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(54) **Title**: TREATMENT OF NUT MIDLINE CARCINOMA

(57) **Abstract**: Disclosed herein is a method of treating nuclear protein in testis (NUT) midline carcinoma (NMC) in a subject in need thereof, comprising administering an effective amount of a bromodomain inhibitor, wherein the effective amount can be determined according to the expression levels of CD11b, which monitors responsiveness of the NMC to the bromodomain inhibitor. Also disclosed herein is a method of determining a bromodomain inhibitor treatment regimen in a subject suffering from NMC.

TREATMENT OF NUT MIDLINE CARCINOMA

RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 62/185,203, filed on June 26, 2015. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] NUT midline carcinoma (or NMC) is a rare form of cancer characterized by a chromosomal rearrangement in which a portion of the NUT (nuclear protein in testis) gene on chromosome 15 is fused to a BRD (bromodomain protein) gene or other, as yet unidentified, gene (French, *et al., Cancer Res.* 63(2):304-307 (2003); French, *et al., J. Clin. Oncol.* 22(20):4135-4139 (2004); French, *et al., Oncogene* 27(15):2237-42 (2008)). NUT fusion genes encode oncoproteins that maintain cells in an undifferentiated state and promote their rapid and uncontrolled growth.

[0003] For the majority of cases, the translocation occurs between NUT and BRD3 or BRD4, leading to a fusion protein consisting of the bromodomains and virtually the entire coding sequence of NUT (French *et al., Ann. Rev. Pathol.* 7:247-265, (2012)). Mechanistically, BRD-NUT appears to block differentiation of the cancer cells in part by decreasing global histone acetylation levels through the sequestration of the histone acetyl transferase p300 in subnuclear foci French, *et al., Oncogene* 27:2237-42 (2008); Schwartz, *et al., Cancer Res.* 71:2686-96, (2011)). Furthermorne, the BRD4-NUT fusion protein binds to the promoter of the *MYC* oncogene and activates expression, contributing to the undifferentiated proliferative state of NMC cells (Grayson, *et al., Oncogene* 33:1736-42 (2014). The frequent involvement of midline structures in the head, neck, mediastinal, and other midline structures, suggest that NMCs arise from primitive neural crest-derived cells. NMCs are very aggressive clinically, respond poorly to conventional chemotherapy, and are almost uniformly fatal. Even with aggressive surgery, radiation therapy, and systemic chemotherapy, the median lifespan is only 6.7 months (French, *et al., Head Neck Pathol.* (2013)). NMC can occur in children and adults of all ages.

[0004] Accordingly, there is a significant unmet need for therapies with increased efficacy in treating NMC. The present application provides such therapies.

SUMMARY OF THE INVENTION

[0005] The present invention relates to a method of nuclear protein in testis (NUT) midline carcinoma (NMC) therapy in a subject in need of treatment, comprising administering an effective amount of an inhibitor of the bromodomain and extra terminal (BET) family of bromodomains. In particular, the methods provided herein are based, in part, on the identification of CD11b expression level on cells (*e.g.*, monocytes) as an indicator of disease responsiveness (or disease activity) to the BET inhibitor.

[0006] In one aspect, the present invention provides a method of treating a patient suffering from nuclear protein in testis (NUT) midline carcinoma (NMC), comprising: administering an effective amount of a bromodomain inhibitor to the patient in a current cycle of a treatment regimen having multiple cycles, each cycle including an on-drug and an off-drug segment, wherein the patient exhibits a CD11b expression reduction of less than about 50% relative to a baseline level, wherein the CD11b expression is measured during the current cycle or a prior cycle.

[0007] In another aspect, the invention provides a method of monitoring a treatment response in a patient suffering from nuclear protein in testis (NUT) midline carcinoma (NMC), comprising: a) administering a predetermined amount of a bromodomain inhibitor to the patient using a treatment regimen having multiple cycles, each cycle comprising an on-drug and an off-drug segment; and b) quantifying a CD11b expression level in a sample collected from the patient; wherein a CD11b expression reduction of about 50% or more relative to a baseline level indicates a positive response to the treatment regimen.

[0008] In other aspects, the invention also provides a method of determining a treatment regimen in a patient suffering from nuclear protein in testis (NUT) midline carcinoma (NMC), comprising: a) administering a predetermined amount of a bromodomain inhibitor to the patient in a first cycle of a treatment regimen having multiple cycles, each cycle including an on-drug and an off-drug segment; b) quantifying a CD11b expression level in a sample collected from the patient during the first cycle; and c) determining whether to modify the first cycle or a subsequent cycle of the treatment regimen, wherein a CD11b expression reduction of less than about 50% relative to a

baseline level indicates that the first cycle or the subsequent cycle should be modified, thereby determining the treatment regimen in a patient suffering from NMC.

[0009] Many cell lines of solid tumor origin, including NMC, are sensitive to bromodomain inhibitors (*e.g.,* TEN-010). Notably, the present invention reveals a relationship between CD11b levels and responsiveness to bromodomain inhibitor therapy that is specific to NMC patients. Thus, CD11b expression levels on cells (*e.g.* monocytes) can be used to monitor responsiveness to a BET inhibitor (*e.g.*, TEN-010) in NMC patients, and to enable modification of a pre-existing BET inhibitor therapy to enhance efficacy of NMC treatment. The ability to monitor and modify an ongoing bromodomain therapy regimen for NMC treatment is particularly desirable given the highly aggressive nature of the disease.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawings will be provided by the Office upon request and payment of the necessary fee.

[0011] The foregoing will be apparent from the following more particular description of example embodiments of the invention, as illustrated in the accompanying drawings in which like reference characters refer to the same parts throughout the different views.

[0012] FIG. 1 shows CD11b levels in patients undergoing treatment with TEN-010. The designation "004-001 (NMC)" indicates the patient as one who is suffering from NMC. "MESF" refers to Molecules of Equivalent Soluble Fluorochrome. Measurements taken at the indicated time points are denoted as "C#D#" wherein C# refers to the cycle number, and D# refers to the number of days in the indicated cycle. For example, C2D1 refers to cycle 2, day 1.

[0013] FIGS. 2A-2F illustrate a comparison of lactate dehydrogenase (LDH) levels and CD11b levels in each patient presented in FIG. 1 undergoing TEN-010 treatment, wherein LDH levels are represented on the left y-axis, and CD11b levels are represented on the right y-axis. "MESF" refers to Molecules of Equivalent Soluble Fluorochrome. Measurements taken at the indicated time points are denoted as "C#D#" wherein C# refers to the cycle number, and D# refers to the number of days in the indicated cycle. For example, C4D22 refers to cycle 4, day 22.

DETAILED DESCRIPTION OF THE INVENTION

[0014] A description of example embodiments of the invention follows.

[0015] A bromodomain is an approximately 110 amino acid protein domain that recognizes monoacetylated lysine residues such as those on the N-terminal tails of histones. Acetylation of lysine residues is a post-translational modification with broad relevance to cellular signalling and disease biology. Enzymes that 'write' (histone acetyltransferases, HATs) and 'erase' (histone deacetylases, HDACs) acetylation sites are an area of extensive research in current drug development, but very few potent inhibitors that modulate the 'reading process' mediated by acetyl lysines have been described. The principal readers of ε-N-acetyl lysine (Kac) marks are bromodomains (BRDs), a diverse family of evolutionary conserved protein-interaction modules. Proteins that contain BRDs have been implicated in the development of a large variety of diseases. Targeting BRD-mediated protein-protein interaction has emerged as a promising avenue for drug development for the large number of diseases that are caused by aberrant acetylation of lysine residues.

[0016] The BET inhibitor class of compounds targets and inhibits the bromodomain and extra terminal (BET) family of proteins. The BET family currently consists of four proteins, the ubiquitously expressed BRD2, BRD3 and BRD4, and the testis specific BRDT (Jones *et al., Genomics* 45:529-34 (1997); Paillisson *et al., Genomics* 89:215-23 (2007)). BET proteins are transcription cofactors that are involved in regulating cell-cycle progression, proliferation, energy homeostasis, spermatogenesis and inflammatory responses (Belkina and Denis, *Nat. Rev. Cancer* 12:465-77, (2012); Matzuk *et al., Cell* 150:673-84, (2012); Nicodeme *et al., Nature* 468:1119-23, (2010); Wang *et al., Biochem. J.* 425:71-83, (2010); Wu and Chiang, *JBC* 282:13141-45, (2007). Each family member contains two amino-terminal tandem bromodomains and a conserved extra-terminal (ET) domain that is also involved in protein-protein interactions (Rahman *et al., Mol. Cell Biol.* 31:2641-52, (2011). BET proteins regulate gene expression by binding acetylated chromatin at promoters and enhancers (see, *e.g.,* Draker *et al., PLoS Genet* 8, e1003047, (2012)). BET proteins stimulate gene expression by recruiting positive transcription elongation factor b (P-TEFb) (see, *e.g.*, Zhang *et al., JBC* 287:43137-55, (2012)). P-TEFb promotes the release of RNA polymerase II from promoters, resulting in productive transcriptional elongation and active gene expression. JQ1 (referred to herein as S-JQ1S), a

known BET inhibitor, specifically binds the bromodomains of the BET family (Bres *et al., Curr. Opin. Cell Biol.* 20:334-340, (2008)).

[0017] The specific BET family member BRD4 has been directly implicated in regulating cell-cycle progression. BRD4 is a bookmarking factor that remains bound to chromosomes during mitosis and recruits P-TEFb to genes to promote activation of an early G1 transcriptional program (Dey *et al., MBC* 20:4899-4909, (2009); Yang *et al., MBC* 28:967-76, (2008)). Decreasing BRD4 protein levels results in the failure of expression of key G1 growth associated genes as the cell exits mitosis, leading to a G1 arrest and apoptosis (Dey *et al., MBC* 20:4899-4909, (2009); Yang *et al., MBC* 28:967-76, (2008); Mochizuki *et al., JBC* 283:9040-48, (2008)). Similar results have been obtained with JQ1 (i.e., JQ1S as described herein) treatment (a known BET inhibitor), which displaces BRD4 from mitotic chromosomes and significantly delays the activation of early G1 genes (Zhao *et al., Nat. Cell Biol.* 13:1295-1304, (2011)).

[0018] BRD3 and BRD4 are also implicated in NMC, which predominantly results from a translocation between the NUT gene and BRD3 and BRD4. NMC occurs in the midline, most commonly in the head, neck, or mediastinum, as poorly differentiated carcinomas with variable degrees of squamous differentiation. This tumor is defined by rearrangement of the "nuclear protein in testis" (NUT) gene on chromosome 15q14. In most cases, NUT is involved in a balanced translocation with the BRD4 gene on chromosome 19p13.1, an event that creates a BRD4-NUT fusion gene. Variant rearrangements, some involving the BRD3 gene, occur in the remaining cases. NMC may be diagnosed by detection of NUT rearrangement by fluorescence in situ hybridization, karyotype analysis, or RT-PCR. Due to its rarity and lack of characteristic histologic features, most cases of NMC currently go unrecognized.

[0019] NMC is defined herein as any malignant epithelial tumor with rearrangement of the NUT gene. In approximately ⅔ of cases, NUT (chromosome 15q14) is fused to BRD4, on chromosome 19p13.1, forming the BRD4-NUT fusion gene. In the remaining ⅓ of cases, the partner gene is BRD3 or other uncharacterized gene. These are referred to as NUT-variant fusion genes. The histologic features of NMC are not distinctive, and diagnosis is based on detection of the NUT rearrangement. NUT rearrangements define NMCs, and for this reason the diagnosis is never in question once rearrangement of NUT has been demonstrated. Methods of detecting such rearrangements are known and available

in the art. Through implication of BRD3 and BRD4 in NMC, BET bromodomain inhibitors also have promise as a targeted therapy for NMC (Filippakopoulos *et al., Nature* 468:1067-73, (2010)).

[0020] Methods of BET Inhibitor Therapy in NUT Midline Carcinoma (NMC)

[0021] The present invention is based, in part, on the identification of CD11b expression level on cells (*e.g.*, monocytes) as an indicator of NMC responsiveness (or disease activity) to a BET inhibitor. CD11b (also known as integrin α_M) is an integrin family member which pairs with CD18 (also known as integrin β_2) to form the CR3 complement heterodimer receptor (also known as Macrophage-1 antigen, Mac-1, integrin $\alpha_M\beta_2$, or macrophage integrin). CD11b is expressed on the surface of leukocytes including monocytes, neutrophils, natural killer cells, granulocytes and macrophages, as well as on some spleen cells and bone marrow cells. Functionally, CD11b regulates leukocyte adhesion and migration to mediate the inflammatory response.

[0022] As exemplified herein, CD11b levels can be used to monitor responsiveness to a bromodomain inhibitor therapy in a patient suffering from NMC, as validated by lactate dehydrogenase (LDH) levels, which is a known clinical marker of cancer progression. Briefly, the present invention demonstrates that, in an NMC patient, CD11b expression levels tracked closely with LDH levels throughout the course of TEN-010 therapy (FIG. 2C). In contrast, CD11b expression levels are independent of LDH levels in non-NMC patients (FIGS. 2A, 2B, and 2D-2F, in particular 2B). Thus, while not wishing to be bound by any theory, monitoring CD11b levels on monocytes enables one to follow NMC disease activity in a patient undergoing a bromodomain inhibitor therapy. As described herein, CD11b levels can be measured to determine whether an NMC patient will require more or less bromodomain inhibitor in subsequent cycle(s) of treatment, or whether an NMC patient will require an earlier or later commencement of a subsequent cycle of bromodomain inhibitor treatment, or any combination thereof.

[0023] Accordingly, in one aspect, the present invention provides a method of treating a patient suffering from nuclear protein in testis (NUT) midline carcinoma (NMC), comprising: administering an effective amount of a bromodomain inhibitor to the patient in a current cycle of a treatment regimen having multiple cycles, each cycle including an on-drug and an off-drug segment, wherein the patient exhibits a CD11b expression reduction

of less than about 50% relative to a baseline level, wherein the CD11b expression is measured during the current cycle or a prior cycle.

[0024] As used herein "treating" includes any evidence of antitumor activity including, but not limited to, delaying or preventing the progression of clinical indications related to the NMC. For example, disease progression can be slowed. Additional, evidence of antitumor activity includes reduction in tumor growth, or prevention of further growth or reduction in tumor metabolic activity, as detected by standard imaging methods known in the art, including, for example, computed tomography (CT) scan, magnetic resonance imaging (MRI), chest x-ray, and CT/positron emission tomography (CT/PET) scans, and evaluated according to guidelines and methods known in the art. For example, responses to treatment can be evaluated through the Response Evaluation Criteria in Solid Tumors (RECIST) (Revised RECIST Guideline version 1.1; see Eisenhauer *et al.*, *Eur. J. Cancer* 45(2):228-47, 2009). Thus, in some embodiments, "treating" refers to a Complete Response (CR), which is defined according to the RECIST guideline as the disappearance of all target lesions, or a Partial Response (PR), which is defined as at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. Other means for evaluating tumor response to treatment include evaluation of tumor markers and evaluation of performance status (*e.g.*, assessment of creatinine clearance; see Cockcroft and Gault, *Nephron.* 16:31-41, 1976). Response evaluation for lymphoma patients is based upon Lugano Classification.

[0025] The terms "bromodomain inhibitor" and "BET inhibitor" are used interchangebly. Both terms refer to a class of compounds that targets and inhibits the bromodomain and extra terminal (BET) family of proteins. Examples of bromodomain inhibitors are described in detail herein. In one embodiment, the bromodomain inhibitor is TEN-010.

[0026] As used herein, the term "patient" refers to a mammal, preferably a human, but can also mean an animal in need of veterinary treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like).

[0027] The term "effective amount" as used herein refers to an effective dosage over a specified treatment cycle within a treatment regimen that includes multiple cycles, each cycle comprising on-drug and off-drug segments, such that the effect of the treatment

regimen achieves and maintains a CD11b expression level during any cycle that is at least 50% reduced as compared to baseline levels of CD11b (*i.e.*, 50% or more reduction in CD11b compared to a baseline level). In certain embodiments, the effect of the treatment regimen achieves and maintains 60%, 70%, 80%, or 90% or more reduction in CD11b compared to a baseline level.

[0028] As used herein, a "cycle" within a treatment regimen refers to a specified period of time (*e.g.*, number of days) that consists of "on-drug" and "off-drug" segments, wherein "on-drug" refers to a period of time during which drug is administered, whereas "off-drug" refers to a period of time during which no drug is administered. In one embodiment, a cycle consists of one on-drug segment and one off-drug segment. In another embodiment, a cycle can consist of one continuous on-drug segment with no off-drug segment (*e.g.*, continuous dosing), wherein the cycle is still defined as having a specified number of days (*e.g.*, 28 days). In this scenario, the delineation of one cycle from the next cycle is determined by the number of specified days (*e.g.*, 28 days); a subsequent cycle can be designed to have the same, higher, or lower dose of bromodomain inhibitor as compared to a prior cycle, as determined according to the methods of the invention.

[0029] As used herein, a "current" cycle refers to the cycle presently ongoing.

[0030] As used herein, a "prior" cycle refers to any prior cycle within a treatment regimen, including a cycle that occurred one cycle prior to the current cycle, as well as a cycle that occurred more than one cycle prior to the current cycle.

[0031] A cycle can consist of a number of days deemed appropriate by a skilled medical professional, and will vary depending on the nature of the disease, the dose of the drug being administered, the health of the patient, the intended result, and the like. By way of example, a cycle of a bromodomain inhibitor treatment regimen for treating NMC can be about 15 to about 35 days. In one embodiment, a cycle can be about 28 days, having 21 on-drug days, and 7 off-drug days. As will be appreciated by those of skill in the art, a cycle having any combination of the number of "on" and "off" drug days (including zero off-drug days) can be designed as deemed appropriate by a skilled medical professional.

[0032] A patient's sample can be obtained and the CD11b expression level measured during any portion of a segment (on or off) of a cycle for comparison against a baseline level to determine and/or administer an effective amount of a bromodomain inhibitor during the current cycle. For example, the CD11b expression level can be measured during the

off-drug segment of a prior cycle. If, by way of example, the CD11b expression level during any portion of the off-drug segment of the prior cycle is reduced by less than about 50% relative to a baseline level (*i.e.*, CD11b level is higher than desired and treatment is not effective), then a higher dose of bromodomain inhibitor can be administered in the current cycle. Alternatively, or in addition, the number of days in the off-drug segment of the prior cycle can be shortened (relative to a pre-determined number of days in the off-segment of a cycle) to begin the current cycle earlier. In contrast, if it is determined that the CD11b expression level is favorable (*i.e.,* treatment is effective), then the bromodomain inhibitor dose can be maintained or decreased.

[0033] As another example, if the CD11b expression level during the on-drug segment of the current cycle is reduced by less than about 50% relative to a baseline level, then a higher dose of bromodomain inhibitor can be administered in the ongoing current cycle. In this second example, it is also possible to increase the number of days in the on-drug segment of the current cycle in addition to, or alternatively to, increasing the dose of bromodomain inhibitor.

[0034] As used herein, the "baseline" level refers to the level of CD11b expression measured in an NMC patient prior to receiving the first dose of treatment (at pre-dose).

[0035] In certain embodiments, the sample obtained from the patient is a blood sample.

[0036] In other aspects, the present invention also provides a method of determining a treatment regimen in a patient suffering from NMC, comprising: a) administering a predetermined amount of a bromodomain inhibitor to the patient in a first cycle of a treatment regimen having multiple cycles, each cycle including an on-drug and an off-drug segment; b) quantifying a CD11b expression level in a sample collected from the patient during the first cycle; and c) determining whether to modify the first cycle or a subsequent cycle of the treatment regimen, wherein a CD11b expression reduction of less than about 50% relative to a baseline level indicates that the first cycle or the subsequent cycle should be modified, thereby determining the treatment regimen in a patient suffering from NMC.

[0037] As used herein, a "predetermined amount" refers to an amount of a bromodomain inhibitor determined for a patient based, for example, on criteria previously determined, but that which is potentially currently not effective due to, for example, a change in disease status.

[0038] As used herein, a "first cycle" refers to a current, ongoing cycle of treatment, and does not necessarily refer to the actual first cycle of a bromodomain inhibitor treatment regimen.

[0039] In certain embodiments, the first cycle or the subsequent cycle is modified by increasing the length of the on-drug segment, decreasing the length of the off-drug segment, increasing the predetermined amount of the bromodomain inhibitor, or a combination thereof. The table below summarizes some examples of possible scenarios and modifications to a treatment regimen, when it is determined that CD11b expression reduction is less than about 50% relative to a baseline level (*i.e.*, CD11b level is higher than desired and disease responsiveness is not at a suitable level). If it is determined that CD11b expression reduction is favorable (*i.e.,* disease responsiveness is at a suitable level), then it can be desirable to, *e.g.,* decrease the bromodomain inhibitor dose, or delay the commencement of the next cycle, or both.

[0040] Table 1. Possible modifications to bromodomain treatment regimen

When CD11b measured	Possible modifications if CD11b expression reduction is less than about 50% relative to baseline level
On-drug segment of current cycle	- increase the number of days in the on-drug segment of the current cycle - increase the dose of bromodomain inhibitor during the on-drug segment of the current cycle - increase the dose of bromodomain inhibitor in the subsequent (*e.g.* next) cycle - shorten number of days in the off-drug segment of the current cycle - any combination of above - if a cycle consists of only an on-drug segment with no off-drug segment (*e.g.* continuous dosing), then increase the dose of bromodomain inhibitor in the current cycle, or the next cycle of "on-drug only" cycle
Off-drug segment of current cycle	- shorten number of days in current off-drug segment (*i.e.*, commence subsequent cycle earlier) - increase number of days on-drug segment of subsequent cycle - increase dose of bromodomain inhibitor in subsequent cycle - shorten off-drug segment of subsequent cycle - any combination of above

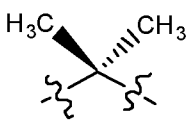
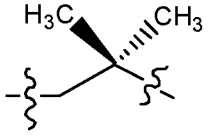
[0041] CD11b expression levels on cells (*e.g.,* monocytes) can be quantified using a variety of methods known and available in the art. In one example, CD11b expression levels on monocytes can be quantitued by flow cytometry.

[0042] In another aspect, the present invention provides a method of monitoring a treatment response in a patient suffering from NMC, comprising: a) administering a predetermined amount of a bromodomain inhibitor to the patient using a treatment regimen having multiple cycles, each cycle comprising an on-drug and an off-drug segment; and b) quantifying a CD11b expression level in a sample collected from the patient; wherein a CD11b expression reduction of about 50% or more relative to a baseline level indicates a positive response to the treatment regimen.

[0043] **BET Inhibitors**

[0044] ***Definitions***

[0045] "Alkyl" means an optionally substituted saturated aliphatic branched or straight-chain monovalent hydrocarbon radical having the specified number of carbon atoms. Thus, "(C_1-C_6) alkyl" means a radical having from 1-6 carbon atoms in a linear or branched arrangement. "(C_1-C_6)alkyl" includes methyl, ethyl, propyl, iso-propyl (or *i*-propyl), butyl, sec-butyl, tert-butyl, pentyl, hexyl and the like. The terms "alkyl", "alkoxy", "hydroxyalkyl", "haloalkyl", "aralkyl", "alkoxyalkyl", "alkylamine", "dialkylamine", "alkylamino", "dialkylamino", "alkoxycarbonyl"and the like, used alone or as part of a larger moiety includes both straight and branched saturated chains containing one to twelve carbon atoms.

[0046] "Alkylene" means an optionally substituted saturated aliphatic branched or straight-chain divalent hydrocarbon radical having the specified number of carbon atoms. Thus, "(C_1-C_6)alkylene" means a divalent saturated aliphatic radical having from 1- 6 carbon atoms in a linear arrangement, *e.g.*, -[$(CH_2)_n$]-, where n is an integer from 1 to 6, "(C_1-C_6)alkylene" includes methylene, ethylene, propylene, butylene, pentylene and hexylene. Alternatively, "(C_1-C_6)alkylene" means a divalent saturated radical having from 1-6 carbon atoms in a branched arrangement, for example: -[$(CH_2CH_2CH_2CH_2CH(CH_3)]$-, -[$(CH_2CH_2CH_2CH_2C(CH_3)_2]$-, -[$(CH_2C(CH_3)_2CH(CH_3))]$-, and the like. A specific branched C_3-alkylene is  and a specific C_4-alkylene is  .

[0047] "Alkenyl" means branched or straight-chain monovalent hydrocarbon radical containing at least one double bond and having specified number of carbon atoms. Alkenyl

may be mono or polyunsaturated, and may exist in the E or Z onfiguration. For example, "(C_2-C_6)alkenyl" means a radical having from 2-6 carbon atoms in a linear or branched arrangement.

[0048] "Alkynyl" means branched or straight-chain monovalent hydrocarbon radical containing at least one triple bond and having specified number of carbon atoms. For example, "(C_2-C_6)alkynyl" means a radical having from 2-6 carbon atoms in a linear or branched arrangement.

[0049] Each alkyl or alkylene in Structural Formulas depicted below can be optionally and independently substituted with one or more substituents.

[0050] "Aryl" or "aromatic" means an aromatic monocyclic or polycyclic (*e.g.* bicyclic or tricyclic) carbon-containing ring system. In one embodiment, "aryl" is a 6-12 membered monocyclic or bicyclic system. Aryl systems include, but are not limited to, phenyl, naphthalenyl, fluorenyl, indenyl, azulenyl, and anthracenyl.

[0051] "Cycloalkyl" means a saturated aliphatic cyclic hydrocarbon ring. "Cycloalkyl" includes 3- to 12- membered saturated aliphatic cyclic hydrocarbon rings. Thus, "(C_3-C_7)cycloalkyl" means a hydrocarbon radical of a 3- to 7-membered saturated aliphatic cyclic hydrocarbon ring. A (C_3-C_7)cycloalkyl includes, but is not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

[0052] A cycloalkyl moiety can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic, or polycyclic. For example, monocyclic (C_3-C_8)cycloalkyl means a radical having from 3 to 8 carbon atoms arranged in a monocyclic ring. Monocyclic (C_3-C_8)cycloalkyl includes, but is not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctane.

[0053] Monocyclic ring systems have a single ring structure. They include saturated or unsaturated aliphatic cyclic hydrocarbon rings (*e.g.*, cycloalkyl, cycloalkenyl, or cycloalkynyl) or aromatic hydrocarbon rings (*e.g.*, aryl) having the specified number of carbon atoms. The monocyclic ring system can optionally contain 1 to 5 heteroatoms in the ring structure wherein each heteroatom is independently selected from the group consisting O, N and S (*e.g.*, heterocycloalkyl, heterocycloalkenyl, heterocycloalkynyl or heteroaryl). When the heteroatom is N, it can be optionally substituted with alkyl, cycloalkyl, alkylene-cycloalkyl, heterocycloalkyl, alkylene-heterocycloalkyl, aryl, alkylene-aryl, heteroaryl, alkylene-heteroaryl, each of which can be optionally substituted with one or more halogen,

=O, hydroxy, alkoxy, haloalkyl, alkyl, etc. When the heteroatom is S, it can be optionally mono- or di-oxygenated (*i.e.*, -S(O)- or -$S(O)_2$-). Examples of monocyclic ring systems include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctane, azetidine, pyrrolidine, piperidine, piperazine, azepane hexahydropyrimidine, tetrahydrofuran, tetrahydropyran, oxepane, tetrahydrothiophene, tetrahydrothiopyran, isoxazolidine, 1,3-dioxolane, 1,3-dithiolane, 1,3-dioxane, 1,4-dioxane, 1,3-dithiane, 1,4-dithiane, morpholine, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-2H-1,2-thiazine, tetrahydro-2H-1,2-thiazine 1,1-dioxide, and isothiazolidine 1,1-dioxide, tetrahydrothiophene 1-oxide, tetrahydrothiophene 1,1-dioxide, thiomorpholine 1-oxide, thiomorpholine 1,1-dioxide, tetrahydro-2H-1,2-thiazine 1,1-dioxide, and isothiazolidine 1,1-dioxide, pyrrolidin-2-one, piperidin-2-one, piperazin-2-one, and morpholin-2-one.

[0054] Bicyclic ring systems have two rings that have at least one ring atom in common. Bicyclic ring systems include fused, bridged and spiro ring systems. The two rings can both be aliphatic (*e.g.*, cycloalkyl, cycloalkene, cycloalkyne, or heterocycloalkyl), both be aromatic (*e.g.*, aryl or heteroaryl), or a combination thereof. The bicyclic ring systems can optionally contain 1 to 5 heteroatoms in the ring structure wherein each heteroatom is independently selected from the group consisting O, N and S. When the heteroatom is N, it can be substituted with H, alkyl, cycloalkyl, alkylene-cycloalkyl, heterocycloalkyl, alkylene-heterocycloalkyl, aryl, alkylene-aryl, heteroaryl, alkylene-heteroaryl, each of which can be optionally substituted with one or more halogen, =O, hydroxy, alkoxy, haloalkyl, alkyl, etc. When the heteroatom is S, it can be optionally mono- or di-oxygenated (i.e. -S(O)- or -$S(O)_2$-).

[0055] A fused bicyclic ring system has two rings which have two adjacent ring atoms in common. The two rings can both be aliphatic (*e.g.*, cycloalkyl, cycloalkene, cycloalkyne, or heterocycloalkyl), both be aromatic (*e.g.*, aryl or heteroaryl), or a combination thereof. For example, the first ring can be cycloalkyl or heterocycloalkyl, and the second ring can be a cycloalkyl, cycloalkene, cycloalkyne, aryl, heteroaryl or a heterocycloalkyl. For example, the second ring can be a (C_3-C_6)cycloalkyl, such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Alternatively, the second ring can be an aryl ring (*e.g.*, phenyl). Examples of fused bicyclic ring systems include, but are not limited to, 6,7,8,9-tetrahydro-5H-benzo[7]annulene, 2,3-dihydro-1H-indene, octahydro-1H-indene, tetrahydronaphthalene,

decahydronaphthalene, indoline, isoindoline, 2,3-dihydro-1H-benzo[d]imidazole, 2,3-dihydrobenzo[d]oxazole, 2,3-dihydrobenzo[d]thiazole, octahydrobenzo[d]oxazole, octahydro-1H-benzo[d]imidazole, octahydrobenzo[d]thiazole, octahydrocyclopenta[c]pyrrole, 3-azabicyclo[3.1.0]hexane, 3-azabicyclo[3.2.0]heptane, 5,6,7,8-tetrahydroquinoline and 5,6,7,8-tetrahydroisoquinoline, and 2,3,4,5-tetrahydrobenzo[b]oxepine.

[0056] A spiro bicyclic ring system has two rings which have only one ring atom in common. The two rings can both be aliphatic (*e.g.*, cycloalkyl, cycloalkene, cycloalkyne, or heterocycloalkyl), both be aromatic (*e.g.*, aryl or heteroaryl), or a combination thereof. For example, the first ring can be a cycloalkyl or a heterocycloalkyl and the second ring can be a cycloalkyl, a cycloalkene, a cycloalkyne, an aryl, a heteroaryl, or a heterocycloalkyl. Examples of spiral bicyclic ring systems include, but are not limited to, spiro[2.2]pentane, spiro[2.3]hexane, spiro[3.3]heptane, spiro[2.4]heptane, spiro[3.4]octane, spiro[2.5]octane, azaspiro[4.4]nonane, 7-azaspiro[4.4]nonane, azaspiro[4.5]decane, 8-azaspiro[4.5]decane, azaspiro[5.5]undecane, 3-azaspiro[5.5]undecane, and 3,9-diazaspiro[5.5]undecane.

[0057] A bridged bicyclic ring system has two rings which have three or more adjacent ring atoms in common. The two rings can both be aliphatic (*e.g.*, cycloalkyl, cycloalkene, cycloalkyne, or heterocycloalkyl), both be aromatic (*e.g.*, aryl or heteroaryl), or a combination thereof. For example, the first ring can be a cycloalkyl or a heterocycloalkyl and the other ring is a cycloalkyl, a cycloalkene, a cycloalkyne, an aryl, a heteroaryl or a heterocycloalkyl. Examples of bridged bicyclic ring systems include, but are not limited to, bicyclo[1.1.0]butane, bicyclo[1.2.0]pentane, bicyclo[2.2.0]hexane, bicyclo[3.2.0]heptane, bicyclo[3.3.0]octane, bicyclo[4.2.0]octane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.1]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, bicyclo[3.3.2]decane bicyclo[3.3.3]undecane, azabicyclo[3.3.1]nonane, 3-azabicyclo[3.3.1]nonane, azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.1]octane, 6-azabicyclo[3.2.1]octane and azabicyclo[2.2.2]octane, 2-azabicyclo[2.2.2]octane, and 2-oxabicyclo[2.2.2]octane.

[0058] Polycyclic ring systems have more than two rings (*e.g.*, three rings resulting in a tricyclic ring system) and adjacent rings have at least one ring atom in common. Polycyclic ring systems include fused, bridged and spiro ring systems. A fused polycyclic ring system has at least two rings that have two adjacent ring atoms in common. A spiro polycyclic ring system has at least two rings that have only one ring atom in common. A bridged

polycyclic ring system has at least two rings that have three or more adjacent ring atoms in common. Examples of polycyclic ring systems include, but are not limited to, tricyclo[3.3.1.$0^{3,7}$]nonane (noradamantane), tricyclo[3.3.1.$1^{3,7}$]decane (adamantane) and 2,3-dihydro-1H-phenalene.

[0059] "Cycloalkene" means an aliphatic cyclic hydrocarbon ring having one or more double bonds in the ring. "Cycloalkene" includes 3- to 12-membered unsaturated aliphatic cyclic hydrocarbon rings. Thus, "(C_3-C_7)cycloalkene" means a hydrocarbon radical of a 3- to 7- membered unsaturated aliphatic cyclic hydrocarbon ring. A (C_3-C_7) cycloalkene includes, but is not limited to cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl.

[0060] A cycloalkene moiety can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic, or polycyclic. For example, monocyclic (C_3-C_8)cycloalkene means a radical having from 3 to 8 carbon atoms arranged in a monocyclic ring. Monocyclic (C_3-C_8)cycloalkene includes, but is not limited to, cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl and cycloheptenyl.

[0061] "Cycloalkyne" means an aliphatic cyclic hydrocarbon ring having one or more triple bonds in the ring. "Cycloalkyne" includes 3- to 12-membered unsaturated aliphatic cyclic hydrocarbon rings. Thus, "(C_3-C_7)cycloalkyne" means a hydrocarbon radical of a 3- to 7-membered unsaturated aliphatic cyclic hydrocarbon ring. A (C_3-C_7) cycloalkyne includes, but is not limited to cyclopropynyl, cyclobutynyl, cyclopentynyl, cyclohexynyl and cycloheptynyl.

[0062] A cycloalkyne moiety can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic, or polycyclic. For example, monocyclic (C_3-C_8)cycloalkyne means a radical having from 3 to 8 carbon atoms arranged in a monocyclic ring. Monocyclic (C_3-C_8)cycloalkyne includes, but is not limited to, cyclopropynyl, cyclobutynyl, cyclopentynyl, cyclohexynyl, and cycloheptynyl.

[0063] "Hetero" refers to the replacement of at least one carbon atom member in a ring system with at least one heteroatom selected from N, S, and O. "Hetero" also refers to the replacement of at least one carbon atom member in an acyclic system. A hetero ring system or a hetero acyclic system may have 1, 2, 3, 4 or 5 carbon atoms members replaced by a heteroatom.

[0064] "Heterocycloalkyl" means a cyclic 4- to 12-membered saturated aliphatic ring containing 1, 2, 3, 4 or 5 heteroatoms independently selected from N, O or S. When one heteroatom is S, it can be optionally mono- or di-oxygenated (*i.e.* -S(O)- or -$S(O)_2$-). When one heteroatom is N, it can be optionally substituted with alkyl, cycloalkyl, alkylene-cycloalkyl, heterocycloalkyl, alkylene-heterocycloalkyl, aryl, alkylene-aryl, heteroaryl, alkylene-heteroaryl, each of which can be optionally substituted with one or more halogen, =O, hydroxy, alkoxy, haloalkyl, alkyl, etc.

[0065] A heterocycloalkyl moiety can be monocyclic, fused bicyclic, bridged bicyclic, spiro bicyclic, or polycyclic. For example, monocyclic (C_3-C_8) heterocycloalkyl means a 3- to 8 membered saturated aliphatic ring containing 1, 2, 3, 4, or 5 heteroatoms independently selected from N, O or S arranged in a monocyclic ring. Examples of monocyclic heterocycloalkyls include, but are not limited to, azetidine, pyrrolidine, piperidine, piperazine, azepane, hexahydropyrimidine, tetrahydrofuran, tetrahydropyran, morpholine, thiomorpholine, thiomorpholine 1,1-dioxide, tetrahydro-2H-1,2-thiazine, tetrahydro-2H-1,2-thiazine 1,1-dioxide, isothiazolidine, isothiazolidine 1,1-dioxide.

[0066] "Heteroaryl" or "heteroaromatic ring" means a 5- to 12-membered monovalent heteroaromatic monocyclic or bicyclic ring radical. A heteroaryl contains 1, 2, 3, 4, or 5 heteroatoms independently selected from N, O, and S. Heteroaryls include, but are not limited to furan, oxazole, thiophene, 1,2,3-triazole, 1,2,4-triazine, 1,2,4-triazole, 1,2,5-thiadiazole 1,1-dioxide, 1,2,5-thiadiazole 1-oxide, 1,2,5-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,3,5-triazine, imidazole, isothiazole, isoxazole, pyrazole, pyridazine, pyridine, pyridine-N-oxide, pyrazine, pyrimidine, pyrrole, tetrazole, and thiazole. Bicyclic heteroaryl rings include, but are not limited to, bicyclo[4.4.0] and bicyclo[4.3.0] fused ring systems such as indolizine, indole, isoindole, indazole, benzimidazole, benzothiazole, purine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, benzofuran, 1,8-naphthyridine, and pteridine.

[0067] In a particular embodiment, each cycloalkyl, cycloalkene, cycloalkyne, cycloheterocycloalkyl, aryl and heteroaryl is optionally and independently substituted with 1 to 4. Exemplary substituents include, but are not limited to, halo, -(C_1-C_4)alkyl, -OH, =O, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, and -C(O)-(C_1-C_4)alkyl.

[0068] "Halogen," as used herein, refers to fluorine, chlorine, bromine, or iodine.

[0069] "Alkoxy" refers to the group –O-R where R is "alkyl", "cycloalkyl", "alkenyl", or "alkynyl". "(C_1-C_6)alkoxy" includes methoxy, ethoxy, ethenoxy, propoxy, butoxy, pentoxy, and the like.

[0070] Haloalkyl and halocycloalkyl include mono, poly, and perhalo-substituted alkyl or cycloalkyl groups where each halogen is independently selected from fluorine, chlorine, and bromine.

[0071] "Halogen" and "halo" are interchangeably used herein and each refers to fluorine, chlorine, bromine, or iodine.

[0072] "Fluoro" means -F.

[0073] As used herein, fluoro-substituted (C_1-C_4)alkyl means a (C_1-C_4)alkyl substituted with one or more -F groups. Examples of fluoro-substituted-(C_1-C_4)alkyl include, but are not limited to, $-CF_3$, $-CH_2CF_3$, $-CH_2CF_2H$, $-CH_2CH_2F$ and $-CH_2CH_2CF_3$.

[0074] "Naturally occurring amino acid side chain moiety" refers to any amino acid side chain moiety present in a natural amino acid.

[0075] The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound disclosed herein, or any other compound delineated herein (*e.g.*, a compound of Formulas I-III), having a basic functional group, such as an amino functional group, and a pharmaceutically acceptable inorganic or organic acid. For example, an acid salt of a compound of the present invention containing an amine or other basic group can be obtained by reacting the compound with a suitable organic or inorganic acid, resulting in pharmaceutically acceptable anionic salt forms. Examples of anionic salts include the acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, glyceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylsulfate, mucate, napsylate, nitrate, pamoate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, and triethiodide salts.

[0076] The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound disclosed herein (*e.g.*, a compound of Formulas I-III) or any other compound delineated herein, having an acidic functional group, such as a carboxylic acid functional group, and a pharmaceutically acceptable inorganic or organic base.

[0077] Salts of the compounds used in the methods of the present invention containing a carboxylic acid or other acidic functional group can be prepared by reacting with a suitable base. Such a pharmaceutically acceptable salt may be made with a base which affords a pharmaceutically acceptable cation, which includes alkali metal salts (especially sodium and potassium), alkaline earth metal salts (especially calcium and magnesium), aluminum salts and ammonium salts, as well as salts made from physiologically acceptable organic bases such as trimethylamine, triethylamine, morpholine, pyridine, piperidine, picoline, dicyclohexylamine, N,N'-dibenzylethylenediamine, 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine, tri-(2-hydroxyethyl)amine, procaine, dibenzylpiperidine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine, collidine, quinine, quinoline, and basic amino acids such as lysine and arginine.

[0078] The invention also includes various isomers of the compounds disclosed herein and mixtures thereof. Certain compounds of the present invention may exist in various stereoisomeric forms. Stereoisomers are compounds which differ only in their spatial arrangement. Enantiomers are pairs of stereoisomers whose mirror images are not superimposable, most commonly because they contain an asymmetrically substituted carbon atom that acts as a chiral center. "Enantiomers" means one of a pair of molecules that are mirror images of each other and are not superimposable. Diastereomers are stereoisomers that are not related as mirror images, most commonly because they contain two or more asymmetrically substituted carbon atoms. "*R*" and "*S*" represent the configuration of substituents around one or more chiral carbon atoms. When a chiral center is not defined as R or S, either a pure enantiomer or a mixture of both configurations is present.

[0079] "Racemate" or "racemic mixture" means a compound of equimolar quantities of two enantiomers, wherein such mixtures exhibit no optical activity (*i.e.*, they do not rotate the plane of polarized light).

[0080] The compounds of the present invention may be prepared as individual isomers by either isomer-specific synthesis or resolved from an isomeric mixture. Conventional resolution techniques include forming the salt of a free base of each isomer of an isomeric pair using an optically active acid (followed by fractional crystallization and regeneration of the free base), forming the salt of the acid form of each isomer of an isomeric pair using an optically active amine (followed by fractional crystallization and regeneration of the free

acid), forming an ester or amide of each of the isomers of an isomeric pair using an optically pure acid, amine or alcohol (followed by chromatographic separation and removal of the chiral auxiliary), or resolving an isomeric mixture of either a starting material or a final product using various well known chromatographic methods.

[0081] When the stereochemistry of a disclosed compound is named or depicted by structure, the named or depicted stereoisomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight pure relative to the other stereoisomers. When a single enantiomer is named or depicted by structure, the depicted or named enantiomer is at least 60%, 70%, 80%, 90%, 99% or 99.9% by weight optically pure. Percent optical purity by weight is the ratio of the weight of the enantiomer that is present divided by the combined weight of the enantiomer that is present and the weight of its optical isomer.

[0082] As used herein, the term "tautomers" refers to isomers of organic molecules that readily interconvert by tautomerization, in which a hydrogen atom or proton migrates in the reaction, accompanied in some occasions by a switch of a single bond and an adjacent double bond.

[0083] Compounds useful for practicing the methods described herein are described in the following paragraphs, for example with references to structural formulas reproduced below. Values and alternative values for the variables in structural formulas reproduced below or an enantiomer, a diastereomer, a tautomer, or a pharmaceutically acceptable salt thereof and for each of the embodiments described herein are provided in the following paragraphs. It is understood that the invention encompasses all combinations of the substituent variables (i.e., R_1, R_2, R_3, etc.) defined herein.

[0084] ***Example BET Inhibitors – Structural Formulas (I) through (VIII)***

[0085] In an example embodiment, bromodomain inhibitors for use in the methods of the invention, as well as methods of preparing same, are described, for example, in the U.S. Patent No. 8,981,083, and in the International Application PCT/US2015/018118, filed on February 27, 2015, published as WO 2015/131113. The teachings of this publication are incorporated herein by reference in its entirety.

[0086] Example compounds suitable for use with the methods of the present invention include those represented by structural formulas (I) through (VIII) or a pharmaceutically acceptable salt thereof. Values and alternative values for the variables in Formulas (I)-(VIII) or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, and

for each of the embodiments described herein are provided in the following paragraphs. It is understood that the invention encompasses all combinations of the substituent variables (i.e., R_1, R_2, R_3, etc.) defined herein.

[0087] X is N or CR_3;

[0088] R_3 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally substituted with 1 to 4 substituents independently selected from -F, -Cl, -Br, -OH, =O, -S(O)-, -$S(O)_2$-, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[0089] Alternatively, R_3 is selected from the group consisting of : H and -(C_1-C_4)alkyl. Further, R_3 is selected from the group consisting of: H, methyl, ethyl, propyl, butyl, sec-butyl and tert-butyl. Specifically, R_3 is H or methyl.

[0090] R_B is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, or –COO–R_4, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6;

[0091] Alternatively, R_B is H, -(C_1-C_4)alkyl, or -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, wherein each is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6.

[0092] Further, R_B is H, methyl, ethyl, propyl, butyl, sec-butyl, tert-butyl, -COOH, -COOMe, -COOEt, -$COOCH_2OC(O)CH_3$, trifluoromethyl, -CF_2-CF_3, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, methoxytrifluoromethyl, -CH_2-O-CF_2-CF_3, hydroxymethyl, hydroxyethyl, -CH_2-NH_2, -$(CH_2)_2$-NH_2, -CH_2-$NHCH_3$, or -$(CH_2)_2$-$NHCH_3$. In another alternative, R_B is H, methyl, ethyl, trifluoromethyl, methoxymethyl, ethoxymethyl, hydroxymethyl, hydroxyethyl, -CH_2-NH_2, or -$(CH_2)_2$-NH_2.

[0093] Specifically, R_B is H, methyl, ethyl, trifluoromethyl, methoxymethyl, ethoxymethyl, hydroxymethyl, or -CH_2-NH_2. Alternatively, R_B is H.

[0094] Ring A is -(C_6-C_{10})aryl or -(C_5-C_{10})heteroaryl. Alternatively, ring A is thiofuranyl, phenyl, naphthyl, biphenyl, tetrahydronaphthyl, indanyl, pyridyl, furanyl,

indolyl, pyrimidinyl, pyridizinyl, pyrazinyl, imidazolyl, oxazolyl, thienyl, thiazolyl, triazolyl, isoxazolyl, quinolinyl, pyrrolyl, pyrazolyl, or 5,6,7,8-tetrahydroisoquinolinyl.

[0095] Alternatively, ring A is 5- or 6-membered aryl or heteroaryl. Ring A is thiofuranyl, phenyl, pyridyl, furanyl, indolyl, pyrimidinyl, pyridizinyl, pyrazinyl, imidazolyl, oxazolyl, thienyl, thiazolyl, triazolyl, isoxazolyl, pyrrolyl, or pyrazolyl. Further, ring A is phenyl or thienyl. Specifically, ring A is thienyl.

[0096] Each R_A is independently H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally substituted with 1 to 4 substituents independently selected from -F, -Cl, -Br, -OH, =O, -S(O)-, -$S(O)_2$-, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O- (C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl); or any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group.

[0097] Alternatively, each R_A is independently H or -(C_1-C_4)alkyl. Each R_A is independently H, methyl, ethyl, propyl, butyl, sec-butyl, or tert-butyl. Specifically, each R_A is independently H or methyl.

[0098] Alternatively, any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group. Further, any two R_A together with the atoms to which each is bound form a fused aryl.

[0099] R is -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O -(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O- (C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro-substituted-(C_1-C_4)alkyl), -$S(O)_o$-(C_1-C_4)alkyl, -NR_7R_8 and CN.

[00100] Alternatively, R is-(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O -(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro-substituted-(C_1-C_4)alkyl), -$S(O)_o$-(C_1-C_4)alkyl, -NR_7R_8 and CN.

[00101] R is phenyl or pyridinyl, wherein each is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O -(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro-substituted-(C_1-C_4)alkyl), -$S(O)_o$-(C_1-C_4)alkyl, -NR_7R_8 and CN.

[00102] Further, R is phenyl or pyridinyl wherein each is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -methyl, ethyl, propyl, butyl, sec-butyl, tert-butyl, -COOH, -COOMe, -COOEt, -$COOCH_2OC(O)CH_3$, trifluoromethyl, -CF_2-CF_3, methoxymethyl, methoxyethyl, methoxypropyl, ethoxymethyl, ethoxyethyl, methoxytrifluoromethyl, -CH_2-O-CF_2-CF_3, hydroxymethyl, hydroxyethyl, -CH_2-NH_2, -$(CH_2)_2$-NH_2, -CH_2-$NHCH_3$, -$(CH_2)_2$-$NHCH_3$ and CN. Alternatively, R is phenyl or pyridinyl wherein each is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -and OH.

[00103] R is phenyl optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -and OH. Alternatively, R is phenyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of: -F, -Cl, -Br, -and OH. Further, R is phenyl optionally substituted with a substituent independently selected from the group consisting of: -F, -Cl, -Br, -and OH. Specifically, R is p-Cl-phenyl, o-Cl-phenyl, m-Cl-phenyl, p-F-phenyl, o-F-phenyl, m-F-phenyl or pyridinyl.

[00104] R_1 is -$(CH_2)_n$-L, in which n is 0-3 and L is H, -C(O)O–R_9, -CO-$N(R_9R_{10})$, -NR_9R_{10}, -$N(R_{10})C(O)OR_9$, or -$N(R_{10})C(O)R_9$.

[00105] Alternatively, R_1 is -$(CH_2)_n$-L, in which n is 0-3, and L is-C(O)O–R_9. R_1 is -$(CH_2)_n$-L, in which n is 1-3, and L is-C(O)O–R_9. Further, R_1 is-$(CH_2)_n$-L, in which n is 1-2, and L is-C(O)O–R_9. Alternatively, R_1 is-$(CH_2)_n$-L, in which n is 1, and L is -C(O)O–R_9.

[00106] Further, R_1 is -$(CH_2)_n$-L, in which n is 0-3, and L is -CO-$N(R_9R_{10})$. R_1 is -$(CH_2)_n$-L, in which n is 1-3, and L is -CO-$N(R_9R_{10})$. R_1 is -$(CH_2)_n$-L, in which n is 1-2, and L is -CO-$N(R_9R_{10})$. Alternatively, R_1 is -$(CH_2)_n$-L, in which n is 1, and L is -CO-$N(R_9R_{10})$.

[00107] In another alternative, R_1 is -$(CH_2)_n$-L, in which n is 0-3, and L is -NR_9R_{10}. R_1 is -$(CH_2)_n$-L, in which n is 1-3, and L is -NR_9R_{10}. Further, R_1 is -$(CH_2)_n$-L, in which n is 1-2, and L is -NR_9R_{10}. Alternatively, R_1 is -$(CH_2)_n$-L, in which n is 1, and L is -NR_9R_{10}.

[00108] R_1 is -$(CH_2)_n$-L, in which n is 0-3, and L is -$N(R_{10})C(O)OR_9$. Alternatively, R_1 is -$(CH_2)_n$-L, in which n is 1-3, and L is -$N(R_{10})C(O)OR_9$. Further, R_1 is -$(CH_2)_n$-L, in which n is 1-2, and L is -$N(R_{10})C(O)OR_9$. Alternatively, R_1 is -$(CH_2)_n$-L, in which n is 1, and L is -$N(R_{10})C(O)OR_9$.

[00109] Further, R_1 is -$(CH_2)_n$-L, in which n is 0-3, and L is -$N(R_{10})C(O)R_9$. Alternatively, R_1 is -$(CH_2)_n$-L, in which n is 1-3, and L is -$N(R_{10})C(O)R_9$. Further, R_1 is -$(CH_2)_n$-L, in which n is 1-2, and L is -$N(R_{10})C(O)R_9$. Alternatively, R_1 is -$(CH_2)_n$-L, in which n is 1, and L is -$N(R_{10})C(O)R_9$.

[00110] Alternatively, R_1 is -$(CH_2)_n$-L, in which n is 0-3 and L is H. R_1 is methyl, ethyl, propyl, iso-propyl. Specifically, R_1 is methyl.

[00111] R_2 is H, D, halogen, or -$(C_1$-$C_4)$alkyl. Alternatively, R_2 is H or -$(C_1$-$C_4)$alkyl. Further, R_2 is H, methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl or tert-butyl. Specifically, R_2 is H or methyl.

[00112] R_4 is selected from the group consisting of: H, -$(C_1$-$C_4)$alkyl, -$(C_3$-$C_8)$cycloalkyl, -$(C_5$-$C_7)$heterocycloalkyl, -$(C_6$-$C_{10})$aryl, and -$(C_5$-$C_7)$heteroaryl, wherein each -$(C_1$-$C_4)$alkyl, -$(C_3$-$C_8)$cycloalkyl, -$(C_5$-$C_7)$heterocycloalkyl, -$(C_6$-$C_{10})$aryl, and -$(C_5$-$C_7)$heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -$(C_1$-$C_4)$alkyl, -O-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkylene-O-$(C_1$-$C_4)$alkyl, halo-substituted-$(C_1$-$C_4)$alkyl, halo-substituted-O-$(C_1$-$C_4)$alkyl, -C(O)-$(C_1$-$C_4)$alkyl, and -C(O)-(fluoro-substituted-$(C_1$-$C_4)$alkyl).

[00113] Alternatively, R_4 is selected from the group consisting of: H and -$(C_1$-$C_4)$alkyl, wherein each -$(C_1$-$C_4)$alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -$(C_1$-$C_4)$alkyl, -O-$(C_1$-$C_4)$alkyl, -$(C_1$-$C_4)$alkylene-O-$(C_1$-$C_4)$alkyl, halo-substituted-$(C_1$-$C_4)$alkyl, halo-substituted-O-$(C_1$-$C_4)$alkyl, -C(O)-$(C_1$-$C_4)$alkyl, and -C(O)-(fluoro- substituted-$(C_1$-$C_4)$alkyl).

[00114] R_4 is selected from the group consisting of: H and -$(C_1$-$C_4)$alkyl, wherein each -$(C_1$-$C_4)$alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, and -OH. In another alternative, R_4 is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, tert-butyl, trifluoromethyl, -CF_2-CF_3, hydroxymethyl, and hydroxyethyl. Alternatively, R_4 is selected from the group consisting of: H, methyl, ethyl, tert-butyl, and trifluoromethyl.

[00115] R_5 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00116] Alternatively, R_5 is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl).

[00117] Further, R_5 is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -OH, -O-(C_1-C_4)alkyl, and halo-substituted-(C_1-C_4)alkyl. In another alternative, R_5 is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, methoxy, hydroxyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00118] R_6 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00119] Alternatively, R_6 is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl).

[00120] Further, R_6 is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -OH, -O-(C_1-C_4)alkyl, and halo-substituted-(C_1-C_4)alkyl. In another alternative, R_6 is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, methoxy, hydroxyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00121] R_7 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00122] Alternatively, R_7 is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00123] Further, R_7 is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -OH, -O-(C_1-C_4)alkyl, and halo-substituted-(C_1-C_4)alkyl. In another alternative, R_7 is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, methoxy, hydroxyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00124] R_8 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00125] Alternatively, R_8 is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl).

[00126] Further, R_8 is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -OH, -O-(C_1-C_4)alkyl, and halo-substituted-(C_1-C_4)alkyl. In another alternative, R_8 is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, methoxy, hydroxyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00127] R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, -(C_0-C_6)alkylene-heteroaryl, and -N=$CR_{11}R_{12}$, wherein each -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-, -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro-substituted-(C_1-C_4)alkyl), -$S(O)_p$-(C_1-C_4)alkyl, -$NR_{13}R_{14}$, and CN.

[00128] Alternatively, R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, -(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl). Further, R_9 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_1-C_3)alkylene-heterocycloalkyl, -(C_1-C_3)alkylene-aryl, and -(C_1-C_3)alkylene-heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_1-C_3)alkylene-, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, -(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl,and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl).

[00129] Further, R_9 is selected from the group consisting of: H, methyl, ethyl, propyl, i-propyl, butyl, sec-butyl, t-butyl, and trifluoromethyl. Alternatively, R_9 is selected from the group consisting of -(C_1-C_3)alkylene-morpholine, -(C_1-C_3)alkylene-piperazine, -(C_1-C_3)alkylene-phenyl, -(C_1-C_3)alkylene-pyridyl, -(C_1-C_3)alkylene-imidazolyl, -(C_1-C_3)alkylene-azetidine, -(C_1-C_3)alkylene-furanyl, -(C_1-C_3)alkylene-pyrazinyl, -(C_1-C_3)alkylene-oxazolyl, -(C_1-C_3)alkylene-thienyl, -(C_1-C_3)alkylene-thiazolyl, -(C_1-C_3)alkylene-triazolyl, and -(C_1-C_3)alkylene-isoxazolyl, wherein each -(C_1-C_3)alkylene-, -morpholine, -piperazine, -phenyl, -pyridyl, and -imidazolyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, OH, =O, -$B(OH)_2$, -(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and halo-substituted- (C_1-C_4)alkyl.

[00130] In another alternative, R_9 is selected from the group consisting of -(C_1-C_3)alkylene-morpholine, -(C_1-C_3)alkylene-piperazine, -(C_1-C_3)alkylene-phenyl, -(C_1-C_3)alkylene-pyridyl, and -(C_1-C_3)alkylene-imidazolyl, wherein each -(C_1-C_3)alkylene-, -morpholine, -piperazine, -phenyl, -pyridyl, and -imidazolyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, OH, =O, -$B(OH)_2$, -(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and halo-substituted- (C_1-C_4)alkyl. Further, R_9 is selected from the group consisting of -(C_1-C_3)alkylene-morpholine, -(C_1-C_3)alkylene-piperazine, -(C_1-C_3)alkylene-phenyl, -(C_1-C_3)alkylene-pyridyl, and -(C_1-C_3)alkylene-imidazolyl, wherein each -(C_1-C_3)alkylene-, -morpholine, -piperazine, -phenyl, -pyridyl, and -imidazolyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -$B(OH)_2$, and -(C_1-C_4)alkyl.

[00131] Alternatively, R_9 is -N=$CR_{11}R_{12}$.

[00132] R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl; and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-, -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro-substituted-(C_1-C_4)alkyl), -$S(O)_q$-(C_1-C_4)alkyl, -$NR_{15}R_{16}$ and CN.

[00133] Alternatively, R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, and -(C_1-C_6)alkylene-heterocycloalkyl, wherein each -(C_1-C_6)alkyl, -(C_1-C_6)alkylene-, and -

heterocycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl,

-C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro- substituted-(C_1-C_4)alkyl), -$S(O)_q$-(C_1-C_4)alkyl, -$NR_{15}R_{16}$ and CN.

[00134] Further, R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, and -(C_1-C_3)alkylene-heterocycloalkyl, wherein each -(C_1-C_6)alkyl, -(C_1-C_6)alkylene-, and -heterocycloalkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, -(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl,and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl). Alternatively, Further, R_{10} is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, sec-butyl, tert-butyl, trifluoromethyl, -(C_1-C_3)alkylene-morpholine, -(C_1-C_3)alkylene-piperazine, -(C_1-C_3)alkylene-phenyl, -(C_1-C_3)alkylene-pyridyl, and -(C_1-C_3)alkylene-imidazolyl, wherein each -(C_1-C_3)alkylene-, -morpholine, -piperazine, -phenyl, -pyridyl, and -imidazolyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -$B(OH)_2$, and -(C_1-C_4)alkyl.

[00135] R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-10-membered ring. Alternatively, R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-6-membered ring. Further, R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-6-membered ring cycloalkyl or heterocycloalkyl.

[00136] R_{11} is H, -(C_1-C_4)alkyl, or -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 3 substituents independently selected from the group consisting of: -F, -Cl, -Br, and -OH. Alternatively, R_{11} is H or -(C_1-C_4)alkyl optionally substituted with 1 to 3 substituents independently selected from the group consisting of: -F, -Cl, -Br, and -OH. Further, R_{11} is H, methyl, ethyl, propyl, butyl, or trifluoromethyl. Specifically, R_{11} is H or methyl.

[00137] R_{12} is H,-(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1

to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro-substituted-(C_1-C_4)alkyl), -$S(O)_r$-(C_1-C_4)alkyl, - $S(O)_2$-Na, and CN.

[00138] Alternatively, R_{12} is H, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro- substituted-(C_1-C_4)alkyl), -$S(O)_r$-(C_1-C_4)alkyl, - $S(O)_2$-Na, and CN. Further, R_{12} is H, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_6-C_{10})aryl and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, (C1-C4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro- substituted-(C_1-C_4)alkyl), -$S(O)_r$-(C_1-C_4)alkyl, - $S(O)_2$-Na, and CN.

[00139] In another alternative, R_{12} is H, thiofuranyl, phenyl, naphthyl, biphenyl, tetrahydronaphthyl, indanyl, pyridyl, imidazolyl, furanyl, indolyl, pyrimidinyl, pyridizinyl, pyrazinyl, imidazolyl, oxazolyl, thienyl, thiazolyl, triazolyl, isoxazolyl, quinolinyl, pyrrolyl, pyrazolyl, or 5,6,7,8-tetrahydroisoquinolinyl, wherein each is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, =O, -$B(OH)_2$, (C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -$S(O)_r$-(C_1-C_4)alkyl, - $S(O)_2$-Na, and CN. Alternatively, R_{12} is H, phenyl, imidazolyl, furanyl, or indolyl, wherein each phenyl, imidazolyl, furanyl, or indolyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -OH, methyl, - $S(O)_2$-Na, or -$B(OH)_2$,

[00140] R_{13} is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-

O-(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl).

[00141] Alternatively, R_{13} is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00142] Further, R_{13} is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -OH, -O-(C_1-C_4)alkyl, and halo-substituted-(C_1-C_4)alkyl. In another alternative, R_{13} is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, methoxy, hydroxyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00143] R_{14} is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl).

[00144] Alternatively, R_{14} is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00145] Further, R_{14} is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -OH, -O-(C_1-C_4)alkyl, and halo-substituted-(C_1-C_4)alkyl. In another alternative, R_{14} is selected

from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, methoxy, hydroxyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00146] R_{15} is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro- substituted-(C_1-C_4)alkyl).

[00147] Alternatively, R_{15} is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00148] Further, R_{15} is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -OH, -O-(C_1-C_4)alkyl, and halo-substituted-(C_1-C_4)alkyl. In another alternative, R_{15} is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, methoxy, hydroxyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00149] R_{16} is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted- (C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00150] Alternatively, R_{16} is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-

substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, and -C(O)-(fluoro-substituted-(C_1-C_4)alkyl).

[00151] Further, R_{16} is selected from the group consisting of: H, -(C_1-C_4)alkyl, and -(C_3-C_8)cycloalkyl, wherein each -(C_1-C_4)alkyl and -(C_3-C_8)cycloalkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -OH, -O-(C_1-C_4)alkyl, and halo-substituted-(C_1-C_4)alkyl. In another alternative, R_{16} is selected from the group consisting of: H, methyl, ethyl, propyl, iso-propyl, butyl, tert-butyl, methoxy, hydroxyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[00152] R_C is selected from the group consisting of: -F, -Cl, -Br, -OH, -(C_1-C_4)alkyl, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O -(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro-substituted -(C_1-C_4)alkyl), -$S(O)_o$-(C_1-C_4)alkyl, -NR_7R_8 and CN.

[00153] Alternatively R_C is selected from the group consisting of: -F, -Cl, -Br, -OH, and -O-(C_1-C_4)alkyl. In another alternative, R_C is selected from the group consisting of F, -Cl, -Br, -OH, methoxy, and ethoxy.

[00154] m is 0, 1, 2, or 3. Alternatively, m is 1 or 2.

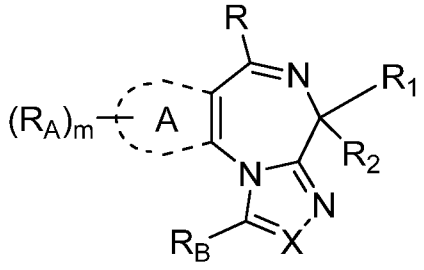
[00155] o is 1 or 2.

[00156] p is 1 or 2.

[00157] q is 1 or 2.

[00158] r is 1 or 2.

[00159] A first embodiment a compound is represented by Structural Formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein:

[00160] X is N or CR_3;

[00161] R_3 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl, wherein

each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00162] R_B is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, or –COO–R_4, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6;

[00163] ring A is -(C_6-C_{10})aryl or -(C_5-C_{10})heteroaryl;

[00164] each R_A is independently H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents; or any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group;

[00165] R is -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each is optionally and independently substituted with 1 to 4 substituents;

[00166] R_1 is -$(CH_2)_n$-L, in which n is 0-3 and L is H, -C(O)O–R_9, -CO-N(R_9R_{10}), -NR_9R_{10}, -N(R_{10})C(O)OR_9, or -N(R_{10})C(O)R_9;

[00167] R_2 is H, D, halogen, or -(C_1-C_4)alkyl;

[00168] R_4, R_5, and R_6 are each independently selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00169] R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, -(C_0-C_6)alkylene-heteroaryl, and -N=C$R_{11}R_{12}$, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00170] R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl; and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and

independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00171] R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-10-membered ring;

[00172] R_{11} is H, -(C_1-C_4)alkyl, or -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally and independently substituted with 1 to 3 substituents selected from the group consisting of: -F, -Cl, -Br, and -OH;

[00173] R_{12} is H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents; and

[00174] m is 0, 1, 2, or 3.

[00175] In a first aspect of the first embodiment or the particular or specific embodiment thereof: X is N.

[00176] In a second aspect of first embodiment or the particular or specific embodiment thereof: R_B is H or -(C_1-C_4)alkyl.

[00177] In a third aspect of the first embodiment or the particular or specific embodiment thereof: ring A is 5- or 6-membered aryl or heteroaryl.

[00178] In a fourth aspect of the first embodiment or the particular or specific embodiment thereof: ring A is phenyl or thienyl.

[00179] In a fifth aspect of the first embodiment or the particular or specific embodiment thereof: R is -(C_6-C_{10})aryl or -(C_5-C_{10})heteroaryl optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, and -Br.

[00180] In a fifth aspect of the first embodiment or the particular or specific embodiment thereof: L is H, –COO–R_9, or –CO-N(R_9R_{10}).

[00181] In a sixth aspect of the first embodiment or the particular or specific embodiment thereof: each R_9 is independently selected from the group consisting of -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, and -(C_0-C_6)alkylene-heteroaryl and each -(C_1-C_6)alkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -(C_1-C_6)alkyl.

[00182] In a seventh aspect of the first embodiment or the particular or specific embodiment thereof: each R_{10} is independently selected from the group consisting of: H and -(C_1-C_6)alkyl.

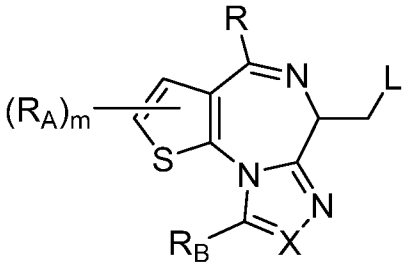
[00183] In an eighth aspect of the first embodiment or the particular or specific embodiment thereof: wherein R_2 is selected from the group consisting of: H and methyl.

[00184] In a ninth aspect of the first embodiment or the particular or specific embodiment thereof: R_A is independently H or -(C_1-C_4)alkyl, or any two R_A together with the atoms to which each is attached, can form a fused aryl.

[00185] In a tenth aspect of the first embodiment or the particular or specific embodiment thereof: m is 2 and and at least one R_A is methyl.

[00186] In an eleventh aspect of the first embodiment or the particular or specific embodiment thereof: m is 2 and each R_A is methyl.

[00187] In a second embodiment, a compound is represented by represented by Structural Formula II:



(II)

or a pharmaceutically acceptable salt thereof, wherein:

[00188] X is N or CR_3;

[00189] R_3 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00190] R_B is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, or –COO–R_4, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6;

[00191] each R_A is independently H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-

C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents; or any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group;

[00192] R is -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each is optionally and independently substituted with 1 to 4 substituents;

[00193] L is H, -C(O)O–R_9, -CO-N(R_9R_{10}), -NR_9R_{10}, -N(R_{10})C(O)OR_9, or -N(R_{10})C(O)R_9;

[00194] R_4, R_5, and R_6 are each independently selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00195] R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, -(C_0-C_6)alkylene-heteroaryl, and -N=C$R_{11}R_{12}$, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00196] R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl; and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00197] R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-10-membered ring;

[00198] R_{11} is H, -(C_1-C_4)alkyl, or -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, wherein each-(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of: -F, -Cl, -Br, and -OH;

[00199] R_{12} is H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-

C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents; and

[00200] m is 0, 1, 2, or 3.

[00201] In a first aspect of the second embodiment or the particular or specific embodiment thereof: X is N.

[00202] In a second aspect of the second embodiment or the particular or specific embodiment thereof: R_B is selected from the group consisting of: H, -(C_1-C_4) alkyl, and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, and each -(C_1-C_4) alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, and -OH.

[00203] In a third aspect of the second embodiment or the particular or specific embodiment thereof: R_B is methyl, ethyl, hydroxy methyl, methoxymethyl, or trifluoromethyl.

[00204] In a fourth aspect of the second embodiment or the particular or specific embodiment thereof: R is -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl optionally substituted with a substituent selected from the group consisting of: -F, -Cl, and -Br.

[00205] In a fifth aspect of the second embodiment or the particular or specific embodiment thereof: R is phenyl or pyridyl optionally substituted with a substituent selected from the group consisting of: -F, -Cl, and -Br.

[00206] In a sixth aspect of the second embodiment or the particular or specific embodiment thereof: R is p-Cl-phenyl, o-Cl-phenyl, m-Cl-phenyl, p-F-phenyl, o-F-phenyl, m-F-phenyl or pyridinyl.

[00207] In a seventh aspect of the second embodiment or the particular or specific embodiment thereof: L is –CO-N(R_9R_{10}), R_9 is -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6) alkylene-aryl, or -(C_0-C_6)alkylene- heteroaryl, wherein each -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 (C_1-C_4)alkyl, and R_{10} is H or -(C_1-C_6)alkyl.

[00208] In an eighth aspect of the second embodiment or the particular or specific embodiment thereof: L is –COO–R_9 and R_9 is independently selected from the group consisting of: -(C_1-C_6)alkyl, -(C_0-C_6)alkylene -heterocycloalkyl, -(C_0-C_6)alkylene-aryl, and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl, -heterocycloalkyl, -aryl, and -

heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, -Br, and -(C_1-C_6)alkyl.

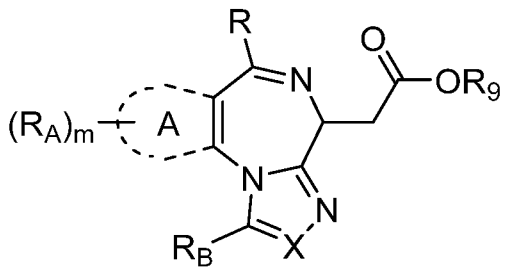
[00209] In a ninth aspect of the second embodiment or the particular or specific embodiment thereof: L is –COO–R_9, and R_9 is selected from the group consisting of: methyl, ethyl, propyl, i-propyl, butyl, sec-butyl, t-butyl, and trifluoromethyl.

[00210] In a tenth aspect of the second embodiment or the particular or specific embodiment thereof: each R_A is independently H or -(C_1-C_4)alkyl, or any two R_A together with the atoms to which each is attached, can form a fused aryl.

[00211] In an eleventh aspect of the second embodiment or the particular or specific embodiment thereof: m is 2, and at least one occurrence of R_A is methyl.

[00212] In a twelfth aspect of the second embodiment or the particular or specific embodiment thereof: m is 2 and each R_A is methyl.

[00213] In a third embodiment, a compound is represented by represented by Structural Formula III:



(III)

or a pharmaceutically acceptable salt thereof, wherein:

[00214] X is N or CR_3;

[00215] R_3 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00216] R_B is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, or –COO–R_4, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6;

[00217] ring A is -(C_6-C_{10})aryl or -(C_5-C_{10})heteroaryl;

[00218] each R_A is independently H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents; or any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group;

[00219] R is -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each is optionally and independently substituted with 1 to 4 substituents;

[00220] R_4, R_5, and R_6 are each independently selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00221] R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents; and

[00222] m is 0, 1, 2, or 3.

[00223] In a first aspect of the third embodiment or the particular or specific embodiment thereof: X is N.

[00224] In a second aspect of the third embodiment or the particular or specific embodiment thereof: R_B is selected from the group consisting of: H, -(C_1-C_4) alkyl, and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, and each -(C_1-C_4) alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -OH.

[00225] In a third aspect of the third embodiment or the particular or specific embodiment thereof: R_B is methyl, ethyl, hydroxy methyl, methoxymethyl, or trifluoromethyl.

[00226] In a fourth aspect of the third embodiment or the particular or specific embodiment thereof: ring A is 5- or 6-membered aryl or heteroaryl.

[00227] In a fifth aspect of the third embodiment or the particular or specific embodiment thereof: ring A is thiofuranyl, phenyl, naphthyl, biphenyl, tetrahydronaphthyl, indanyl, pyridyl, furanyl, indolyl, pyrimidinyl, pyridizinyl, pyrazinyl, imidazolyl, oxazolyl, thienyl, thiazolyl, triazolyl, isoxazolyl, quinolinyl, pyrrolyl, pyrazolyl, or 5,6,7,8-tetrahydroisoquinolinyl.

[00228] In a sixth aspect of the third embodiment or the particular or specific embodiment thereof: ring A is phenyl or thienyl.

[00229] In a seventh aspect of the third embodiment or the particular or specific embodiment thereof: R is -(C_6-C_{10})aryl or -(C_5-C_{10})heteroaryl optionally substituted with a substituent selected from the group consisting of: -F, -Cl, and -Br.

[00230] In an eighth aspect of the third embodiment or the particular or specific embodiment thereof: R is phenyl or pyridyl optionally substituted with 1-4 substituents independently selected from the group consisting of: -F, -Cl, and -Br.

[00231] In a ninth aspect of the third embodiment or the particular or specific embodiment thereof: R is p-Cl-phenyl, o-Cl-phenyl, m-Cl-phenyl, p-F-phenyl, o-F-phenyl, m-F-phenyl or pyridinyl.

[00232] In a tenth aspect of the third embodiment or the particular or specific embodiment thereof: each R_A is independently H or -(C_1-C_4)alkyl, or any two R_A together with the atoms to which each is attached, can form a fused aryl.

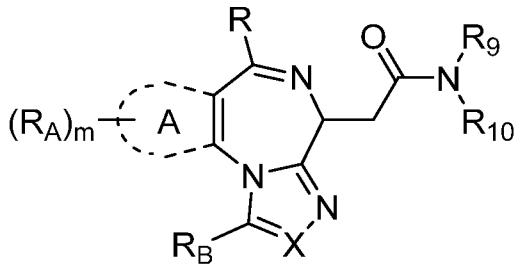
[00233] In an eleventh aspect of the third embodiment or the particular or specific embodiment thereof: m is 2, and at least one occurrence of R_A is methyl.

[00234] In a twelfth aspect of the third embodiment or the particular or specific embodiment thereof: m is 2 and each R_A is methyl.

[00235] In a thirteenth aspect of the third embodiment or the particular or specific embodiment thereof: R_9 is independently selected from the group consisting of -(C_1-C_6)alkyl, -(C_0-C_6)alkylene -heterocycloalkyl, -(C_0-C_6)alkylene-aryl, and -(C_0-C_6)alkylene-heteroaryl and each -(C_1-C_6)alkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -(C_1-C_6)alkyl.

[00236] In a fourteenth aspect of the third embodiment or the particular or specific embodiment thereof: R_9 is selected from the group consisting of: methyl, ethyl, propyl, i-propyl, butyl, sec-butyl, t-butyl, and trifluoromethyl.

[00237] In a fourth embodiment, a compound is represented by represented by Structural Formula IV:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

[00238] X is N or CR_3;

[00239] R_3 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00240] R_B is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, or –COO–R_4, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6;

[00241] ring A is aryl or heteroaryl;

[00242] each R_A is independently H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents; or any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group;

[00243] R is -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each is optionally and independently substituted with 1 to 4 substituents;

[00244] R_4, R_5, and R_6 are each independently selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00245] R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, -(C_0-C_6)alkylene-heteroaryl, and -N=C$R_{11}R_{12}$, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00246] R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl; and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00247] R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-10-membered ring;

[00248] R_{11} is H, -(C_1-C_4)alkyl, or -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of: -F, -Cl, -Br, and -OH;

[00249] R_{12} is H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents; and

[00250] m is 0, 1, 2, or 3.

[00251] In a first aspect of the fourth embodiment or the particular or specific embodiment thereof: X is N.

[00252] In a second aspect of the fourth embodiment or the particular or specific embodiment thereof: R_B is selected from the group consisting of: H, -(C_1-C_4) alkyl, and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, and each -(C_1-C_4) alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -OH.

[00253] In a third aspect of the fourth embodiment or the particular or specific embodiment thereof: R_B is methyl, ethyl, hydroxy methyl, methoxymethyl, or trifluoromethyl.

[00254] In a fourth aspect of the fourth embodiment or the particular or specific embodiment thereof: ring A is 5- or 6-membered aryl or heteroaryl.

[00255] In a fifth aspect of the fourth embodiment or the particular or specific embodiment thereof: ring A is thiofuranyl, phenyl, naphthyl, biphenyl, tetrahydronaphthyl, indanyl, pyridyl, furanyl, indolyl, pyrimidinyl, pyridizinyl, pyrazinyl, imidazolyl, oxazolyl, thienyl, thiazolyl, triazolyl, isoxazolyl, quinolinyl, pyrrolyl, pyrazolyl, or 5,6,7,8-tetrahydroisoquinolinyl.

[00256] In a sixth aspect of the fourth embodiment or the particular or specific embodiment thereof: ring A is phenyl or thienyl.

[00257] In a seventh aspect of the fourth embodiment or the particular or specific embodiment thereof: R is -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, and -Br.

[00258] In an eighth aspect of the fourth embodiment or the particular or specific embodiment thereof: R is phenyl or pyridyl optionally substituted with 1 to 4 substituents independently selected from the group consisting of: -F, -Cl, and -Br.

[00259] In a ninth aspect of the fourth embodiment or the particular or specific embodiment thereof: R is p-Cl-phenyl, o-Cl-phenyl, m-Cl-phenyl, p-F-phenyl, o-F-phenyl, m-F-phenyl or pyridinyl.

[00260] In a tenth aspect of the fourth embodiment or the particular or specific embodiment thereof: each R_A is independently H or -(C_1-C_4)alkyl, or any two R_A together with the atoms to which each is attached, can form a fused aryl.

[00261] In an eleventh aspect of the fourth embodiment or the particular or specific embodiment thereof: m is 2, and at least one occurrence of R_A is methyl.

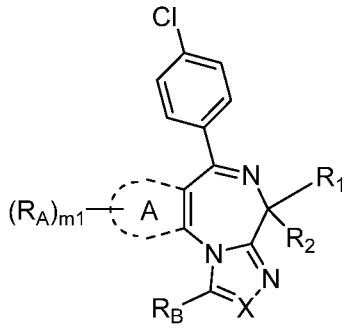
[00262] In a twelfth aspect of the fourth embodiment or the particular or specific embodiment thereof: m is 2 and each R_A is methyl.

[00263] In a thirteenth aspect of the fourth embodiment or the particular or specific embodiment thereof: R_9 is independently selected from the group consisting of -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, and -(C_0-C_6)alkylene-heteroaryl and each -(C_1-C_6)alkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -(C_1-C_6)alkyl.

[00264] In a fourteenth aspect of the fourth embodiment or the particular or specific embodiment thereof: R_{10} is selected from the group consisting of: H and -(C_1-C_6)alkyl optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, and -O-(C_1-C_6)alkyl.

[00265] In a fifteenth aspect of the fourth embodiment or the particular or specific embodiment thereof: R_9 is N=C$R_{11}R_{12}$, R_{11} is H or -(C_1-C_4)alkyl and R_{12} is -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl or -(C_5-C_7)heteroaryl, optionally substituted with 1 to 4 substituents independently selected from -(C_1-C_4)alkyl, -F, -Cl, -SO_2Na, or -B(OH)$_2$.

[00266] In a fifth embodiment, a compound is represented by represented by Structural Formula V:



(V)

or a pharmaceutically acceptable salt thereof, wherein:

[00267] X is N or CR_3;

[00268] R_3 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00269] R_B is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, or –COO–R_4, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6;

[00270] ring A is -(C_6-C_{10})aryl or -(C_5-C_{10})heteroaryl;

[00271] each R_A is independently H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is

optionally and independently substituted with 1 to 4 substituents; or any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group;

[00272] R_1 is -$(CH_2)_n$-L, in which n is 0-3 and L is H, -C(O)O–R_9, -CO-N(R_9R_{10}), -NR_9R_{10}, -N(R_{10})C(O)OR_9, or -N(R_{10})C(O)R_9;

[00273] R_2 is H, D, halogen, or -(C_1-C_4)alkyl;

[00274] R_4, R_5, and R_6 are each independently selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00275] R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, -(C_0-C_6)alkylene-heteroaryl, and -N=C$R_{11}R_{12}$, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00276] R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl; and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00277] R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-10-membered ring;

[00278] R_{11} is H, -(C_1-C_4)alkyl, or -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, wherein each -(C_1-C_4)alkyl, and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally and independently substituted with 1 to 3 substituents selected from the group consisting of: -F, -Cl, -Br, and -OH;

[00279] R_{12} is H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents; and

[00280] m is 0, 1, 2, or 3.

[00281] In a first aspect of the fifth embodiment or the particular or specific embodiment thereof: X is N.

[00282] In a second aspect of the fifth embodiment or the particular or specific embodiment thereof: R_B is selected from the group consisting of: H, -(C_1-C_4) alkyl, and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, and each -(C_1-C_4) alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -OH.

[00283] In a third aspect of the fifth embodiment or the particular or specific embodiment thereof: R_B is methyl, ethyl, hydroxy methyl, methoxymethyl, or trifluoromethyl.

[00284] In a fourth aspect of the fifth embodiment or the particular or specific embodiment thereof: ring A is 5- or 6-membered aryl or heteroaryl.

[00285] In a fifth aspect of the fifth embodiment or the particular or specific embodiment thereof: ring A is thiofuranyl, phenyl, naphthyl, biphenyl, tetrahydronaphthyl, indanyl, pyridyl, furanyl, indolyl, pyrimidinyl, pyridizinyl, pyrazinyl, imidazolyl, oxazolyl, thienyl, thiazolyl, triazolyl, isoxazolyl, quinolinyl, pyrrolyl, pyrazolyl, or 5,6,7,8-tetrahydroisoquinolinyl.

[00286] In a sixth aspect of the fifth embodiment or the particular or specific embodiment thereof: ring A is phenyl or thienyl.

[00287] In a seventh aspect of the fifth embodiment or the particular or specific embodiment thereof: R_A is independently H or -(C_1-C_4)alkyl, or any two R_A together with the atoms to which each is attached, can form a fused aryl.

[00288] In an eighth aspect of the fifth embodiment or the particular or specific embodiment thereof: m is 2, and at least one occurrence of R_A is methyl.

[00289] In a ninth aspect of the fifth embodiment or the particular or specific embodiment thereof: m is 2 and each R_A is methyl.

[00290] In a tenth aspect of the fifth embodiment or the particular or specific embodiment thereof: L is –CO-N(R_9R_{10}), R_9 is -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6) alkylene-aryl, or -(C_0-C_6)alkylene-heteroaryl, optionally and independently substituted with 1 to 4 (C_1-C_4)alkyl, and R_{10} is H or -(C_1-C_6)alkyl.

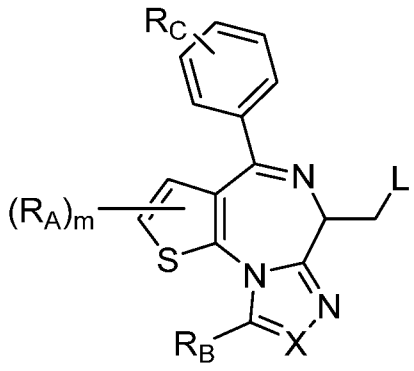
[00291] In a eleventh aspect of the fifth embodiment or the particular or specific embodiment thereof: L is –COO–R_9, and R_9 is independently selected from the group

consisting of -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, and -(C_0-C_6)alkylene-heteroaryl and each -(C_1-C_6)alkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -(C_1-C_6)alkyl.

[00292] In a twelfth aspect of the fifth embodiment or the particular or specific embodiment thereof: L is –COO–R_9, and R_9 is selected from the group consisting of: methyl, ethyl, propyl, i-propyl, butyl, sec-butyl, t-butyl, and trifluoromethyl.

[00293] In a thirteenth aspect of the fifth embodiment or the particular or specific embodiment thereof: R_2 is H or -(C_1-C_4)alkyl.

[00294] In a sixth embodiment, a compound is represented by represented by Structural Formula VI:



(VI)

or a pharmaceutically acceptable salt thereof, wherein:

[00295] X is N or CR_3;

[00296] R_3 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00297] R_B is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, or –COO–R_4, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6;

[00298] each R_A is independently H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is

optionally and independently substituted with 1 to 4 substituents; or any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group;

[00299] L is H, -C(O)O–R_9, -CO-N(R_9R_{10}), -NR_9R_{10}, -N(R_{10})C(O)OR_9, or -N(R_{10})C(O)R_9;

[00300] R_C is selected from the group consisting of: -F, -Cl, -Br, -OH, -O-(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, halo-substituted-(C_1-C_4)alkyl, halo-substituted-O-(C_1-C_4)alkyl, -C(O)-(C_1-C_4)alkyl, -C(O)-(fluoro-substituted-(C_1-C_4)alkyl), -S(O)$_o$-(C_1-C_4)alkyl, -NR_7R_8 and CN;

[00301] R_4, R_5, R_6, R_7 and R_8 are each independently selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00302] R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, -(C_0-C_6)alkylene-heteroaryl, and -N=C$R_{11}R_{12}$, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00303] R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl; and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00304] R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-10-membered ring;

[00305] R_{11} is H, -(C_1-C_4)alkyl, or -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, wherein each -(C_1-C_4)alkyl, and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally and independently substituted with 1 to 3 substituents selected from the group consisting of: -F, -Cl, -Br, and -OH;

[00306] R_{12} is H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-

C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents;

[00307] m is 0, 1, 2, or 3; and

[00308] o is 1 or 2.

[00309] In a first aspect of the sixth embodiment or the particular or specific embodiment thereof: X is N.

[00310] In a second aspect of the sixth embodiment or the particular or specific embodiment thereof: R_B is selected from the group consisting of: H, -(C_1-C_4) alkyl, and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, and each -(C_1-C_4) alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -OH.

[00311] In a third aspect of the sixth embodiment or the particular or specific embodiment thereof: R_B is methyl, ethyl, hydroxy methyl, methoxymethyl, or trifluoromethyl.

[00312] In a fourth aspect of the sixth embodiment or the particular or specific embodiment thereof: each R_A is independently H or -(C_1-C_4)alkyl, or any two R_A together with the atoms to which each is attached, can form a fused aryl.

[00313] In a fifth aspect of the sixth embodiment or the particular or specific embodiment thereof: m is 1 or 2, and at least one occurrence of R_A is methyl.

[00314] In a sixth aspect of the sixth embodiment or the particular or specific embodiment thereof: m is 2 and each R_A is methyl.

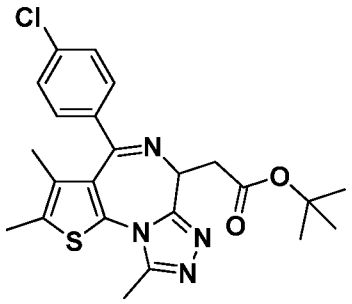
[00315] In a seventh aspect of the sixth embodiment or the particular or specific embodiment thereof: L is –CO-N(R_9R_{10}), R_9 is -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6) alkylene-aryl, or -(C_0-C_6)alkylene-heteroaryl and each -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 (C_1-C_4)alkyl, and R_{10} is H or -(C_1-C_6)alkyl.

[00316] In an eighth aspect of the sixth embodiment or the particular or specific embodiment thereof: L is –COO–R_9, and R_9 is independently selected from the group consisting of -(C_1-C_6)alkyl, -(C_0-C_6)alkylene -heterocycloalkyl, -(C_0-C_6)alkylene-aryl, and -(C_0-C_6)alkylene-heteroaryl and each -(C_1-C_6)alkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, and -(C_1-C_6)alkyl.

[00317] In a ninth aspect of the sixth embodiment or the particular or specific embodiment thereof: L is –COO–R_9, and R_9 is selected from the group consisting of: methyl, ethyl, propyl, i-propyl, butyl, sec-butyl, t-butyl, and trifluoromethyl.

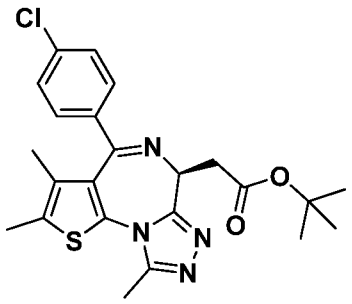
[00318] In a tenth aspect of the sixth embodiment or the particular or specific embodiment thereof: R_C is selected from the group consisting of: -F, -Cl, -Br, -OH, and -O-(C_1-C_4)alkyl.

[00319] In a seventh embodiment, a compound is represented following structural formula:



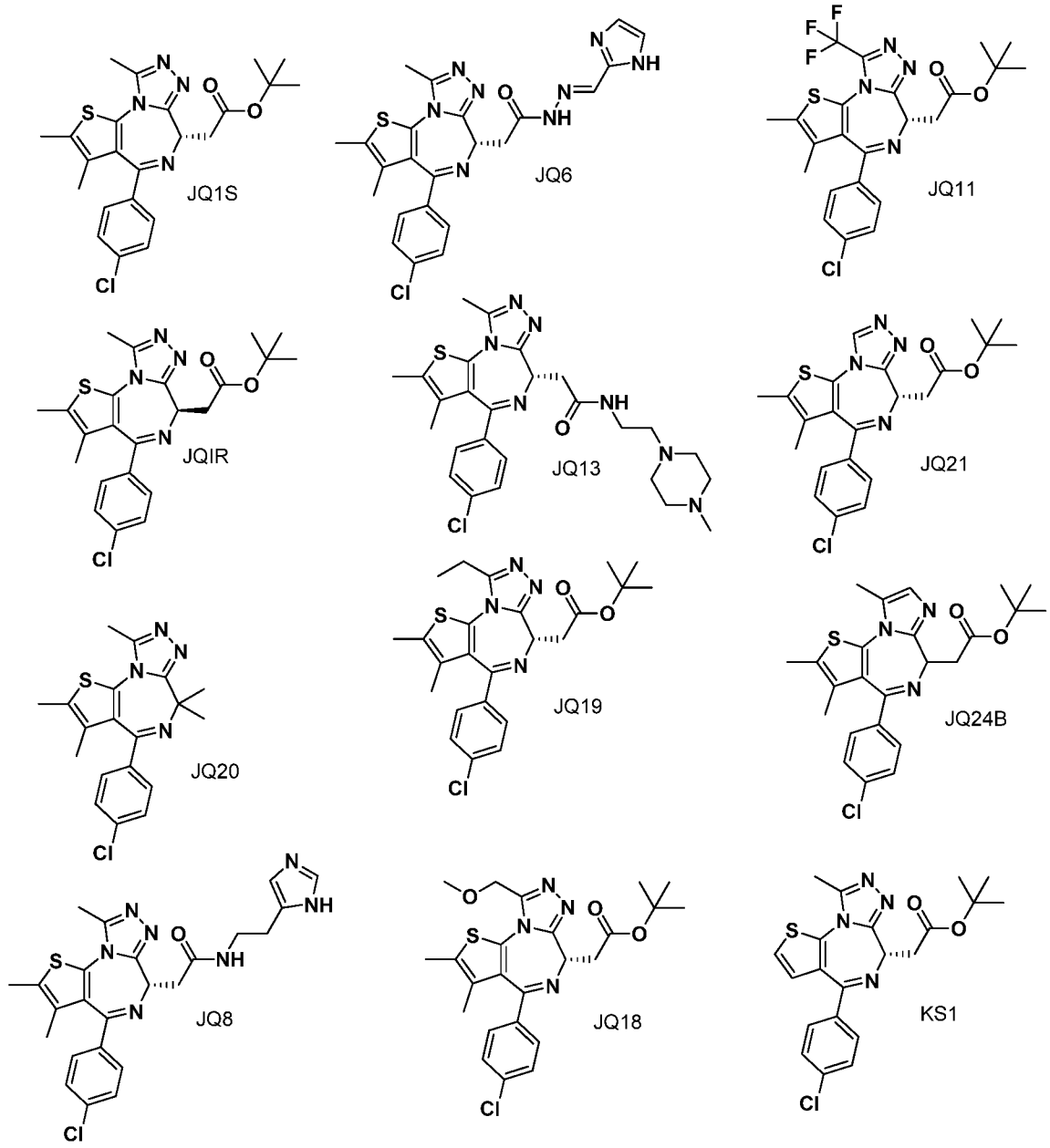
or a pharmaceutically acceptable salt thereof.

[00320] In first aspect of the seventh embodiment or the particular or specific embodiments thereof, the compound is represented following structural formula:



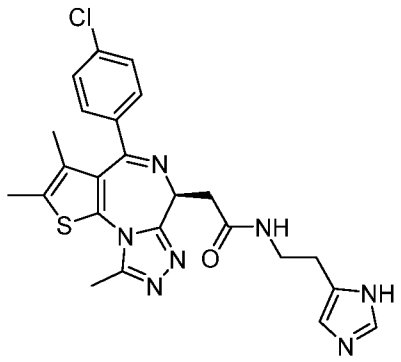
or a pharmaceutically acceptable salt thereof.

[00321] In an eighth embodiment, a compound is represented by represented by any one of the following structural formulas:



or a pharmaceutically acceptable salt thereof.

[00322] In a ninth embodiment, a compound is represented by represented by any one of the following structural formulas: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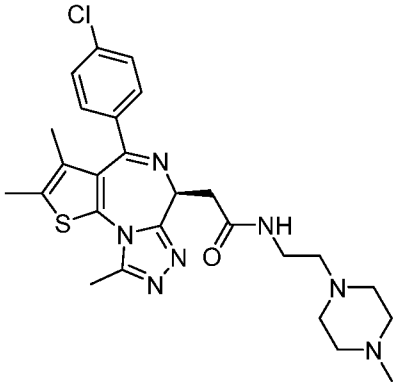
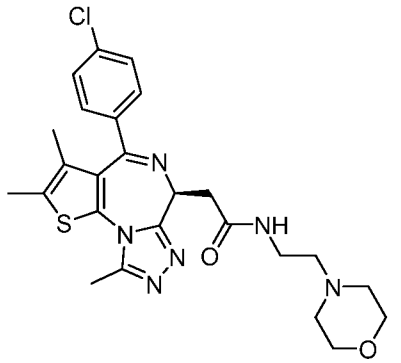

,

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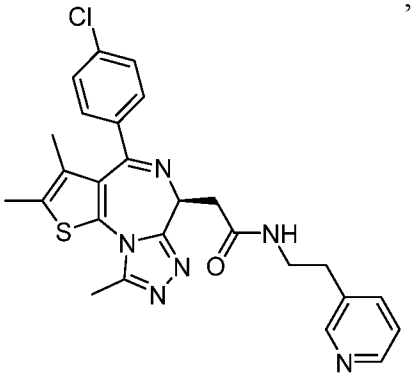
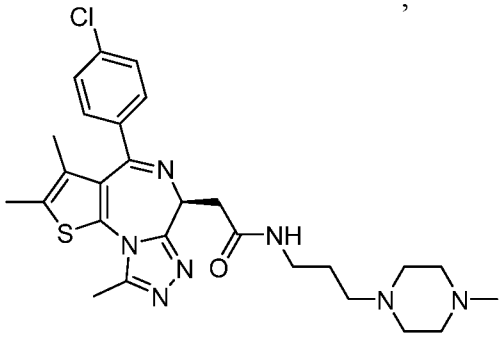
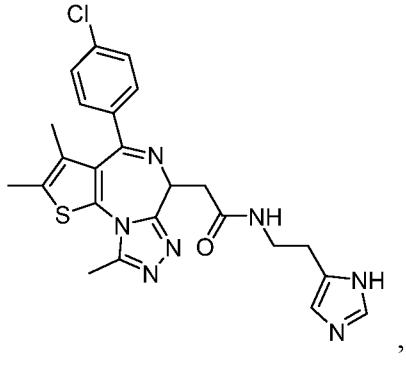

, or


or a pharmaceutically acceptable salt thereof.

[00323] In a tenth embodiment, a compound is represented by represented by any one of the following structural formulas: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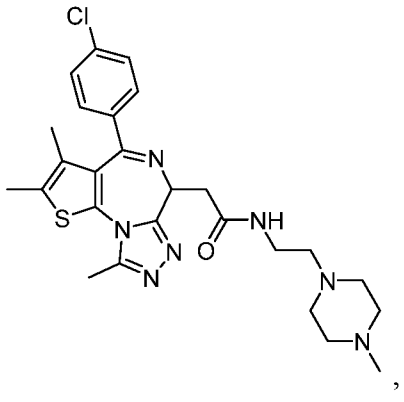
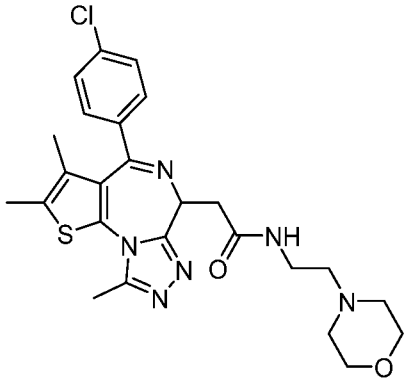

,



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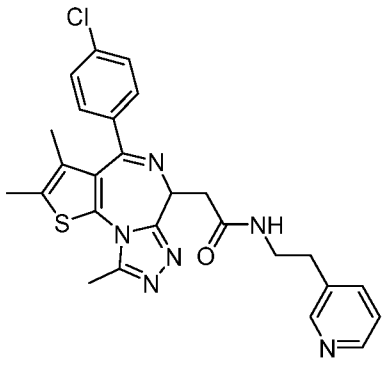
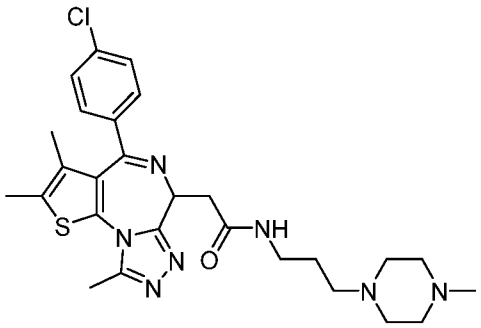


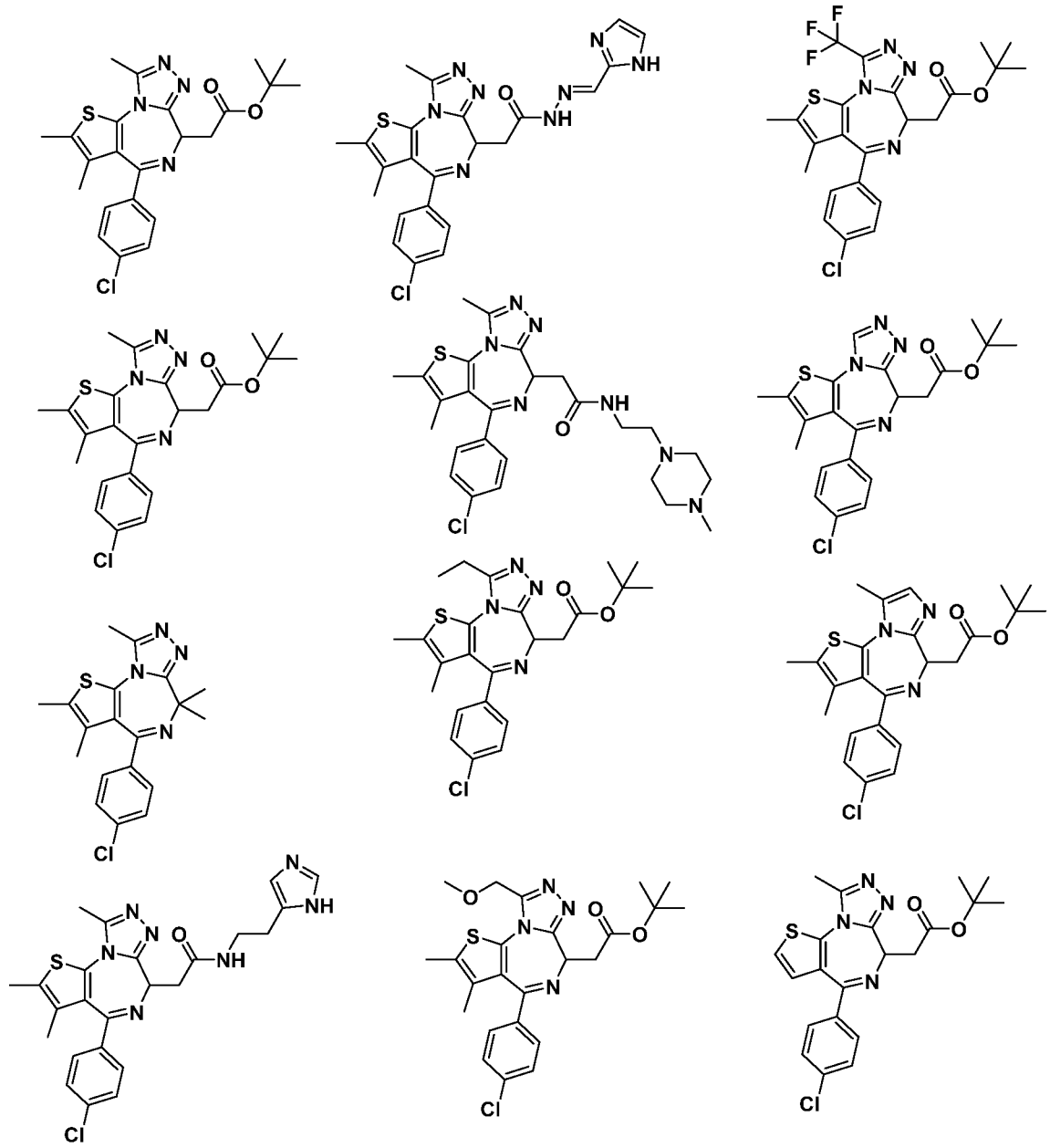
, or



;

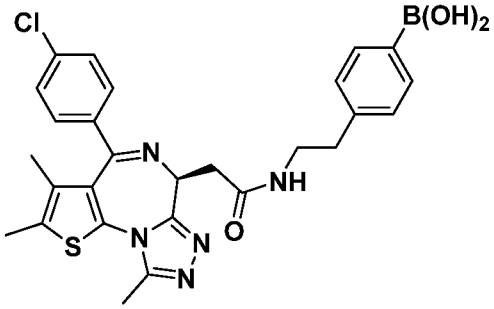
or a pharmaceutically acceptable salt thereof.

[00324] In an eleventh embodiment, a compound is represented by represented by any one of the following structural formulas:

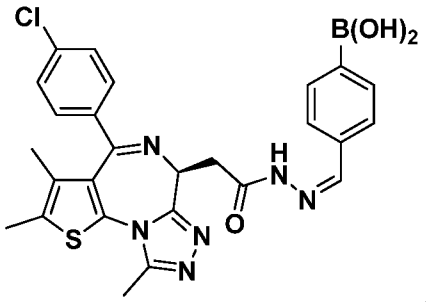


or a pharmaceutically acceptable salt thereof.

[00325] In a twelfth embodiment, a compound is represented by represented by any one of the following structural formulas:



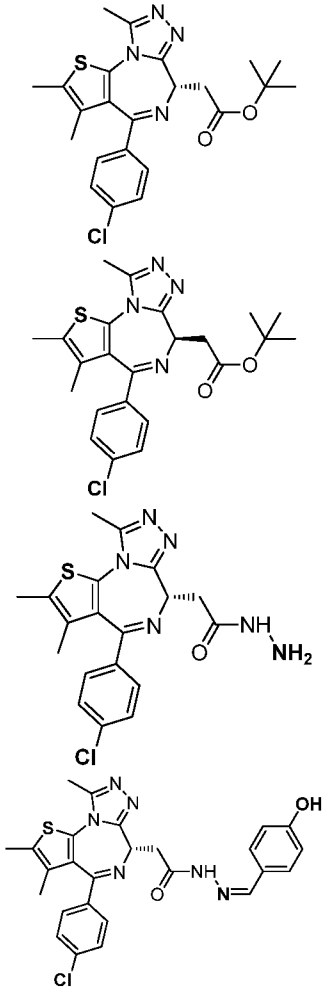
or

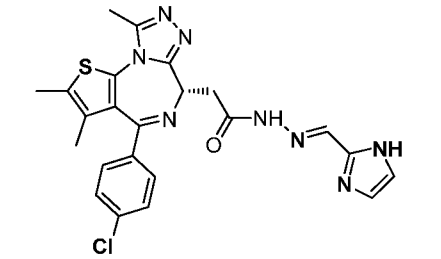


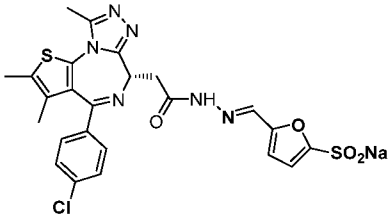
,

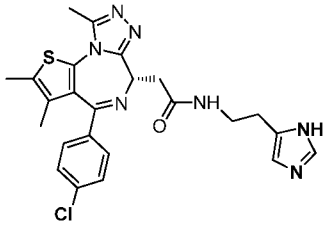
or a pharmaceutically acceptable salt thereof.

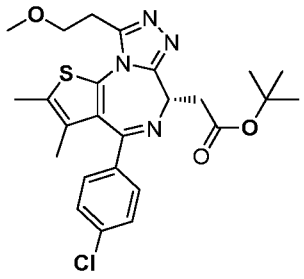
[00326] In a thirteenth embodiment, a compound is represented by represented by any one of the following structural formulas:

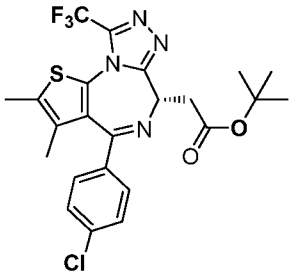


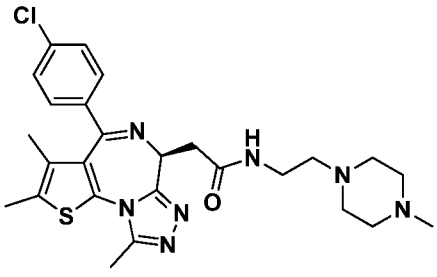


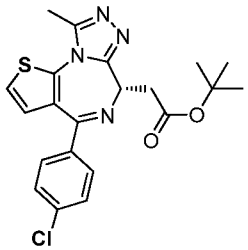


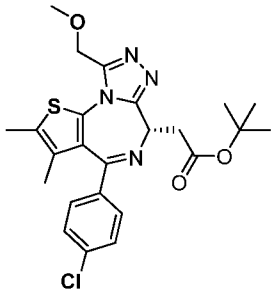


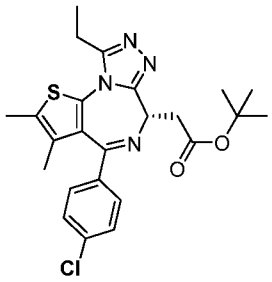


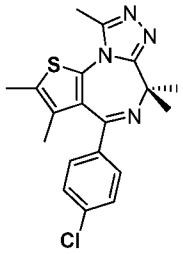


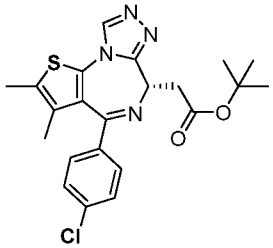


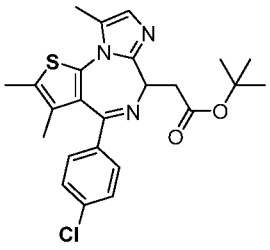


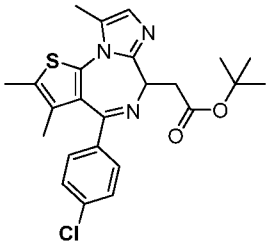


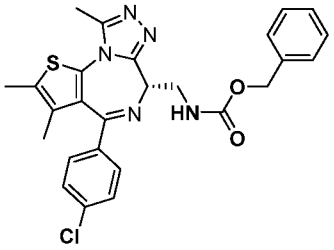


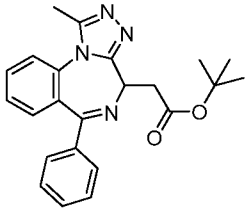


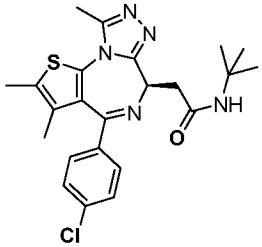


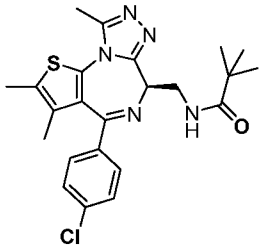


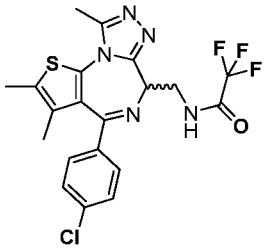


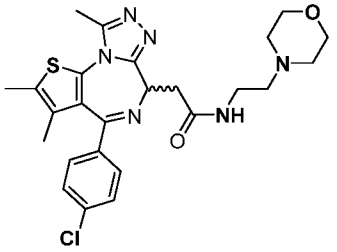


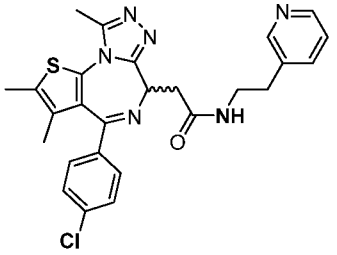


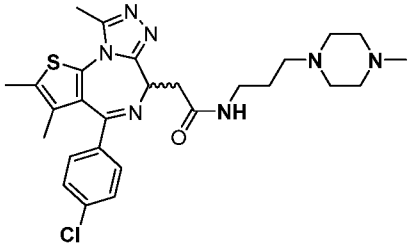


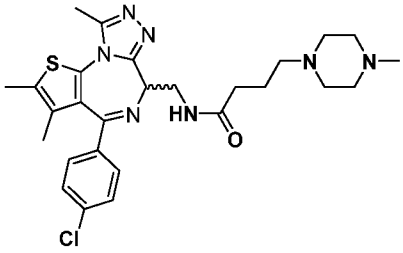


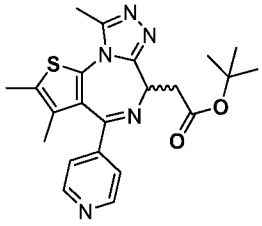


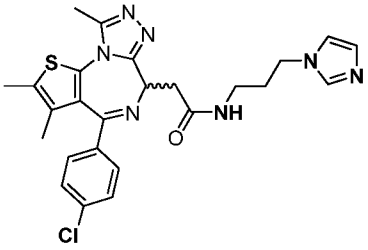


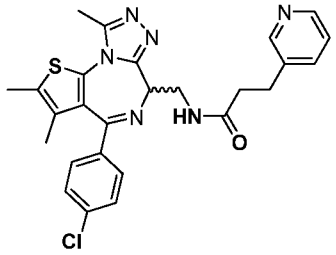


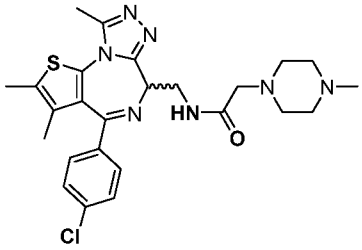












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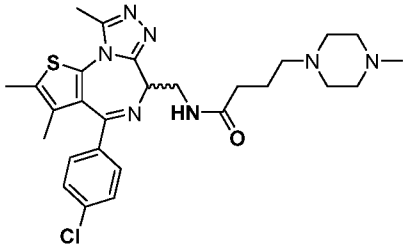
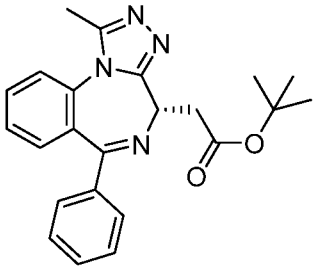


;

or a pharmaceutically acceptable salt thereof.

[00327] In a fourteenth embodiment, a compound is represented by represented by any one of the following structural formulas:



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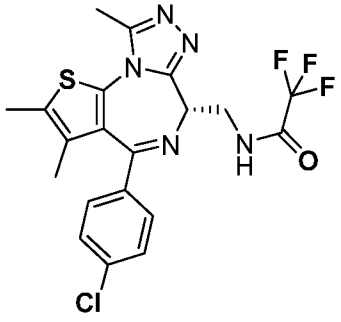

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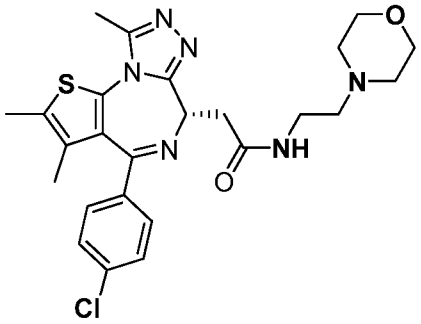

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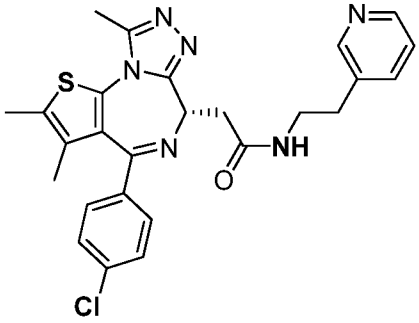

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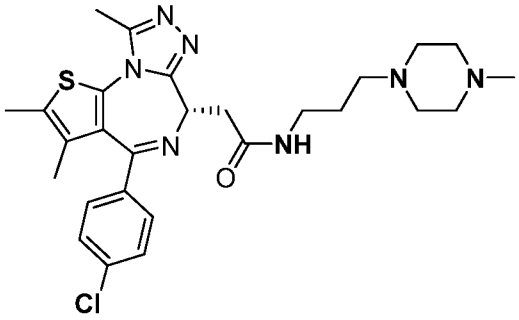

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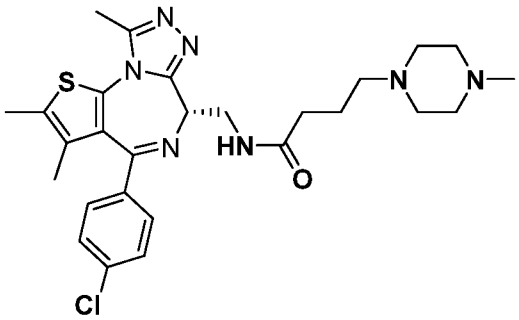

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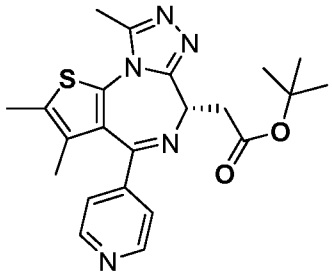

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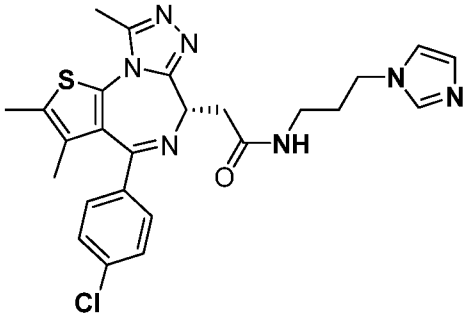

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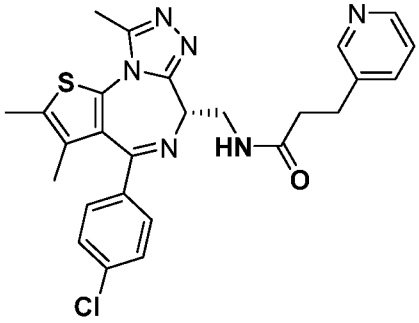

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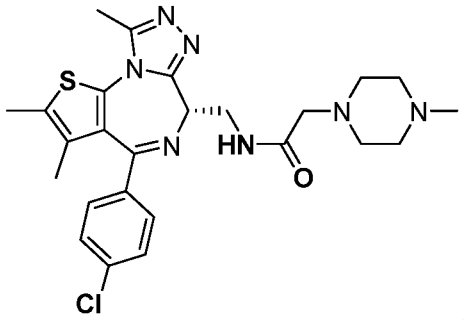

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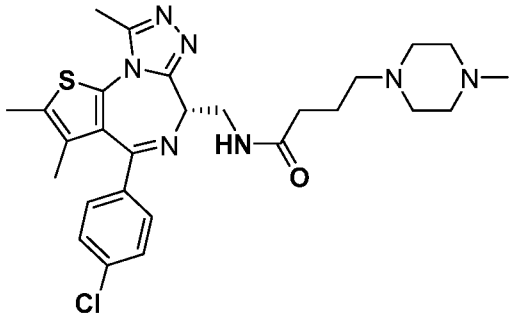

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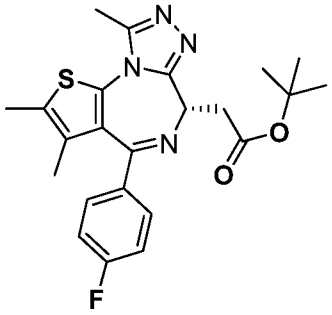
N
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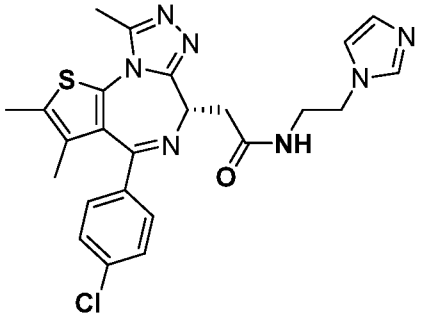
O
O
F

,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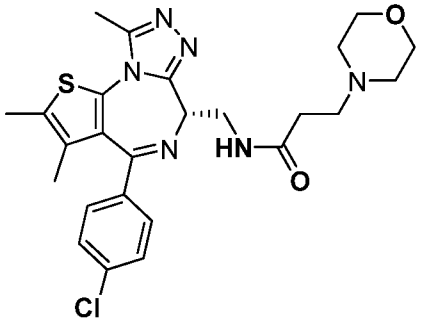
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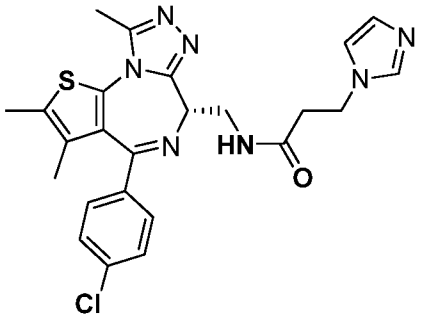
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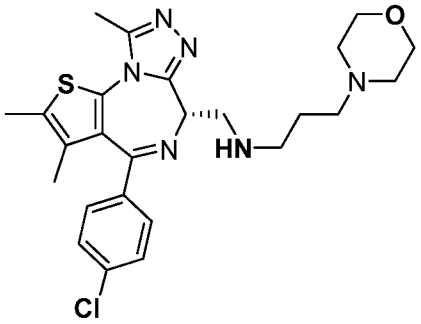
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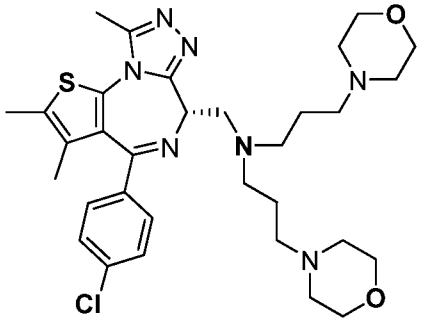
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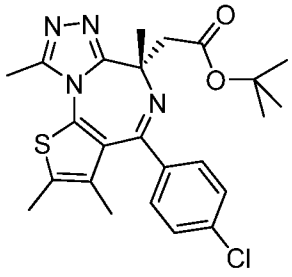
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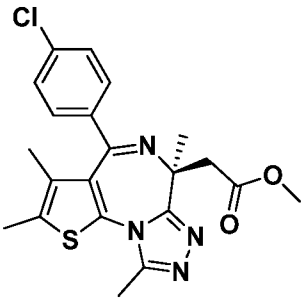
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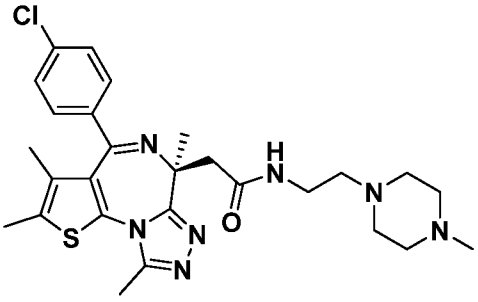
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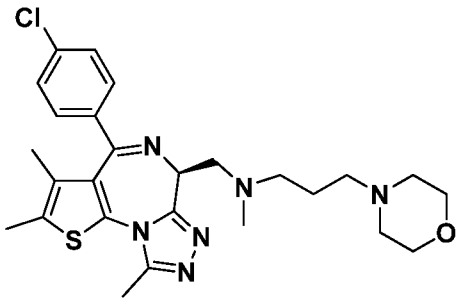
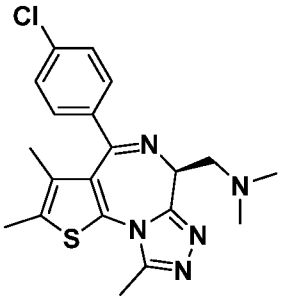
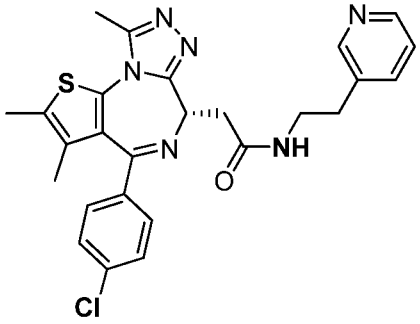

, or


;

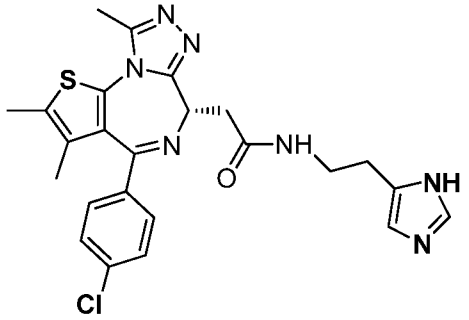
or a pharmaceutically acceptable salt thereof.

[00328] In a fifteenth embodiment, a compound is represented by the structure:


;

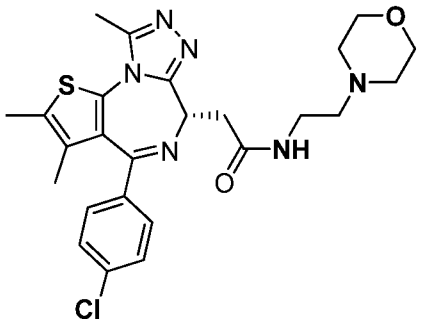
or a pharmaceutically acceptable salt thereof.

[00329] In a sixteenth embodiment, a compound is represented by the structure:



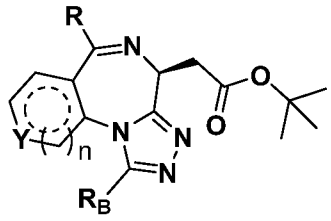
or a pharmaceutically acceptable salt thereof

[00330] In a seventeenth embodiment, a compound is represented by the structure:

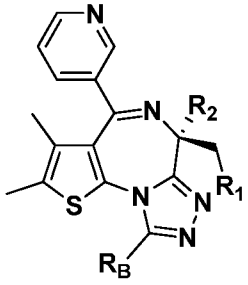


or a pharmaceutically acceptable salt thereof.

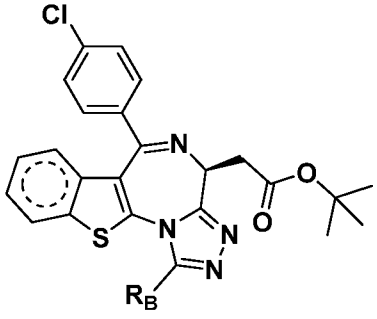
[00331] In an eighteenth embodiment, a compound is represented by Structural Formula (VI), (VII), or (VIII):



(VI),



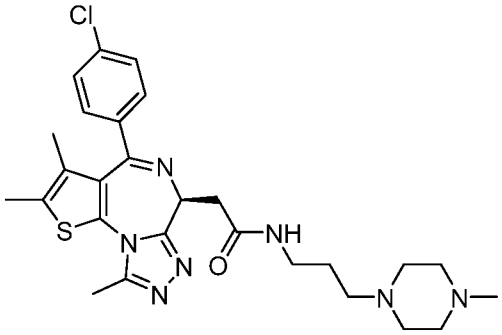
(VII),



(VIII);

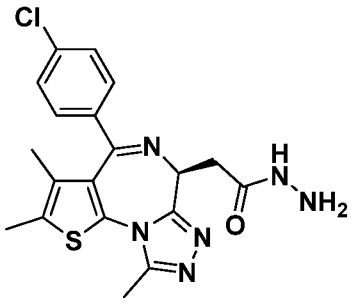
in which R, R_1, and R_2 and R_B have the same meaning as in Formula (I); Y is O, N, S, or CR_3, in which R_3 has the same meaning as in Formula (I); n is 0 or 1; and the dashed circle in Formula (VIII) indicates an aromatic or non-aromatic ring; or a pharmaceutically acceptable salt thereof.

[00332] In a nineteenth embodiment, a compound is represented by the structure:



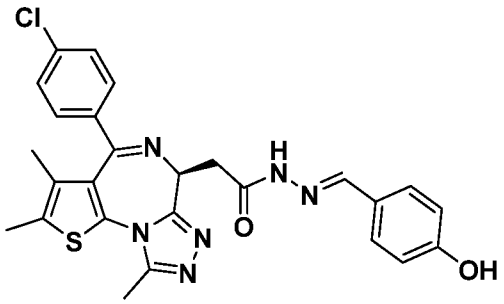
or a pharmaceutically acceptable salt thereof.

[00333] In certain embodiments, the compound for use in the methods of the invention is a compound selected from the group consisting of :



(3)

and



(4)

;

or a pharmaceutically acceptable salt thereof.

[00334] ***Example BET Inhibitors – Structural Formulas (IX) to (XI)***

[00335] In another example embodiment, bromodomain inhibitors for use in the methods of the invention, as well as methods of preparing same, are described in U.S. Provisional Application No. 62/068,983, filed on October 27, 2014. The teachings of this application are incorporated herein by referejce in its entirety.

[00336] Example compounds suitable for use with the methods of the present invention include those represented by structural formulas (IX), (X), and (XI), or a pharmaceutically

acceptable salt thereof. Values and alternative values for the variables in Formulas (IX-XI) or an enantiomer, a diastereomer, or a pharmaceutically acceptable salt thereof, and for each of the embodiments described herein are provided in the following paragraphs. It is understood that the invention encompasses all combinations of the substituent variables (i.e., R_1, R_2, R_{20}, etc.) defined herein.

[00337] A is selected from the group consisting of a $(C_1$-$C_6)$alkyl, a $(C_2$-$C_6)$alkenyl, a $(C_2$-$C_6)$alkynyl, a $(C_3$-$C_{12})$cycloalkyl, and a $(C_5$-$C_7)$heterocycloalkyl, wherein moiety A is optionally substituted with 1 to R_2 groups.

[00338] Alternatively, A is selected from the group consisting of a $(C_1$-$C_6)$alkyl, a $(C_3$-$C_{12})$cycloalkyl, and a $(C_5$-$C_7)$heterocycloalkyl, wherein moiety A is optionally substituted with 1 to 4 R_2 groups. In another alternative, A is selected from the group consisting of a $(C_1$-$C_6)$alkyl, a $(C_3$-$C_{12})$cycloalkyl, and a $(C_5$-$C_7)$heterocycloalkyl. Further, A is ethyl or cyclohexyl.

[00339] R_1 is selected from the group consisting of -OH, a halogen, -CN, a $(C_1$-$C_4)$ alkoxy, -C(O)$(C_1$-$C_4)$alkyl, -C(O)O$(C_1$-$C_4)$alkyl, -OC(O)$(C_1$-C_4 alkyl), -C(O)NR_3R_4, -NR_5C(=O)R_6, a $(C_1$-$C_6)$alkyl, a $(C_2$-$C_6)$alkenyl, a $(C_3$-$C_{12})$cycloalkyl, and a $(C_5$-$C_7)$heterocycloalkyl.

[00340] Alternatively, R_1 is selected from the group consisting of -OH, a halogen, a $(C_1$-$C_4)$ alkoxy, -C(O)$(C_1$-$C_4)$alkyl, -C(O)O$(C_1$-$C_4)$alkyl, -OC(O)$(C_1$-C_4 alkyl) and a $(C_1$-$C_6)$alkyl. Further, R_1 is selected from the group consisting of -OH, a halogen, $(C_1$-$C_4)$ alkoxy, and a $(C_1$-$C_6)$alkyl. Alternatively, R_1 is selected from the group consisting of a halogen and a $(C_1$-$C_6)$alkyl. In another alternative, R_1 is selected from the group consisting of -F, -Cl, -Br, or -I.

[00341] R_2 is a $(C_1$-$C_6)$alkyl, a $(C_2$-$C_6)$alkenyl, a halo$(C_1$-$C_6)$alkoxy, a halo$(C_1$-$C_6)$alkyl, a hydroxy$(C_1$-$C_6)$alkyl, a $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, a $(C_3$-$C_{12})$ cycloalkyl, a -$(C_1$-$C_6)$alkylene-$(C_3$-$C_{12})$cycloalkyl, a $(C_3$-$C_{12})$ heterocycloalkyl, a -$(C_1$-$C_6)$alkylene-$(C_3$-$C_{12})$heterocycloalkyl, a $(C_1$-$C_6)$alkoxy, -C(O)$(C_1$-C_6 alkyl), -C(O)O$(C_1$-C_6 alkyl), -OC(O)$(C_1$-C_6 alkyl), -C(O)NR_7R_8, -NR_9C(=O)R_{10}, -$NR_{11}R_{12}$, a halogen, an oxo, or –OH.

[00342] Alternatively, R_2 is a $(C_1$-$C_6)$alkyl, a halo$(C_1$-$C_6)$alkoxy, a halo$(C_1$-$C_6)$alkyl, a hydroxy$(C_1$-$C_6)$alkyl, a $(C_1$-$C_6)$alkoxy$(C_1$-$C_6)$alkyl, a $(C_1$-$C_6)$alkoxy, -C(O)$(C_1$-C_6 alkyl), -C(O)O$(C_1$-C_6 alkyl), -OC(O)$(C_1$-C_6 alkyl), a halogen, an oxo, or –OH. Further, R_2 is a

(C_1-C_6)alkyl, a halo(C_1-C_6)alkoxy, a halo(C_1-C_6)alkyl, a hydroxy(C_1-C_6)alkyl, a (C_1-C_6)alkoxy(C_1-C_6)alkyl, a (C_1-C_6)alkoxy, a halogen, an oxo, or –OH.

[00343] R_3 is H or a (C_1-C_4)alkyl. Alternatively, R_3 is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00344] R_4 is H or a (C_1-C_4)alkyl. Alternatively, R_4 is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00345] R_5 is H or a (C_1-C_4)alkyl. Alternatively, R_5 is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00346] R_6 is H or a (C_1-C_4)alkyl. Alternatively, R_6 is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00347] R_7 is H or a (C_1-C_4)alkyl. Alternatively, R_7 is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00348] R_8 is H or a (C_1-C_4)alkyl. Alternatively, R_8 is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00349] R_9 is H or a (C_1-C_4)alkyl. Alternatively, R_9 is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00350] R_{10} is H or a (C_1-C_4)alkyl. Alternatively, R_{10} is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00351] R_{11} is H or a (C_1-C_4)alkyl. Alternatively, R_{11} is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00352] R_{12} is H or a (C_1-C_4)alkyl. Alternatively, R_{12} is H, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, or tert-butyl.

[00353] R_{20} is -H, -OH, a (C_1-C_3) alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl. Alternatively, R_{20} is H or a (C_1-C_3)alkyl. Further, R_{20} is H, methyl, ethyl, propyl, or iso-propyl.

[00354] R_{30} is -H, -OH, a (C_1-C_3)alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl. Alternatively, R_{30} is H or a (C_1-C_3)alkyl. Further, R_{30} is H, methyl, ethyl, propyl, or iso-propyl.

[00355] R_{40}, for each occurence independently, is -H, -OH, a (C_1-C_3)alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl. R_{40} is H or a (C_1-C_3)alkyl. Further, R_{40} is H, methyl, ethyl, propyl, or iso-propyl.

[00356] m is 0, 1, 2, 3, or 4. Alternatively, m is 0, 1, or 2. Further, m is 1 or 2. Alternatively, m is 1.

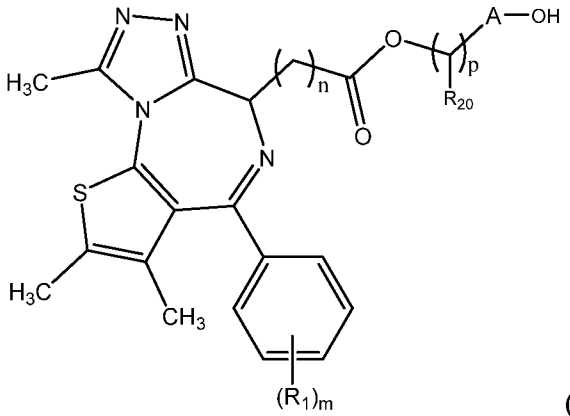
[00357] n is 0, 1, 2, 3, or 4. Alternatively, n is 0, 1, or 2. Further, n is 0 or 1. Alternatively, n is 1.

[00358] p is 0, 1, 2, 3 or 4. Alternatively, p is 0, 1, or 2. Further, p is 0 or 1.

[00359] q is 0, 1, 2, 3 or 4. Alternatively, q is 0, 1, or 2. Further, q is 0 or 1.

[00360] A description of example embodiments of the invention follows.

[00361] A first embodiment of the present invention is directed to a compound of Structural Formula (IX):



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

[00362] A is selected from the group consisting of a (C_1-C_6)alkyl, a (C_2-C_6)alkenyl, a (C_2-C_6)alkynyl, a (C_3-C_{12})cycloalkyl, and a (C_5-C_7)heterocycloalkyl, wherein moiety A is optionally substituted with 1 to 4 R_2 groups;

[00363] R_{20}, for each occurence independently, is -H, -OH, a (C_1-C_3) alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl;

[00364] R_1 for each occurence independently is selected from the group consisting of -OH, a halogen, -CN, a (C_1-C_4) alkoxy, -C(O)(C_1-C_4)alkyl, -C(O)O(C_1-C_4)alkyl, -OC(O)(C_1-C_4 alkyl), -C(O)NR_3R_4, -NR_5C(=O)R_6, a (C_1-C_6)alkyl, a (C_2-C_6)alkenyl, a (C_3-C_{12})cycloalkyl, and a (C_5-C_7)heterocycloalkyl;

[00365] R_2 for each occurence independently is a (C_1-C_6)alkyl, a (C_2-C_6)alkenyl, a halo(C_1-C_6)alkoxy, a halo(C_1-C_6)alkyl, a hydroxy(C_1-C_6)alkyl, a (C_1-C_6)alkoxy(C_1-C_6)alkyl, a (C_3-C_{12}) cycloalkyl, a -(C_1-C_6)alkylene-(C_3-C_{12})cycloalkyl, a (C_3-C_{12}) heterocycloalkyl, a -(C_1-C_6)alkylene-(C_3-C_{12})heterocycloalkyl, a (C_1-C_6)alkoxy, -C(O)(C_1-

C_6 alkyl), -C(O)O(C_1-C_6 alkyl), -OC(O)(C_1-C_6 alkyl), -C(O)NR_7R_8, -NR_9C(=O)R_{10}, -$NR_{11}R_{12}$, a halogen, an oxo, or -OH;

[00366] R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are each independently H or a (C_1-C_4)alkyl; and

[00367] each m, n and p is independently 0, 1, 2, 3, or 4.

[00368] In a first aspect of the first embodiment: A is a (C_1-C_6)alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl.

[00369] In a second aspect of the first embodiment: A is ethyl or cyclohexyl.

[00370] In a third aspect of the first embodiment: R_2 is –OH or a (C_1-C_6)alkyl. In a particular example of the third aspect, the remaining variables are as set forth in the first or second aspect of the first embodiment.

[00371] In a fourth aspect of the first embodiment: R_2 is –OH or methyl. In a particular example of the third aspect, the remaining variables are as set forth in the first or second aspect of the first embodiment.

[00372] In a fifth aspect of the first embodiment: R_1 is -F, -Cl, -Br, or –I. In a particular example of the fifth aspect, the remaining variables are as in the first, second, third or fourth aspect of the first embodiment or any of the particular examples of the third or fourth aspect.

[00373] In a sixth aspect of the first embodiment: R_{20} is H or a (C_1-C_3)alkyl. In a particular example of the sixth aspect, the remaining variables are as in the first, second, third, fourth or fifth aspect of the first embodiment or any of the particular examples of the third, fourth or fifth aspect.

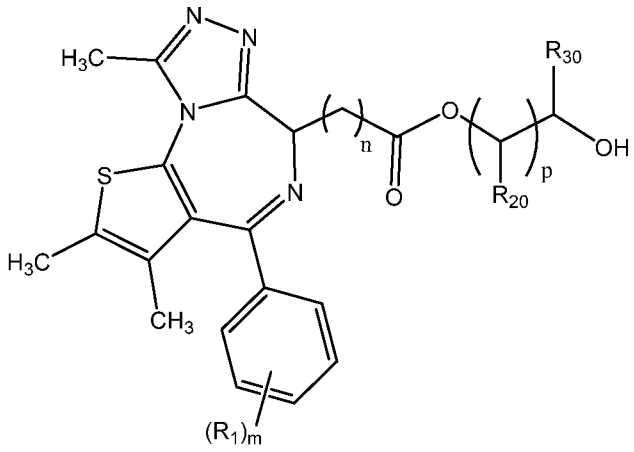
[00374] In a seventh aspect of the first embodiment: p is 0. In a particular example of the seventh aspect, the remaining variables are as in the first, second, third, fourth, fifth or sixth aspect of the first embodiment or any of the particular examples of the third, fourth or fifth or sixth aspect.

[00375] In an eighth aspect of the first embodiment: m is 1. In a particular example of the eighth aspect, the remaining variables are as in the first, second, third, fourth, fifth, sixth or seventh aspect of the first embodiment or any of the particular examples of the third, fourth, fifth, sixth or seventh aspect.

[00376] In a ninth aspect of the first embodiment: n is 1. In a particular example of the ninth aspect, the remaining variables are as in the first, second, third, fourth, fifth, sixth,

seventh or eighth aspect of the first embodiment or any of the particular examples of the third, fourth, fifth, sixth, seventh or eighth aspect.

[00377] In a second embodiment, the present invention is directed to a compound of Structural Formula (X):



(X)

or a pharmaceutically acceptable salt thereof, wherein:

[00378] R_1 for each occurence independently is selected from the group consisting of -OH, a halogen, -CN, a (C_1-C_4) alkoxy, -C(O)(C_1-C_4)alkyl, -C(O)O(C_1-C_4)alkyl, -OC(O)(C_1-C_4 alkyl), -C(O)NR_3R_4, -NR_5C(=O)R_6, a (C_1-C_6)alkyl, a (C_2-C_6)alkenyl, a (C_3-C_{12})cycloalkyl, and a (C_5-C_7)heterocycloalkyl;

[00379] R_3, R_4, R_5, and R_6 are each independently H or a (C_1-C_4)alkyl

[00380] R_{20}, for each occurence independently, is -H, -OH, a (C_1-C_3) alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl;

[00381] R_{30}, for each occurence independently, is -H, -OH, a (C_1-C_3)alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl; and

[00382] each m, n and p is independently 0, 1, 2, 3, or 4.

[00383] In a first aspect of the second embodiment: R_1 is -F, -Cl, -Br, or –I.

[00384] In a second aspect of second embodiment: R_{20} is H or a (C_1-C_3)alkyl. In a particular example of the second aspect, the remaining variables are as set forth in the first aspect of the second embodiment.

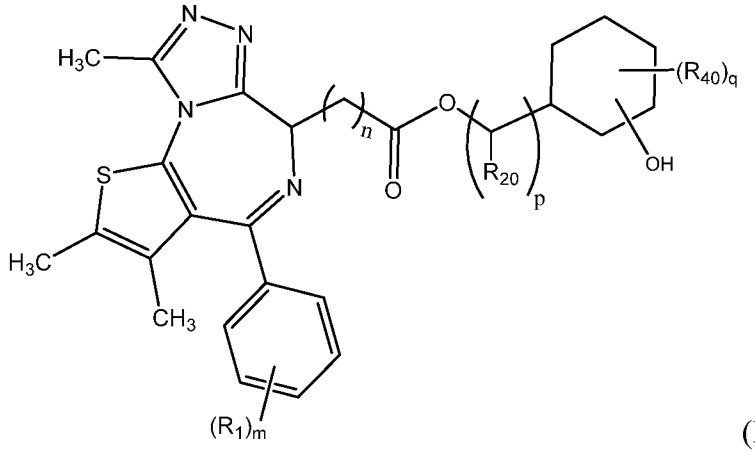
[00385] In a third aspect of the second embodiment: R_{30} is H or a (C_1-C_3)alkyl. In a particular example of the third aspect, the remaining variables are as set forth in the first or second aspect of the second embodiment or any of the particular examples of the second aspect.

[00386] In a fourth aspect of the second embodiment: p is 1. In a particular example of the fourth aspect, the remaining variables are as set forth in the first, second or third aspect of the second embodiment or any of the particular examples of the second or third aspect.

[00387] In a fifth aspect of the second embodiment: m is 1. In a particular example of the fifth aspect, the remaining variables are as set forth in the first, second, third or fourth aspect of the second embodiment or any of the particular examples of the second, third or fourth aspect.

[00388] In a sixth aspect of the second embodiment: n is 1. In a particular example of the sixth aspect, the remaining variables are as set forth in the first, second, third, fourth or fifith aspect of the second embodiment or any of the particular examples of the second, third, fourth or fifth aspect.

[00389] In a third embodiment, the present invention is directed to a compound of Structural Formula (XI):



(XI)

or a pharmaceutically acceptable salt thereof, wherein:

[00390] R_1 for each occurence independently is selected from the group consisting of -OH, a halogen, -CN, a (C_1-C_4) alkoxy, -C(O)(C_1-C_4)alkyl, -C(O)O(C_1-C_4)alkyl, -OC(O)(C_1-C_4 alkyl), -C(O)NR_3R_4, -NR_5C(=O)R_6, a (C_1-C_6)alkyl, a (C_2-C_6)alkenyl, a (C_3-C_{12})cycloalkyl, and a (C_5-C_7)heterocycloalkyl;

[00391] R_3, R_4, R_5, and R_6 are each independently H or a (C_1-C_4)alkyl

[00392] R_{20}, for each occurence independently, is -H, -OH, a (C_1-C_3) alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl;

[00393] R_{40}, for each occurence independently, is -H, -OH, a (C_1-C_3)alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl; and

[00394] each q, m, n and p is independently 0, 1, 2, 3 or 4.

[00395] In one aspect of the third embodiment: R_1 is -F, -Cl, -Br, or –I.

[00396] In a second aspect of third embodiment: R_{20} is H or a $(C_1\text{-}C_3)$alkyl. In a particular example of the second aspect, the remaining variables are as set forth in the first aspect of the third embodiment.

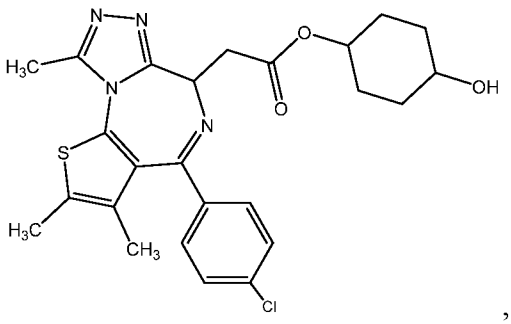
[00397] In a third aspect of the third embodiment: R_{40} is H or a $(C_1\text{-}C_3)$alkyl. In a particular example of the third aspect, the remaining variables are as set forth in the first or second aspect of the third embodiment or any of the particular examples of the second aspect.

[00398] In a fourth aspect of the third embodiment: p is 0. In a particular example of the fourth aspect, the remaining variables are as set forth in the first, second or third aspect of the third embodiment or any of the particular examples of the second or third aspect.

[00399] In a fifth aspect of the third embodiment: m is 1. In a particular example of the fifth aspect, the remaining variables are as set forth in the first, second, third or fourth aspect of the third embodiment or any of the particular examples of the second, third or fourth aspect.

[00400] In a sixth aspect of the third embodiment: n is 1. In a particular example of the sixth aspect, the remaining variables are as set forth in the first, second, third, fourth or fifth aspect of the third embodiment or any of the particular examples of the second, third, fourth or fifth aspect.

[00401] In another aspect, the invention provides a compound represented by any one of the following formulae:



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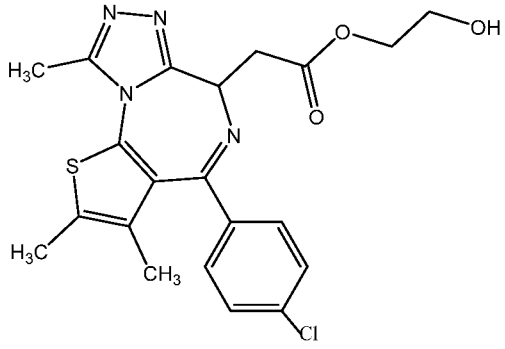
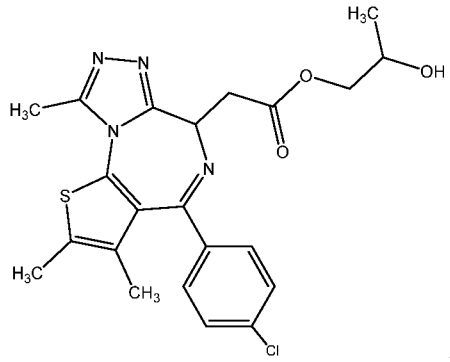


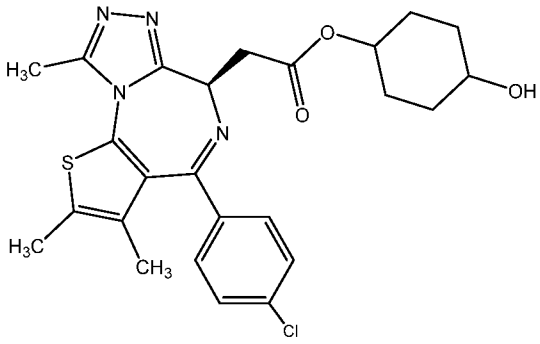
, or



,

or a pharmaceutically acceptable salt thereof.

[00402] In another aspect, the invention provides a compound represented by any one of the following formulae:



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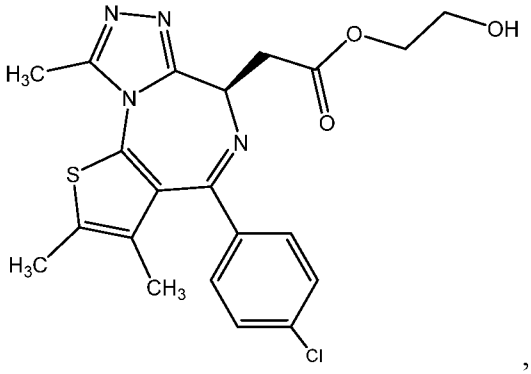
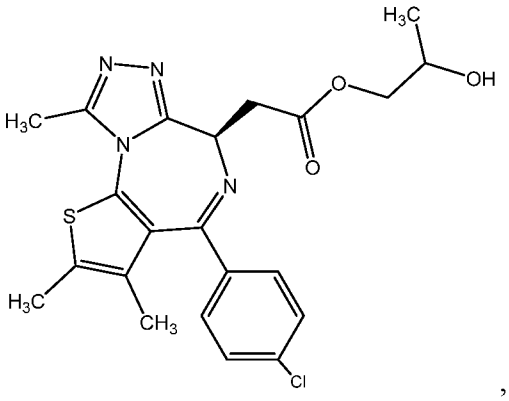


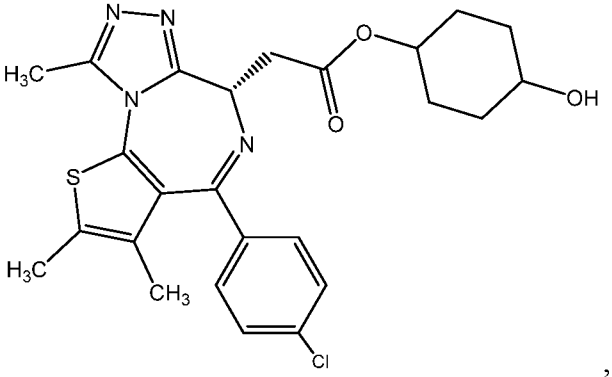
, or



,

or a pharmaceutically acceptable salt thereof.

[00403] In another aspect, the invention provides a compound represented by any one of the following formulae:



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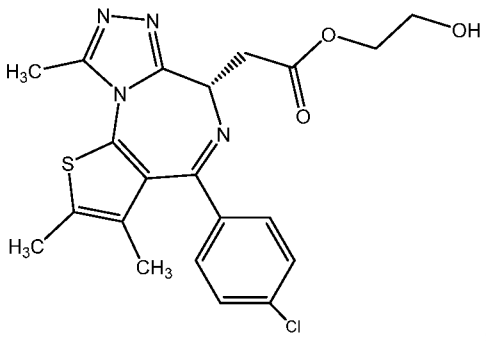
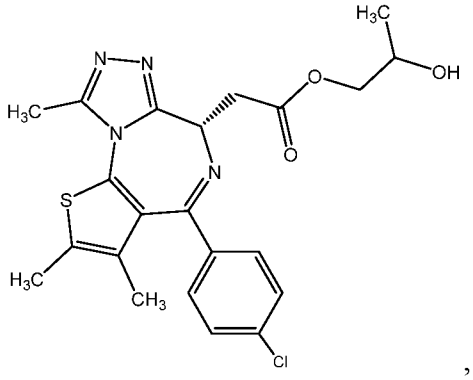


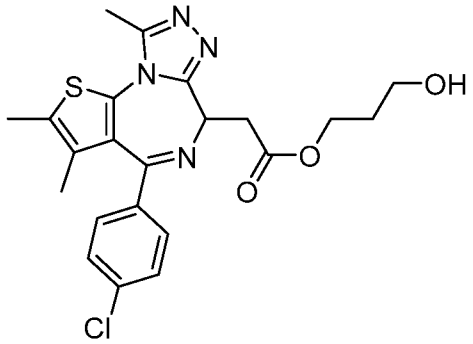
, or



,

or a pharmaceutically acceptable salt thereof.

[00404] In another aspect, the invention provides a compound represented by any one of the following formulae:



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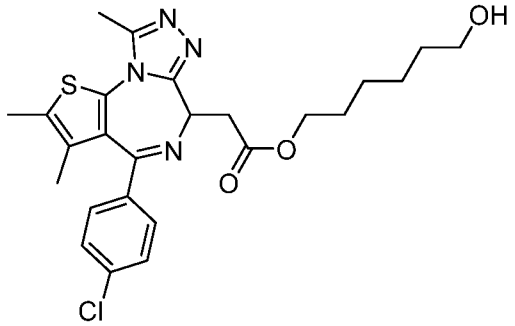

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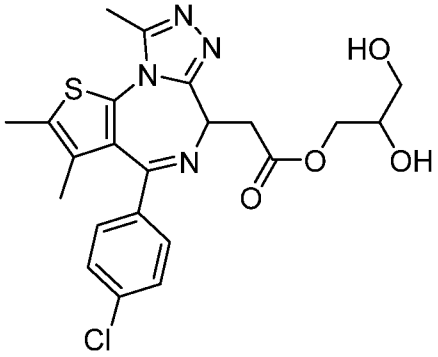
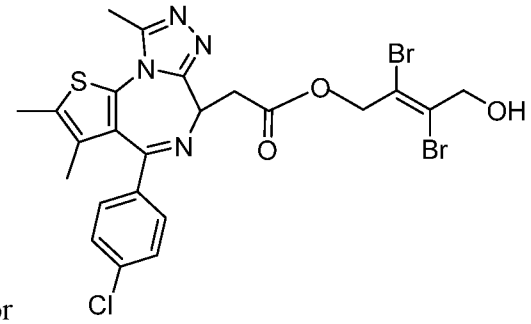
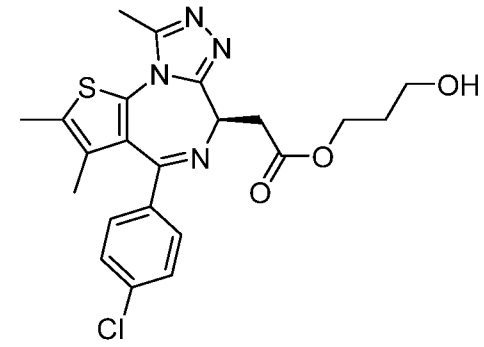


, or



[00405] or a pharmaceutically acceptable salt thereof.

[00406] In another aspect, the invention provides a compound represented by any one of the following formulae:



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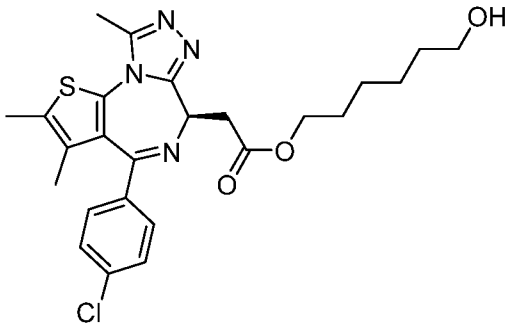

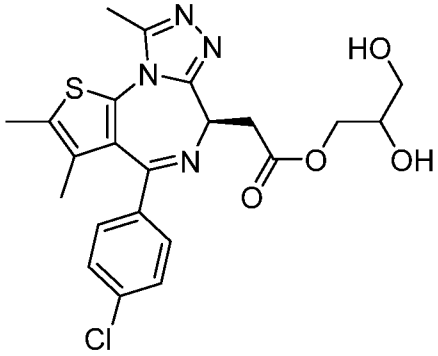

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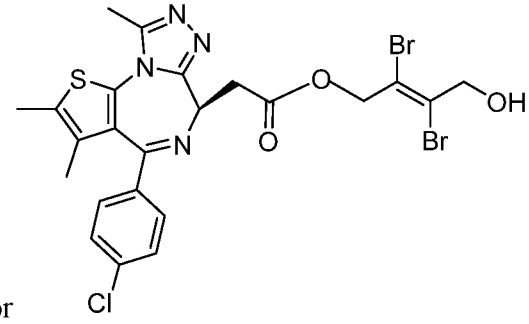
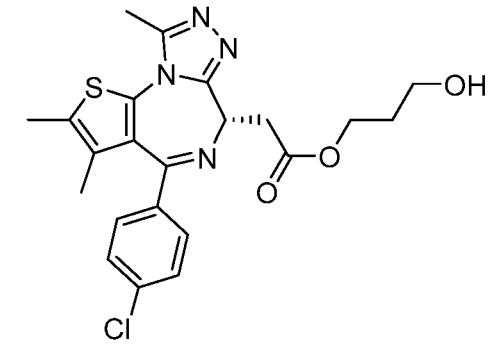


or

[00407] or a pharmaceutically acceptable salt thereof.

[00408] In another aspect, the invention provides a compound represented by any one of the following formulae:



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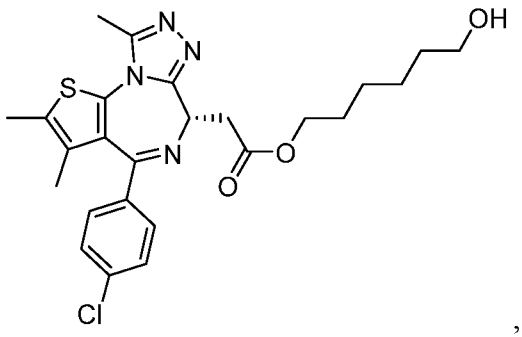

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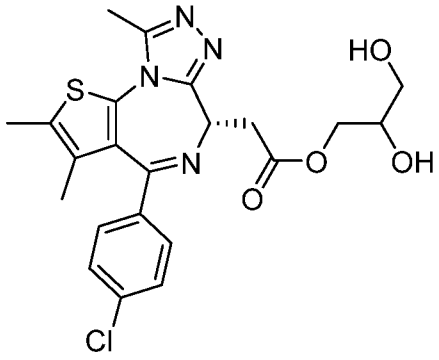
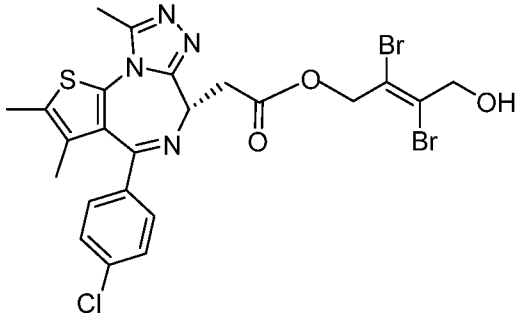


, or



or a pharmaceutically acceptable salt thereof.

[00409] Further examples of BET inhibitors suitable for using with the methods disclosed herein include the compounds and compositions disclosed in WO 2011/054843 (Glaxosmithkline), WO 2009/084693 (Mitsubishi Tanabe Pharma Corporation), WO 2012/075383 (Constellation Pharmaceuticals, Inc.), WO 2011/054553 (Glaxosmithkline),

WO 2011/054841 (Glaxosmithkline), WO 2011/054844 (Glaxosmithkline), WO 2011/054845 (Glaxosmithkline), WO 2011/054846 (Glaxosmithkline), WO 2011/054848 (Glaxosmithkline), WO 2011/161031 (Glaxosmithkline), US2015/0148337 (Constellation Pharmaceuticals, Inc.), US2014/0371206 (Constellation Pharmaceuticals, Inc.), US2014/0296243 (Constellation Pharmaceuticals, Inc.), US2014/0135316 (Constellation Pharmaceuticals, Inc.), US2014/0005169 (Constellation Pharmaceuticals, Inc.), US2012/0157428 (Constellation Pharmaceuticals, Inc.), and U.S. Pat No. 8,796,261 (Constellation Pharmaceuticals, Inc.). The relevant teachings of each of these documents are incorporated herein by reference.

[00410] Modes of Administration

[00411] The bromodomain inhibitors (*e.g.*, TEN-010) for use in the methods or compositions of the invention can be formulated for parenteral, oral, transdermal, sublingual, buccal, rectal, intranasal, intrabronchial or intrapulmonary administration.

[00412] For parenteral administration, the compounds for use in the methods or compositions of the invention can be formulated for injection or infusion, for example, intravenous, intramuscular or subcutaneous injection or infusion, or for administration in a bolus dose and/or infusion (*e.g.*, continuous infusion). Suspensions, solutions or emulsions in an oily or aqueous vehicle, optionally containing other formulatory agents such as suspending, stabilizing and/or dispersing agents can be used.

[00413] For oral administration the bromodomain inhibitor can be of the form of tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (*e.g.*, polyvinylpyrrolidone or hydroxypropylmethylcellulose); fillers (*e.g.*, lactose, microcrystalline cellulose or calcium phosphate); lubricants (e.g., magnesium stearate, talc or silica); disintegrates (*e.g.*, sodium starch glycollate); or wetting agents (*e.g.*, sodium lauryl sulphate). If desired, the tablets can be coated using suitable methods. Liquid preparation for oral administration can be in the form of solutions, syrups or suspensions. The liquid preparations can be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g., sorbitol syrup, methyl cellulose or hydrogenated edible fats); emulsifying agent (*e.g.*, lecithin or acacia); non-aqueous vehicles (*e.g.,* almond oil, oily esters or ethyl alcohol); and preservatives (*e.g.*, methyl or propyl p-hydroxy benzoates or sorbic acid).

[00414] For buccal administration, the compounds for use in the methods or compositions of the invention can be in the form of tablets or lozenges formulated in a conventional manner.

[00415] For rectal administration, the compounds for use in the methods or compositions of the invention can be in the form of suppositories.

[00416] For sublingual administration, tablets can be formulated in conventional manner.

[00417] For intranasal, intrabronchial or intrapulmonary administration, conventional formulations can be employed.

[00418] Further, the compounds for use in the methods or compositions of the invention can be formulated in a sustained release preparation. For example, the compounds can be formulated with a suitable polymer or hydrophobic material which provides sustained and/or controlled release properties to the active agent compound. As such, the compounds for use in the method of the invention can be administered in the form of microparticles, for example, by injection or in the form of wafers or discs by implantation. Various methods of formulating controlled release drug preparations are known in the art.

[00419] Administration of a bromodomain inhibitor, or pharmaceutically acceptable salt thereof, disclosed herein useful to practice the methods described herein, can be continuous, hourly, four times daily, three time daily, twice daily, once daily, once every other day, twice weekly, once weekly, once every two weeks, once a month, or once every two months, or longer, or some other intermittent dosing regimen. In a particular embodiment, the bromodomain inhibitor is administered in cycles, as described herein.

[00420] Examples of administration of a bromodomain inhibitor, or pharmaceutical salt thereof, of the invention include peripheral administration. Examples of peripheral administration include oral, subcutaneous, intraperitoneal, intramuscular, intravenous, rectal, transdermal, or intranasal forms of administration.

[00421] As used herein, peripheral administration includes all forms of administration of a bromodomain inhibitor or a composition comprising a bromodomain inhibitor disclosed herein which excludes intracranial administration. Examples of peripheral administration include, but are not limited to, oral, parenteral (*e.g.*, intramuscular, intraperitoneal, intravenous or subcutaneous injection, extended release, slow release implant, depot and the like), nasal, vaginal, rectal, sublingual or topical routes of administration, including transdermal patch applications and the like.

[00422] Pharmaceutical Composition

[00423] The bromodomain inhibitors disclosed herein can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the bromodomain inhibitor (*e.g.*, TEN-010) and a pharmaceutically acceptable carrier. As used herein the language "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated.

[00424] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. As described herein, examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[00425] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL(TM) (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a

solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyetheylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[00426] Sterile injectable solutions can be prepared by incorporating the active compound (*e.g.*, TEN-010) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle which contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying which yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[00427] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the bromodomain inhibitor can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such

as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[00428] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser which contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[00429] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories.

[00430] For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[00431] The compounds can also be prepared in the form of suppositories (*e.g.,* with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[00432] In one embodiment, the bromodomain inhibitors are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[00433] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical

carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[00434] Suitable doses per administration for a bromodomain inhibitor include doses of about or greater than about 250 ng/kg, about 500 ng/kg, about 750 ng/kg, about 1 ug/kg, about 10 ug/kg, about 20 ug/kg, about 30 ug/kg, about 40 ug/kg, about 50 ug/kg, about 60 ug/kg, about 70 ug/kg, about 80 ug/kg, about 90 ug/kg, about 0.1 mg/kg, about 0.15 mg/kg, about 0.2 mg/kg, about 0.25 mg/kg, about 0.3 mg/kg, about 0.35 mg/kg, about 0.4 mg/kg, about 0.45 mg/kg, about 0.5 mg/kg, about 0.55 mg/kg, about 0.6 mg/kg, about 0.65 mg/kg, about 0.7 mg/kg, about 0.75 mg/kg, about 0.8 mg/kg, about 0.85 mg/kg, about 0.9 mg/kg, about 0.95 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, or about 2.0 mg/kg. Each suitable dose can be administered over a period time deemed appropriate by a skilled practitioner. In one example, each suitable dose of TEN-010 can be administered in a single injection, at about 0.45 mg/kg, or about 0.65 mg/kg. In other embodiments, each suitable dose can be administered (*e.g.,* infused) over a period of time deemed appropriate by a skilled professional.

[00435] Combination Therapy

[00436] The bromodomain inhibitors (*e.g.,* TEN-010) disclosed herein can be used for treating NMC in combination with a second amount of an anti-cancer agent (sometime referred to herein as a "second agent"), *e.g.,* chemotherapeutic agents or HDAC inhibitors. Such combination administration can be by means of a single dosage form which includes a bromodomain inhibitor and the second agent, such single dosage form including a tablet, capsule, spray, inhalation powder, injectable liquid or the like. Combination administration can comprise a further second agent (*e.g.,* chemotherapeutic agent or HDAC inhibitor) in addition to the single dosage form. Alternatively, combination administration can be by means of administration of two different dosage forms, with one dosage form containing a bromodomain inhibitor, and the other dosage form including a second amount of an anti-cancer agent. In this instance, the dosage forms may be the same or different. Without wishing to limit combination therapies, the following exemplifies certain combination

therapies which may be employed. It is understood that additional anti-cancer agents beyond the required second amount of an anti-cancer agent can be employed in the method described herein.

[00437] The second amount of the anti-cancer agent (sometimes referred to herein as the second agent) can be administered before, simultaneously with, or after the administration of a bromodomain inhibitor. Accordingly, a bromodomain inhibitor and a second agent can be administered together in a single formulation or can be administered in separate formulations, *e.g.*, either simultaneously or sequentially, or both. For example, if a bromodomain inhibitor and a second agent are administered sequentially in separate compositions, the bromodomain inhibitor can be administered before or after the anti-cancer agent. The duration of time between the administration of a bromodomain inhibitor and the second amount of the anti-cancer agent will depend on the nature of the anti-cancer agent. In certain embodiments, the bromodomain inhibitor can precede or follow a chemotherapeutic agent immediately, or after some duration of time deemed to be appropriate by a skilled practitioner.

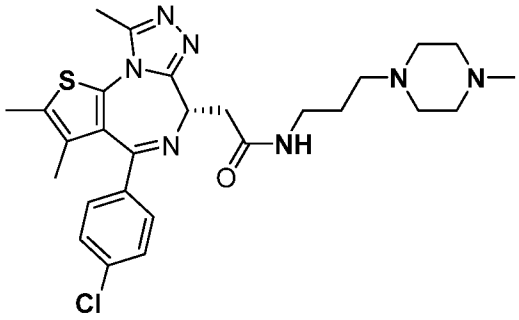
[00438] In addition, the bromodomain inhibitor and the second amount of the anti-cancer agent may or may not be administered on similar dosing schedules. For example, the brmodomain inhibitor and the anti-cancer agent may have different half-lives and/or act on different time-scales such that the bromodomain inhibitor is administered with greater frequency than the anti-cancer agent or vice-versa. For example, the bromodomain inhibitor and the anti-cancer agent can be administered together (*e.g.*, in a single dosage or sequentially) on one day, followed by administration of only the bromodomain inhibitor for a set number of subsequent days. The number of days in between administration of therapeutic agents can be appropriately determined according to the safety and pharmacodynamics of each drug. Either the bromodomain inhibitor or the anti-cancer agent can be administered acutely or chronically.

[00439] Suitable doses per administration of a bromodomain inhibitor have been described herein. An effective amount of the second active agent (*e.g.,* chemotherapeutic agent or HDAC inhibitor) will depend on the age, gender, and weight of the patient, the current medical condition of the patient, and the nature of the NMC being treated. Those of skill in the art will be able to determine appropriate dosages depending on these and other factors. Suitable doses per administration for a second amount of an anti-cancer agent in a

combination therapy can be determined based on the recommended dosing found on the label, as appropriate by a skilled medical professional.

EXAMPLES OF THE INVENTION

[00440] **Compound TEN-010: The Compound TEN-010 used in the following examples and disclosed herein has the following structural formula:**



[00441] **CD11b Expression Levels in NMC Patient is Indicative of Disease Activity**

[00442] The present study was designed to evaluate whether the BET bromodomain inhibitor TEN-010 could have potential to be of benefit in solid tumor oncology indications. As demonstrated herein, the levels of CD11b expressed on the surface of monocytes serve as a marker of responsiveness in TEN-010 NMC therapy.

[00443] The clinical studies disclosed herein were performed in compliance with Good Clinical Practice (GCP), the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

[00444] **Materials and Methods**

[00445] Study Population

[00446] Patients aged 18 years or older with histologically confirmed advanced solid tumors with progressive disease requiring therapy were enrolled in the study. In particular, patients with histologically confirmed advanced solid malignancy with progressive disease, NMC, or advanced aggressive diffuse large B cell lymphoma (DLBCL) were enrolled in the study. Patients with hemotologic malignancies were not enrolled in the study.

[00447] Administration of TEN-010

[00448] TEN-010 was formulated as a sterile, preserved isotonic solution for subcutaneous (SC) administration. A dose of 0.45 mg/kg was administered on Days 1

through 21 ("ON segment") of each cycle without interruption, followed by a 7-day dose-free interval ("OFF segment") in a 28-day treatment cycle. Injections were rotated amongst several sites including bilateral upper arms and thighs and mid and lower abdomen and buttocks.

[00449] Sample collection and assay for CD11b expression levels

[00450] Whole blood specimens were collected at specified time points (*e.g.*, see FIG. 1) in sodium heparin vacutainers. Briefly, two 12x75 mm test tubes per donor were labeled with specimen ID and appropriate cocktail name (see Table 2 below). 100 µl of sodium heparin anticoagulated whole blood was pipetted into the test tubes. The appropriate titrated volume of antibody cocktails was pipetted into the correspondingly labeled tubes. The appropriate titrated amount of CD14 PerCP, was added to all tubes to identify CD14 positive monocytes. The tubes were vortexed and were allowed to incubate for 30 minutes at room temperature in the dark. The red blood cells were lysed by adding 4 ml of an ammonium chloride-based whole blood lysing reagent to each tube. The tubes were capped and inverted to mix well prior to incubating in the dark at room temperature for 5 minutes. After the incubation, the tubes were centrifuged at 400 RCF for 5 minutes, the supernatant decanted and the tubes rack-raked to disperse cell pellet. The cells were washed with 2 ml of PBS with 1% BSA and centrifuged. To detect biotin conjugated CD45 RO antibody, the appropriate titrated amount of SA-BV605 (streptavidin (SA) conjugated to brilliant violet (BV) 605) was added to each tube and tubes were vortexed. After a 20 minute incubation in the dark at room temperature, the cells were washed with 2 ml of PBS with 1% BSA and centrifuged. The supernatant was decanted and the cells were rack-raked to disperse the cell pellet. Each tube received 500 µl of 1% paraformaldehyde and stored at 2-8 C until acquisition on the day of preparation. The tubes were acquired on a Becton Dickinson (BD) FACSCanto™ II flow cytometer with appropriate instrument settings, acquiring approximately 250,000 total events per tube.

[00451] Table 2. Flow cytometry labeling mix

	Content of Cocktail Mixture
Cocktail #1 (control to determine background fluorescence)	MsIgG1 FITC, MsIgG2a phycoerythrin (PE), MsIgG1 Allophycocyanin (APC), CD4 Alexa Fluor® 700 (AF700), MsIgG1 mFluor™ Violet 450 (V450), CD3 Violet 500 (V500), and CD45RO Biotin-SA BV605
Cocktail #2	CD127 FITC, E-Selectin(CD62E) PE, MAC-1 (CD11b) APC, CD4 AF700, CD25 V450, CD3 V500 and CD45RO Biotin-SA BV605

[00452] All labeled antibody reagents for flow cytometric assay were purchased from Becton Dickinson; E-Selectin (CD62E) PE and CD45RO Biotin were purchased from Biolegend.

[00453] Other reagents used is the study include PBS with 1% BSA, ammonium chloride-based whole blood lysing reagent, 1% paraformaldehyde solution, and Quantum MESF fluorescein isothiocyanate (FITC), phycoerythrin (PE), Allophycocyanin (APC) Calibration Beads.

Assay for measuring LDH levels

[00454] LDH levels were measured using standard protocols, using a chemistry analyzer, *e.g.,* Beckman Coulter. See, *e.g.*, Lactate OSR6193 procedure published March 2012 (webcache.googleusercontent.com/search?q=cache:iyYi7vCetH4J:https://www.beckmancoulter.com/wsrportal/techdocs%3Fdocname%3D/cis/BAOSR6x93/%2525%2525/EN_LACTATE_BAOSR6x93_US.doc+&cd=2&hl=en&ct=clnk&gl=us), incorporated by reference in its entirety.

[00455] Data analysis

[00456] All analyses for flow cytometry were performed on WinList 7.0 (Verity Software House, Topsham, Maine) with a direct data exchange link to Microsoft® Excel 2003 or equivalent. For FIG. 1, baseline value (pre-dose at cycle 1, day 1, *i.e.,* C1D1) was set at an arbitrary MESF value (*e.g.,* 100) for each patient; all subsequent values obtained from the study were normalized to the baseline value. For FIG. 2, unnormalized MESF values are shown. The MESF values obtained for the pre-dose, 2, 4 and 8 hour time points on C1D1 were averaged and have been displayed as a single value for C1D1. The MESF values obtained for the pre-dose, 2 and 4 hour time points on C1D15 were averaged and

have been displayed as a single value for C1D15. Patients that did not have C1D1 or C1D15 data available are not shown.

[00457] Results

[00458] As described herein, CD11b levels on CD14+ monocytes were measured in all 6 patients in the present study. FIG. 1 shows a representative data set collected for each patient at the indicated timepoints. CD11b levels in all patients decreased by at least 50% of the baseline value (pre-dose at cycle 1 day 1 – C1D1) by cycle 1 day 15 (C1D15). At the completion of one cycle (*e.g.*, 21 days of on-drug segment followed by 7 days of off-drug segment), and at the start of the second cycle (C2D1), CD11b levels held steady in all patients except patient 004-001, who suffered from NMC (FIG. 1). The CD11b levels in this patient dramatically increased following the off-drug segment, suggesting that TEN-010 was not effective in this patient by C2D1. Patient 004-001 died shortly thereafter.

[00459] In conjunction with the measurement of CD11b expression levels, lactate dehydrogenase (LDH) levels were also measured along similar timepoints. LDH is a known clinical biomarker for cancer progression, and is routinely measured as part of cancer diagnosis and disease progression. Notably, as shown in FIG. 2C, CD11b levels in the NMC patient tracked with LDH levels, validating CD11b levels as a marker for responsiveness in the NMC patient. In contrast, CD11b levels were independent of LDH levels in non-NMC patients. In fact, for non-NMC Patent 002-021 (FIG. 2B), LDH levels remained constant despite a significant rise in CD11b levels.

[00460] Taken together, these results suggest, in part, that CD11b levels can be used to monitor NMC responsiveness to a bromodomain inhibitor therapy. Further, while not wishing to be bound by any theory, monitoring CD11b levels on monocytes enables one to follow NMC disease activity. Accordingly, CD11b levels can be measured to determine whether an NMC patient will require more or less bromodomain inhibitor in subsequent cycle(s) of treatment, or whether an NMC patient will require an earlier or delayed commencement of a subsequent cycle of bromodomain inhibitor treatment, or any combination thereof.

[00461] The teachings of all patents, published applications and references cited herein are incorporated by reference in their entirety.

[00462] While this invention has been particularly shown and described with references to example embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of treating a patient suffering from nuclear protein in testis (NUT) midline carcinoma (NMC), comprising:

administering an effective amount of a bromodomain inhibitor to the patient in a current cycle of a treatment regimen having multiple cycles, each cycle including an on-drug and an off-drug segment,

wherein the patient exhibits a CD11b expression reduction of less than about 50% relative to a baseline level, and wherein the CD11b expression is measured during the current cycle or a prior cycle.

2. The method of claim 1, wherein the CD11b expression is measured during the off-drug segment of the prior cycle.

3. The method of claim 1, wherein the CD11b expression is measured during the on-drug segment of the current cycle.

4. A method of monitoring a treatment response in a patient suffering from nuclear protein in testis (NUT) midline carcinoma (NMC), comprising:

a) administering a predetermined amount of a bromodomain inhibitor to the patient using a treatment regimen having multiple cycles, each cycle comprising an on-drug and an off-drug segment; and

b) quantifying a CD11b expression level in a sample collected from the patient;

wherein a CD11b expression reduction of about 50% or more relative to a baseline level indicates a positive response to the treatment regimen.

5. The method of claim 4, wherein the CD11b expression level is quantified during the off-drug segment of at least one cycle.

6. A method of determining a treatment regimen in a patient suffering from nuclear protein in testis (NUT) midline carcinoma (NMC), comprising:

a) administering a predetermined amount of a bromodomain inhibitor to the patient in a first cycle of a treatment regimen having multiple cycles, each cycle including an on-drug and an off-drug segment;

b) quantifying a CD11b expression level in a sample collected from the patient during the first cycle; and

c) determining whether to modify the first cycle or a subsequent cycle of the treatment regimen, wherein a CD11b expression reduction of less than about 50% relative to a baseline level indicates that the first cycle or the subsequent cycle should be modified,

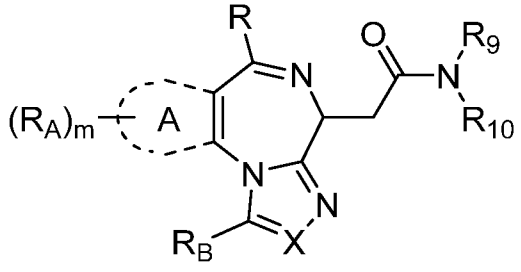
thereby determining the treatment regimen in a patient suffering from NMC.

7. The method of claim 6, wherein the first cycle or the subsequent cycle is modified by increasing the length of the on-drug segment, decreasing the length of the off-drug segment, increasing the predetermined amount of the bromodomain inhibitor, or a combination thereof.

8. The method of claim 6, wherein the CD11b expression level is quantified during the off-drug segment of the first or subsequent cycles.

9. The method of claim 6, wherein the CD11b expression level is quantified during the on-drug segment of the first cycle.

10. The method of any one of Claims 1-9, wherein the bromodomain inhibitor is represented by Structural Formula IV:



(IV)

or a pharmaceutically acceptable salt thereof, wherein:

X is N or CR_3;

R_3 is selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents;

R_B is H, -(C_1-C_4)alkyl, -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, or –COO–R_4, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 4 substituents independently selected from the group consisting of -F, -Cl, -Br, -OH, and -NR_5R_6;

ring A is aryl or heteroaryl;

each R_A is independently H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7) heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_{10})heteroaryl is optionally and independently substituted with 1 to 4 substituents; or any two R_A together with the atoms to which each is bound form a fused aryl or heteroaryl group;

R is -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_{10})heteroaryl, wherein each is optionally and independently substituted with 1 to 4 substituents;

R_4, R_5, and R_6 are each independently selected from the group consisting of: H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents;

R_9 is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl, -(C_0-C_6)alkylene-heteroaryl, and -N=$CR_{11}R_{12}$, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and

each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

R_{10} is selected from the group consisting of: H, -(C_1-C_6)alkyl, -(C_0-C_6)alkylene-cycloalkyl, -(C_0-C_6)alkylene-heterocycloalkyl, -(C_0-C_6)alkylene-aryl; and -(C_0-C_6)alkylene-heteroaryl, wherein each -(C_1-C_6)alkyl and -(C_0-C_6)alkylene- is optionally and independently substituted with 1 to 4 substituents and each -cycloalkyl, -heterocycloalkyl, -aryl, and -heteroaryl is optionally and independently substituted with 1 to 4 substituents;

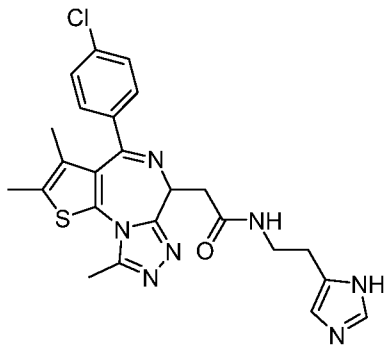
R_9 and R_{10} are taken together with the nitrogen atom to which they are bound form a 4-10-membered ring;

R_{11} is H, -(C_1-C_4)alkyl, or -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl, wherein each -(C_1-C_4)alkyl and -(C_1-C_4)alkylene-O-(C_1-C_4)alkyl is optionally substituted with 1 to 3 substituents selected from the group consisting of: -F, -Cl, -Br, and -OH;

R_{12} is H, -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, or -(C_5-C_7)heteroaryl, wherein each -(C_1-C_4)alkyl, -(C_3-C_8)cycloalkyl, -(C_5-C_7)heterocycloalkyl, -(C_6-C_{10})aryl, and -(C_5-C_7)heteroaryl is optionally and independently substituted with 1 to 4 substituents; and

m is 0, 1, 2, or 3.

11. The method of any one of Claims 1-10, wherein the bromodomain inhibitor is a compound is represented by represented by any one of the following structural formulas:



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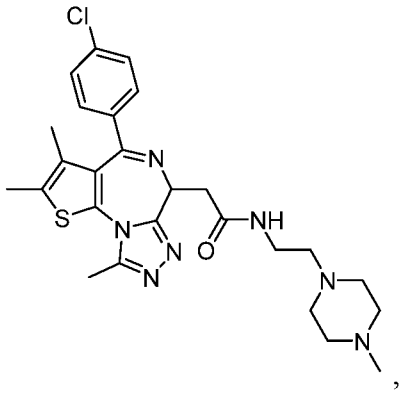

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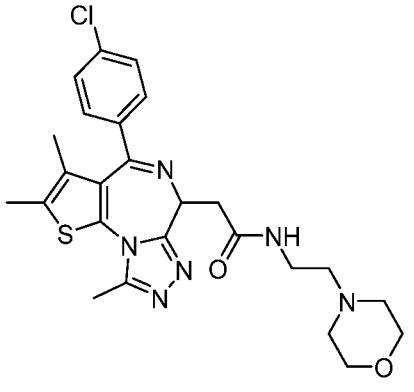
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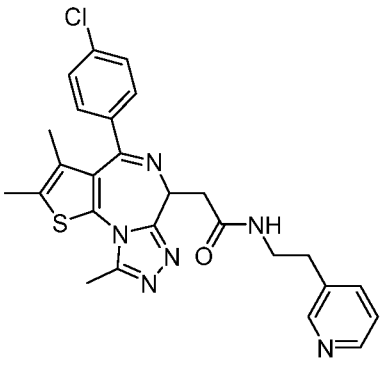
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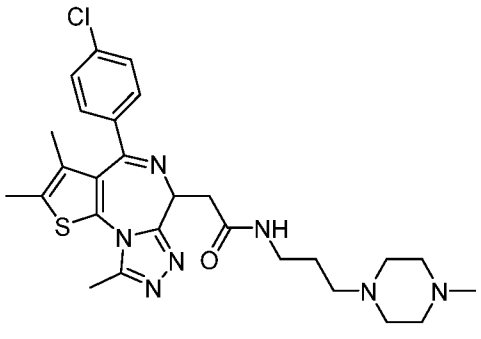
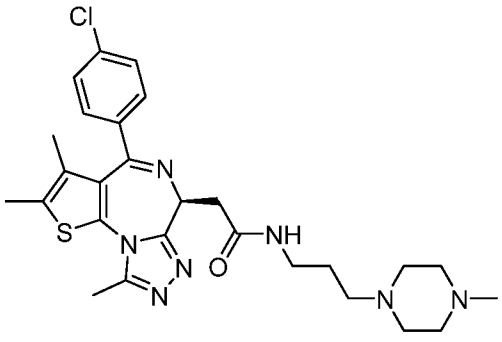

;

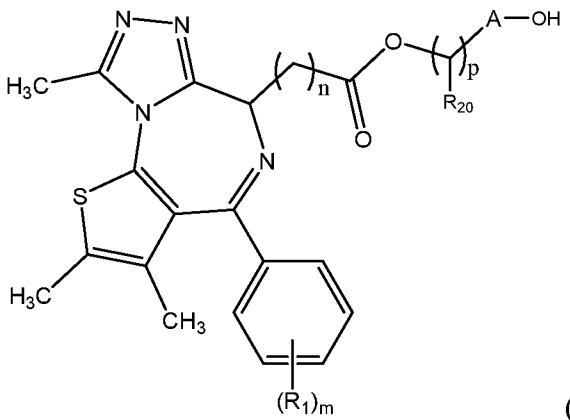
or a pharmaceutically acceptable salt thereof.

12. The method of any one of Claims 1-11, wherein the bromodomain inhibitor is a compound represented by the structural formula:



or a pharmaceutically acceptable salt thereof.

13. The method of any one of Claims 1-9, wherein the bromodomain inhibitor is a compound represented by Structural Formula (IX):



(IX)

or a pharmaceutically acceptable salt thereof, wherein:

A is selected from the group consisting of a (C_1-C_6)alkyl, a (C_2-C_6)alkenyl, a (C_2-C_6)alkynyl, a (C_3-C_{12})cycloalkyl, and a (C_5-C_7)heterocycloalkyl, wherein moiety A is optionally substituted with 1 to 4 R_2 groups;

R_{20}, for each occurence independently, is -H, -OH, a (C_1-C_3) alkyl, a (C_3-C_{12})cycloalkyl, or a (C_5-C_7)heterocycloalkyl;

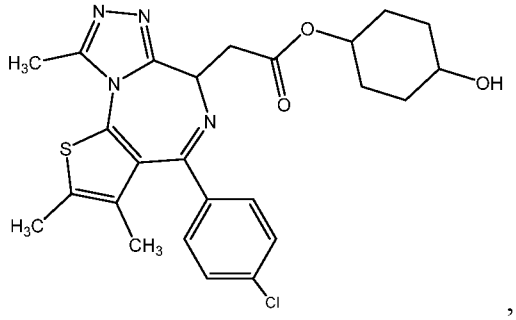
R_1 for each occurence independently is selected from the group consisting of -OH, a halogen, -CN, a (C_1-C_4) alkoxy, -C(O)(C_1-C_4)alkyl, -C(O)O(C_1-C_4)alkyl, -OC(O)(C_1-C_4 alkyl), -C(O)NR_3R_4, -NR_5C(=O)R_6, a (C_1-C_6)alkyl, a (C_2-C_6)alkenyl, a (C_3-C_{12})cycloalkyl, and a (C_5-C_7)heterocycloalkyl;

R_2 for each occurence independently is a (C_1-C_6)alkyl, a (C_2-C_6)alkenyl, a halo(C_1-C_6)alkoxy, a halo(C_1-C_6)alkyl, a hydroxy(C_1-C_6)alkyl, a (C_1-C_6)alkoxy(C_1-C_6)alkyl, a (C_3-C_{12}) cycloalkyl, a -(C_1-C_6)alkylene-(C_3-C_{12})cycloalkyl, a (C_3-C_{12}) heterocycloalkyl, a -(C_1-C_6)alkylene-(C_3-C_{12})heterocycloalkyl, a (C_1-C_6)alkoxy, -C(O)(C_1-C_6 alkyl), -C(O)O(C_1-C_6 alkyl), -OC(O)(C_1-C_6 alkyl), -C(O)NR_7R_8, -NR_9C(=O)R_{10}, -N$R_{11}R_{12}$, a halogen, an oxo, or -OH;

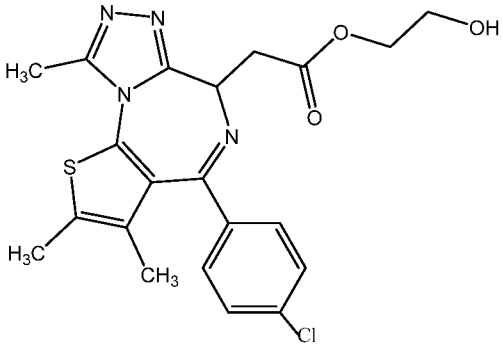
R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, and R_{12} are each independently H or a (C_1-C_4)alkyl; and

each m, n and p is independently 0, 1, 2, 3, or 4.

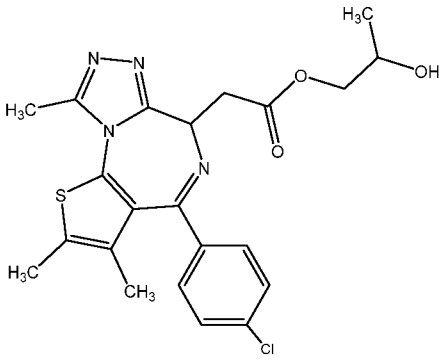
14. The method of any one of the Claims 1-9 or 13, wherein the bromodomain inhibitor is a compound represented by any one of the following structural formulae:



,



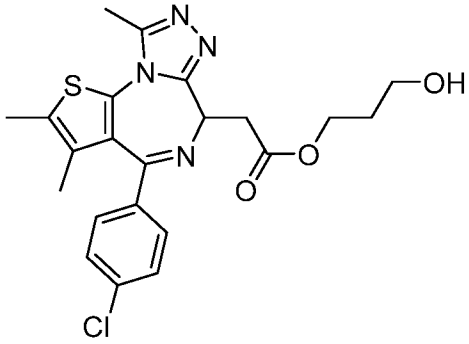
, or



,

or a pharmaceutically acceptable salt thereof.

15. The method of any one of the Claims 1-9 or 13, wherein the bromodomain inhibitor is a compound represented by by any one of the following formulae:



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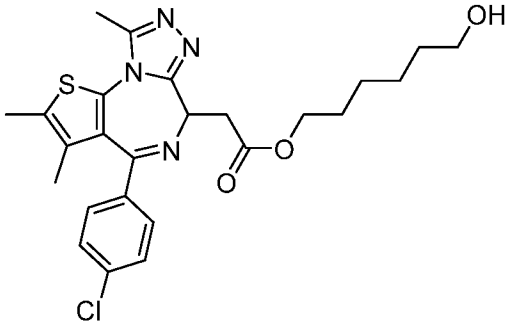
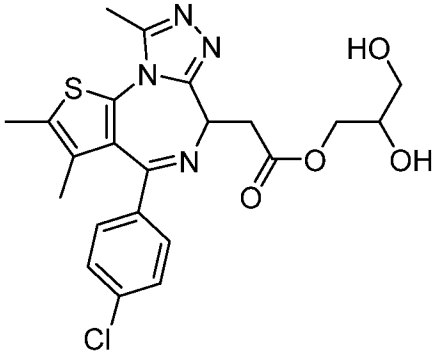
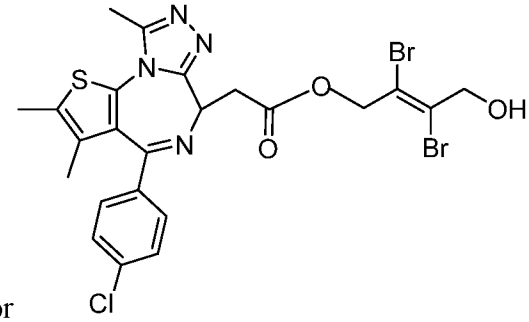




, or



or a pharmaceutically acceptable salt thereof.

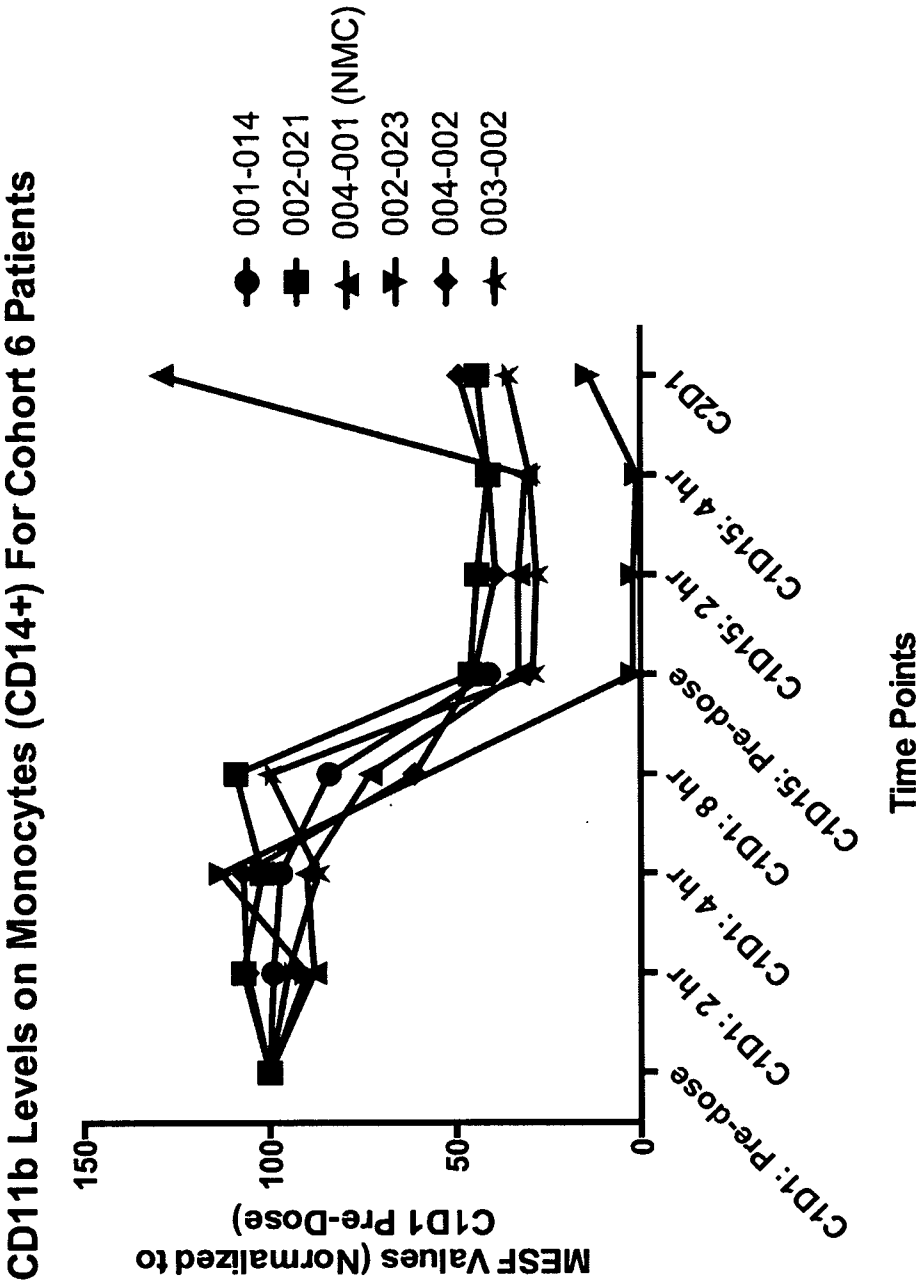

CD11b Levels on Monocytes (CD14+) For Cohort 6 Patients
001-014
002-021
004-001 (NMC)
002-023
004-002
003-002
MESF Values (Normalized to C1D1 Pre-Dose)
150
100
50
0
C1D1: Pre-dose
C1D1: 2 hr
C1D1: 4 hr
C1D1: 8 hr
C1D15: Pre-dose
C1D15: 2 hr
C1D15: 4 hr
C2D1
Time Points

FIG. 1

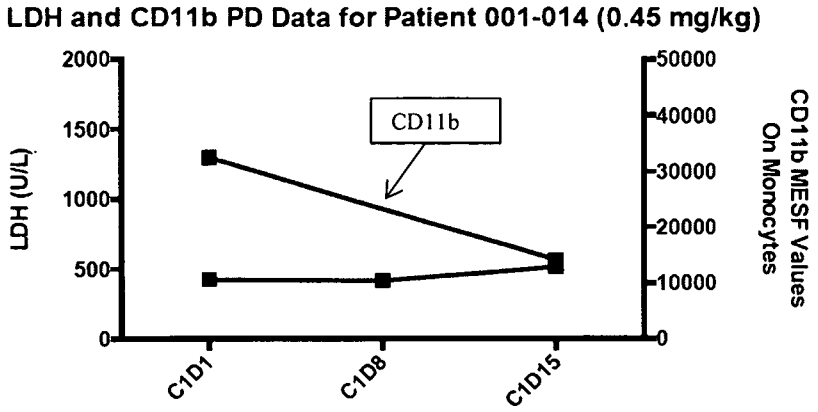


FIG. 2A

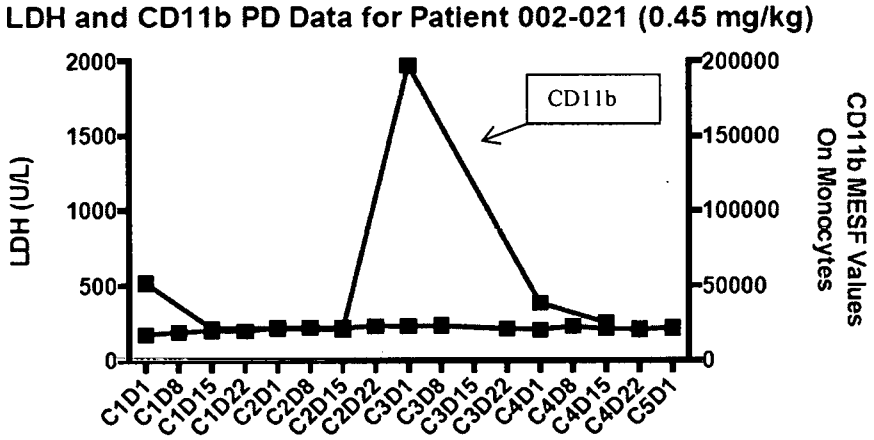


FIG. 2B

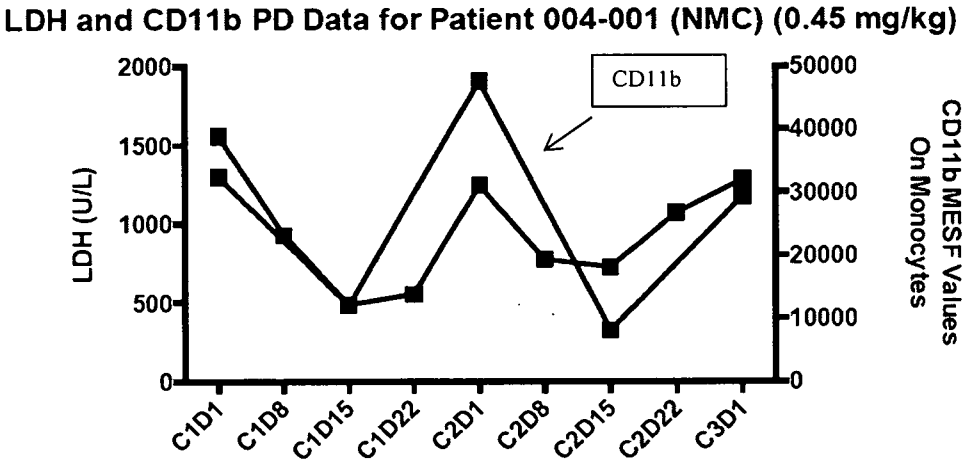


FIG. 2C

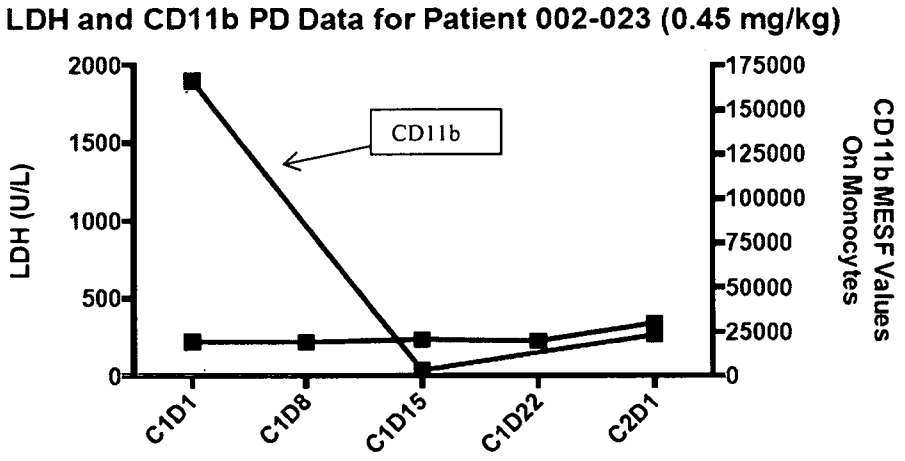


FIG. 2D

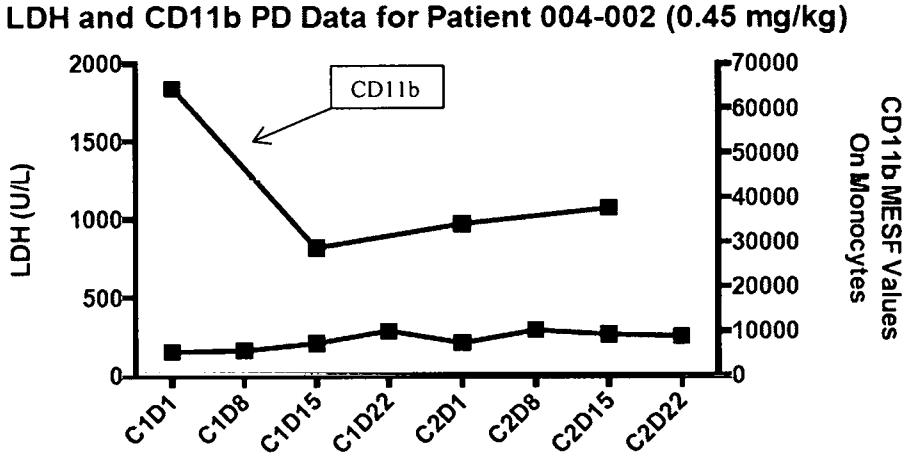


FIG. 2E

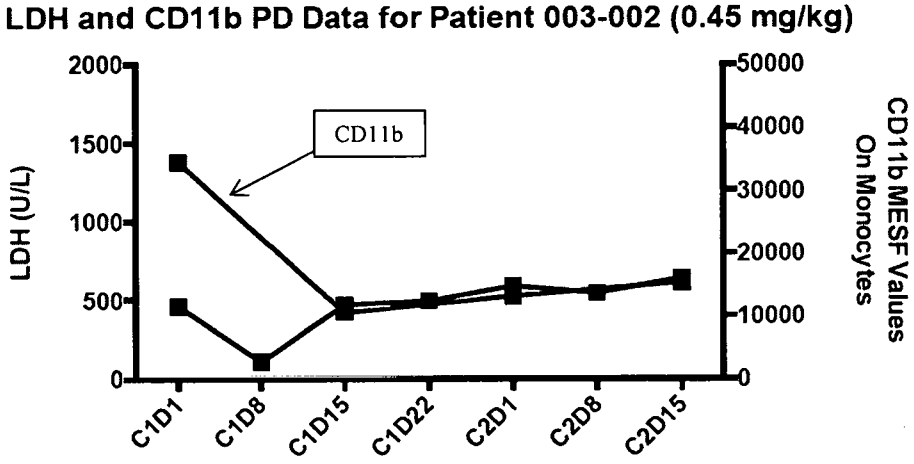


FIG. 2F

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/039270

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12Q1/00 G01N33/574 A61K31/5517 A61P35/00
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12Q G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEM ABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011/143669 A2 (DANA FARBER CANCER INST INC) 17 November 2011 (2011-11-17) abstract page 120; compound jq35 page 125; example 6 page 123; examples 2,5 page 131; tables; compound jg35 claims	1-15
A	US 2013/261109 A1 (MIYOSHI SHINJI [JP] ET AL) 3 October 2013 (2013-10-03) abstract paragraphs [0006], [0100] claims	1-15

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 October 2016	18/10/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Garabatos-Perera, J

3

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R. WANG ET AL: "Activation of SOX2 Expression by BRD4-NUT Oncogenic Fusion Drives Neoplastic Transformation in NUT Midline Carcinoma", CANCER RESEARCH, vol. 74, no. 12, 15 April 2014 (2014-04-15), pages 3332-3343, XP055296872, US ISSN: 0008-5472, DOI: 10.1158/0008-5472.CAN-13-2658 abstract page 3334, right-hand column, last paragraph - page 3335, left-hand column, paragraph 1 page 3342, left-hand column, paragraph 1 -----	1-15
A	P. RHEIN ET AL: "CD11b is a therapy resistance- and minimal residual disease-specific marker in precursor B-cell acute lymphoblastic leukemia", BLOOD, vol. 115, no. 18, 12 March 2010 (2010-03-12), pages 3763-3771, XP055184874, ISSN: 0006-4971, DOI: 10.1182/blood-2009-10-247585 abstract page 3763, right-hand column - page 3764, left-hand column, paragraph 2 page 3766, right-hand column, last paragraph page 3767; figure 1 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2016/039270

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011143669 A2	17-11-2011	AU 2011252808 A1	10-01-2013
		BR 112012029005 A2	26-07-2016
		CA 2799420 A1	17-11-2011
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		EP 2571503 A2	27-03-2013
		EP 2902030 A1	05-08-2015
		ES 2534521 T3	23-04-2015
		HK 1183620 A1	18-09-2015
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		US 2010286127 A1	11-11-2010
		US 2013261109 A1	03-10-2013
		US 2015335656 A1	26-11-2015
		WO 2009084693 A1	09-07-2009

(19)中华人民共和国国家知识产权局

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2017.12.20

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PCT/US2016/039270 2016.06.24

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(71)申请人 腾沙治疗公司
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(74)专利代理机构 北京市金杜律师事务所 11256
代理人 陈文平 侯宝光

(51)Int.Cl.
A61K 31/551(2006.01)
G01N 33/574(2006.01)
A61P 35/00(2006.01)

权利要求书6页 说明书62页 附图4页

(54)发明名称

NUT中线癌的治疗

(57)摘要

本文公开了治疗有需要的受试者的睾丸中的核蛋白(NUT)中线癌(NMC)的方法,其包括施用有效量的布罗莫结构域抑制剂,其中可根据监测NMC对布罗莫结构域抑制剂的反应性的CD11b的表达水平来确定有效量。本文还公开了确定罹患NMC的受试者的布罗莫结构域抑制剂治疗方案的方法。

CN 107787227 A

1.一种治疗罹患睾丸中的核蛋白(NUT)中线癌(NMC)的患者的方法,其包括:

在具有多个周期的治疗方案的当前周期中对所述患者施用有效量的布罗莫结构域抑制剂,每个周期包括上药和离药段,

其中所述患者相对于基线水平表现出不到约50%的CD11b表达降低,且其中所述CD11b表达是在所述当前周期或先前周期期间测量的。

2.如权利要求1所述的方法,其中所述CD11b表达是在所述先前周期的所述离药段期间测量的。

3.如权利要求1所述的方法,其中所述CD11b表达是在所述当前周期的所述上药段期间测量的。

4.一种监测罹患睾丸中的核蛋白(NUT)中线癌(NMC)的患者的治疗反应的方法,其包括:

a)采用具有多个周期的治疗方案对所述患者施用预定量的布罗莫结构域抑制剂,每个周期包括上药和离药段;和

b)量化收集自所述患者的样品中的CD11b表达水平;

其中相对于基线水平约50%或更多的CD11b表达降低指示对所述治疗方案的阳性反应。

5.如权利要求4所述的方法,其中在至少一个周期的所述离药段期间量化所述CD11b表达水平。

6.一种确定罹患睾丸中的核蛋白(NUT)中线癌(NMC)的患者的治疗方案的方法,其包括:

a)在具有多个周期的治疗方案的第一周期中对所述患者施用预定量的布罗莫结构域抑制剂,每个周期包括上药和离药段;

b)量化在所述第一周期期间收集自所述患者的样品中的CD11b表达水平;和

c)确定是否修改所述治疗方案的所述第一周期或后续周期,其中相对于基线水平不到约50%的CD11b表达降低表明应修改所述第一周期或所述后续周期,

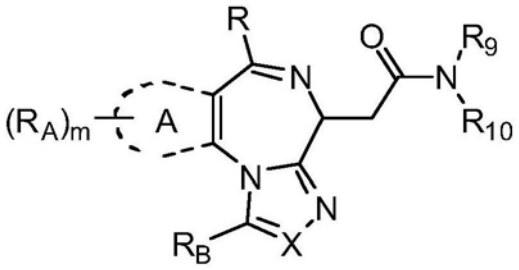
从而确定罹患NMC的患者的治疗方案。

7.如权利要求6所述的方法,其中通过增加所述上药段的长度、减少所述离药段的长度、增加所述布罗莫结构域抑制剂的所述预定量或其组合的方式来修改所述第一周期或所述后续周期。

8.如权利要求6所述的方法,其中在所述第一或后续周期的所述离药段期间量化所述CD11b表达水平。

9.如权利要求6所述的方法,其中在所述第一周期的所述上药段期间量化所述CD11b表达水平。

10.如权利要求1-9中任一项所述的方法,其中所述布罗莫结构域抑制剂由结构式IV表示:



(IV)

或其药学上可接受的盐，其中：

X是N或CR_3；

R_3选自由以下组成的组：H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C10)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C10)杂芳基任选且独立地被1至4个取代基取代；

R_B是H、-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基或-COO-R_4，其中每个-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代；

环A是芳基或杂芳基；

每个R_A独立地为H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基或-(C5-C10)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C10)杂芳基任选且独立地被1至4个取代基取代；或者任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团；

R是-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基或-(C5-C10)杂芳基，其中每个任选且独立地被1至4个取代基取代；

R_4、R_5和R_6各自独立地选自由以下组成的组：H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选且独立地被1至4个取代基取代；

R_9选自由以下组成的组：H、-(C1-C6)烷基、-(C0-C6)亚烷基-环烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基、-(C0-C6)亚烷基-杂芳基和-N=$CR_{11}R_{12}$，其中每个-(C1-C6)烷基和-(C0-C6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

R_{10}选自由以下组成的组：H、-(C1-C6)烷基、-(C0-C6)亚烷基-环烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基；和-(C0-C6)亚烷基-杂芳基，其中每个-(C1-C6)烷基和-(C0-C6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

R_9和R_{10}与它们所结合的氮原子一起形成4-10元环；

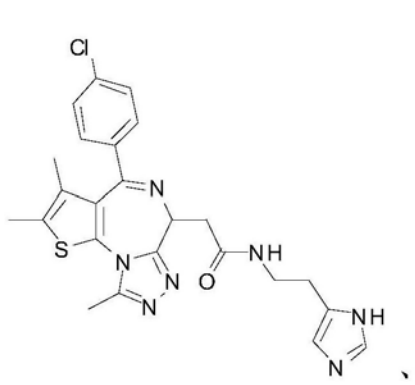
R_{11}是H、-(C1-C4)烷基或-(C1-C4)亚烷基-O-(C1-C4)烷基，其中每个-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基任选被1至3个选自由以下组成的组的取代基取代：-F、-Cl、-Br和-OH；

R_{12}是H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基或-(C5-C7)杂

芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选且独立地被1至4个取代基取代；且

m是0、1、2或3。

11.如权利要求1-10中任一项所述的方法，其中所述布罗莫结构域抑制剂是由以下结构式中的任一者表示的化合物：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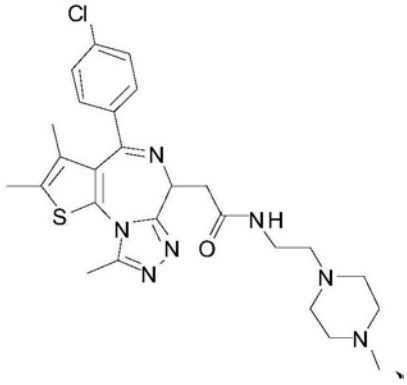
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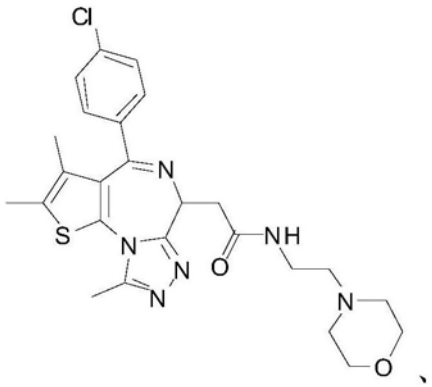
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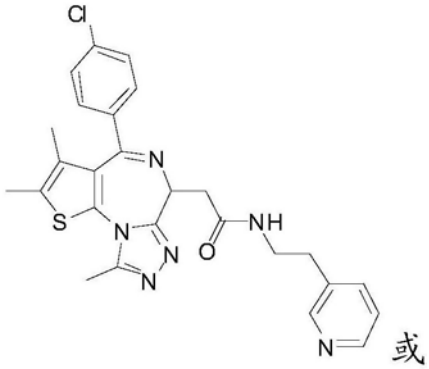
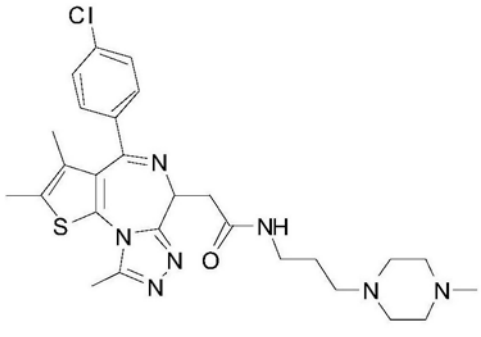
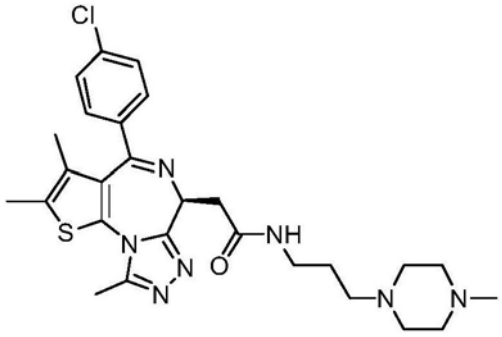

或

；

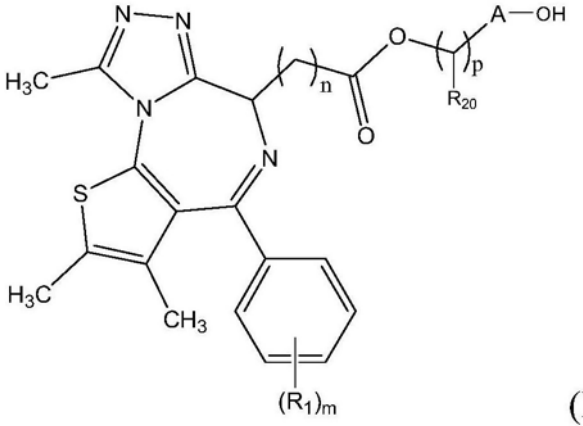
或其药学上可接受的盐。

12.如权利要求1-11中任一项所述的方法，其中所述布罗莫结构域抑制剂是由以下结构式表示的化合物：



或其药学上可接受的盐。

13.如权利要求1-9中任一项所述的方法，其中所述布罗莫结构域抑制剂是由结构式(IX)表示的化合物：



(IX)

或其药学上可接受的盐，其中：

A选自由(C_1-C_6)烷基、(C_2-C_6)烯基、(C_2-C_6)炔基、(C_3-C_{12})环烷基和(C_5-C_7)杂环烷基组成的组，其中部分A任选被1至4个R_2基团取代；

每次出现的R_{20}独立地为-H、-OH、(C_1-C_3)烷基、(C_3-C_{12})环烷基或(C_5-C_7)杂环烷基；

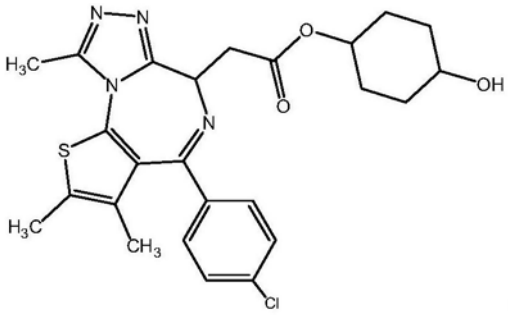
每次出现的R_1独立地选自由-OH、卤素、-CN、(C_1-C_4)烷氧基、-C(O)(C_1-C_4)烷基、-C(O)O(C_1-C_4)烷基、-OC(O)$(C_1-C_4$烷基)、-C(O)NR_3R_4、$-NR_5C(=O)R_6$、(C_1-C_6)烷基、(C_2-C_6)烯基、(C_3-C_{12})环烷基和(C_5-C_7)杂环烷基组成的组；

每次出现的R_2独立地为(C_1-C_6)烷基、(C_2-C_6)烯基、卤代(C_1-C_6)烷氧基、卤代(C_1-C_6)烷基、羟基(C_1-C_6)烷基、(C_1-C_6)烷氧基(C_1-C_6)烷基、(C_3-C_{12})环烷基、-(C_1-C_6)亚烷基-(C_3-C_{12})环烷基、(C_3-C_{12})杂环烷基、-(C_1-C_6)亚烷基-(C_3-C_{12})杂环烷基、(C_1-C_6)烷氧基、-C(O)$(C_1-C_6$烷基)、-C(O)O$(C_1-C_6$烷基)、-OC(O)$(C_1-C_6$烷基)、-C(O)NR_7R_8、$-NR_9C(=O)R_{10}$、$-NR_{11}R_{12}$、卤素、氧代或-OH；

R_3、R_4、R_5、R_6、R_7、R_8、R_9、R_{10}、R_{11}和R_{12}各自独立地为H或(C_1-C_4)烷基；且

每个m、n和p独立地为0、1、2、3或4。

14.如权利要求1-9或13中任一项所述的方法，其中所述布罗莫结构域抑制剂是由以下结构式中的任一者表示的化合物：



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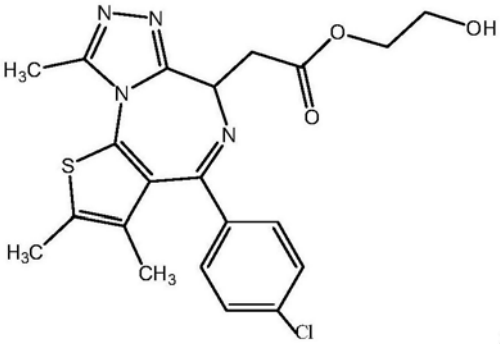
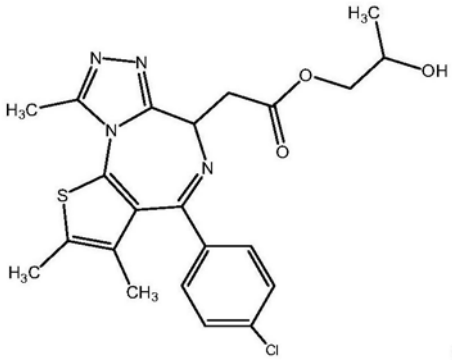


或



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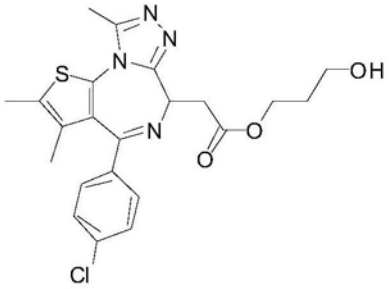
或其药学上可接受的盐。

15.如权利要求1-9或13中任一项所述的方法，其中所述布罗莫结构域抑制剂是由下式中的任一者表示的化合物：



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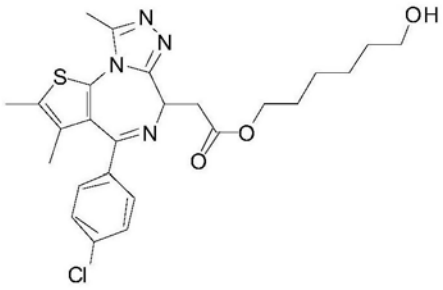
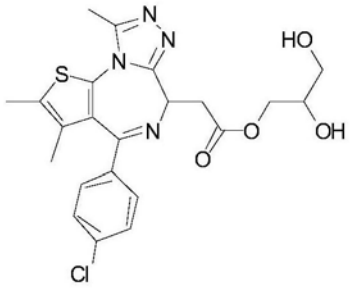
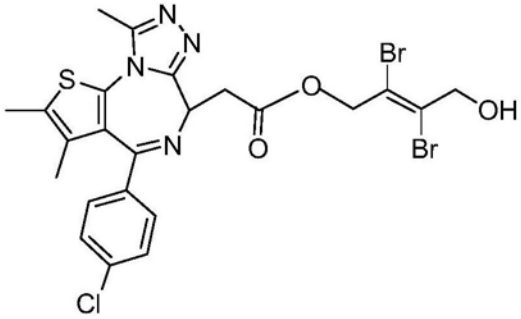




或



或其药学上可接受的盐。

NUT中线癌的治疗

[0001] 相关申请

[0002] 本申请要求2015年6月26日提交的第62/185,203号美国临时申请的权益。上述申请的全部教导以引用的方式并入本文。

[0003] 发明背景

[0004] NUT中线癌(或NMC)是罕见形式的癌症,其特征在于染色体重排,其中染色体15上的NUT(睾丸中的核蛋白)基因的一部分与BRD(布罗莫结构域蛋白)基因或其它迄今尚未确认的基因融合(French等人,Cancer Res.63(2):304-307(2003);French等人,J.Clin.Oncol.22(20):4135-4139(2004);French等人,Oncogene 27(15):2237-42(2008))。NUT融合基因编码保持细胞处于未分化状态并促使它们快速且不受控制地生长的癌蛋白。

[0005] 对于大多数情况,易位发生在NUT与BRD3或BRD4之间,得到由布罗莫结构域和NUT的几乎整个编码序列组成的融合蛋白(French等人,Ann.Rev.Pathol.7:247-265,(2012))。机理上讲,BRD-NUT似乎部分地通过亚核灶中的组蛋白乙酰转移酶p300的隔离而降低总体组蛋白乙酰化水平,由此阻断癌细胞的分化(French等人,Oncogene 27:2237-42(2008);Schwartz等人,Cancer Res.71:2686-96,(2011))。此外,BRD4-NUT融合蛋白与MYC致癌基因的启动子结合并激活表达,促成了NMC细胞的未分化的增殖状态(Grayson等人,Oncogene 33:1736-42(2014)。头部、颈部、纵隔中的中线结构及其它中线结构的频繁参与表明NMC由原始神经嵴衍生的细胞引起。NMC在临床上非常具有侵袭性,对常规的化学疗法反应很差,并且几乎一贯是致命的。即使是采用侵袭性的外科手术、放射疗法和全身化疗,中值寿命也仅为6.7个月(French等人,Head Neck Pathol.(2013))。NMC可在所有年龄的儿童和成年人中发生。

[0006] 因此,在治疗NMC中,对于提高疗效的疗法的需求没有显著地得到满足。本申请提供这类疗法。

[0007] 发明概述

[0008] 本发明涉及需要治疗的受试者的睾丸中的核蛋白(NUT)中线癌(NMC)治疗的方法,其包括施用有效量的布罗莫结构域及布罗莫结构域的额外末端(BET)家族的抑制剂。特别地,本文提供的方法部分地基于鉴定细胞(例如,单核细胞)上的CD11b表达水平作为对BET抑制剂的疾病反应性(或疾病活动性)的指标。

[0009] 一方面,本发明提供治疗罹患睾丸中的核蛋白(NUT)中线癌(NMC)的患者的方法,其包括:在具有多个周期的治疗方案的当前周期中对患者施用有效量的布罗莫结构域抑制剂,每个周期包括上药和离药段,其中患者相对于基线水平表现出不到约50%的CD11b表达降低,其中CD11b表达是在当前周期或先前周期期间测量的。

[0010] 另一方面,本发明提供监测罹患睾丸中的核蛋白(NUT)中线癌(NMC)的患者的治疗反应的方法,其包括:a)采用具有多个周期的治疗方案对患者施用预定量的布罗莫结构域抑制剂,每个周期包括上药和离药段;和b)量化收集自患者的样品中的CD11b表达水平;其中相对于基线水平约50%或更多的CD11b表达降低指示对治疗方案的阳性反应。

[0011] 在其它方面，本发明还提供确定罹患睾丸中的核蛋白(NUT)中线癌(NMC)的患者的治疗方案的方法，其包括：a)在具有多个周期的治疗方案的第一周期中对患者施用预定量的布罗莫结构域抑制剂，每个周期包括上药和离药段；b)量化在第一周期期间收集自患者的样品中的CD11b表达水平；和c)确定是否修改治疗方案的第一周期或后续周期，其中相对于基线水平不到约50％的CD11b表达降低表明应修改第一周期或后续周期，从而确定罹患NMC的患者的治疗方案。

[0012] 包括NMC在内的实体肿瘤源的许多细胞系对布罗莫结构域抑制剂(例如，TEN-010)敏感。值得注意的是，本发明揭示了CD11b水平与对针对NMC患者具有特异性的布罗莫结构域抑制剂疗法的反应性之间的关系。因此，细胞(例如单核细胞)上的CD11b表达水平可用于监测NMC患者对BET抑制剂(例如，TEN-010)的反应性，并且使得能够修改已有的BET抑制剂疗法以提高NMC治疗的疗效。考虑到疾病的高侵袭性质，监测和修改目前用于NMC治疗的布罗莫结构域治疗方案的能力是特别可取的。

[0013] 附图简述

[0014] 本专利或申请文件含至少一张彩色绘制附图。根据请求并支付必要的费用后，本专利或专利申请公布的带彩色附图的副本将由专利局提供。

[0015] 从本发明的示例实施方案的以下更具体的描述中来看，上述内容将是显而易见的，如附图中所示，其中贯穿不同视图的同样的参考字符指的是相同的部分。

[0016] 图1显示经受TEN-010治疗的患者中的CD11b水平。标记“004-001(NMC)”指示患者为罹患NMC的患者。“MESF”是指等效可溶性荧光染料的分子。将在指示的时间点进行的测量表示为“C#D#”，其中C#指的是周期数，且D#指的是在指示的周期中的天数。例如，C2D1是指第2周期的第1天。

[0017] 图2A-2F示出在图1中出现的经受TEN-010治疗的每一患者中的乳酸脱氢酶(LDH)水平和CD11b水平的比较，其中左y轴上表示LDH水平，且右y轴上表示CD11b水平。“MESF”是指等效可溶性荧光染料的分子。将在指示的时间点进行的测量表示为“C#D#”，其中C#指的是周期数，且D#指的是在指示的周期中的天数。例如，C4D22是指第4周期的第22天。

[0018] 发明详述

[0019] 以下描述本发明的示例实施方案。

[0020] 布罗莫结构域是大约110个氨基酸的蛋白质结构域，其识别诸如组蛋白的N-末端尾部上的那些的单乙酰化赖氨酸残基。赖氨酸残基的乙酰化是与细胞信号传导和疾病生物学广泛关联的翻译后修饰。“写”(组蛋白乙酰转移酶，HAT)和“擦”(组蛋白脱乙酰酶，HDAC)乙酰化位点的酶是当前药物开发中广泛研究的领域，但很少有描述调节由乙酰赖氨酸介导的“阅读过程”的有效抑制剂。ε-N-乙酰赖氨酸(Kac)标记的主要阅读器是布罗莫结构域(BRD)，其是进化保守型蛋白质相互作用模块的不同家族。含有BRD的蛋白质已牵涉到许多种疾病的发生。靶向BRD介导的蛋白质-蛋白质相互作用已成为有望用于许多种由赖氨酸残基的异常乙酰化引起的疾病的药物开发途径。

[0021] BET抑制剂类别的化合物靶向并抑制蛋白质的布罗莫结构域和额外末端(BET)家族。BET家族目前由四种蛋白质组成，即普遍表达的BRD2、BRD3和BRD4以及睾丸特异性的BRDT(Jones等人，Genomics 45:529-34(1997)；Paillisson等人，Genomics 89:215-23(2007))。BET蛋白是参与调节细胞周期进程、增殖、能量体内平衡、精子发生和炎症反应的

转录辅因子(Belkina和Denis,Nat.Rev.Cancer12:465-77,(2012);Matzuk等人,Cell 150:673-84,(2012);Nicodeme等人,Nature 468:1119-23,(2010);Wang等人,Biochem.J.425:71-83,(2010);Wu和Chiang,JBC 282:13141-45,(2007)。每个家族成员含有两个氨基末端串联布罗莫结构域和也参与蛋白质-蛋白质相互作用的保守型额外末端(ET)结构域(Rahman等人,Mol.Cell Biol.31:2641-52,(2011)。BET蛋白通过结合启动子和增强子处的乙酰化染色质来调节基因表达(参见例如Draker等人,PLoS Genet 8,e1003047,(2012))。BET蛋白通过募集阳性转录延伸因子b(P-TEFb)来刺激基因表达(参见例如Zhang等人,JBC 287:43137-55,(2012))。P-TEFb促进由启动子释放RNA聚合酶II,导致生产性转录延伸和活性基因表达。一种已知的BET抑制剂JQ1(本文中被称为S-JQ1S)特异性地结合BET家族的布罗莫结构域(Bres等人,Curr.Opin.Cell Biol.20:334-340,(2008))。

[0022] 特异性BET家族成员BRD4已直接牵涉到调节细胞周期进程。BRD4是书签因子,其在有丝分裂期间保持与染色体结合,并将P-TEFb募集到基因以促进早期G1转录程序的激活(Dey等人,MBC20:4899-4909,(2009);Yang等人,MBC 28:967-76,(2008))。降低BRD4蛋白水平导致随着细胞退出有丝分裂,关键的G1生长相关基因的表达失败,引起G1阻滞和细胞凋亡(Dey等人,MBC 20:4899-4909,(2009);Yang等人,MBC 28:967-76,(2008);Mochizuki等人,JBC283:9040-48,(2008))。用JQ1(即,如本文所述的JQ1S)治疗(已知的BET抑制剂)已获得了类似的结果,其从有丝分裂染色体中置换BRD4并显著延迟早期G1基因的激活(Zhao等人,Nat.Cell Biol.13:1295-1304,(2011))。

[0023] BRD3和BRD4也涉及NMC,这主要起因于NUT基因与BRD3和BRD4之间的易位。NMC在中线、最常见在头部、颈部或纵隔中作为分化不良的癌发生,伴随可变程度的鳞状分化。这种肿瘤是通过染色体15q14上的“睾丸中的核蛋白”(NUT)基因的重排定义的。在大多数情况下,NUT参与与染色体19p13.1上的BRD4基因的平衡易位,这是产生BRD4-NUT融合基因的事件。在其余的情况下发生变异重排,一些涉及BRD3基因。可通过借助荧光原位杂交、核型分析或RT-PCR检测NUT重排来诊断NMC。由于罕见且缺乏特性组织学特征的原因,目前无法识别NMC的大多数病例。

[0024] NMC在本文中被定义为具有NUT基因的重排的任何恶性上皮肿瘤。在大约2/3的病例中,NUT(染色体15q14)与染色体19p13.1上的BRD4融合,形成BRD4-NUT融合基因。在其余的1/3病例中,伴侣基因是BRD3或其它未表征的基因。这些被称为NUT-变体融合基因。NMC的组织学特征并不独特,并且诊断是基于检测NUT重排。NUT重排定义NMC,为此一旦已证实了NUT的重排,则诊断就不会有问题。检测这类重排的方法是本领域中已知和可用的。由于BRD3和BRD4牵涉NMC,BET布罗莫结构域抑制剂也有望成为NMC的靶向疗法(Filippakopoulos等人,Nature 468:1067-73,(2010))。

[0025] NUT中线癌(NMC)的BET抑制剂治疗的方法

[0026] 本发明部分地基于鉴定细胞(例如,单核细胞)上的CD11b表达水平作为NMC对BET抑制剂的反应性(或疾病活动性)的指标。CD11b(也称为整联蛋白α_M)是与CD18(也称为整联蛋白β_2)配对以形成CR3补体异二聚体受体(也称为巨噬细胞-1抗原、Mac-1、整联蛋白$\alpha_M\beta_2$或巨噬细胞整联蛋白)的整联蛋白家族成员。CD11b在包括单核细胞在内的白细胞、嗜中性粒细胞、天然杀伤细胞、粒细胞和巨噬细胞以及一些脾细胞和骨髓细胞的表面上表达。在功能上,CD11b调节白细胞粘附和迁移以介导炎症反应。

[0027] 如本文所例示,CD11b水平可用于在罹患NMC的患者中监测对布罗莫结构域抑制剂疗法的反应性,如通过乳酸脱氢酶(LDH)水平所验证的那样,后者是已知的癌症进展的临床标志物。简言之,本发明显示在NMC患者中,CD11b表达水平在整个TEN-010疗法的过程中与LDH水平密切相关(图2C)。相比之下,在非NMC患者中CD11b表达水平与LDH水平无关(图2A、2B和2D-2F,特别是2B)。因此,虽然不希望受任何理论的约束,但监测单核细胞上的CD11b水平使得能够在经受布罗莫结构域抑制剂疗法的患者中追踪NMC疾病活动性。如本文所述,可测量CD11b水平以确定NMC患者在治疗的后续周期中是否将需要更多或更少的布罗莫结构域抑制剂,或者NMC患者是否将需要更早或更晚开始布罗莫结构域抑制剂治疗的后续周期,或其任意组合的情况。

[0028] 因此,一方面,本发明提供治疗罹患睾丸中的核蛋白(NUT)中线癌(NMC)的患者的方法,其包括:在具有多个周期的治疗方案的当前周期中对患者施用有效量的布罗莫结构域抑制剂,每个周期包括上药和离药段,其中患者相对于基线水平显示出不到约50%的CD11b表达降低,其中CD11b表达是在当前周期或先前周期期间测量的。

[0029] 如本文所用,“治疗”包括任何抗肿瘤活性的迹象,其包括但不限于延迟或阻止与NMC有关的临床指征的进展。例如,可减慢疾病进展。另外,抗肿瘤活性的迹象包括如通过本领域中已知的标准成像方法检测到并根据本领域中已知的指导原则和方法评估的肿瘤生长减少或防止进一步生长或肿瘤代谢活性降低,所述方法包括例如计算机断层(CT)扫描、磁共振成像(MRI)、胸部x光和CT/正电子发射断层(CT/PET)扫描。例如,可通过实体肿瘤中的反应评估标准(Response Evaluation Criteria in Solid Tumors,RECIST)(修订的RECIST指南第1.1版;参见Eisenhauer等人,Eur.J.Cancer 45(2):228-47,2009)来评估对治疗的反应。因此,在一些实施方案中,“治疗”是指根据RECIST指南定义为所有靶病变消失的完全反应(CR)或定义为靶病变的直径总和减少至少30%的部分反应(PR)(以基线总和直径为参考)。评估肿瘤对治疗反应的其它方法包括评估肿瘤标志物和评估体能状态(例如,评价肌酐清除率;参见Cockcroft和Gault,Nephron.16:31-41,1976)。淋巴瘤患者的反应评估是基于Lugano分类。

[0030] 术语“布罗莫结构域抑制剂”和“BET抑制剂”可互换使用。这两个术语是指靶向并抑制蛋白质的布罗莫结构域和额外末端(BET)家族的一类化合物。布罗莫结构域抑制剂的实例详述于本文中。在一个实施方案中,布罗莫结构域抑制剂是TEN-010。

[0031] 如本文所用,术语“患者”是指哺乳动物,优选人,但也可指需要兽医治疗的动物,例如伴侣动物(例如,狗、猫等)、农场动物(例如,牛、绵羊、猪、马等)和实验室动物(例如,大鼠、小鼠、豚鼠等)。

[0032] 如本文所用的术语“有效量”是指在包括多个周期的治疗方案内的指定治疗周期上的有效剂量,每个周期包括上药和离药段,使得治疗方案的效果实现在任何周期期间的CD11b表达水平与CD11b的基线水平相比降低至少50%(即,与基线水平相比CD11b减少50%或更多)并维持之。在某些实施方案中,治疗方案的效果实现与基线水平相比CD11b减少60%、70%、80%或90%或更多并维持之。

[0033] 如本文所用,治疗方案内的“周期”是指由“上药”和“离药”段组成的指定时间段(例如,天数),其中“上药”是指期间施用药物的时间段,而“离药”是指期间不施用药物的时间段。在一个实施方案中,周期由一个上药段和一个离药段组成。在另一实施方案中,周期

可由一个连续的上药段组成,没有离药段(例如,连续给药),其中所述周期仍被定义为具有指定的天数(例如,28天)。在这种情形中,一个周期与下一个周期的划分由指定天数(例如,28天)确定;可将后续周期设计成与先前周期相比具有相同、更高或更低的布罗莫结构域抑制剂剂量,如根据本发明的方法确定的那样。

[0034] 如本文所用,“当前”周期是指目前正在进行的周期。

[0035] 如本文所用,“先前”周期是指治疗方案内的任何先前周期,其包括在当前周期之前一个周期发生的周期,以及在当前周期之前不止一个周期发生的周期。

[0036] 周期可由熟练的医疗专业人员认为适当的天数组成,并且将根据疾病的性质、所施用的药物的剂量、患者的健康状况、预期结果等而有所不同。举例而言,治疗NMC的布罗莫结构域抑制剂治疗方案的周期可以是约15至约35天。在一个实施方案中,周期可以是约28天,具有21个上药天和7个离药天。如本领域技术人员将会理解的那样,可将具有“上”和“离”药天数(包括零离药天数)的数目的任意组合的周期设计为熟练的医疗专业人员认为是适当的。

[0037] 可获得患者的样品,并在周期的段(上药或离药)的任何部分期间测量CD11b表达水平,用来与基线水平进行比较,以确定和/或施用当前周期期间布罗莫结构域抑制剂的有效量。例如,可在先前周期的离药段期间测量CD11b表达水平。如果举例而言在先前周期的离药段的任何部分期间CD11b表达水平相对于基线水平降低不到约50%(即,CD11b水平高于期望值,并且治疗不是有效的),则可在当前周期中施用更高剂量的布罗莫结构域抑制剂。或者或另外,可缩短先前周期的离药段中的天数(相对于周期的离药段中的预定天数)以更早地开始当前周期。相比之下,如果确定CD11b表达水平是有利的(即,治疗是有效的),则可维持或减少布罗莫结构域抑制剂剂量。

[0038] 作为另一个例子,如果当前周期的上药段期间的CD11b表达水平相对于基线水平降低不到约50%,则可在正在进行的当前周期中施用更高剂量的布罗莫结构域抑制剂。在此第二个例子中,除了增加布罗莫结构域抑制剂的剂量之外或者代替增加布罗莫结构域抑制剂的剂量的是,也可以增加当前周期的上药段中的天数。

[0039] 如本文所用,“基线”水平是指在NMC患者接受第一剂量的治疗之前(在给药前)测量的CD11b表达的水平。

[0040] 在某些实施方案中,获自患者的样品是血液样品。

[0041] 在其它方面,本发明还提供确定罹患NMC的患者的治疗方案的方法,其包括:a)在具有多个周期的治疗方案的第一周期中对患者施用预定量的布罗莫结构域抑制剂,每个周期包括上药和离药段;b)量化在第一周期期间收集自患者的样品中的CD11b表达水平;和c)确定是否修改治疗方案的第一周期或后续周期,其中相对于基线水平不到约50%的CD11b表达降低表明应修改第一周期或后续周期,从而确定罹患NMC的患者的治疗方案。

[0042] 如本文所用,“预定量”是指基于例如先前确定的标准为患者确定的布罗莫结构域抑制剂的量,但其由于例如疾病状态变化的原因而可能当前并不是有效的。

[0043] 如本文所用,“第一周期”是指当前正在进行的治疗的周期,并不一定是指布罗莫结构域抑制剂治疗方案的实际第一周期。

[0044] 在某些实施方案中,通过增加上药段的长度、减少离药段的长度、增加布罗莫结构域抑制剂的预定量或其组合的方式来修改第一周期或后续周期。下表汇总了当确定CD11b

表达降低相对于基线水平不到约50％(即,CD11b水平高于期望值且疾病反应性不处于合适的水平)时的可能情形和对治疗方案修改的一些实例。如果确定CD11b表达降低是有利的(即,疾病反应性处于合适的水平),则可取的是例如减少布罗莫结构域抑制剂剂量或延迟开始下一个周期或两者兼有。

[0045] 表1.对布罗莫结构域治疗方案的可能修改

[0046]

当测量 CD11b 时	在 CD11b 表达降低相对于基线水平不到约 50% 情况下的可能修改
当前周期的上药段	-增加当前周期的上药段中的天数 -增加当前周期的上药段期间布罗莫结构域抑制剂的剂量 -增加后续(例如,下一个)周期中布罗莫结构域抑制剂的剂量 -缩短当前周期的离药段中的天数 -上述的任意组合 -如果周期仅由上药段组成而没有离药段(例如,连续给药),则增加“仅上药”周期的当前周期或下一个周期中的布罗莫结构域抑制剂的剂量
当前周期的离药段	-缩短当前离药段中的天数(即,更早地开始后续周期) -增加后续周期的上药段天数

[0047]

	-增加后续周期中的布罗莫结构域抑制剂的剂量 -缩短后续周期的离药段 -上述的任意组合

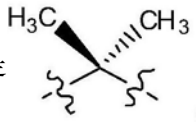
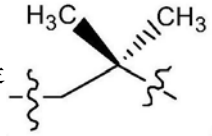
[0048] 可采用本领域中已知和可用的多种方法来量化细胞(例如,单核细胞)上的CD11b表达水平。在一个实例中,可通过流式细胞术来量化单核细胞上的CD11b表达水平。

[0049] 另一方面,本发明提供监测罹患NMC的患者的治疗反应的方法,其包括:a)采用具有多个周期的治疗方案对患者施用预定量的布罗莫结构域抑制剂,每个周期包括上药和离药段;和b)量化收集自患者的样品中的CD11b表达水平;其中相对于基线水平约50％或更多的CD11b表达降低指示对治疗方案的阳性反应。

[0050] BET抑制剂

[0051] 定义

[0052] “烷基”意指具有指定碳原子数的任选取代的饱和脂族支链或直链单价烃基。因此，“(C_1-C_6)烷基”意指具有以直链或支链排列的1-6个碳原子的基团。“(C_1-C_6)烷基”包括甲基、乙基、丙基、异丙基(或i-丙基)、丁基、仲丁基、叔丁基、戊基、己基等。单独或作为较大部分的一部分使用的术语“烷基”、“烷氧基”、“羟烷基”、“卤代烷基”、“芳烷基”、“烷氧基烷基”、“烷基胺”、“二烷基胺”、“烷基氨基”、“二烷基氨基”、“烷氧基羰基”等包括含有一至十二个碳原子的直链和支链饱和链。

[0053] “亚烷基”意指具有指定碳原子数的任选取代的饱和脂族支链或直链二价烃基。因此，“(C_1-C_6)亚烷基”意指具有以直链排列的1-6个碳原子的二价饱和脂族基，例如-[(CH_2)$_n$]-，其中n是1至6的整数，“(C_1-C_6)亚烷基”包括亚甲基、亚乙基、亚丙基、亚丁基、亚戊基和亚己基。或者，“(C_1-C_6)亚烷基”意指具有以支链排列的1-6个碳原子的二价饱和基，例如：-[($CH_2CH_2CH_2CH_2CH(CH_3)$]-、-[($CH_2CH_2CH_2CH_2C(CH_3)_2$]-、-[($CH_2C(CH_3)_2CH(CH_3)$)]-等。一个特定的支链$C_3$-亚烷基是  ，且一个特定的C_4-亚烷基是  。

[0054] “烯基”意指含有至少一个双键且具有指定的碳原子数的支链或直链单价烃基。烯基可以是单或多不饱和的，并且可以E或Z构型存在。例如，“(C_2-C_6)烯基”意指具有以直链或支链排列的2-6个碳原子的基团。

[0055] “炔基”意指含有至少一个三键且具有指定的碳原子数的支链或直链单价烃基。例如，“(C_2-C_6)炔基”意指具有以直链或支链排列的2-6个碳原子的基团。

[0056] 下面描述的结构式中的每个烷基或亚烷基可任选和独立地被一个或多个取代基取代。

[0057] “芳基”或“芳族”意指芳族单环或多环(例如双环或三环)含碳环体系。在一个实施方案中，“芳基”是6-12元单环或双环体系。芳基体系包括但不限于苯基、萘基、芴基、茚基、蒽基和蒽基。

[0058] “环烷基”意指饱和脂族环状烃环。“环烷基”包括3至12元饱和脂族环状烃环。因此，“(C_3-C_7)环烷基”意指3至7元饱和脂族环状烃环的烃基。(C_3-C_7)环烷基包括但不限于环丙基、环丁基、环戊基、环己基和环庚基。

[0059] 环烷基部分可以是单环、稠合双环、桥连双环、螺双环或多环的。例如，单环(C_3-C_8)环烷基意指具有以单环状环排列的3至8个碳原子的基团。单环(C_3-C_8)环烷基包括但不限于环丙基、环丁基、环戊基、环己基、环庚基和环辛烷。

[0060] 单环状环体系具有单环结构。它们包括具有指定碳原子数的饱和或不饱和脂族环状烃环(例如，环烷基、环烯基或环炔基)或芳族烃环(例如，芳基)。单环状环体系可任选在环结构中含有1至5个杂原子，其中每个杂原子独立地选自由O、N和S组成的组(例如，杂环烷基、杂环烯基、杂环炔基或杂芳基)。当杂原子是N时，其可任选被烷基、环烷基、亚烷基-环烷基、杂环烷基、亚烷基-杂环烷基、芳基、亚烷基-芳基、杂芳基、亚烷基-杂芳基取代，这些取代基中的每一个可任选被一个或多个卤素、=O、羟基、烷氧基、卤代烷基、烷基等取代。当杂原子是S时，其可任选是单或二氧化的(即，-S(O)-或-S(O)$_2$-)。单环状环体系的实例包括但不限于环丙基、环丁基、环戊基、环己基、环庚基、环辛烷、氮杂环丁烷、吡咯烷、哌啶、哌嗪、

氮杂环庚烷六氢嘧啶、四氢呋喃、四氢吡喃、氧杂环庚烷、四氢噻吩、四氢噻喃、异噁唑烷、1,3-二氧戊环、1,3-二硫戊环、1,3-二噁烷、1,4-二噁烷、1,3-二噻烷、1,4-二噻烷、吗啉、硫代吗啉、硫代吗啉1,1-二氧化物、四氢-2H-1,2-噻嗪、四氢-2H-1,2-噻嗪1,1-二氧化物和异噻唑烷1,1-二氧化物、四氢噻吩1-氧化物、四氢噻吩1,1-二氧化物、硫代吗啉1-氧化物、硫代吗啉1,1-二氧化物、四氢-2H-1,2-噻嗪1,1-二氧化物和异噻唑烷1,1-二氧化物、吡咯烷-2-酮、哌啶-2-酮、哌嗪-2-酮和吗啉-2-酮。

[0061] 双环状环体系具有两个环，所述两个环具有至少一个共同环原子。双环状环体系包括稠合、桥连和螺环体系。两个环可均为脂族的(例如，环烷基、环烯烃、环炔烃或杂环烷基)、均为芳族的(例如，芳基或杂芳基)或其组合。双环状环体系可任选在环结构中含有1至5个杂原子，其中每个杂原子独立地选自由O、N和S组成的组。当杂原子是N时，其可被H、烷基、环烷基、亚烷基-环烷基、杂环烷基、亚烷基-杂环烷基、芳基、亚烷基-芳基、杂芳基、亚烷基-杂芳基取代，这些取代基中的每一个可任选被一个或多个卤素、=O、羟基、烷氧基、卤代烷基、烷基等取代。当杂原子是S时，其可任选是单或二氧化的(即-S(O)-或-S(O)$_2$-)。

[0062] 稠合双环状环体系具有两个环，所述两个环具有两个相邻的共同环原子。两个环可均为脂族的(例如，环烷基、环烯烃、环炔烃或杂环烷基)、均为芳族的(例如，芳基或杂芳基)或其组合。例如，第一个环可以是环烷基或杂环烷基，且第二个环可以是环烷基、环烯烃、环炔烃、芳基、杂芳基或杂环烷基。例如，第二个环可以是(C_3-C_6)环烷基，如环丙基、环丁基、环戊基和环己基。或者，第二个环可以是芳基环(例如，苯基)。稠合双环状环体系的实例包括但不限于6,7,8,9-四氢-5H-苯并[7]轮烯、2,3-二氢-1H-茚、八氢-1H-茚、四氢萘、十氢萘、二氢吲哚、异二氢吲哚、2,3-二氢-1H-苯并[d]咪唑、2,3-二氢苯并[d]噁唑、2,3-二氢苯并[d]噻唑、八氢苯并[d]噁唑、八氢-1H-苯并[d]咪唑、八氢苯并[d]噻唑、八氢环戊并[c]吡咯、3-氮杂双环[3.1.0]己烷、3-氮杂双环[3.2.0]庚烷、5,6,7,8-四氢喹啉和5,6,7,8-四氢异喹啉以及2,3,4,5-四氢苯并[b]氧杂环庚三烯。

[0063] 螺双环状环体系具有两个环，所述两个环仅具有一个共同环原子。两个环可均为脂族的(例如，环烷基、环烯烃、环炔烃或杂环烷基)、均为芳族的(例如，芳基或杂芳基)或其组合。例如，第一个环可以是环烷基或杂环烷基，且第二个环可以是环烷基、环烯烃、环炔烃、芳基、杂芳基或杂环烷基。螺双环状环体系的实例包括但不限于螺[2.2]戊烷、螺[2.3]己烷、螺[3.3]庚烷、螺[2.4]庚烷、螺[3.4]辛烷、螺[2.5]辛烷、氮杂螺[4.4]壬烷、7-氮杂螺[4.4]壬烷、氮杂螺[4.5]癸烷、8-氮杂螺[4.5]癸烷、氮杂螺[5.5]十一烷、3-氮杂螺[5.5]十一烷和3,9-二氮杂螺[5.5]十一烷。

[0064] 桥连双环状环体系具有两个环，所述两个环具有三个或更多个相邻的共同环原子。两个环可均为脂族的(例如，环烷基、环烯烃、环炔烃或杂环烷基)、均为芳族的(例如，芳基或杂芳基)或其组合。例如，第一个环可以是环烷基或杂环烷基，且另一个环是环烷基、环烯烃、环炔烃、芳基、杂芳基或杂环烷基。桥连双环状环体系的实例包括但不限于双环[1.1.0]丁烷、双环[1.2.0]戊烷、双环[2.2.0]己烷、双环[3.2.0]庚烷、双环[3.3.0]辛烷、双环[4.2.0]辛烷、双环[2.2.1]庚烷、双环[2.2.2]辛烷、双环[3.2.1]辛烷、双环[3.2.2]壬烷、双环[3.3.1]壬烷、双环[3.3.2]癸烷双环[3.3.3]十一烷、氮杂双环[3.3.1]壬烷、3-氮杂双环[3.3.1]壬烷、氮杂双环[3.2.1]辛烷、3-氮杂双环[3.2.1]辛烷、6-氮杂双环[3.2.1]辛烷和氮杂双环[2.2.2]辛烷、2-氮杂双环[2.2.2]辛烷和2-氧杂双环[2.2.2]辛烷。

[0065] 多环状环体系具有不止两个环(例如,产生三环状环体系的三个环)且相邻的环具有至少一个共同环原子。多环状环体系包括稠合、桥连和螺环体系。稠合多环状环体系具有至少两个环,所述至少两个环具有两个相邻的共同环原子。螺多环状环体系具有至少两个环,所述至少两个环仅具有一个共同环原子。桥连多环状环体系具有至少两个环,所述至少两个环具有三个或更多个相邻的共同环原子。多环状环体系的实例包括但不限于三环[3.3.1.$0^{3,7}$]壬烷(降金刚烷)、三环[3.3.1.$1^{3,7}$]癸烷(金刚烷)和2,3-二氢-1H-非那烯。

[0066] “环烯烃”意指在环中具有一个或多个双键的脂族环状烃环。“环烯烃”包括3至12元不饱和脂族环状烃环。因此,“(C_3-C_7)环烯烃”意指3至7元不饱和脂族环状烃环的烃基。(C_3-C_7)环烯烃包括但不限于环丙烯基、环丁烯基、环戊烯基、环己烯基和环庚烯基。

[0067] 环烯烃部分可以是单环、稠合双环、桥连双环、螺双环或多环的。例如,单环(C_3-C_8)环烯烃意指具有以单环状环排列的3至8个碳原子的基团。单环(C_3-C_8)环烯烃包括但不限于环丙烯基、环丁烯基、环戊烯基、环己烯基和环庚烯基。

[0068] “环炔烃”意指在环中具有一个或多个三键的脂族环状烃环。“环炔烃”包括3至12元不饱和脂族环状烃环。因此,“(C_3-C_7)环炔烃”意指3至7元不饱和脂族环状烃环的烃基。(C_3-C_7)环炔烃包括但不限于环丙炔基、环丁炔基、环戊炔基、环己炔基和环庚炔基。

[0069] 环炔烃部分可以是单环、稠合双环、桥连双环、螺双环或多环的。例如,单环(C_3-C_8)环炔烃意指具有以单环状环排列的3至8个碳原子的基团。单环(C_3-C_8)环炔烃包括但不限于环丙炔基、环丁炔基、环戊炔基、环己炔基和环庚炔基。

[0070] “杂”是指用至少一个选自N、S和O的杂原子替换环体系中的至少一个碳原子成员。“杂”还指替换无环体系中的至少一个碳原子成员。杂环体系或杂无环体系可被杂原子替换1、2、3、4或5个碳原子成员。

[0071] “杂环烷基”意指含有1、2、3、4或5个独立地选自N、O或S的杂原子的环状4至12元饱和脂族环。当一个杂原子是S时,其可任选是单或二氧化的(即-S(O)-或-S$(O)_2$-)。当一个杂原子是N时,其可任选被烷基、环烷基、亚烷基-环烷基、杂环烷基、亚烷基-杂环烷基、芳基、亚烷基-芳基、杂芳基、亚烷基-杂芳基取代,这些取代基中的每一个可任选被一个或多个卤素、=O、羟基、烷氧基、卤代烷基、烷基等取代。

[0072] 杂环烷基部分可以是单环、稠合双环、桥连双环、螺双环或多环的。例如,单环(C_3-C_8)杂环烷基意指含有1、2、3、4或5个以单环状环排列的独立地选自N、O或S的杂原子的3至8元饱和脂族环。单环杂环烷基的实例包括但不限于氮杂环丁烷、吡咯烷、哌啶、哌嗪、氮杂环庚烷、六氢嘧啶、四氢呋喃、四氢吡喃、吗啉、硫代吗啉、硫代吗啉1,1-二氧化物、四氢-2H-1,2-噻嗪、四氢-2H-1,2-噻嗪1,1-二氧化物、异噻唑烷、异噻唑烷1,1-二氧化物。

[0073] “杂芳基”或“杂芳族环”意指5至12元单价杂芳族单环或双环状环基。杂芳基含有1、2、3、4或5个独立地选自N、O和S的杂原子。杂芳基包括但不限于呋喃、噁唑、噻吩、1,2,3-三唑、1,2,4-三嗪、1,2,4-三唑、1,2,5-噻二唑1,1-二氧化物、1,2,5-噻二唑1-氧化物、1,2,5-噻二唑、1,3,4-噁二唑、1,3,4-噻二唑、1,3,5-三嗪、咪唑、异噻唑、异噁唑、吡唑、哒嗪、吡啶、吡啶-N-氧化物、吡嗪、嘧啶、吡咯、四唑和噻唑。双环杂芳基环包括但不限于双环[4.4.0]和双环[4.3.0]稠环体系,如吲哚嗪、吲哚、异吲哚、吲唑、苯并咪唑、苯并噻唑、嘌呤、喹啉、异喹啉、噌啉、酞嗪、喹唑啉、喹喔啉、苯并呋喃、1,8-萘啶和蝶啶。

[0074] 在特定的实施方案中,每个环烷基、环烯烃、环炔烃、环杂环烷基、芳基和杂芳基任

选且独立地被1至4个取代。示例性取代基包括但不限于卤代、-(C1-C4)烷基、-OH、=O、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基和-C(O)-(C1-C4)烷基。

[0075] 如本文所用的"卤素"是指氟、氯、溴或碘。

[0076] "烷氧基"是指基团-O-R,其中R是"烷基"、"环烷基"、"烯基"或"炔基"。"(C1-C6)烷氧基"包括甲氧基、乙氧基、乙烯氧基、丙氧基、丁氧基、戊氧基等。

[0077] 卤代烷基和卤代环烷基包括单卤、多卤和全卤取代的烷基或环烷基基团,其中各卤素独立地选自氟、氯和溴。

[0078] "卤素"和"卤代"在本文中可互换使用,并且各自指氟、氯、溴或碘。

[0079] "氟代"意指-F。

[0080] 如本文所用,氟取代的(C1-C4)烷基意指被一个或多个-F基团取代的(C1-C4)烷基。氟取代的(C1-C4)烷基的实例包括但不限于$-CF_3$、$-CH_2CF_3$、$-CH_2CF_2H$、$-CH_2CH_2F$和$-CH_2CH_2CF_3$。

[0081] "天然存在的氨基酸侧链部分"是指天然氨基酸中存在的任何氨基酸侧链部分。

[0082] 术语"药学上可接受的盐"也指由本文公开的化合物或本文记述的任何其它化合物(例如,式I-III的化合物)制备的盐,其具有诸如氨基官能团的碱性官能团和药学上可接受的无机或有机酸。例如,可通过使化合物与合适的有机或无机酸反应得到含有胺或其它碱性基团的本发明的化合物的酸式盐,产生药学上可接受的阴离子盐形式。阴离子盐的实例包括乙酸盐、苯磺酸盐、苯甲酸盐、碳酸氢盐、酒石酸氢盐、溴化物、依地酸钙、樟脑磺酸盐、碳酸盐、氯化物、柠檬酸盐、二盐酸盐、依地酸盐、乙二磺酸盐、依托酸盐(estolate)、乙磺酸盐、富马酸盐、葡庚糖酸盐(glyceptate)、葡糖酸盐、谷氨酸盐、对羟乙酰氨基苯胂酸盐(glycollylarsanilate)、己基间苯二酚盐(hexylresorcinate)、氢溴酸盐、盐酸盐、羟基萘甲酸盐、碘化物、羟乙基磺酸盐、乳酸盐、乳糖醛酸盐、苹果酸盐、马来酸盐、扁桃酸盐、甲磺酸盐、甲基硫酸盐、粘酸盐、萘磺酸盐、硝酸盐、双羟萘酸盐、泛酸盐、磷酸盐/二磷酸盐、聚半乳糖醛酸盐、水杨酸盐、硬脂酸盐、碱式乙酸盐、琥珀酸盐、硫酸盐、鞣酸盐、酒石酸盐、茶氯酸盐(teoclate)、甲苯磺酸盐和三乙基碘盐。

[0083] 术语"药学上可接受的盐"也指由本文公开的化合物(例如,式I-III的化合物)或本文记述的任何其它化合物制备的盐,其具有诸如羧酸官能团的酸性官能团和药学上可接受的无机或有机碱。

[0084] 可通过与合适的碱反应来制备含有羧酸或其它酸性官能团的本发明方法中使用的化合物的盐。可用提供药学上可接受的阳离子的碱制备这种药学上可接受的盐,其包括碱金属盐(特别是钠和钾)、碱土金属盐(特别是钙和镁)、铝盐和铵盐以及由诸如以下的生理上可接受的有机碱制成的盐:三甲胺、三乙胺、吗啉、吡啶、哌啶、甲基吡啶、二环己胺、N,N'-二苄基乙二胺、2-羟乙胺、双-(2-羟乙基)胺、三-(2-羟乙基)胺、普鲁卡因、二苄基哌啶、脱氢松香胺、N,N'-双脱氢松香胺、葡糖胺、N-甲基葡糖胺、可力丁、奎宁、喹啉和诸如赖氨酸和精氨酸的碱性氨基酸。

[0085] 本发明还包括本文公开的化合物的各种异构体及其混合物。本发明的某些化合物可呈各种立体异构形式存在。立体异构体是仅在其空间排列上不同的化合物。对映异构体是镜像不可重叠的立体异构体对,最常见是因为它们含有充当手性中心的不对称取代的碳原子。"对映异构体"意指彼此为镜像且不可重叠的分子对中的一个。非对映异构体是不与

镜像相关的立体异构体，最常见是因为它们含有两个或更多个不对称取代的碳原子。“R”和“S”表示一个或多个手性碳原子周围的取代基的构型。当手性中心不被定义为R或S时，存在纯的对映异构体或两种构型的混合物。

[0086] “外消旋体”或“外消旋混合物”意指等摩尔量的两种对映异构体的化合物，其中这类混合物不表现出光学活性(即，它们不旋转偏振光的平面)。

[0087] 可通过异构体特异性合成或由异构混合物拆分而将本发明的化合物制备成单独的异构体。常规的拆分技术包括使用光学活性酸形成异构对的每种异构体的游离碱的盐(接着是分级结晶和游离碱的再生)、使用光学活性胺形成异构对的每种异构体的酸形式的盐(接着是分级结晶和游离酸的再生)、使用光学纯的酸、胺或醇形成异构对的各异构体的酯或酰胺(接着是色谱分离和除去手性助剂)或采用各种熟知的色谱方法拆分起始材料或终产物的异构混合物。

[0088] 当通过结构对所公开的化合物的立体化学进行命名或描述时，所命名或描述的立体异构体相对于其它立体异构体为按重量计至少60％、70％、80％、90％、99％或99.9％纯的。当通过结构命名或描述单一对映异构体时，所描述或命名的对映异构体为按重量计至少60％、70％、80％、90％、99％或99.9％光学纯的。按重量计的光学纯度百分比是存在的对映异构体的重量除以存在的对映异构体及其光学异构体的重量的合并重量的比率。

[0089] 如本文所用，术语“互变异构体”是指容易通过互变异构化而互变的有机分子的异构体，在互变异构化中氢原子或质子在反应中迁移，在一些场合下伴随单键和相邻双键的转换。

[0090] 在以下段落中例如参考下面复述的结构式描述可用于实施本文所述方法的化合物。在以下段落中提供下面复述的结构式或其对映异构体、非对映异构体、互变异构体或药学上可接受的盐中的变量以及本文描述的各实施方案的值和替代值。要理解的是，本发明涵盖本文定义的取代基变量(即，R_1、R_2、R_3等)的所有组合。

[0091] 示例BET抑制剂-结构式(I)至(VIII)

[0092] 在示例实施方案中，用于本发明方法的布罗莫结构域抑制剂以及其制备方法描述于例如第8,981,083号美国专利中以及2015年2月27日提交的公布为WO 2015/131113的国际申请PCT/US2015/018118中。此公布的教导内容以引用的方式整体并入本文。

[0093] 适用于本发明方法的示例化合物包括由结构式(I)至(VIII)表示的化合物或其药学上可接受的盐。在以下段落中提供式(I)-(VIII)或其对映异构体、非对映异构体或药学上可接受的盐中的变量以及本文描述的各实施方案的值和替代值。要理解的是，本发明涵盖本文定义的取代基变量(即，R_1、R_2、R_3等)的所有组合。

[0094] X是N或CR_3；

[0095] R_3选自由以下组成的组：H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选被1至4个独立地选自-F、-Cl、-Br、-OH、=O、-S(O)-、-$S(O)_2$-、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)的取代基取代。

[0096] 或者，R_3选自由以下组成的组：H和-(C_1-C_4)烷基。进一步地，R_3选自由以下组成的

组:H、甲基、乙基、丙基、丁基、仲丁基和叔丁基。具体地,R_3是H或甲基。

[0097] R_B是H、-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基或-COO-R_4,其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代;

[0098] 或者,R_B是H、-(C_1-C_4)烷基或-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基,其中每个任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代。

[0099] 进一步地,R_B是H、甲基、乙基、丙基、丁基、仲丁基、叔丁基、-COOH、-COOMe、-COOEt、-$COOCH_2OC(O)CH_3$、三氟甲基、-CF_2-CF_3、甲氧基甲基、甲氧基乙基、甲氧基丙基、乙氧基甲基、乙氧基乙基、甲氧基三氟甲基、-$CH_2-O-CF_2-CF_3$、羟甲基、羟乙基、-CH_2-NH_2、-$(CH_2)_2-NH_2$、-CH_2-NHCH_3或-$(CH_2)_2-NHCH_3$。在另一种替代方案中,R_B是H、甲基、乙基、三氟甲基、甲氧基甲基、乙氧基甲基、羟甲基、羟乙基、-CH_2-NH_2或-$(CH_2)_2-NH_2$。

[0100] 具体地,R_B是H、甲基、乙基、三氟甲基、甲氧基甲基、乙氧基甲基、羟甲基或-CH_2-NH_2。或者,R_B是H。

[0101] 环A是-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基。或者,环A是硫代呋喃基、苯基、萘基、联苯基、四氢萘基、茚满基、吡啶基、呋喃基、吲哚基、嘧啶基、吡啶嗪基(pyridizinyl)、吡嗪基、咪唑基、噁唑基、噻吩基、噻唑基、三唑基、异噁唑基、喹啉基、吡咯基、吡唑基或5,6,7,8-四氢异喹啉基。

[0102] 或者,环A是5或6元芳基或杂芳基。环A是硫代呋喃基、苯基、吡啶基、呋喃基、吲哚基、嘧啶基、吡啶嗪基、吡嗪基、咪唑基、噁唑基、噻吩基、噻唑基、三唑基、异噁唑基、吡咯基或吡唑基。进一步地,环A是苯基或噻吩基。具体地,环A是噻吩基。

[0103] 每个R_A独立地为H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选被1至4个独立地选自-F、-Cl、-Br、-OH、=O、-S(O)-、-$S(O)_2$-、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)的取代基取代;或者任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团。

[0104] 或者,每个R_A独立地为H或-(C_1-C_4)烷基。每个R_A独立地为H、甲基、乙基、丙基、丁基、仲丁基或叔丁基。具体地,每个R_A独立地为H或甲基。

[0105] 或者,任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团。进一步地,任何两个R_A与各自所结合的原子一起形成稠合芳基。

[0106] R是-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基,其中每个任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基、-C(O)-(氟取代的-(C_1-C_4)烷基)、-$S(O)_o$-(C_1-C_4)烷基、-NR_7R_8和CN。

[0107] 或者,R是-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基,其中每个任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基、-C(O)-(氟取代的-(C_1-C_4)烷基)、-$S(O)_o$-(C_1-C_4)烷基、-NR_7R_8和CN。

[0108] R是苯基或吡啶基，其中每个任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基、-C(O)-(氟取代的-(C1-C4)烷基)、-S(O)o-(C1-C4)烷基、-NR7R8和CN。

[0109] 进一步地，R是苯基或吡啶基，其中每个任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-Br、-OH、-甲基、乙基、丙基、丁基、仲丁基、叔丁基、-COOH、-COOMe、-COOEt、-COOCH2OC(O)CH3、三氟甲基、-CF2-CF3、甲氧基甲基、甲氧基乙基、甲氧基丙基、乙氧基甲基、乙氧基乙基、甲氧基三氟甲基、-CH2-O-CF2-CF3、羟甲基、羟乙基、-CH2-NH2、-(CH2)2-NH2、-CH2-NHCH3、-(CH2)2-NHCH3和CN。或者，R是苯基或吡啶基，其中每个任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-Br、-和OH。

[0110] R是任选被1至4个独立地选自由以下组成的组的取代基取代的苯基：-F、-Cl、-Br、-和OH。或者，R是任选被1至3个独立地选自由以下组成的组的取代基取代的苯基：-F、-Cl、-Br、-和OH。进一步地，R是任选被独立地选自由以下组成的组的取代基取代的苯基：-F、-Cl、-Br、-和OH。具体地，R是对-Cl-苯基、邻-Cl-苯基、间-Cl-苯基、对-F-苯基、邻-F-苯基、间-F-苯基或吡啶基。

[0111] R1是-(CH2)n-L，其中n是0-3且L是H、-C(O)O-R9、-CO-N(R9R10)、-NR9R10、-N(R10)C(O)OR9或-N(R10)C(O)R9。

[0112] 或者，R1是-(CH2)n-L，其中n是0-3，且L是-C(O)O-R9。R1是-(CH2)n-L，其中n是1-3，且L是-C(O)O-R9。进一步地，R1是-(CH2)n-L，其中n是1-2，且L是-C(O)O-R9。或者，R1是-(CH2)n-L，其中n是1，且L是-C(O)O-R9。

[0113] 进一步地，R1是-(CH2)n-L，其中n是0-3，且L是-CO-N(R9R10)。R1是-(CH2)n-L，其中n是1-3，且L是-CO-N(R9R10)。R1是-(CH2)n-L，其中n是1-2，且L是-CO-N(R9R10)。或者，R1是-(CH2)n-L，其中n是1，且L是-CO-N(R9R10)。

[0114] 在另一种替代方案中，R1是-(CH2)n-L，其中n是0-3，且L是-NR9R10。R1是-(CH2)n-L，其中n是1-3，且L是-NR9R10。进一步地，R1是-(CH2)n-L，其中n是1-2，且L是-NR9R10。或者，R1是-(CH2)n-L，其中n是1，且L是-NR9R10。

[0115] R1是-(CH2)n-L，其中n是0-3，且L是-N(R10)C(O)OR9。或者，R1是-(CH2)n-L，其中n是1-3，且L是-N(R10)C(O)OR9。进一步地，R1是-(CH2)n-L，其中n是1-2，且L是-N(R10)C(O)OR9。或者，R1是-(CH2)n-L，其中n是1，且L是-N(R10)C(O)OR9。

[0116] 进一步地，R1是-(CH2)n-L，其中n是0-3，且L是-N(R10)C(O)R9。或者，R1是-(CH2)n-L，其中n是1-3，且L是-N(R10)C(O)R9。进一步地，R1是-(CH2)n-L，其中n是1-2，且L是-N(R10)C(O)R9。或者，R1是-(CH2)n-L，其中n是1，且L是-N(R10)C(O)R9。

[0117] 或者，R1是-(CH2)n-L，其中n是0-3且L是H。R1是甲基、乙基、丙基、异丙基。具体地，R1是甲基。

[0118] R2是H、D、卤素或-(C1-C4)烷基。或者，R2是H或-(C1-C4)烷基。进一步地，R2是H、甲基、乙基、丙基、异丙基、丁基、仲丁基或叔丁基。具体地，R2是H或甲基。

[0119] R4选自由以下组成的组：H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取

代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0120] 或者,R4选自由以下组成的组:H和-(C1-C4)烷基,其中每个-(C1-C4)烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0121] R4选自由以下组成的组:H和-(C1-C4)烷基,其中每个-(C1-C4)烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br和-OH。在另一种替代方案中,R4选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基、三氟甲基、-CF2-CF3、羟甲基和羟乙基。或者,R4选自由以下组成的组:H、甲基、乙基、叔丁基和三氟甲基。

[0122] R5选自由以下组成的组:H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基,其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0123] 或者,R5选自由以下组成的组:H、-(C1-C4)烷基和-(C3-C8)环烷基,其中每个-(C1-C4)烷基和-(C3-C8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0124] 进一步地,R5选自由以下组成的组:H、-(C1-C4)烷基和-(C3-C8)环烷基,其中每个-(C1-C4)烷基和-(C3-C8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-OH、-O-(C1-C4)烷基和卤取代的-(C1-C4)烷基。在另一种替代方案中,R5选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、叔丁基、甲氧基、羟基、环丁基、环戊基和环己基。

[0125] R6选自由以下组成的组:H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基,其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0126] 或者,R6选自由以下组成的组:H、-(C1-C4)烷基和-(C3-C8)环烷基,其中每个-(C1-C4)烷基和-(C3-C8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0127] 进一步地,R6选自由以下组成的组:H、-(C1-C4)烷基和-(C3-C8)环烷基,其中每个-

(C1-C4)烷基和-(C3-C8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-OH、-O-(C1-C4)烷基和卤取代的-(C1-C4)烷基。在另一种替代方案中,R6选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、叔丁基、甲氧基、羟基、环丁基、环戊基和环己基。

[0128] R7选自由以下组成的组:H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基,其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0129] 或者,R7选自由以下组成的组:H、-(C1-C4)烷基和-(C3-C8)环烷基,其中每个-(C1-C4)烷基和-(C3-C8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0130] 进一步地,R7选自由以下组成的组:H、-(C1-C4)烷基和-(C3-C8)环烷基,其中每个-(C1-C4)烷基和-(C3-C8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-OH、-O-(C1-C4)烷基和卤取代的-(C1-C4)烷基。在另一种替代方案中,R7选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、叔丁基、甲氧基、羟基、环丁基、环戊基和环己基。

[0131] R8选自由以下组成的组:H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基,其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0132] 或者,R8选自由以下组成的组:H、-(C1-C4)烷基和-(C3-C8)环烷基,其中每个-(C1-C4)烷基和-(C3-C8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C1-C4)烷基、-O-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基、卤取代的-(C1-C4)烷基、卤取代的-O-(C1-C4)烷基、-C(O)-(C1-C4)烷基和-C(O)-(氟取代的-(C1-C4)烷基)。

[0133] 进一步地,R8选自由以下组成的组:H、-(C1-C4)烷基和-(C3-C8)环烷基,其中每个-(C1-C4)烷基和-(C3-C8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-OH、-O-(C1-C4)烷基和卤取代的-(C1-C4)烷基。在另一种替代方案中,R8选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、叔丁基、甲氧基、羟基、环丁基、环戊基和环己基。

[0134] R9选自由以下组成的组:H、-(C1-C6)烷基、-(C0-C6)亚烷基-环烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基、-(C0-C6)亚烷基-杂芳基和-N=CR11R12,其中每个-(C1-C6)烷基、-(C0-C6)亚烷基-、-环烷基、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自

由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、-(C$_1$-C$_4$)烷基、-O-(C$_1$-C$_4$)烷基、-(C$_1$-C$_4$)亚烷基-O-(C$_1$-C$_4$)烷基、卤取代的-(C$_1$-C$_4$)烷基、卤取代的-O-(C$_1$-C$_4$)烷基、-C(O)-(C$_1$-C$_4$)烷基、-C(O)-(氟取代的-(C$_1$-C$_4$)烷基)、-S(O)$_p$-(C$_1$-C$_4$)烷基、-NR$_{13}$R$_{14}$和CN。

[0135] 或者,R$_9$选自由以下组成的组:H、-(C$_1$-C$_6$)烷基、-(C$_0$-C$_6$)亚烷基-杂环烷基、-(C$_0$-C$_6$)亚烷基-芳基和-(C$_0$-C$_6$)亚烷基-杂芳基,其中每个-(C$_1$-C$_6$)烷基、-(C$_0$-C$_6$)亚烷基-、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、-(C$_1$-C$_4$)烷基、卤取代的-(C$_1$-C$_4$)烷基、-C(O)-(C$_1$-C$_4$)烷基和-C(O)-(氟取代的-(C$_1$-C$_4$)烷基)。进一步地,R$_9$选自由以下组成的组:H、-(C$_1$-C$_4$)烷基、-(C$_1$-C$_3$)亚烷基-杂环烷基、-(C$_1$-C$_3$)亚烷基-芳基和-(C$_1$-C$_3$)亚烷基-杂芳基,其中每个-(C$_1$-C$_4$)烷基、-(C$_1$-C$_3$)亚烷基-、-杂环烷基、-芳基和-杂芳基任选被1至3个独立地选自由-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、-(C$_1$-C$_4$)烷基、卤取代的-(C$_1$-C$_4$)烷基、-C(O)-(C$_1$-C$_4$)烷基和-C(O)-(氟取代的-(C$_1$-C$_4$)烷基)组成的组的取代基取代。

[0136] 进一步地,R$_9$选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基和三氟甲基。或者,R$_9$选自由-(C$_1$-C$_3$)亚烷基-吗啉、-(C$_1$-C$_3$)亚烷基-哌嗪、-(C$_1$-C$_3$)亚烷基-苯基、-(C$_1$-C$_3$)亚烷基-吡啶基、-(C$_1$-C$_3$)亚烷基-咪唑基、-(C$_1$-C$_3$)亚烷基-氮杂环丁烷、-(C$_1$-C$_3$)亚烷基-呋喃基、-(C$_1$-C$_3$)亚烷基-吡嗪基、-(C$_1$-C$_3$)亚烷基-噁唑基、-(C$_1$-C$_3$)亚烷基-噻吩基、-(C$_1$-C$_3$)亚烷基-噻唑基、-(C$_1$-C$_3$)亚烷基-三唑基和-(C$_1$-C$_3$)亚烷基-异噁唑基组成的组,其中每个-(C$_1$-C$_3$)亚烷基-、-吗啉、-哌嗪、-苯基、-吡啶基和-咪唑基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、OH、=O、-B(OH)$_2$、-(C$_1$-C$_4$)烷基、-C(O)-(C$_1$-C$_4$)烷基和卤取代的-(C$_1$-C$_4$)烷基。

[0137] 在另一种替代方案中,R$_9$选自由-(C$_1$-C$_3$)亚烷基-吗啉、-(C$_1$-C$_3$)亚烷基-哌嗪、-(C$_1$-C$_3$)亚烷基-苯基、-(C$_1$-C$_3$)亚烷基-吡啶基和-(C$_1$-C$_3$)亚烷基-咪唑基组成的组,其中每个-(C$_1$-C$_3$)亚烷基-、-吗啉、-哌嗪、-苯基、-吡啶基和-咪唑基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、OH、=O、-B(OH)$_2$、-(C$_1$-C$_4$)烷基、-C(O)-(C$_1$-C$_4$)烷基和卤取代的-(C$_1$-C$_4$)烷基。进一步地,R$_9$选自由-(C$_1$-C$_3$)亚烷基-吗啉、-(C$_1$-C$_3$)亚烷基-哌嗪、-(C$_1$-C$_3$)亚烷基-苯基、-(C$_1$-C$_3$)亚烷基-吡啶基和-(C$_1$-C$_3$)亚烷基-咪唑基组成的组,其中每个-(C$_1$-C$_3$)亚烷基-、-吗啉、-哌嗪、-苯基、-吡啶基和-咪唑基任选被1至4个独立地选自由-B(OH)$_2$和-(C$_1$-C$_4$)烷基组成的组的取代基取代。

[0138] 或者,R$_9$是-N=CR$_{11}$R$_{12}$。

[0139] R$_{10}$选自由以下组成的组:H、-(C$_1$-C$_6$)烷基、-(C$_0$-C$_6$)亚烷基-环烷基、-(C$_0$-C$_6$)亚烷基-杂环烷基、-(C$_0$-C$_6$)亚烷基-芳基;和-(C$_0$-C$_6$)亚烷基-杂芳基,其中每个-(C$_1$-C$_6$)烷基、-(C$_0$-C$_6$)亚烷基-、-环烷基、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、(C$_1$-C$_4$)烷基、-O-(C$_1$-C$_4$)烷基、-(C$_1$-C$_4$)亚烷基-O-(C$_1$-C$_4$)烷基、卤取代的-(C$_1$-C$_4$)烷基、卤取代的-O-(C$_1$-C$_4$)烷基、-C(O)-(C$_1$-C$_4$)烷基、-C(O)-(氟取代的-(C$_1$-C$_4$)烷基)、-S(O)$_q$-(C$_1$-C$_4$)烷基-NR$_{15}$R$_{16}$和CN。

[0140] 或者,R$_{10}$选自由以下组成的组:H、-(C$_1$-C$_6$)烷基和-(C$_1$-C$_6$)亚烷基-杂环烷基,其中每个-(C$_1$-C$_6$)烷基、-(C$_1$-C$_6$)亚烷基-和-杂环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、-(C$_1$-C$_4$)烷基、-O-(C$_1$-C$_4$)烷基、-(C$_1$-C$_4$)亚烷基-O-(C$_1$-C$_4$)烷基、卤取代的-(C$_1$-C$_4$)烷基、卤取代的-O-(C$_1$-C$_4$)烷基、-C(O)-(C$_1$-C$_4$)烷

基、-C(O)-(氟取代的-(C_1-C_4)烷基)、-S(O)$_q$-(C_1-C_4)烷基、-$NR_{15}R_{16}$和CN。

[0141] 进一步地,R_{10}选自由以下组成的组:H、-(C_1-C_6)烷基和-(C_1-C_3)亚烷基-杂环烷基,其中每个-(C_1-C_6)烷基、-(C_1-C_6)亚烷基-和-杂环烷基任选被1至3个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。或者,进一步地,R_{10}选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基、三氟甲基、-(C_1-C_3)亚烷基-吗啉、-(C_1-C_3)亚烷基-哌嗪、-(C_1-C_3)亚烷基-苯基、-(C_1-C_3)亚烷基-吡啶基和-(C_1-C_3)亚烷基-咪唑基,其中每个-(C_1-C_3)亚烷基-、-吗啉、-哌嗪、-苯基、-吡啶基和-咪唑基任选被1至4个独立地选自由-B(OH)$_2$和-(C_1-C_4)烷基组成的组的取代基取代。

[0142] R_9和R_{10}与它们所结合的氮原子一起形成4-10元环。或者,R_9和R_{10}与它们所结合的氮原子一起形成4-6元环。进一步地,R_9和R_{10}与它们所结合的氮原子一起形成4-6元环环烷基或杂环烷基。

[0143] R_{11}是H、-(C_1-C_4)烷基或-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基,其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至3个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br和-OH。或者,R_{11}是H或任选被1至3个独立地选自由以下组成的组的取代基取代的-(C_1-C_4)烷基:-F、-Cl、-Br和-OH。进一步地,R_{11}是H、甲基、乙基、丙基、丁基或三氟甲基。具体地,R_{11}是H或甲基。

[0144] R_{12}是H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_7)杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基、-C(O)-(氟取代的-(C_1-C_4)烷基)、-S(O)$_r$-(C_1-C_4)烷基、-S(O)$_2$-Na和CN。

[0145] 或者,R_{12}是H、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_7)杂芳基,其中每个-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基、-C(O)-(氟取代的-(C_1-C_4)烷基)、-S(O)$_r$-(C_1-C_4)烷基、-S(O)$_2$-Na和CN。进一步地,R_{12}是H、-(C_6-C_{10})芳基或-(C_5-C_7)杂芳基,其中每个-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、(C1-C4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基、-C(O)-(氟取代的-(C_1-C_4)烷基)、-S(O)$_r$-(C_1-C_4)烷基、-S(O)$_2$-Na和CN。

[0146] 在另一种替代方案中,R_{12}是H、硫代呋喃基、苯基、萘基、联苯基、四氢萘基、茚满基、吡啶基、咪唑基、呋喃基、吲哚基、嘧啶基、吡啶嗪基、吡嗪基、咪唑基、噁唑基、噻吩基、噻唑基、三唑基、异噁唑基、喹啉基、吡咯基、吡唑基或5,6,7,8-四氢异喹啉基,其中每个任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、=O、-B(OH)$_2$、(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-S(O)$_r$-(C_1-C_4)烷基、-S(O)$_2$-Na和CN。或者,R_{12}是H、苯基、咪唑基、呋喃基或吲哚基,其中每个苯基、咪唑基、呋喃基或吲哚基任选被1至4个独立地选自由以下组成

的组的取代基取代:-F、-OH、甲基、-S(O)$_2$-Na或-B(OH)$_2$,

[0147] R_{13}选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。

[0148] 或者,R_{13}选自由以下组成的组:H、-(C_1-C_4)烷基和-(C_3-C_8)环烷基,其中每个-(C_1-C_4)烷基和-(C_3-C_8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。

[0149] 进一步地,R_{13}选自由以下组成的组:H、-(C_1-C_4)烷基和-(C_3-C_8)环烷基,其中每个-(C_1-C_4)烷基和-(C_3-C_8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-OH、-O-(C_1-C_4)烷基和卤取代的-(C_1-C_4)烷基。在另一种替代方案中,R_{13}选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、叔丁基、甲氧基、羟基、环丁基、环戊基和环己基。

[0150] R_{14}选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。

[0151] 或者,R_{14}选自由以下组成的组:H、-(C_1-C_4)烷基和-(C_3-C_8)环烷基,其中每个-(C_1-C_4)烷基和-(C_3-C_8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。

[0152] 进一步地,R_{14}选自由以下组成的组:H、-(C_1-C_4)烷基和-(C_3-C_8)环烷基,其中每个-(C_1-C_4)烷基和-(C_3-C_8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-OH、-O-(C_1-C_4)烷基和卤取代的-(C_1-C_4)烷基。在另一种替代方案中,R_{14}选自由以下组成的组:H、甲基、乙基、丙基、异丙基、丁基、叔丁基、甲氧基、羟基、环丁基、环戊基和环己基。

[0153] R_{15}选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。

[0154] 或者，R_{15}选自由以下组成的组：H、-(C_1-C_4)烷基和-(C_3-C_8)环烷基，其中每个-(C_1-C_4)烷基和-(C_3-C_8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。

[0155] 进一步地，R_{15}选自由以下组成的组：H、-(C_1-C_4)烷基和-(C_3-C_8)环烷基，其中每个-(C_1-C_4)烷基和-(C_3-C_8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-OH、-O-(C_1-C_4)烷基和卤取代的-(C_1-C_4)烷基。在另一种替代方案中，R_{15}选自由以下组成的组：H、甲基、乙基、丙基、异丙基、丁基、叔丁基、甲氧基、羟基、环丁基、环戊基和环己基。

[0156] R_{16}选自由以下组成的组：H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。

[0157] 或者，R_{16}选自由以下组成的组：H、-(C_1-C_4)烷基和-(C_3-C_8)环烷基，其中每个-(C_1-C_4)烷基和-(C_3-C_8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基和-C(O)-(氟取代的-(C_1-C_4)烷基)。

[0158] 进一步地，R_{16}选自由以下组成的组：H、-(C_1-C_4)烷基和-(C_3-C_8)环烷基，其中每个-(C_1-C_4)烷基和-(C_3-C_8)环烷基任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-OH、-O-(C_1-C_4)烷基和卤取代的-(C_1-C_4)烷基。在另一种替代方案中，R_{16}选自由以下组成的组：H、甲基、乙基、丙基、异丙基、丁基、叔丁基、甲氧基、羟基、环丁基、环戊基和环己基。

[0159] R_C选自由以下组成的组：-F、-Cl、-Br、-OH、-(C_1-C_4)烷基、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基、-C(O)-(氟取代的-(C_1-C_4)烷基)、-S(O)$_o$-(C_1-C_4)烷基、-NR_7R_8和CN。

[0160] 或者R_C选自由以下组成的组：-F、-Cl、-Br、-OH和-O-(C_1-C_4)烷基。在另一种替代方案中，R_C选自由F、-Cl、-Br、-OH、甲氧基和乙氧基组成的组。

[0161] m是0、1、2或3。或者，m是1或2。

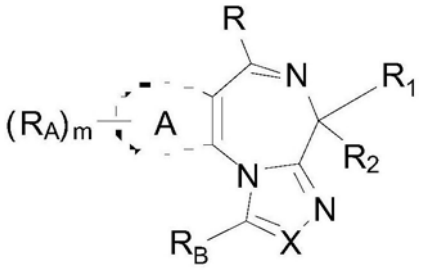
[0162] o是1或2。

[0163] p是1或2。

[0164] q是1或2。

[0165] r是1或2。

[0166] 第一实施方案化合物由结构式I表示：

[0167] 

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[0168] 或其药学上可接受的盐，其中：

[0169] X是N或CR_3；

[0170] R_3选自由以下组成的组：H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C10)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C10)杂芳基任选且独立地被1至4个取代基取代；

[0171] R_B是H、-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基或-COO-R_4，其中每个-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代；

[0172] 环A是-(C6-C10)芳基或-(C5-C10)杂芳基；

[0173] 每个R_A独立地为H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基或-(C5-C10)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C10)杂芳基任选且独立地被1至4个取代基取代；或者任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团；

[0174] R是-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基或-(C5-C10)杂芳基，其中每个任选且独立地被1至4个取代基取代；

[0175] R_1是-$(CH_2)_n$-L，其中n是0-3且L是H、-C(O)O-R_9、-CO-N(R_9R_{10})、-NR_9R_{10}、-N(R_{10})C(O)OR_9或-N(R_{10})C(O)R_9；

[0176] R_2是H、D、卤素或-(C1-C4)烷基；

[0177] R_4、R_5和R_6各自独立地选自由以下组成的组：H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选且独立地被1至4个取代基取代；

[0178] R_9选自由以下组成的组：H、-(C1-C6)烷基、-(C0-C6)亚烷基-环烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基、-(C0-C6)亚烷基-杂芳基和-N=$CR_{11}R_{12}$，其中每个-(C1-C6)烷基和-(C0-C6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

[0179] R_{10}选自由以下组成的组：H、-(C1-C6)烷基、-(C0-C6)亚烷基-环烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基；和-(C0-C6)亚烷基-杂芳基，其中每个-(C1-C6)烷基和-(C0-C6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

[0180] R_9和R_{10}与它们所结合的氮原子一起形成4-10元环；

[0181] R_{11}是H、-(C_1-C_4)烷基或-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基，其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选且独立地被1至3个选自由以下组成的组的取代基取代：-F、-Cl、-Br和-OH；

[0182] R_{12}是H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_7)杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选且独立地被1至4个取代基取代；且

[0183] m是0、1、2或3。

[0184] 在第一实施方案的第一方面或其特定或具体实施方案中：X是N。

[0185] 在第一实施方案的第二方面或其特定或具体实施方案中：R_B是H或-(C_1-C_4)烷基。

[0186] 在第一实施方案的第三方面或其特定或具体实施方案中：环A是5或6元芳基或杂芳基。

[0187] 在第一实施方案的第四方面或其特定或具体实施方案中：环A是苯基或噻吩基。

[0188] 在第一实施方案的第五方面或其特定或具体实施方案中：R是任选被1至4个独立地选自由以下组成的组的取代基取代的-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基：-F、-Cl和-Br。

[0189] 在第一实施方案的第五方面或其特定或具体实施方案中：L是H、-COO-R_9或-CO-N(R_9R_{10})。

[0190] 在第一实施方案的第六方面或其特定或具体实施方案中：每个R_9独立地选自由-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基和-(C_0-C_6)亚烷基-杂芳基组成的组，且每个-(C_1-C_6)烷基、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自由-F、-Cl、-Br和-(C_1-C_6)烷基组成的组的取代基取代。

[0191] 在第一实施方案的第七方面或其特定或具体实施方案中：每个R_{10}独立地选自由以下组成的组：H和-(C_1-C_6)烷基。

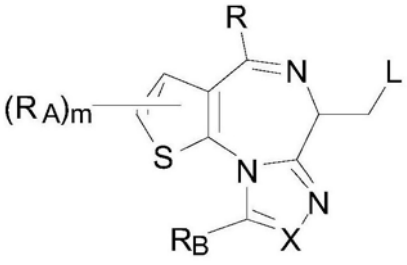
[0192] 在第一实施方案的第八方面或其特定或具体实施方案中：其中R_2选自由以下组成的组：H和甲基。

[0193] 在第一实施方案的第九方面或其特定或具体实施方案中：R_A独立地为H或-(C_1-C_4)烷基，或者任何两个R_A与各自所连接的原子一起可形成稠合芳基。

[0194] 在第一实施方案的第十方面或其特定或具体实施方案中：m是2且至少一个R_A是甲基。

[0195] 在第一实施方案的第十一方面或其特定或具体实施方案中：m是2且每个R_A是甲基。

[0196] 在第二实施方案中，化合物由结构式II表示：

[0197] 

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[0198] 或其药学上可接受的盐，其中：

[0199] X是N或CR_3；

[0200] R_3选自由以下组成的组：H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代；

[0201] R_B是H、-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基或-COO-R_4，其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代；

[0202] 每个R_A独立地为H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代；或者任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团；

[0203] R是-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基，其中每个任选且独立地被1至4个取代基取代；

[0204] L是H、-C(O)O-R_9、-CO-N(R_9R_{10})、-NR_9R_{10}、-N(R_{10})C(O)OR_9或-N(R_{10})C(O)R_9；

[0205] R_4、R_5和R_6各自独立地选自由以下组成的组：H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选且独立地被1至4个取代基取代；

[0206] R_9选自由以下组成的组：H、-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-环烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基、-(C_0-C_6)亚烷基-杂芳基和-N=$CR_{11}R_{12}$，其中每个-(C_1-C_6)烷基和-(C_0-C_6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

[0207] R_{10}选自由以下组成的组：H、-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-环烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基；和-(C_0-C_6)亚烷基-杂芳基，其中每个-(C_1-C_6)烷基和-(C_0-C_6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

[0208] R_9和R_{10}与它们所结合的氮原子一起形成4-10元环；

[0209] R_{11}是H、-(C_1-C_4)烷基或-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基，其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至3个选自由以下组成的组的取代基取代：-F、-Cl、-Br和-OH；

[0210] R_{12}是H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_7)杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选且独立地被1至4个取代基取代；且

[0211] m是0、1、2或3。

[0212] 在第二实施方案的第一方面或其特定或具体实施方案中：X是N。

[0213] 在第二实施方案的第二方面或其特定或具体实施方案中：R_B选自由以下组成的组：H、-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基，且每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由以下组成的组的取代基取代：-F、-Cl、-Br和-

OH。

[0214] 在第二实施方案的第三方面或其特定或具体实施方案中:R_B是甲基、乙基、羟甲基、甲氧基甲基或三氟甲基。

[0215] 在第二实施方案的第四方面或其特定或具体实施方案中:R是任选被选自由以下组成的组的取代基取代的-(C6-C10)芳基或-(C5-C10)杂芳基:-F、-Cl和-Br。

[0216] 在第二实施方案的第五方面或其特定或具体实施方案中:R是任选被选自由以下组成的组的取代基取代的苯基或吡啶基:-F、-Cl和-Br。

[0217] 在第二实施方案的第六方面或其特定或具体实施方案中:R是对-Cl-苯基、邻-Cl-苯基、间-Cl-苯基、对-F-苯基、邻-F-苯基、间-F-苯基或吡啶基。

[0218] 在第二实施方案的第七方面或其特定或具体实施方案中:L是-CO-N(R_9R_{10}),R_9是-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基或-(C0-C6)亚烷基-杂芳基,其中每个-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个(C1-C4)烷基取代,且R_{10}是H或-(C1-C6)烷基。

[0219] 在第二实施方案的第八方面或其特定或具体实施方案中:L是-COO-R_9且R_9独立地选自由以下组成的组:-(C1-C6)烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基和-(C0-C6)亚烷基-杂芳基,其中每个-(C1-C6)烷基、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自由以下组成的组的取代基取代:-F、-Cl、-Br和-(C1-C6)烷基。

[0220] 在第二实施方案的第九方面或其特定或具体实施方案中:L是-COO-R_9,且R_9选自由以下组成的组:甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基和三氟甲基。

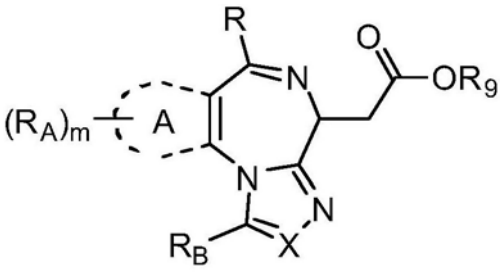
[0221] 在第二实施方案的第十方面或其特定或具体实施方案中:每个R_A独立地为H或-(C1-C4)烷基,或者任何两个R_A与各自所连接的原子一起可形成稠合芳基。

[0222] 在第二实施方案的第十一方面或其特定或具体实施方案中:m是2,且至少一次出现的R_A是甲基。

[0223] 在第二实施方案的第十二方面或其特定或具体实施方案中:m是2且每个R_A是甲基。

[0224] 在第三实施方案中,化合物由结构式III表示:

[0225]



(III)

[0226] 或其药学上可接受的盐,其中:

[0227] X是N或CR_3;

[0228] R_3选自由以下组成的组:H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C10)杂芳基,其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C10)杂芳基任选且独立地被1至4个取代基取代;

[0229] R_B是H、-(C1-C4)烷基、-(C1-C4)亚烷基-O-(C1-C4)烷基或-COO-R_4,其中每个-(C1-

C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代；

[0230] 环A是-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基；

[0231] 每个R_A独立地为H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代；或者任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团；

[0232] R是-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基，其中每个任选且独立地被1至4个取代基取代；

[0233] R_4、R_5和R_6各自独立地选自由以下组成的组：H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基，其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选且独立地被1至4个取代基取代；

[0234] R_9选自由以下组成的组：H、-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-环烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基和-(C_0-C_6)亚烷基-杂芳基，其中每个-(C_1-C_6)烷基和-(C_0-C_6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；且

[0235] m是0、1、2或3。

[0236] 在第三实施方案的第一方面或其特定或具体实施方案中：X是N。

[0237] 在第三实施方案的第二方面或其特定或具体实施方案中：R_B选自由以下组成的组：H、-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基，且每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由-F、-Cl、-Br和-OH组成的组的取代基取代。

[0238] 在第三实施方案的第三方面或其特定或具体实施方案中：R_B是甲基、乙基、羟甲基、甲氧基甲基或三氟甲基。

[0239] 在第三实施方案的第四方面或其特定或具体实施方案中：环A是5或6元芳基或杂芳基。

[0240] 在第三实施方案的第五方面或其特定或具体实施方案中：环A是硫代呋喃基、苯基、萘基、联苯基、四氢萘基、茚满基、吡啶基、呋喃基、吲哚基、嘧啶基、吡啶嗪基、吡嗪基、咪唑基、噁唑基、噻吩基、噻唑基、三唑基、异噁唑基、喹啉基、吡咯基、吡唑基或5,6,7,8-四氢异喹啉基。

[0241] 在第三实施方案的第六方面或其特定或具体实施方案中：环A是苯基或噻吩基。

[0242] 在第三实施方案的第七方面或其特定或具体实施方案中：R是任选被选自由以下组成的组的取代基取代的-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基：-F、-Cl和-Br。

[0243] 在第三实施方案的第八方面或其特定或具体实施方案中：R是任选被1-4个独立地选自由以下组成的组的取代基取代的苯基或吡啶基：-F、-Cl和-Br。

[0244] 在第三实施方案的第九方面或其特定或具体实施方案中：R是对-Cl-苯基、邻-Cl-苯基、间-Cl-苯基、对-F-苯基、邻-F-苯基、间-F-苯基或吡啶基。

[0245] 在第三实施方案的第十方面或其特定或具体实施方案中：每个R_A独立地为H或-(C_1-C_4)烷基，或者任何两个R_A与各自所连接的原子一起可形成稠合芳基。

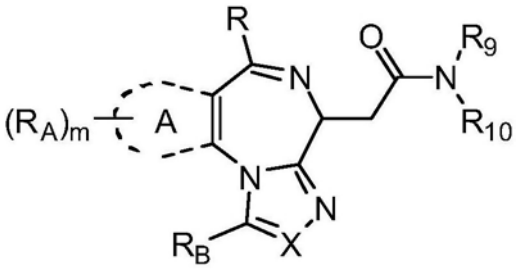
[0246] 在第三实施方案的第十一方面或其特定或具体实施方案中:m是2,且至少一次出现的R_A是甲基。

[0247] 在第三实施方案的第十二方面或其特定或具体实施方案中:m是2且每个R_A是甲基。

[0248] 在第三实施方案的第十三方面或其特定或具体实施方案中:R_9独立地选自由-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基和-(C_0-C_6)亚烷基-杂芳基组成的组,且每个-(C_1-C_6)烷基、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自由-F、-Cl、-Br和-(C_1-C_6)烷基组成的组的取代基取代。

[0249] 在第三实施方案的第十四方面或其特定或具体实施方案中:R_9选自由以下组成的组:甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基和三氟甲基。

[0250] 在第四实施方案中,化合物由结构式IV表示:

[0251] 

(IV)

[0252] 或其药学上可接受的盐,其中:

[0253] X是N或CR_3;

[0254] R_3选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代;

[0255] R_B是H、-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基或-COO-R_4,其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代;

[0256] 环A是芳基或杂芳基;

[0257] 每个R_A独立地为H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代;或者任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团;

[0258] R是-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基,其中每个任选且独立地被1至4个取代基取代;

[0259] R_4、R_5和R_6各自独立地选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选且独立地被1至4个取代基取代;

[0260] R_9选自由以下组成的组:H、-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-环烷基、-(C_0-C_6)亚烷

基-杂环烷基、-(C0-C6)亚烷基-芳基、-(C0-C6)亚烷基-杂芳基和-N=CR11R12，其中每个-(C1-C6)烷基和-(C0-C6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

[0261] R10选自由以下组成的组：H、-(C1-C6)烷基、-(C0-C6)亚烷基-环烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基；和-(C0-C6)亚烷基-杂芳基，其中每个-(C1-C6)烷基和-(C0-C6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

[0262] R9和R10与它们所结合的氮原子一起形成4-10元环；

[0263] R11是H、-(C1-C4)烷基或-(C1-C4)亚烷基-O-(C1-C4)烷基，其中每个-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基任选被1至3个选自由以下组成的组的取代基取代：-F、-Cl、-Br和-OH；

[0264] R12是H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基或-(C5-C7)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选且独立地被1至4个取代基取代；且

[0265] m是0、1、2或3。

[0266] 在第四实施方案的第一方面或其特定或具体实施方案中：X是N。

[0267] 在第四实施方案的第二方面或其特定或具体实施方案中：RB选自由以下组成的组：H、-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基，且每个-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基任选被1至4个独立地选自由-F、-Cl、-Br和-OH组成的组的取代基取代。

[0268] 在第四实施方案的第三方面或其特定或具体实施方案中：RB是甲基、乙基、羟甲基、甲氧基甲基或三氟甲基。

[0269] 在第四实施方案的第四方面或其特定或具体实施方案中：环A是5或6元芳基或杂芳基。

[0270] 在第四实施方案的第五方面或其特定或具体实施方案中：环A是硫代呋喃基、苯基、萘基、联苯基、四氢萘基、茚满基、吡啶基、呋喃基、吲哚基、嘧啶基、吡啶嗪基、吡嗪基、咪唑基、噁唑基、噻吩基、噻唑基、三唑基、异噁唑基、喹啉基、吡咯基、吡唑基或5,6,7,8-四氢异喹啉基。

[0271] 在第四实施方案的第六方面或其特定或具体实施方案中：环A是苯基或噻吩基。

[0272] 在第四实施方案的第七方面或其特定或具体实施方案中：R是任选被1至4个独立地选自由以下组成的组的取代基取代的-(C6-C10)芳基或-(C5-C10)杂芳基：-F、-Cl和-Br。

[0273] 在第四实施方案的第八方面或其特定或具体实施方案中：R是任选被1至4个独立地选自由以下组成的组的取代基取代的苯基或吡啶基：-F、-Cl和-Br。

[0274] 在第四实施方案的第九方面或其特定或具体实施方案中：R是对-Cl-苯基、邻-Cl-苯基、间-Cl-苯基、对-F-苯基、邻-F-苯基、间-F-苯基或吡啶基。

[0275] 在第四实施方案的第十方面或其特定或具体实施方案中：每个RA独立地为H或-(C1-C4)烷基，或者任何两个RA与各自所连接的原子一起可形成稠合芳基。

[0276] 在第四实施方案的第十一方面或其特定或具体实施方案中：m是2，且至少一次出现的RA是甲基。

[0277] 在第四实施方案的第十二方面或其特定或具体实施方案中：m是2且每个RA是甲

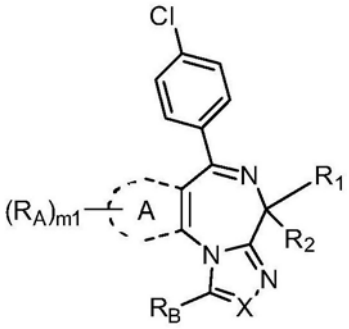
基。

[0278] 在第四实施方案的第十三方面或其特定或具体实施方案中:R_9独立地选自由-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基和-(C_0-C_6)亚烷基-杂芳基组成的组,且每个-(C_1-C_6)烷基、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自由-F、-Cl、-Br和-(C_1-C_6)烷基组成的组的取代基取代。

[0279] 在第四实施方案的第十四方面或其特定或具体实施方案中:R_{10}选自由以下组成的组:H和任选被1至4个独立地选自由-F和-O-(C_1-C_6)烷基组成的组的取代基取代的-(C_1-C_6)烷基。

[0280] 在第四实施方案的第十五方面或其特定或具体实施方案中:R_9是N=$CR_{11}R_{12}$,R_{11}是H或-(C_1-C_4)烷基,且R_{12}是任选被1至4个独立地选自-(C_1-C_4)烷基、-F、-Cl、-SO_2Na或-B(OH)$_2$的取代基取代的-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_7)杂芳基。

[0281] 在第五实施方案中,化合物由结构式V表示:

[0282] 

(V)

[0283] 或其药学上可接受的盐,其中:

[0284] X是N或CR_3;

[0285] R_3选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代;

[0286] R_B是H、-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基或-COO-R_4,其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代;

[0287] 环A是-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基;

[0288] 每个R_A独立地为H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代;或者任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团;

[0289] R_1是-(CH_2)$_n$-L,其中n是0-3且L是H、-C(O)O-R_9、-CO-N(R_9R_{10})、-NR_9R_{10}、-N(R_{10})C(O)OR_9或-N(R_{10})C(O)R_9;

[0290] R_2是H、D、卤素或-(C_1-C_4)烷基;

[0291] R_4、R_5和R_6各自独立地选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷

基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选且独立地被1至4个取代基取代；

[0292] R9选自由以下组成的组：H、-(C1-C6)烷基、-(C0-C6)亚烷基-环烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基、-(C0-C6)亚烷基-杂芳基和-N＝CR11R12，其中每个-(C1-C6)烷基和-(C0-C6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

[0293] R10选自由以下组成的组：H、-(C1-C6)烷基、-(C0-C6)亚烷基-环烷基、-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基；和-(C0-C6)亚烷基-杂芳基，其中每个-(C1-C6)烷基和-(C0-C6)亚烷基-任选且独立地被1至4个取代基取代，且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代；

[0294] R9和R10与它们所结合的氮原子一起形成4-10元环；

[0295] R11是H、-(C1-C4)烷基或-(C1-C4)亚烷基-O-(C1-C4)烷基，其中每个-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基任选且独立地被1至3个选自由以下组成的组的取代基取代：-F、-Cl、-Br和-OH；

[0296] R12是H、-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基或-(C5-C7)杂芳基，其中每个-(C1-C4)烷基、-(C3-C8)环烷基、-(C5-C7)杂环烷基、-(C6-C10)芳基和-(C5-C7)杂芳基任选且独立地被1至4个取代基取代；且

[0297] m是0、1、2或3。

[0298] 在第五实施方案的第一方面或其特定或具体实施方案中：X是N。

[0299] 在第五实施方案的第二方面或其特定或具体实施方案中：RB选自由以下组成的组：H、-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基，且每个-(C1-C4)烷基和-(C1-C4)亚烷基-O-(C1-C4)烷基任选被1至4个独立地选自由-F、-Cl、-Br和-OH组成的组的取代基取代。

[0300] 在第五实施方案的第三方面或其特定或具体实施方案中：RB是甲基、乙基、羟甲基、甲氧基甲基或三氟甲基。

[0301] 在第五实施方案的第四方面或其特定或具体实施方案中：环A是5或6元芳基或杂芳基。

[0302] 在第五实施方案的第五方面或其特定或具体实施方案中：环A是硫代呋喃基、苯基、萘基、联苯基、四氢萘基、茚满基、吡啶基、呋喃基、吲哚基、嘧啶基、吡啶嗪基、吡嗪基、咪唑基、噁唑基、噻吩基、噻唑基、三唑基、异噁唑基、喹啉基、吡咯基、吡唑基或5,6,7,8-四氢异喹啉基。

[0303] 在第五实施方案的第六方面或其特定或具体实施方案中：环A是苯基或噻吩基。

[0304] 在第五实施方案的第七方面或其特定或具体实施方案中：RA独立地为H或-(C1-C4)烷基，或者任何两个RA与各自所连接的原子一起可形成稠合芳基。

[0305] 在第五实施方案的第八方面或其特定或具体实施方案中：m是2，且至少一次出现的RA是甲基。

[0306] 在第五实施方案的第九方面或其特定或具体实施方案中：m是2且每个RA是甲基。

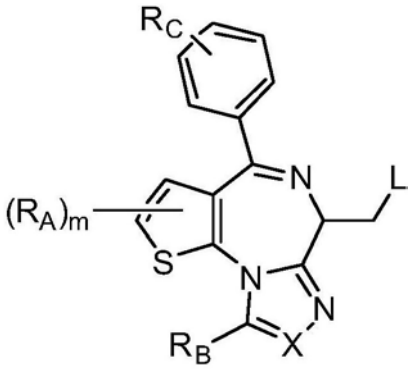
[0307] 在第五实施方案的第十方面或其特定或具体实施方案中：L是-CO-N(R9R10)，R9是任选且独立地被1至4个(C1-C4)烷基取代的-(C0-C6)亚烷基-杂环烷基、-(C0-C6)亚烷基-芳基或-(C0-C6)亚烷基-杂芳基，，且R10是H或-(C1-C6)烷基。

[0308] 在第五实施方案的第十一方面或其特定或具体实施方案中:L是-COO-R_9,且R_9独立地选自由-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基和-(C_0-C_6)亚烷基-杂芳基组成的组,且每个-(C_1-C_6)烷基、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自由-F、-Cl、-Br和-(C_1-C_6)烷基组成的组的取代基取代。

[0309] 在第五实施方案的第十二方面或其特定或具体实施方案中:L是-COO-R_9,且R_9选自由以下组成的组:甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基和三氟甲基。

[0310] 在第五实施方案的第十三方面或其特定或具体实施方案中:R_2是H或-(C_1-C_4)烷基。

[0311] 在第六实施方案中,化合物由结构式VI表示:

[0312] 

(VI)

[0313] 或其药学上可接受的盐,其中:

[0314] X是N或CR_3;

[0315] R_3选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代;

[0316] R_B是H、-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基或-COO-R_4,其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由-F、-Cl、-Br、-OH和-NR_5R_6组成的组的取代基取代;

[0317] 每个R_A独立地为H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_{10})杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_{10})杂芳基任选且独立地被1至4个取代基取代;或者任何两个R_A与各自所结合的原子一起形成稠合芳基或杂芳基基团;

[0318] L是H、-C(O)O-R_9、-CO-N(R_9R_{10})、-NR_9R_{10}、-N(R_{10})C(O)OR_9或-N(R_{10})C(O)R_9;

[0319] R_C选自由以下组成的组:-F、-Cl、-Br、-OH、-O-(C_1-C_4)烷基、-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基、卤取代的-(C_1-C_4)烷基、卤取代的-O-(C_1-C_4)烷基、-C(O)-(C_1-C_4)烷基、-C(O)-(氟取代的-(C_1-C_4)烷基)、-S(O)$_o$-(C_1-C_4)烷基、-NR_7R_8和CN;

[0320] R_4、R_5、R_6、R_7和R_8各自独立地选自由以下组成的组:H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选且独立地被1至4个取代基取代;

[0321] R_9选自由以下组成的组:H、-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-环烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基、-(C_0-C_6)亚烷基-杂芳基和-N=$CR_{11}R_{12}$,其中每个-(C_1-C_6)烷基和-(C_0-C_6)亚烷基-任选且独立地被1至4个取代基取代,且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代;

[0322] R_{10}选自由以下组成的组:H、-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-环烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基;和-(C_0-C_6)亚烷基-杂芳基,其中每个-(C_1-C_6)烷基和-(C_0-C_6)亚烷基-任选且独立地被1至4个取代基取代,且每个-环烷基、-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个取代基取代;

[0323] R_9和R_{10}与它们所结合的氮原子一起形成4-10元环;

[0324] R_{11}是H、-(C_1-C_4)烷基或-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基,其中每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选且独立地被1至3个选自由以下组成的组的取代基取代:-F、-Cl、-Br和-OH;

[0325] R_{12}是H、-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基或-(C_5-C_7)杂芳基,其中每个-(C_1-C_4)烷基、-(C_3-C_8)环烷基、-(C_5-C_7)杂环烷基、-(C_6-C_{10})芳基和-(C_5-C_7)杂芳基任选且独立地被1至4个取代基取代;

[0326] m是0、1、2或3;且

[0327] o是1或2。

[0328] 在第六实施方案的第一方面或其特定或具体实施方案中:X是N。

[0329] 在第六实施方案的第二方面或其特定或具体实施方案中:R_B选自由以下组成的组:H、-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基,且每个-(C_1-C_4)烷基和-(C_1-C_4)亚烷基-O-(C_1-C_4)烷基任选被1至4个独立地选自由-F、-Cl、-Br和-OH组成的组的取代基取代。

[0330] 在第六实施方案的第三方面或其特定或具体实施方案中:R_B是甲基、乙基、羟甲基、甲氧基甲基或三氟甲基。

[0331] 在第六实施方案的第四方面或其特定或具体实施方案中:每个R_A独立地为H或-(C_1-C_4)烷基,或者任何两个R_A与各自所连接的原子一起可形成稠合芳基。

[0332] 在第六实施方案的第五方面或其特定或具体实施方案中:m是1或2,且至少一次出现的R_A是甲基。

[0333] 在第六实施方案的第六方面或其特定或具体实施方案中:m是2且每个R_A是甲基。

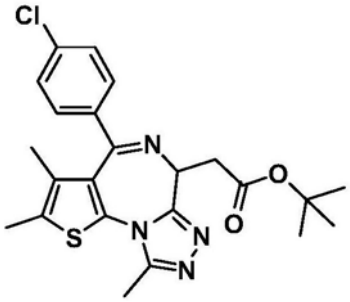
[0334] 在第六实施方案的第七方面或其特定或具体实施方案中:L是-CO-N(R_9R_{10}),R_9是-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基或-(C_0-C_6)亚烷基-杂芳基,且每个-杂环烷基、-芳基和-杂芳基任选且独立地被1至4个(C_1-C_4)烷基取代,且R_{10}是H或-(C_1-C_6)烷基。

[0335] 在第六实施方案的第八方面或其特定或具体实施方案中:L是-COO-R_9,且R_9独立地选自由-(C_1-C_6)烷基、-(C_0-C_6)亚烷基-杂环烷基、-(C_0-C_6)亚烷基-芳基和-(C_0-C_6)亚烷基-杂芳基组成的组,且每个-(C_1-C_6)烷基、-杂环烷基、-芳基和-杂芳基任选被1至4个独立地选自由-F、-Cl、-Br和-(C_1-C_6)烷基组成的组的取代基取代。

[0336] 在第六实施方案的第九方面或其特定或具体实施方案中:L是-COO-R_9,且R_9选自由以下组成的组:甲基、乙基、丙基、异丙基、丁基、仲丁基、叔丁基和三氟甲基。

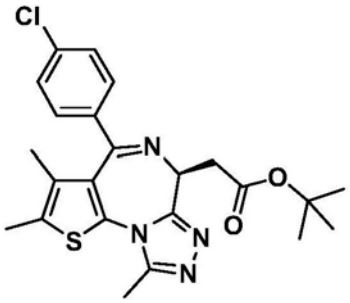
[0337] 在第六实施方案的第十方面或其特定或具体实施方案中:R_C选自由以下组成的组:-F、-Cl、-Br、-OH和-O-(C_1-C_4)烷基。

[0338] 在第七实施方案中,化合物由以下结构式表示:

[0339] 

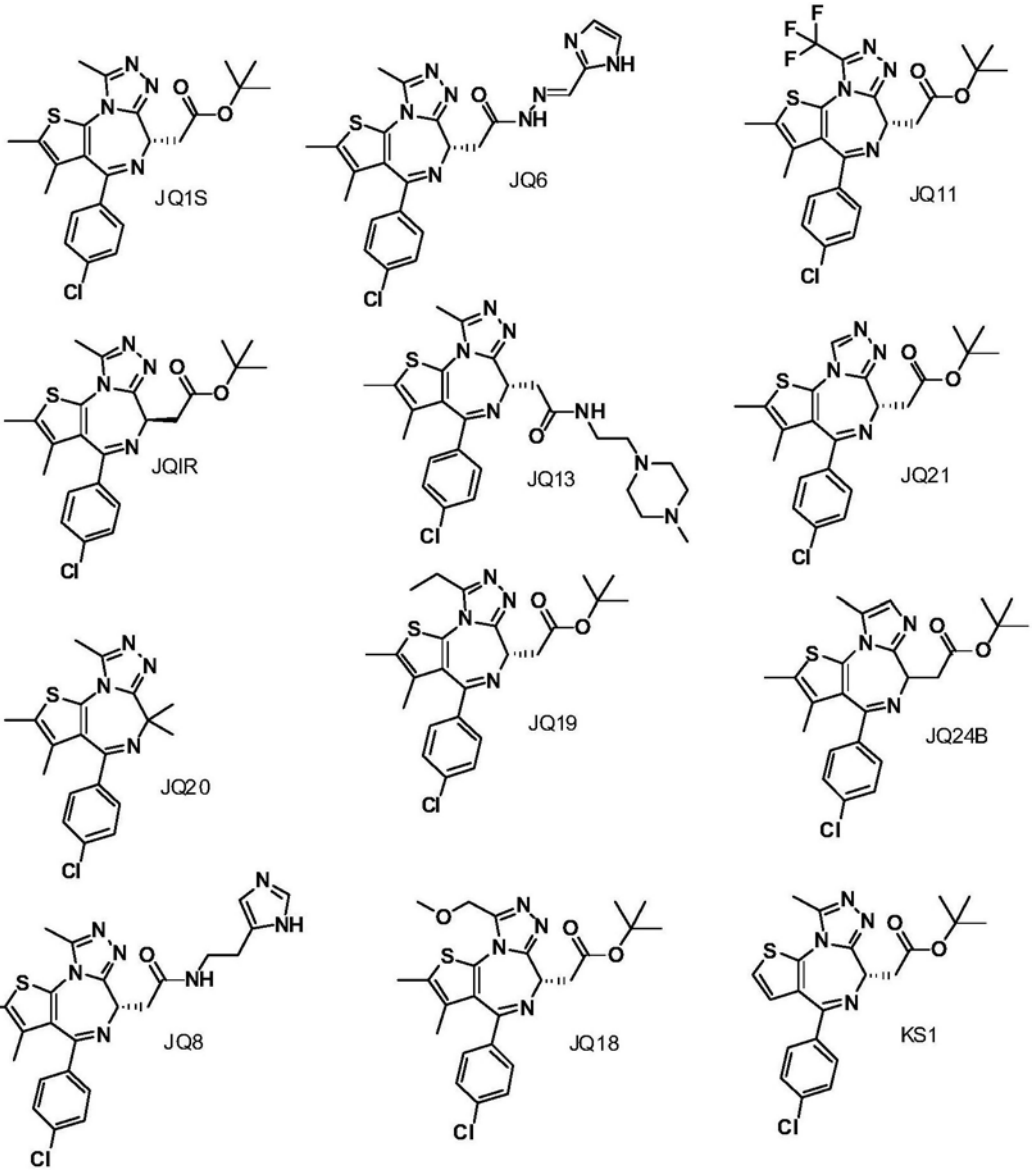
[0340] 或其药学上可接受的盐。

[0341] 在第七实施方案的第一方面或其特定或具体实施方案中,化合物由以下结构式表示:

[0342] 

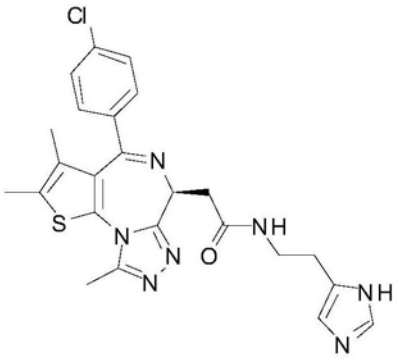
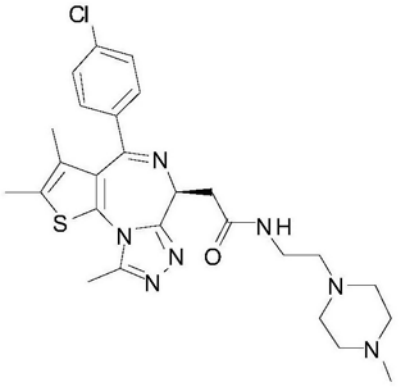
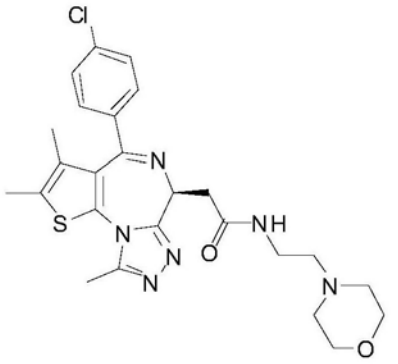
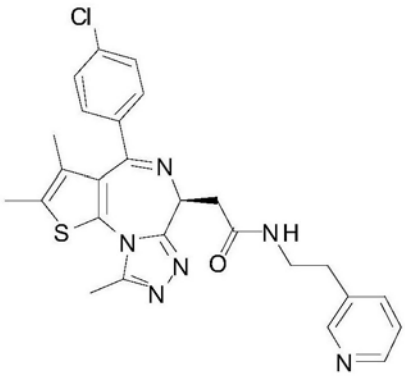
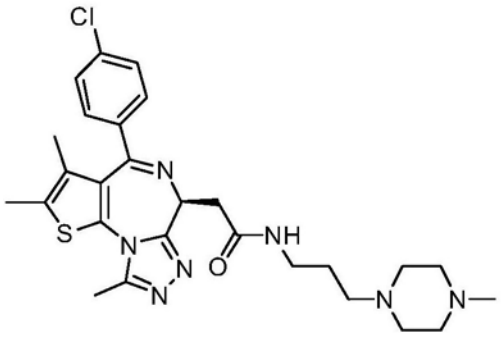
[0343] 或其药学上可接受的盐。

[0344] 在第八实施方案中,化合物由以下结构式中的任一者表示:

[0345] 

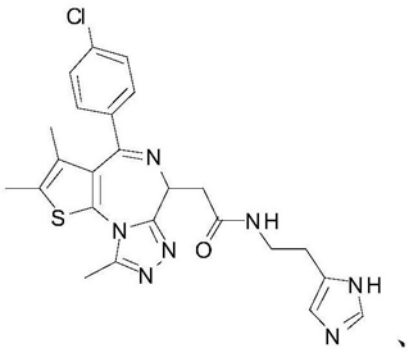
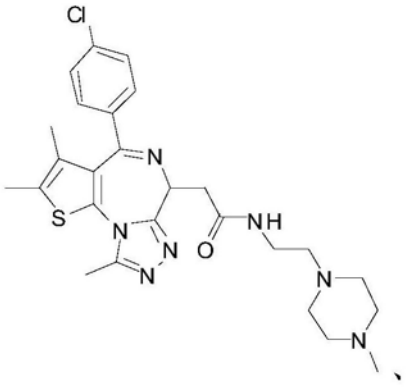
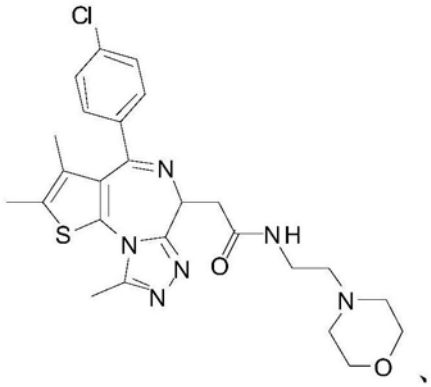
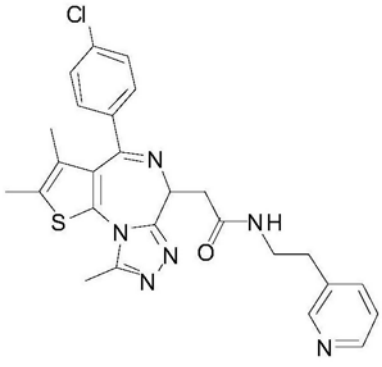
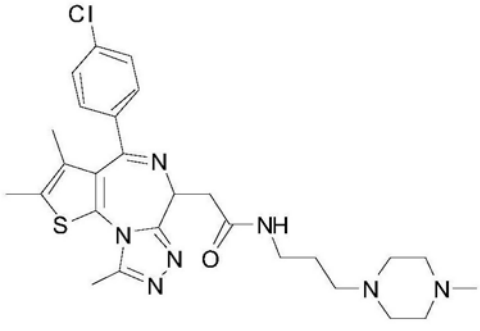
[0346] 或其药学上可接受的盐。

[0347] 在第九实施方案中,化合物由以下结构式中的任一者表示:

[0348]  、  、  、  或 

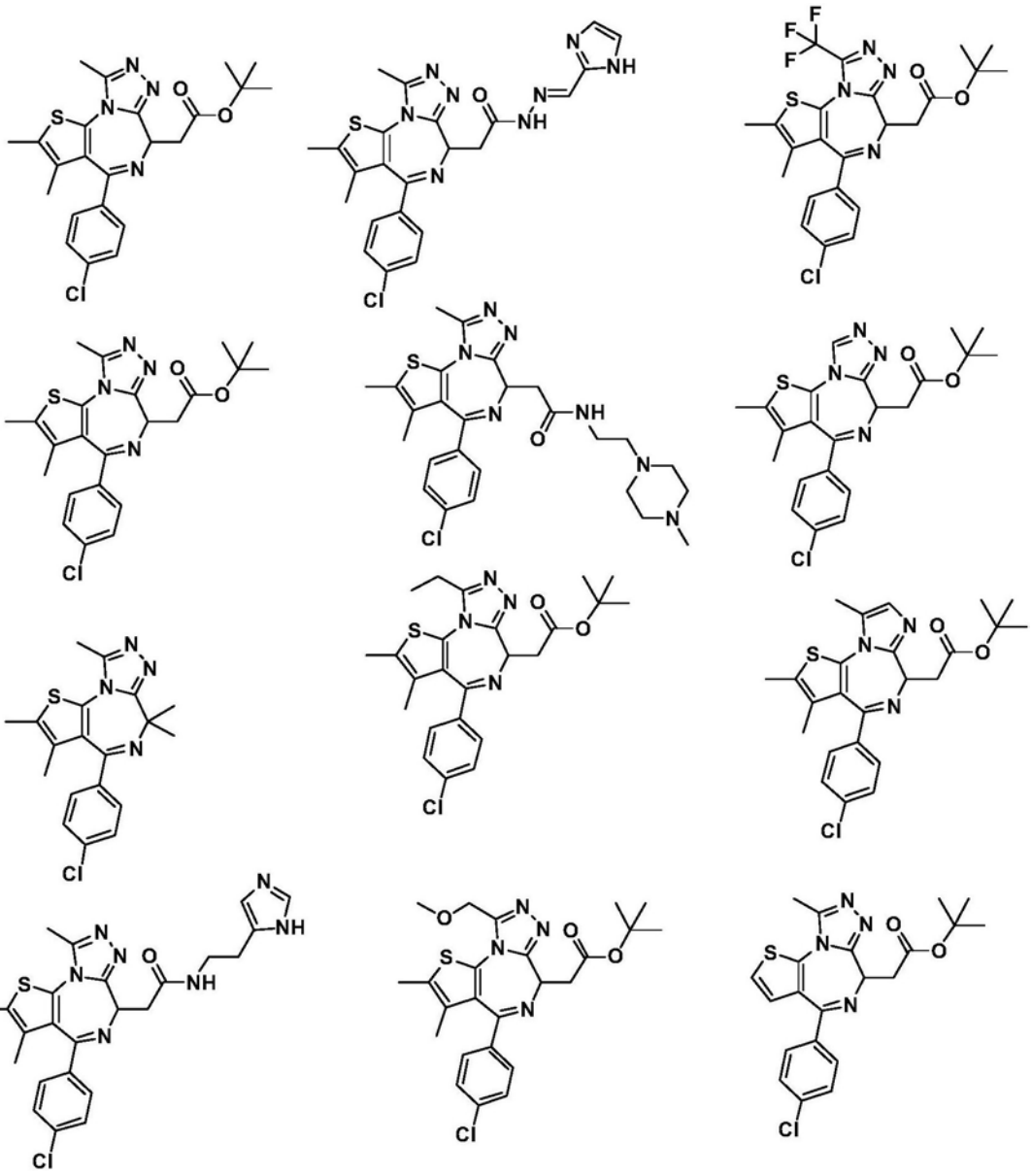
[0349] 或其药学上可接受的盐。

[0350] 在第十实施方案中,化合物由以下结构式中的任一者表示:

[0351]  、  、  、  或  ；

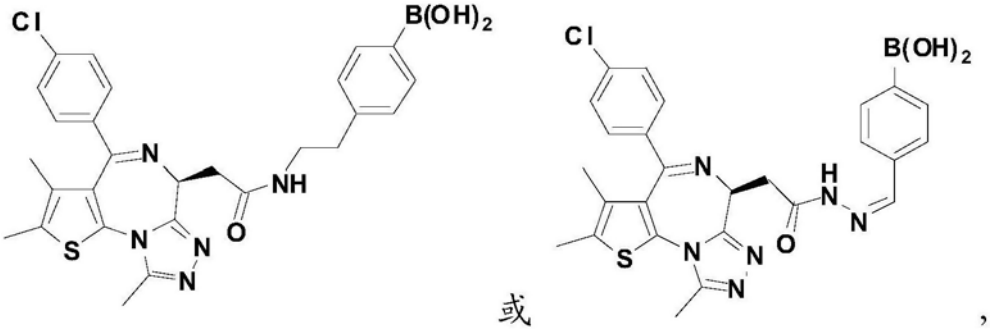
[0352] 或其药学上可接受的盐。

[0353] 在第十一实施方案中，化合物由以下结构式中的任一者表示：

[0354] 

[0355] 或其药学上可接受的盐。

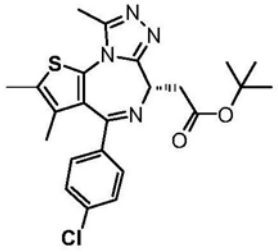
[0356] 在第十二实施方案中,化合物由以下结构式中的任一者表示:

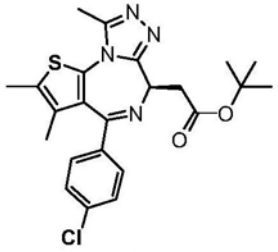
[0357] 

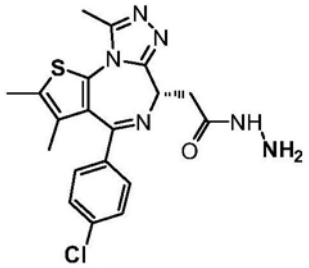
[0358] 或其药学上可接受的盐。

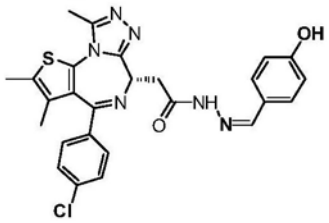
[0359] 在第十三实施方案中,化合物由以下结构式中的任一者表示:

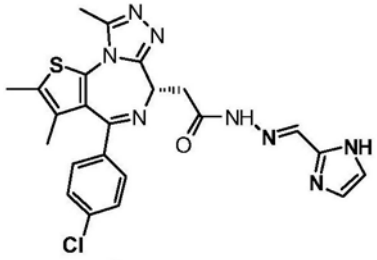
[0360]

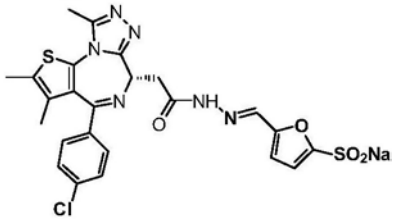


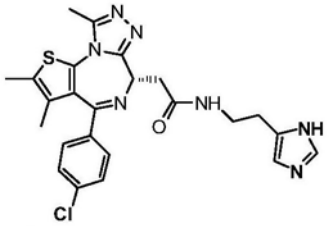


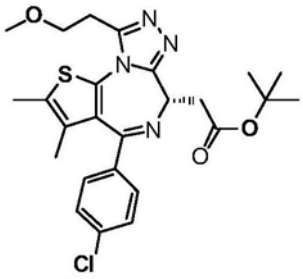


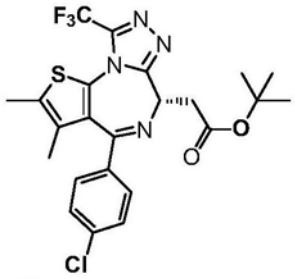




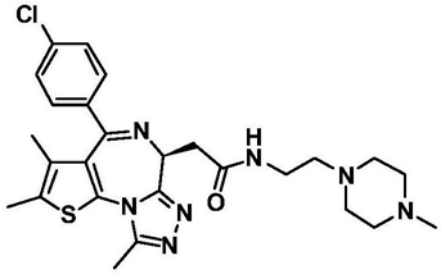


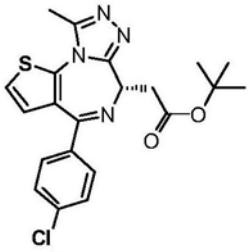


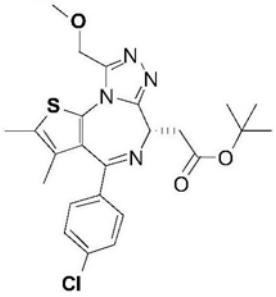


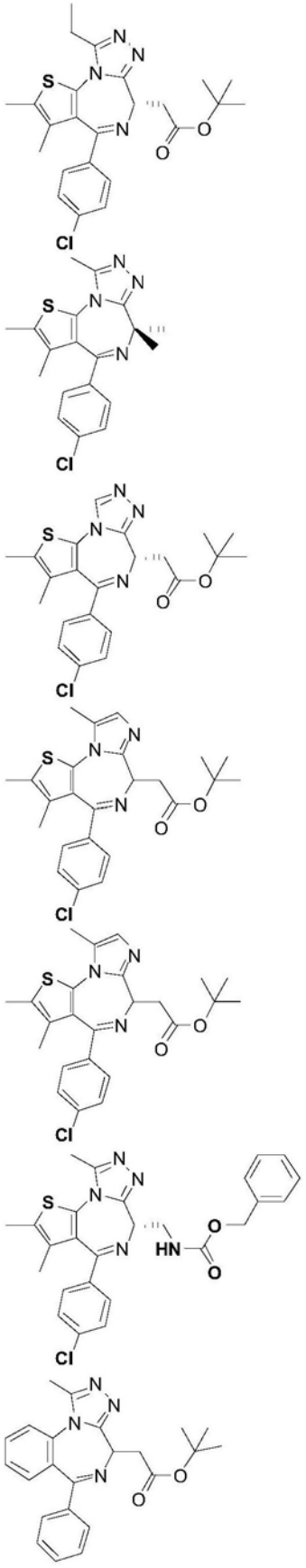


[0361]

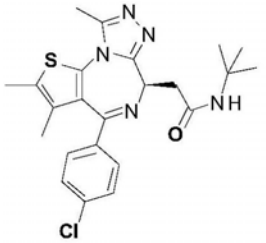


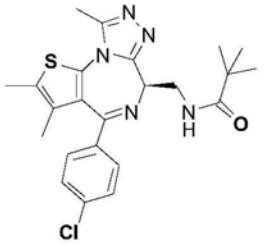


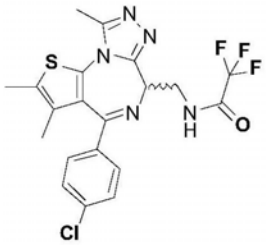


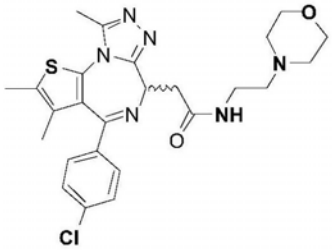
[0362] 

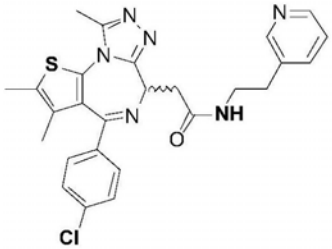
[0363]

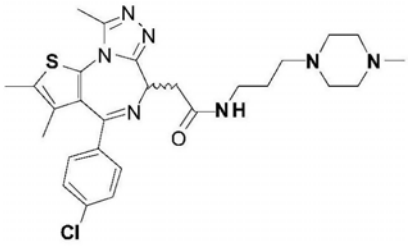


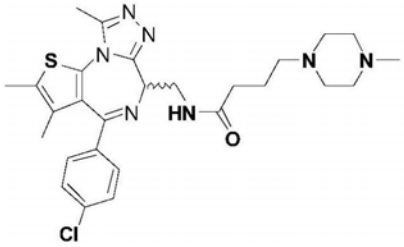


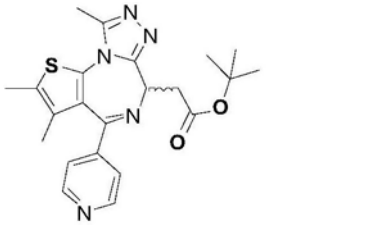
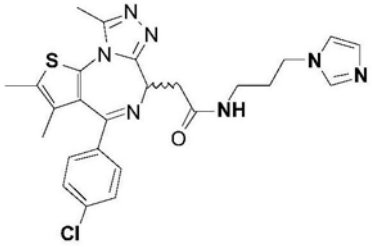
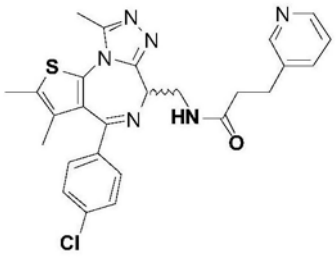
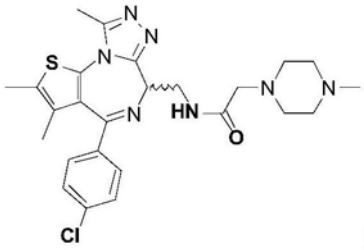
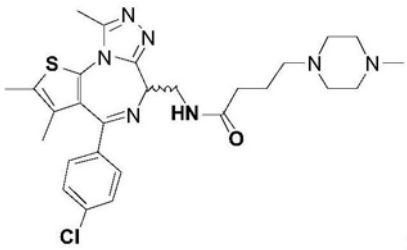






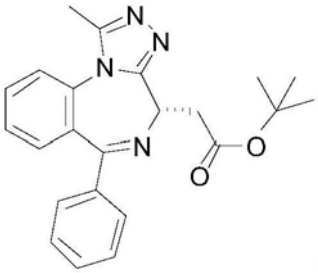


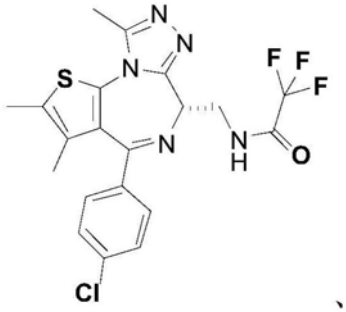


[0364] 



或

;

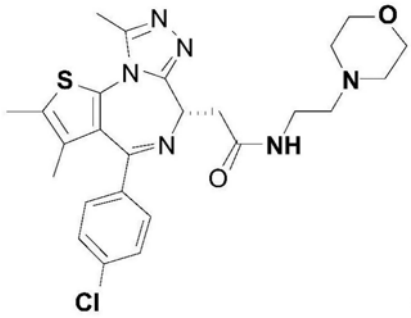
[0365] 或其药学上可接受的盐。

[0366] 在第十四实施方案中,化合物由以下结构式中的任一者表示:

[0367] 
、

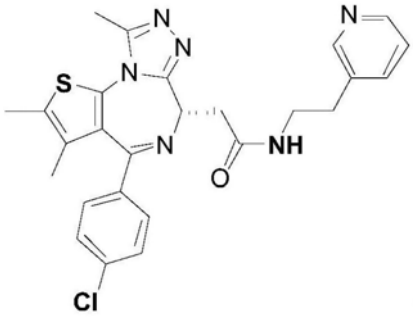


、



、

[0368]



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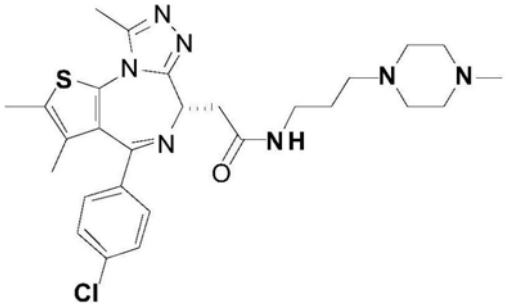

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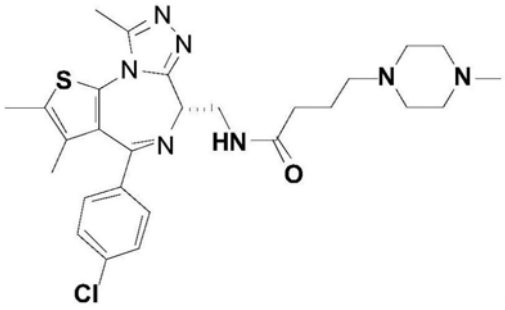

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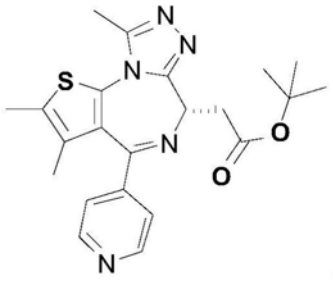
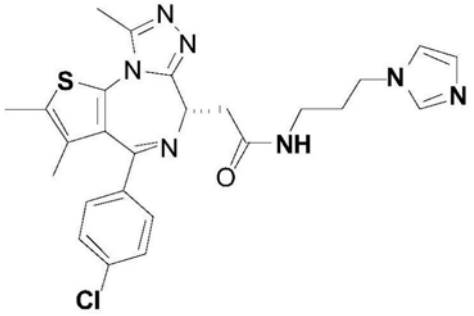
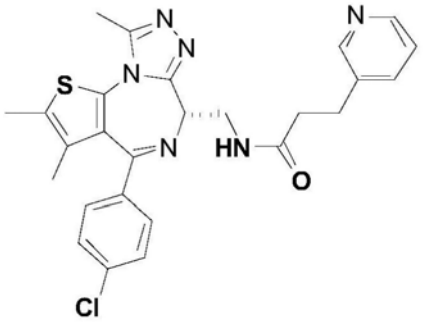
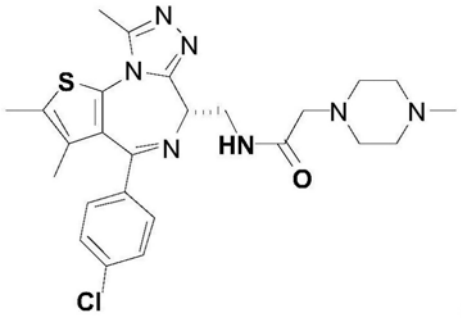
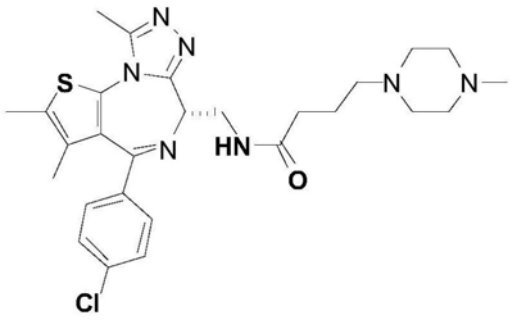


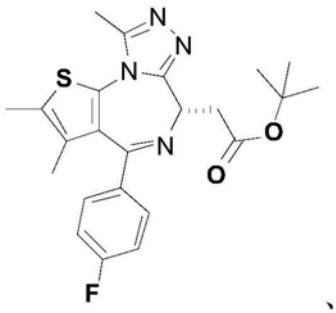


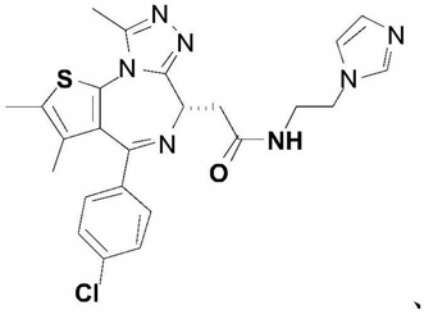
[0369]



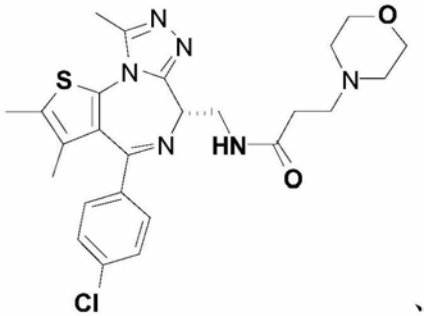


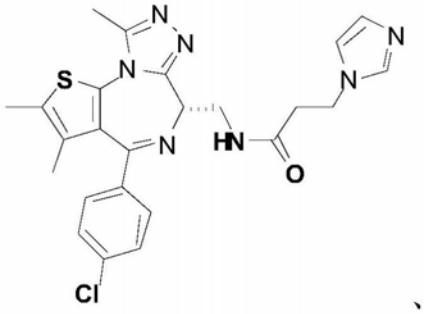


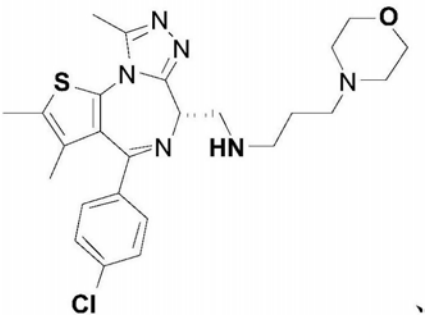


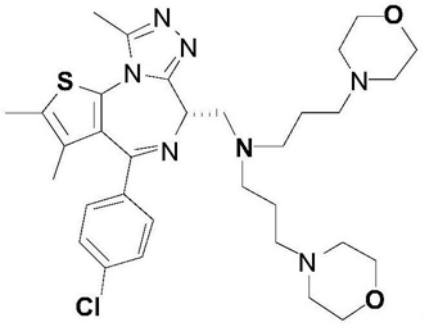


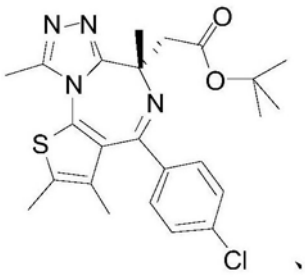
[0370]



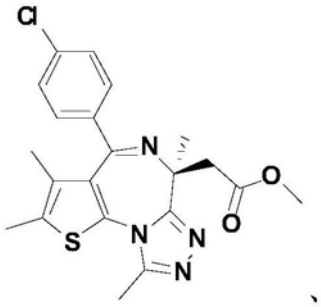


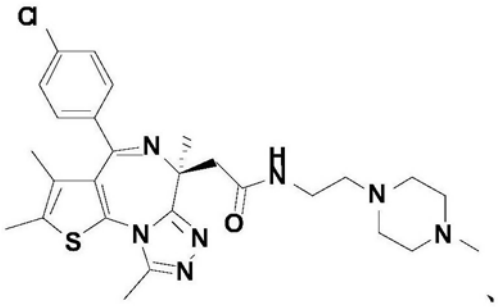


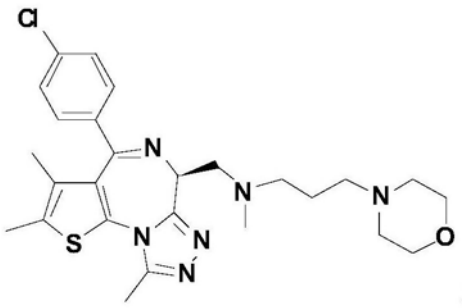




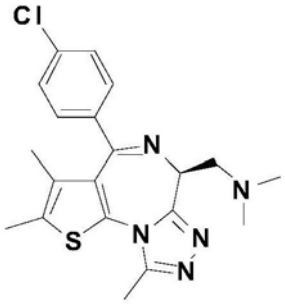
[0371]







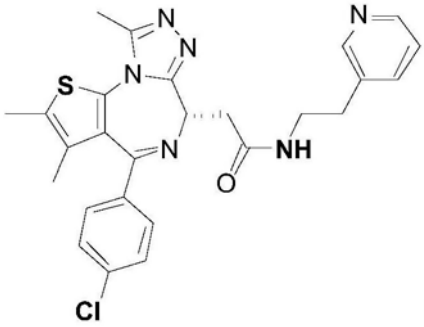
或

[0372] 

;

[0373] 或其药学上可接受的盐。

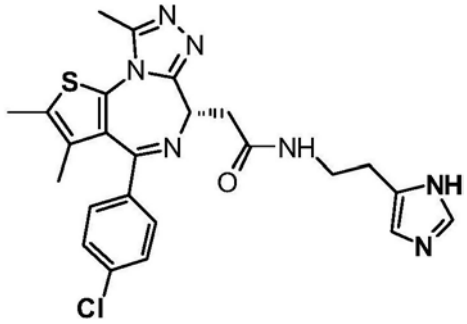
[0374] 在第十五实施方案中,化合物由以下结构表示:

[0375] 

;

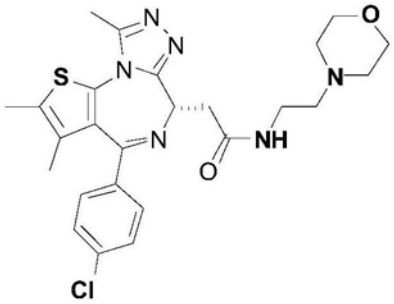
[0376] 或其药学上可接受的盐。

[0377] 在第十六实施方案中,化合物由以下结构表示:

[0378] 

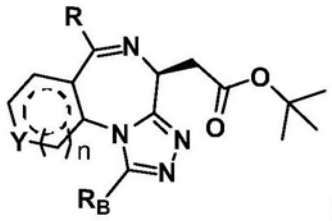
[0379] 或其药学上可接受的盐

[0380] 在第十七实施方案中,化合物由以下结构表示:

[0381] 

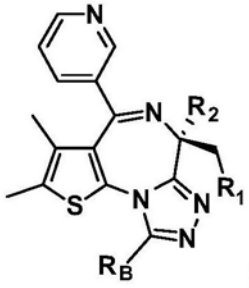
[0382] 或其药学上可接受的盐。

[0383] 在第十八实施方案中,化合物由结构式(VI)、(VII)或(VIII)表示:

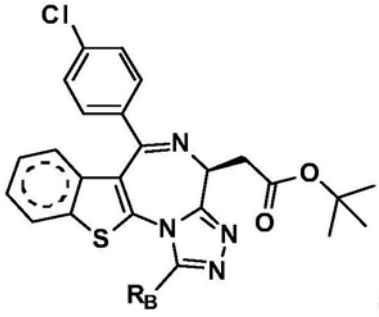


(VI)、

[0384]



(VII)、

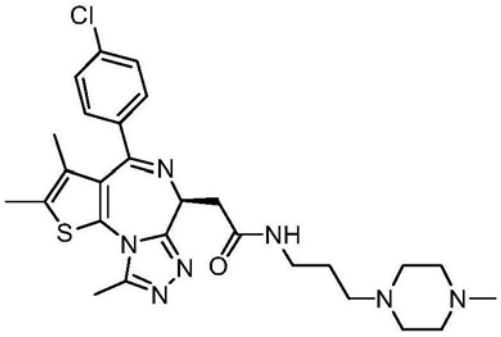


(VIII);

[0385] 其中R、R_1和R_2及R_B具有与式(I)中相同的含义;Y是O、N、S或CR_3,其中R_3具有与式(I)中相同的含义;n是0或1;且式(VIII)中的虚线圆圈表示芳族或非芳族环;或其药学上可接受的盐。

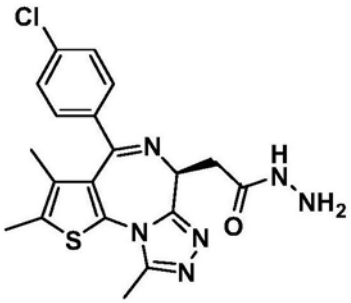
[0386] 在第十九实施方案中,化合物由以下结构表示:

[0387]



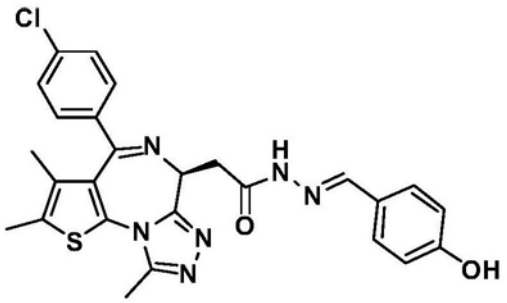
[0388] 或其药学上可接受的盐。

[0389] 在某些实施方案中,用于本发明方法的化合物是选自由以下组成的组的化合物:



(3) 和

[0390]



(4) ;

[0391] 或其药学上可接受的盐。

[0392] 示例BET抑制剂-结构式(IX)至(XI)

[0393] 在另一示例实施方案中,用于本发明方法的布罗莫结构域抑制剂以及其制备方法描述于2014年10月27日提交的第62/068,983号美国临时申请中。此申请的教导内容以引用的方式整体并入本文。

[0394] 适用于本发明方法的示例化合物包括由结构式(IX)、(X)和(XI)表示的那些或其药学上可接受的盐。在以下段落中提供式(IX-XI)或其对映异构体、非对映异构体或药学上可接受的盐中的变量以及本文描述的各实施方案的值和替代值。要理解的是,本发明涵盖本文定义的取代基变量(即,R_1、R_2、R_{20}等)的所有组合。

[0395] A选自由(C_1-C_6)烷基、(C_2-C_6)烯基、(C_2-C_6)炔基、(C_3-C_{12})环烷基和(C_5-C_7)杂环烷基组成的组,其中部分A任选被1至个R_2基团取代。

[0396] 或者,A选自由(C_1-C_6)烷基、(C_3-C_{12})环烷基和(C_5-C_7)杂环烷基组成的组,其中部分A任选被1至4个R_2基团取代。在另一种替代方案中,A选自由(C_1-C_6)烷基、(C_3-C_{12})环烷基和(C_5-C_7)杂环烷基组成的组。进一步地,A是乙基或环己基。

[0397] R_1选自由-OH、卤素、-CN、(C_1-C_4)烷氧基、-C(O)(C_1-C_4)烷基、-C(O)O(C_1-C_4)烷基、-OC(O)(C_1-C_4烷基)、-C(O)NR_3R_4、-NR_5C(=O)R_6、(C_1-C_6)烷基、(C_2-C_6)烯基、(C_3-C_{12})环烷基和(C_5-C_7)杂环烷基组成的组。

[0398] 或者,R_1选自由-OH、卤素、(C_1-C_4)烷氧基、-C(O)(C_1-C_4)烷基、-C(O)O(C_1-C_4)烷基、-OC(O)(C_1-C_4烷基)和(C_1-C_6)烷基组成的组。进一步地,R_1选自由-OH、卤素、(C_1-C_4)烷氧基和(C_1-C_6)烷基组成的组。或者,R_1选自由卤素和(C_1-C_6)烷基组成的组。在另一种替代方案中,R_1选自由-F、-Cl、-Br或-I组成的组。

[0399] R_2是(C_1-C_6)烷基、(C_2-C_6)烯基、卤代(C_1-C_6)烷氧基、卤代(C_1-C_6)烷基、羟基(C_1-C_6)

烷基、(C1-C6)烷氧基(C1-C6)烷基、(C3-C12)环烷基、-(C1-C6)亚烷基-(C3-C12)环烷基、(C3-C12)杂环烷基、-(C1-C6)亚烷基-(C3-C12)杂环烷基、(C1-C6)烷氧基、-C(O)(C1-C6烷基)、-C(O)O(C1-C6烷基)、-OC(O)(C1-C6烷基)、-C(O)NR7R8、-NR9C(=O)R10、-NR11R12、卤素、氧代或-OH。

[0400] 或者,R2是(C1-C6)烷基、卤代(C1-C6)烷氧基、卤代(C1-C6)烷基、羟基(C1-C6)烷基、(C1-C6)烷氧基(C1-C6)烷基、(C1-C6)烷氧基、-C(O)(C1-C6烷基)、-C(O)O(C1-C6烷基)、-OC(O)(C1-C6烷基)、卤素、氧代或-OH。进一步地,R2是(C1-C6)烷基、卤代(C1-C6)烷氧基、卤代(C1-C6)烷基、羟基(C1-C6)烷基、(C1-C6)烷氧基(C1-C6)烷基、(C1-C6)烷氧基、卤素、氧代或-OH。

[0401] R3是H或(C1-C4)烷基。或者,R3是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0402] R4是H或(C1-C4)烷基。或者,R4是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0403] R5是H或(C1-C4)烷基。或者,R5是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0404] R6是H或(C1-C4)烷基。或者,R6是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0405] R7是H或(C1-C4)烷基。或者,R7是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0406] R8是H或(C1-C4)烷基。或者,R8是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0407] R9是H或(C1-C4)烷基。或者,R9是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0408] R10是H或(C1-C4)烷基。或者,R10是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0409] R11是H或(C1-C4)烷基。或者,R11是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0410] R12是H或(C1-C4)烷基。或者,R12是H、甲基、乙基、丙基、异丙基、丁基、异丁基或叔丁基。

[0411] R20是-H、-OH、(C1-C3)烷基、(C3-C12)环烷基或(C5-C7)杂环烷基。或者,R20是H或(C1-C3)烷基。进一步地,R20是H、甲基、乙基、丙基或异丙基。

[0412] R30是-H、-OH、(C1-C3)烷基、(C3-C12)环烷基或(C5-C7)杂环烷基。或者,R30是H或(C1-C3)烷基。进一步地,R30是H、甲基、乙基、丙基或异丙基。

[0413] 每次出现的R40独立地为-H、-OH、(C1-C3)烷基、(C3-C12)环烷基或(C5-C7)杂环烷基。R40是H或(C1-C3)烷基。进一步地,R40是H、甲基、乙基、丙基或异丙基。

[0414] m是0、1、2、3或4。或者,m是0、1或2。进一步地,m是1或2。或者,m是1。

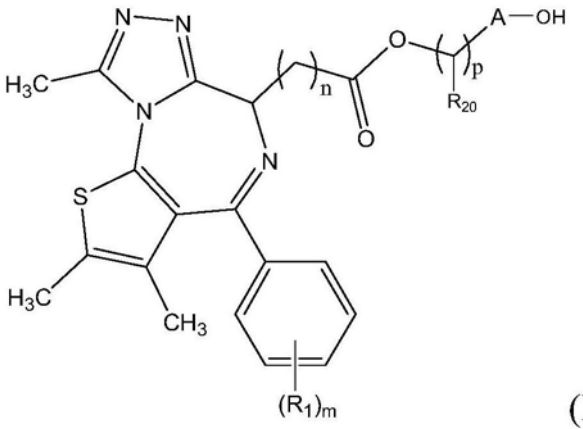
[0415] n是0、1、2、3或4。或者,n是0、1或2。进一步地,n是0或1。或者,n是1。

[0416] p是0、1、2、3或4。或者,p是0、1或2。进一步地,p是0或1。

[0417] q是0、1、2、3或4。或者,q是0、1或2。进一步地,q是0或1。

[0418] 接着描述本发明的示例实施方案。

[0419] 本发明的第一实施方案涉及结构式(IX)的化合物:

[0420] 

(IX)

[0421] 或其药学上可接受的盐，其中：

[0422] A选自由(C1-C6)烷基、(C2-C6)烯基、(C2-C6)炔基、(C3-C12)环烷基和(C5-C7)杂环烷基组成的组，其中部分A任选被1至4个R2基团取代；

[0423] 每次出现的R20独立地为-H、-OH、(C1-C3)烷基、(C3-C12)环烷基或(C5-C7)杂环烷基；

[0424] 每次出现的R1独立地选自由-OH、卤素、-CN、(C1-C4)烷氧基、-C(O)(C1-C4)烷基、-C(O)O(C1-C4)烷基、-OC(O)(C1-C4烷基)、-C(O)NR3R4、-NR5C(=O)R6、(C1-C6)烷基、(C2-C6)烯基、(C3-C12)环烷基和(C5-C7)杂环烷基组成的组；

[0425] 每次出现的R2独立地为(C1-C6)烷基、(C2-C6)烯基、卤代(C1-C6)烷氧基、卤代(C1-C6)烷基、羟基(C1-C6)烷基、(C1-C6)烷氧基(C1-C6)烷基、(C3-C12)环烷基、-(C1-C6)亚烷基-(C3-C12)环烷基、(C3-C12)杂环烷基、-(C1-C6)亚烷基-(C3-C12)杂环烷基、(C1-C6)烷氧基、-C(O)(C1-C6烷基)、-C(O)O(C1-C6烷基)、-OC(O)(C1-C6烷基)、-C(O)NR7R8、-NR9C(=O)R10、-NR11R12、卤素、氧代或-OH；

[0426] R3、R4、R5、R6、R7、R8、R9、R10、R11和R12各自独立地为H或(C1-C4)烷基；且

[0427] 每个m、n和p独立地为0、1、2、3或4。

[0428] 在第一实施方案的第一方面中：A是(C1-C6)烷基、(C3-C12)环烷基或(C5-C7)杂环烷基。

[0429] 在第一实施方案的第二方面中：A是乙基或环己基。

[0430] 在第一实施方案的第三方面中：R2是-OH或(C1-C6)烷基。在第三方面的特定实施例中，其余的变量如第一实施方案的第一或第二方面中所陈述。

[0431] 在第一实施方案的第四方面中：R2是-OH或甲基。在第三方面的特定实施例中，其余的变量如第一实施方案的第一或第二方面中所陈述。

[0432] 在第一实施方案的第五方面中：R1是-F、-Cl、-Br或-I。在第五方面的特定实施例中，其余的变量如第一实施方案的第一、第二、第三或第四方面或第三或第四方面的任何特定实施例中所述。

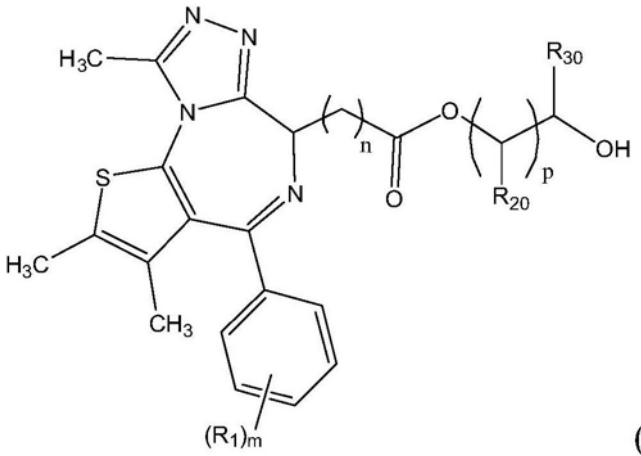
[0433] 在第一实施方案的第六方面中：R20是H或(C1-C3)烷基。在第六方面的特定实施例中，其余的变量如第一实施方案的第一、第二、第三、第四或第五方面或第三、第四或第五方面的任何特定实施例中所述。

[0434] 在第一实施方案的第七方面中：p是0。在第七方面的特定实施例中，其余的变量如第一实施方案的第一、第二、第三、第四、第五或第六方面或第三、第四或第五或第六方面的任何特定实施例中所述。

[0435] 在第一实施方案的第八方面中:m是1。在第八方面的特定实施例中,其余的变量如第一实施方案的第一、第二、第三、第四、第五、第六或第七方面或第三、第四、第五、第六或第七方面的任何特定实施例中所述。

[0436] 在第一实施方案的第九方面中:n是1。在第九方面的特定实施例中,其余的变量如第一实施方案的第一、第二、第三、第四、第五、第六、第七或第八方面或第三、第四、第五、第六、第七或第八方面的任何特定实施例中所述。

[0437] 在第二实施方案中,本发明涉及结构式(X)的化合物:

[0438] 

(X)

[0439] 或其药学上可接受的盐,其中:

[0440] 每次出现的R_1独立地选自由-OH、卤素、-CN、(C_1-C_4)烷氧基、-C(O)(C_1-C_4)烷基、-C(O)O(C_1-C_4)烷基、-OC(O)$(C_1-C_4$烷基)、-C(O)NR_3R_4、-NR_5C(=O)R_6、(C_1-C_6)烷基、(C_2-C_6)烯基、(C_3-C_{12})环烷基和(C_5-C_7)杂环烷基组成的组;

[0441] R_3、R_4、R_5和R_6各自独立地为H或(C_1-C_4)烷基

[0442] 每次出现的R_{20}独立地为-H、-OH、(C_1-C_3)烷基、(C_3-C_{12})环烷基或(C_5-C_7)杂环烷基;

[0443] 每次出现的R_{30}独立地为-H、-OH、(C_1-C_3)烷基、(C_3-C_{12})环烷基或(C_5-C_7)杂环烷基;且

[0444] 每个m、n和p独立地为0、1、2、3或4。

[0445] 在第二实施方案的第一方面中:R_1是-F、-Cl、-Br或-I。

[0446] 在第二实施方案的第二方面中:R_{20}是H或(C_1-C_3)烷基。在第二方面的特定实施例中,其余的变量如第二实施方案的第一方面中所陈述。

[0447] 在第二实施方案的第三方面中:R_{30}是H或(C_1-C_3)烷基。在第三方面的特定实施例中,其余的变量如第二实施方案的第一或第二方面或第二方面的任何特定实施例中所陈述。

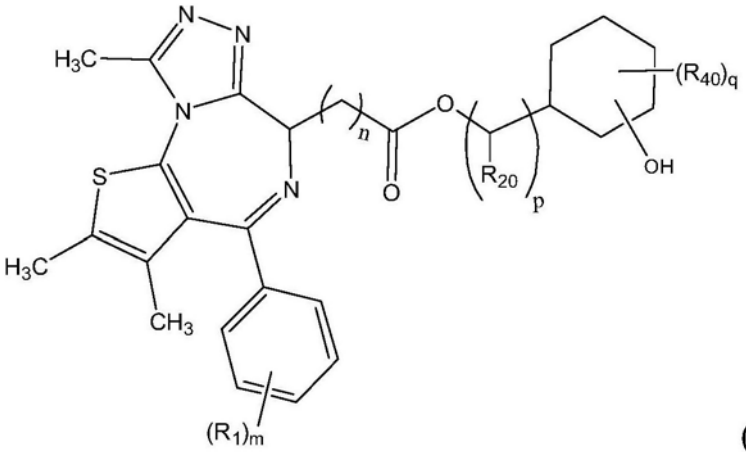
[0448] 在第二实施方案的第四方面中:p是1。在第四方面的特定实施例中,其余的变量如第二实施方案的第一、第二或第三方面或第二或第三方面的任何特定实施例中所陈述。

[0449] 在第二实施方案的第五方面中:m是1。在第五方面的特定实施例中,其余的变量如第二实施方案的第一、第二、第三或第四方面或第二、第三或第四方面的任何特定实施例中所陈述。

[0450] 在第二实施方案的第六方面中:n是1。在第六方面的特定实施例中,其余的变量如第二实施方案的第一、第二、第三、第四或第五方面或第二、第三、第四或第五方面的任何特

定实施例中所陈述。

[0451] 在第三实施方案中，本发明涉及结构式(XI)的化合物：

[0452] 

(XI)

[0453] 或其药学上可接受的盐，其中：

[0454] 每次出现的R_1独立地选自由-OH、卤素、-CN、(C_1-C_4)烷氧基、-C(O)(C_1-C_4)烷基、-C(O)O(C_1-C_4)烷基、-OC(O)$(C_1-C_4$烷基)、-C(O)NR_3R_4、$-NR_5C(=O)R_6$、(C_1-C_6)烷基、(C_2-C_6)烯基、(C_3-C_{12})环烷基和(C_5-C_7)杂环烷基组成的组；

[0455] R_3、R_4、R_5和R_6各自独立地为H或(C_1-C_4)烷基

[0456] 每次出现的R_{20}独立地为-H、-OH、(C_1-C_3)烷基、(C_3-C_{12})环烷基或(C_5-C_7)杂环烷基；

[0457] 每次出现的R_{40}独立地为-H、-OH、(C_1-C_3)烷基、(C_3-C_{12})环烷基或(C_5-C_7)杂环烷基；且

[0458] 每个q、m、n和p独立地为0、1、2、3或4。

[0459] 在第三实施方案的一方面中：R_1是-F、-Cl、-Br或-I。

[0460] 在第三实施方案的第二方面中：R_{20}是H或(C_1-C_3)烷基。在第二方面的特定实施例中，其余的变量如第三实施方案的第一方面中所陈述。

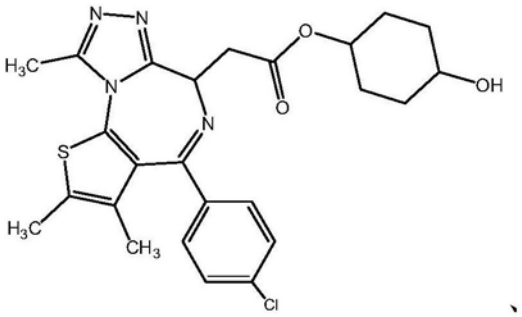
[0461] 在第三实施方案的第三方面中：R_{40}是H或(C_1-C_3)烷基。在第三方面的特定实施例中，其余的变量如第三实施方案的第一或第二方面或第二方面的任何特定实施例中所陈述。

[0462] 在第三实施方案的第四方面中：p是0。在第四方面的特定实施例中，其余的变量如第三实施方案的第一、第二或第三方面或第二或第三方面的任何特定实施例中所陈述。

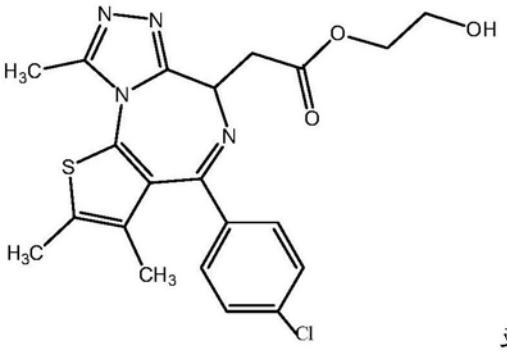
[0463] 在第三实施方案的第五方面中：m是1。在第五方面的特定实施例中，其余的变量如第三实施方案的第一、第二、第三或第四方面或第二、第三或第四方面的任何特定实施例中所陈述。

[0464] 在第三实施方案的第六方面中：n是1。在第六方面的特定实施例中，其余的变量如第三实施方案的第一、第二、第三、第四或第五方面或第二、第三、第四或第五方面的任何特定实施例中所陈述。

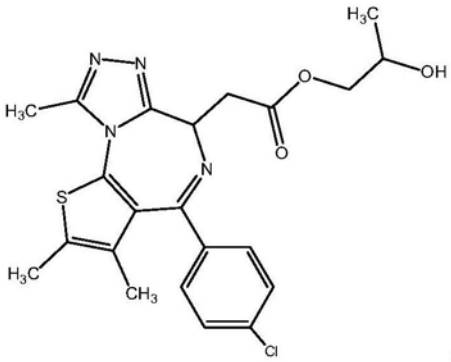
[0465] 另一方面，本发明提供由下式中的任一者表示的化合物：



[0466]

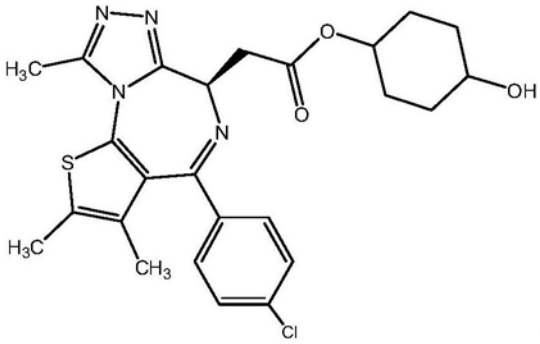


或



[0467] 或其药学上可接受的盐。

[0468] 另一方面,本发明提供由下式中的任一者表示的化合物:



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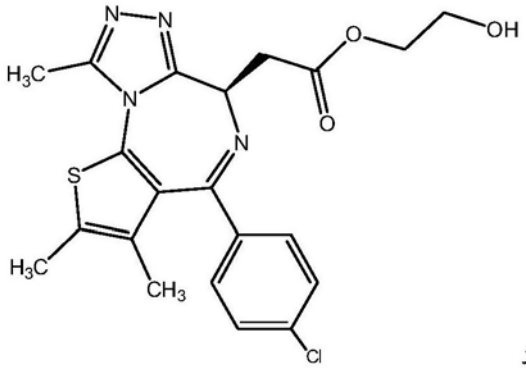
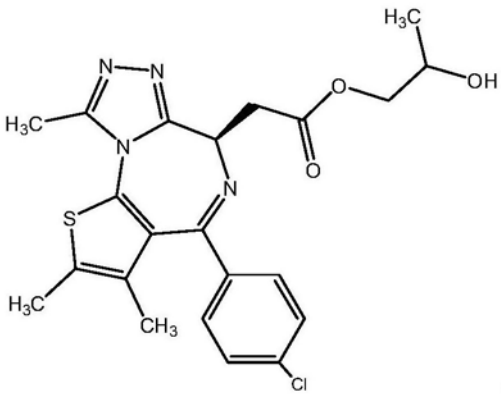
[0469]



或



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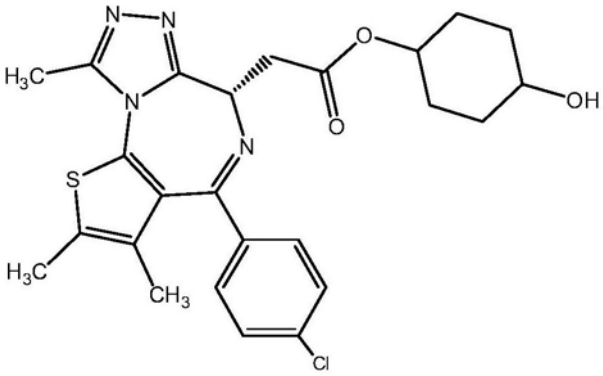
[0470] 或其药学上可接受的盐。

[0471] 另一方面，本发明提供由下式中的任一者表示的化合物：

[0472]



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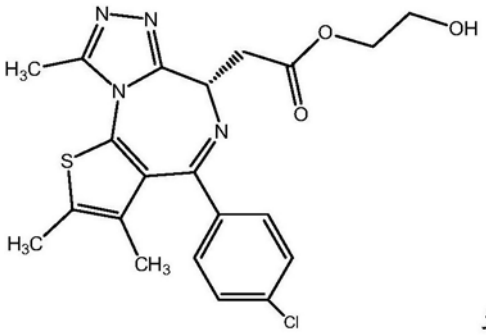
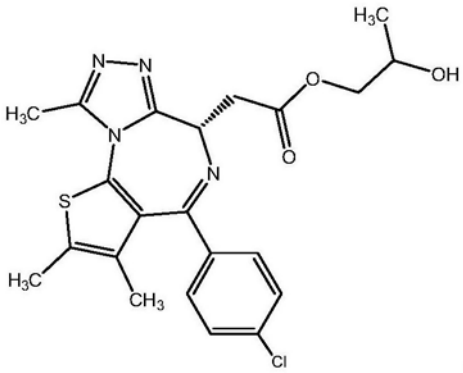


或

[0473]



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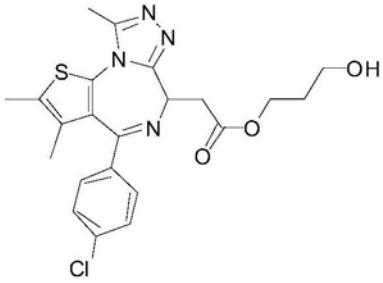
[0474] 或其药学上可接受的盐。

[0475] 另一方面，本发明提供由下式中的任一者表示的化合物：



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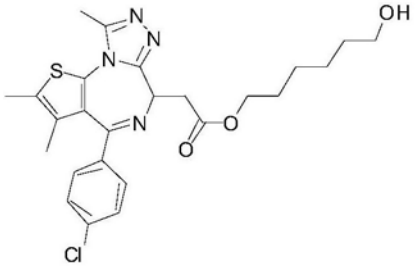
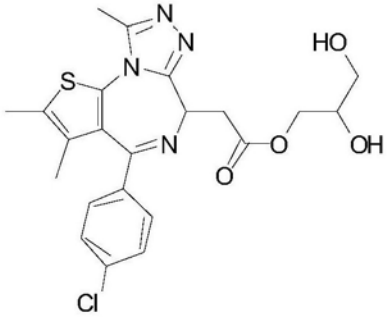
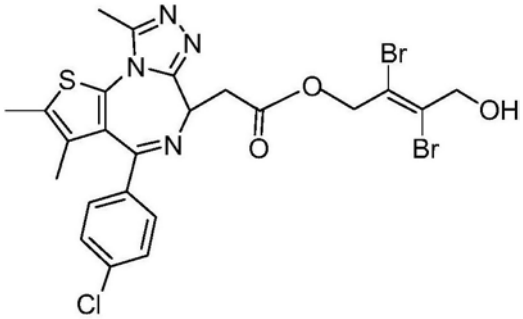
[0476]





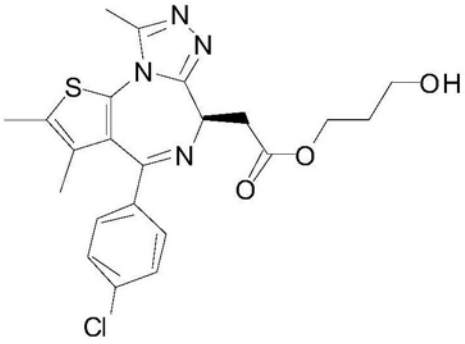
或

[0477]

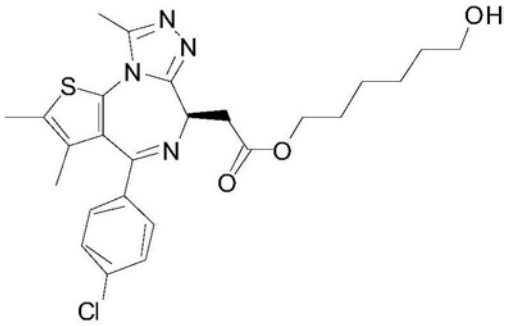


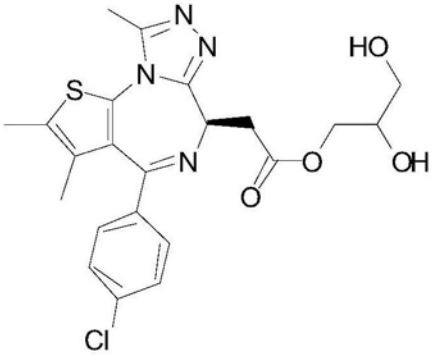
[0478] 或其药学上可接受的盐。

[0479] 另一方面，本发明提供由下式中的任一者表示的化合物：

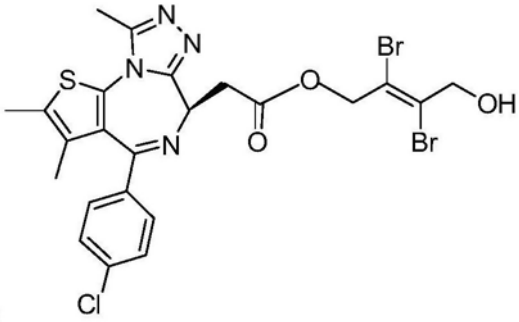


[0480]





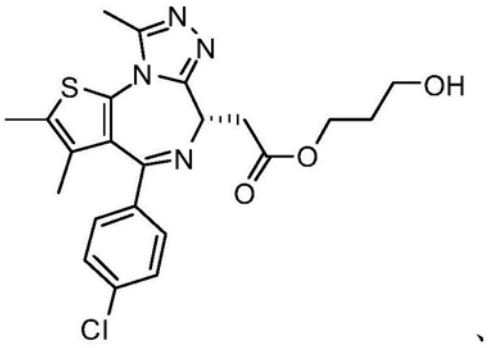
[0481]



或

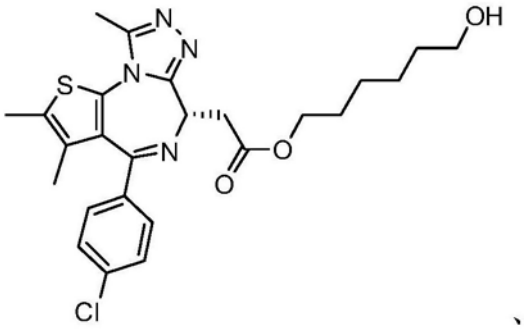
[0482] 或其药学上可接受的盐。

[0483] 另一方面，本发明提供由下式中的任一者表示的化合物：



、

[0484]



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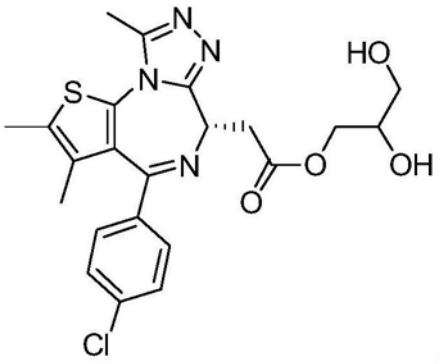
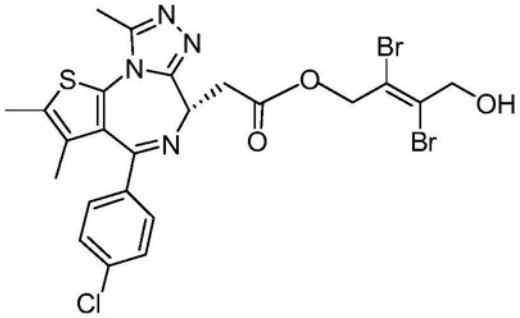


或

[0485]



[0486] 或其药学上可接受的盐。

[0487] 适用于本文公开的方法的BET抑制剂的进一步实例包括以下文献中所公开的化合物和组合物:WO 2011/054843(Glaxosmithkline)、WO 2009/084693(Mitsubishi Tanabe Pharma Corporation)、WO2012/075383(Constellation Pharmaceuticals,Inc.)、WO 2011/054553(Glaxosmithkline)、WO 2011/054841(Glaxosmithkline)、WO2011/054844(Glaxosmithkline)、WO 2011/054845(Glaxosmithkline)、WO 2011/054846(Glaxosmithkline)、WO 2011/054848(Glaxosmithkline)、WO 2011/161031(Glaxosmithkline)、US2015/0148337(Constellation Pharmaceuticals,Inc.)、US2014/

0371206(Constellation Pharmaceuticals,Inc.)、US2014/0296243(Constellation Pharmaceuticals,Inc.)、US2014/0135316(Constellation Pharmaceuticals,Inc.)、US2014/0005169(Constellation Pharmaceuticals,Inc.)、US2012/0157428(Constellation Pharmaceuticals,Inc.)和第8,796,261号美国专利(Constellation Pharmaceuticals,Inc.)。这些文献中的每一者的相关教导内容以引用的方式并入本文。

[0488] 施用方式

[0489] 可将用于本发明的方法或组合物的布罗莫结构域抑制剂(例如,TEN-010)配制成用于胃肠外、口服、透皮、舌下、经颊、经直肠、鼻内、支气管内或肺内施用。

[0490] 对于肠胃外施用,可将用于本发明的方法或组合物的化合物配制成用于注射或输注,例如静脉内、肌内或皮下注射或输注,或者用于以单次剂量(bolus dose)和/或输注施用(例如,连续输注)。可使用在油性或水性媒介物中的混悬剂、溶液剂或乳剂,任选含有其它配制剂,如助悬剂、稳定剂和/或分散剂。

[0491] 对于口服施用,布罗莫结构域抑制剂的形式可以是通过常规方法制备的片剂或胶囊,采用了药学上可接受的赋形剂,如粘结剂(例如,聚乙烯吡咯烷酮或羟丙基甲基纤维素);填充剂(例如,乳糖、微晶纤维素或磷酸钙);润滑剂(例如,硬脂酸镁、滑石或二氧化硅);崩解物(例如,淀粉乙醇酸钠);或润湿剂(例如,十二烷基硫酸钠)。如果需要的话,可采用合适的方法对片剂进行包衣。用于口服施用的液体制剂可呈溶液剂、糖浆剂或混悬剂的形式。可通过常规方法制备液体制剂,采用药学上可接受的添加剂,如助悬剂(例如,山梨醇糖浆、甲基纤维素或氢化食用脂肪);乳化剂(例如,卵磷脂或阿拉伯树胶);非水性媒介物(例如,杏仁油、油性酯或乙醇);和防腐剂(例如,对羟基苯甲酸甲酯或丙酯或山梨酸)。

[0492] 对于经颊施用,用于本发明的方法或组合物的化合物可呈按常规方式配制的片剂或锭剂的形式。

[0493] 对于经直肠施用,用于本发明的方法或组合物的化合物可呈栓剂的形式。

[0494] 对于舌下施用,可按常规方式配制片剂。

[0495] 对于鼻内、支气管内或肺内施用,可使用常规制剂。

[0496] 进一步地,可将用于本发明的方法或组合物的化合物配制为持续释放制剂。例如,可用对活性剂化合物提供持续和/或受控释放特性的合适聚合物或疏水物质配制化合物。如此,可例如通过注射以微粒的形式或通过植入以薄饼或盘片的形式施用供本发明的方法中使用的化合物。配制控释药物制剂的各种方法是本领域中已知的。

[0497] 可用于实施本文所述方法的本文公开的布罗莫结构域抑制剂或其药学上可接受的盐的施用可以是连续的按小时、每日四次、每日三次、每日两次、每日一次、每隔一天一次、每周两次、每周一次、每两周一次、每月一次或每两个月或更久一次或按某种其它的间歇给药方案进行。在特定的实施方案中,如本文所述按周期施用布罗莫结构域抑制剂。

[0498] 本发明的布罗莫结构域抑制剂或其药用盐的施用实例包括外周施用。外周施用的实例包括口服、皮下、腹膜内、肌内、静脉内、经直肠、透皮或鼻内施用形式。

[0499] 如本文所用,外周施用包括本文公开的布罗莫结构域抑制剂或包含布罗莫结构域抑制剂的组合物的所有施用形式,但不包括颅内施用。外周施用的实例包括但不限于口服、肠胃外(例如,肌内、腹膜内、静脉内或皮下注射、延长释放、缓释植入物、贮库等)、经鼻、经阴道、经直肠、舌下或局部途径的施用,其包括透皮贴剂应用等。

[0500] 药物组合物

[0501] 可将本文公开的布罗莫结构域抑制剂掺入到适合施用的药物组合物当中。这类组合物通常包含布罗莫结构域抑制剂(例如,TEN-010)和药学上可接受的载体。如本文所用,表述“药学上可接受的载体”旨在包括与药物施用相容的任何及所有溶剂、分散介质、包衣、抗细菌和抗真菌剂、等渗和吸收延迟剂等。用于药物活性物质的这类介质和试剂的使用是本领域中熟知的。除了任何常规介质或试剂与活性化合物不相容的情况之外,其在组合物中的用途是预期的。

[0502] 本发明的药物组合物被配制成与其预期的施用途径相容。如本文所述,施用途径的实例包括肠胃外例如静脉内、皮内、皮下、口服(例如,吸入)、透皮(局部)、经粘膜和经直肠施用。用于胃肠外、皮内或皮下施加的溶液剂或混悬剂可包括以下组分:无菌稀释剂,如注射用水、盐水溶液、固定油、聚乙二醇、甘油、丙二醇或其它合成溶剂;抗细菌剂,如苄醇或对羟基苯甲酸甲酯;抗氧化剂,如抗坏血酸或亚硫酸氢钠;螯合剂,如乙二胺四乙酸;缓冲剂,如乙酸盐、柠檬酸盐或磷酸盐以及用于调节张力的试剂,如氯化钠或右旋糖。可用诸如盐酸或氢氧化钠的酸或碱调节pH。可将肠胃外制剂封闭在由玻璃或塑料制成的安瓿、一次性注射器或多剂量小瓶中。

[0503] 适合可注射用途的药物组合物包括无菌水溶液剂(水溶性的情况下)或分散剂以及用于临时制备无菌可注射溶液剂或分散剂的无菌粉末。对于静脉内施用,合适的载体包括生理盐水、抑菌水、Cremophor EL(TM)(BASF,Parsippany,N.J.)或磷酸盐缓冲盐水(PBS)。在所有情况下,组合物必须是无菌的,并且应该是达到容易注射的程度的流体。其在制造和储存的条件下必须是稳定的,并且必须在防止诸如细菌和真菌的微生物的污染作用下保存。载体可以是含有例如水、乙醇、多元醇(例如,甘油、丙二醇和液体聚乙二醇等)的溶剂或分散介质及其合适的混合物。可例如通过使用诸如卵磷脂的包衣、在分散剂的情况下通过维持所需的粒度和通过使用表面活性剂来维持适当的流动性。可通过各种抗细菌和抗真菌剂来防止微生物的作用,例如通过对羟基苯甲酸酯、氯丁醇、苯酚、抗坏血酸、硫柳汞等。在许多情况下,优选在组合物中包括等渗剂,例如糖、诸如甘露糖醇、山梨糖醇的多元醇、氯化钠。可通过在组合物中包括例如单硬脂酸铝和明胶的延迟吸收的试剂来使可注射组合物的吸收延长。

[0504] 可通过根据需要将适当溶剂中的所需量的活性化合物(例如,TEN-010)与以上列举的成分中的一种或组合掺混、接着过滤灭菌来制备无菌可注射溶液剂。一般地,通过将活性化合物掺入到含有基本分散介质的无菌媒介物和来自以上列举的那些的所需其它成分当中来制备分散剂。在用于制备无菌可注射溶液剂的无菌粉末的情况下,制备的优选方法是真空干燥和冷冻干燥,其产生活性成分的粉末加上来自其先前无菌过滤的溶液剂的任何附加的所需成分。

[0505] 口服组合物通常包括惰性稀释剂或可食用载体。可将它们封闭在明胶胶囊中或压缩成片剂。为了口服治疗施用的目的,可将布罗莫结构域抑制剂与赋形剂掺混,并以片剂、糖锭或胶囊的形式使用。也可使用用作漱口水的流体载体制备口服组合物,其中流体载体中的化合物被口服施加并含漱和吐出或吞咽。可包括药学上相容的粘结剂和/或佐剂物质作为组合物的一部分。片剂、丸剂、胶囊、糖锭等可含有任何以下成分或类似性质的化合物:粘结剂,如微晶纤维素、黄蓍胶或明胶;赋形剂,如淀粉或乳糖,崩解剂,如藻酸、Primogel或

玉米淀粉;润滑剂,如硬脂酸镁或Sterotes;助流剂,如胶体二氧化硅;甜味剂,如蔗糖或糖精;或调味剂,如薄荷、水杨酸甲酯或橙香精(orange flavoring)。

[0506] 对于通过吸入施用,由含有例如诸如二氧化碳的气体的合适推进剂的加压容器或分配器或者喷雾器以气溶胶喷雾的形式递送化合物。

[0507] 全身施用也可通过经粘膜或透皮方式进行。对于经粘膜或透皮施用,在制剂中使用适于要透过的屏障的渗透剂。这类渗透剂通常是本领域中已知的,并且包括例如对于经粘膜施用的洗涤剂、胆汁盐和夫西地酸衍生物。可通过使用鼻用喷雾剂或栓剂来实现经粘膜施用。

[0508] 对于透皮施用,将活性化合物配制成本领域中通常已知的油膏、药膏、凝胶或乳膏。

[0509] 也可按用于直肠递送的栓剂(例如,具有诸如可可脂及其它甘油酯的常规栓剂基质)或保留灌肠剂的形式制备化合物。

[0510] 在一个实施方案中,将布罗莫结构域抑制剂制备成与将防范化合物自身体快速消除的载体一起,如控释制剂,其包括植入物和微胶囊化递送系统。可使用可生物降解的生物相容性聚合物,如乙烯乙酸乙烯酯、聚酸酐、聚乙醇酸、胶原、聚原酸酯和聚乳酸。制备这类制剂的方法对于本领域技术人员而言是显而易见的。所述物质也可从Alza Corporation和Nova Pharmaceuticals,Inc商购获得。脂质体混悬剂(包括用针对病毒抗原的单克隆抗体靶向感染细胞的脂质体)也可用作药学上可接受的载体。可根据例如描述于第4,522,811号美国专利的本领域技术人员已知的方法制备这些。

[0511] 特别有利的是以剂量单位形式配制口服或肠胃外组合物以利于施用和剂量的均匀性。如本文所用的剂量单位形式是指适合作为单一剂量用于待治疗的受试者的物理上离散的单位;每个单位含有经计算产生与所需药物载体相关联的所需治疗效果的预定量的活性化合物。本发明的剂量单位形式的规格由以下因素决定并直接取决于以下因素:活性化合物的特质和要达到的特定治疗效果以及配混用于治疗个体的这种活性化合物的领域中固有的局限性。

[0512] 布罗莫结构域抑制剂每次施用的合适剂量包括约或大于约250ng/kg、约500ng/kg、约750ng/kg、约1ug/kg、约10ug/kg、约20ug/kg、约30ug/kg、约40ug/kg、约50ug/kg、约60ug/kg、约70ug/kg、约80ug/kg、约90ug/kg、约0.1mg/kg、约0.15mg/kg、约0.2mg/kg、约0.25mg/kg、约0.3mg/kg、约0.35mg/kg、约0.4mg/kg、约0.45mg/kg、约0.5mg/kg、约0.55mg/kg、约0.6mg/kg、约0.65mg/kg、约0.7mg/kg、约0.75mg/kg、约0.8mg/kg、约0.85mg/kg、约0.9mg/kg、约0.95mg/kg、约1.0mg/kg、约1.1mg/kg、约1.2mg/kg、约1.3mg/kg、约1.4mg/kg、约1.5mg/kg、约1.6mg/kg、约1.7mg/kg、约1.8mg/kg、约1.9mg/kg或约2.0mg/kg的剂量。可经熟练的从业人员认为适当的时间段施用每个合适的剂量。在一个实施例中,可按约0.45mg/kg或约0.65mg/kg以单次注射施用TEN-010的每个合适剂量。在其它实施方案中,可经熟练的专业人员认为适当的时间段施用(例如,输注)每个合适的剂量。

[0513] 组合疗法

[0514] 本文公开的布罗莫结构域抑制剂(例如,TEN-010)可用于与例如化学治疗剂或HDAC抑制剂的第二量的抗癌剂(本文中有时称为“第二种药剂”)组合来治疗NMC。这种组合施用可借助于包括布罗莫结构域抑制剂和第二药剂的单一剂型,这种单一剂型包括片剂、

胶囊、喷雾剂、吸入粉末、可注射液体等。组合施用可包含除单一剂型以外进一步的第二种药剂(例如,化学治疗剂或HDAC抑制剂)。或者,组合施用可借助于施用两种不同剂型,其中一种剂型含有布罗莫结构域抑制剂,且另一种剂型包括第二量的抗癌剂。在这种情况下,剂型可以是相同的或不同的。不希望限制组合疗法,以下例示可用的某些组合疗法。要理解的是,在本文所述的方法中可使用除所需第二量的抗癌剂以外的附加抗癌剂。

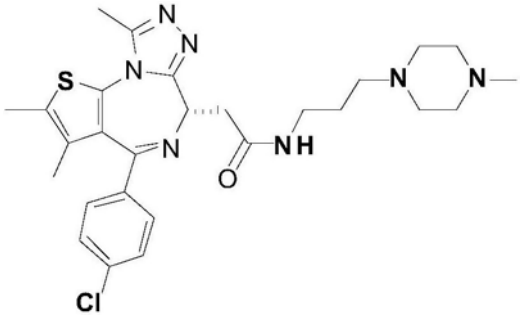
[0515] 可在布罗莫结构域抑制剂的施用之前、同时或之后施用第二量的抗癌剂(本文中有时称为第二种药剂)。因此,布罗莫结构域抑制剂和第二种药剂可在单一制剂中被一起施用,或者可在分开的制剂中被施用,例如同时地或顺序地施用或两种方式兼而有之。例如,如果在分开的组合物中顺序地施用布罗莫结构域抑制剂和第二种药剂,则可在抗癌剂之前或之后施用布罗莫结构域抑制剂。施用布罗莫结构域抑制剂与第二量的抗癌剂之间的持续时间将取决于抗癌剂的性质。在某些实施方案中,布罗莫结构域抑制剂可紧先于或后于化学治疗剂,或者在熟练的从业者认为适当的一段持续时间之后。

[0516] 此外,布罗莫结构域抑制剂和第二量的抗癌剂可以或可以不按类似的给药方案施用。例如,布罗莫结构域抑制剂和抗癌剂可具有不同的半衰期和/或按不同的时间尺度起作用,使得以比抗癌剂更高的频度或反之施用布罗莫结构域抑制剂。例如,可将布罗莫结构域抑制剂和抗癌剂在一天一起施用(例如,按单剂量或顺序地),接着仅施用布罗莫结构域抑制剂持续设定的后续天数。可根据每种药物的安全性和药效学来适当地确定施用治疗剂之间的天数。可急性或慢性地施用布罗莫结构域抑制剂或抗癌剂。

[0517] 本文已描述了每次施用布罗莫结构域抑制剂的合适剂量。第二活性剂(例如,化学治疗剂或HDAC抑制剂)的有效量将取决于患者的年龄、性别和体重、患者的当前医疗状况以及所治疗的NMC的性质。本领域技术人员将能够根据这些及其它因素确定适当的剂量。熟练的医疗专业人员可适当地基于见于标签的推荐剂量来确定组合疗法中第二量的抗癌剂的每次施用的合适剂量。

[0518] 本发明的实施例

[0519] 化合物TEN-010:以下实施例中使用和本文公开的化合物TEN-010具有以下结构式:

[0520] 

[0521] NMC患者中的CD11b表达水平指示疾病活动性

[0522] 本研究被设计用于评估BET布罗莫结构域抑制剂TEN-010是否可能具有在实体肿瘤的肿瘤学适应症中有益的潜力。如本文所证实,在单核细胞的表面上表达的CD11b的水平用作TEN-010NMC疗法中的反应性的标志。

[0523] 本文公开的临床研究是按照良好临床规范(Good Clinical Practice,GCP)进行的,这是赫尔辛基宣言(Declaration of Helsinki)及其它适用性法规要求中规定的伦理

原则。

[0524] 材料和方法

[0525] 研究群体

[0526] 18岁以上患有需要治疗的组织学确诊的晚期实体肿瘤与进行性疾病的患者被纳入研究。特别地，患有组织学确诊的晚期实体恶性肿瘤与进行性疾病NMC或晚期侵袭性弥漫性大B细胞淋巴瘤(DLBCL)的患者被纳入研究。患有血液恶性肿瘤的患者未被纳入研究。

[0527] 施用TEN-010

[0528] 将TEN-010配制为用于皮下(SC)施用的无菌保存的等渗溶液。在28天的治疗周期中，在每个周期的第1至21天(“上药段”)不间断地施用0.45mg/kg的剂量，接着是7天无剂量间隔(“离药段”)。在包括双侧上臂和大腿以及中下腹和臀部在内的若干部位当中轮换注射。

[0529] 样品采集和CD11b表达水平的测定

[0530] 将指定时间点(例如，参见图1)的全血样本收集在肝素钠真空采血管(vacutainer)中。简言之，将每个供体的两个12x75mm试管用样本ID和适当的混杂物(cocktail)名称(见下表2)标记。将100μl肝素钠抗凝全血吸取到试管当中。将适当滴定体积的抗体混杂物吸取到相应标记的管当中。将适当滴定量的CD14 PerCP添加到所有管中以鉴定CD14阳性单核细胞。将管涡旋并使之在黑暗中于室温下温育30分钟。通过向每个管中添加4ml基于氯化铵的全血裂解试剂来裂解红细胞。将管封盖并倒置以充分混合，之后才在室温下于黑暗中温育5分钟。温育后，将管以400RCF离心5分钟，倾析上清液并将管的架子倾斜以分散细胞团。将细胞用2ml含1％BSA的PBS洗涤并离心。为检测生物素缀合的CD45RO抗体，向每个管中添加适当滴定量的SA-BV605(与亮紫(BV)605缀合的链霉亲和素(SA))并将管涡旋。在室温下于黑暗中进行20分钟温育后，将细胞用2ml含1％BSA的PBS洗涤并离心。倾析上清液并将细胞的架子倾斜以分散细胞团。每个管接收500μl的1％多聚甲醛并在2-8℃下储存，直到在制备的当天拿取。在具有适当仪器设置的Becton Dickinson(BD) FACSCanto™II流式细胞仪上拿取管，每管获得大约250,000次总事件。

[0531] 表2.流式细胞术标记混合物

[0532]

	混杂混合物的含量
混杂物 #1	MsIgG1 FITC、MsIgG2a 藻红素(PE)、MsIgG1 别藻

[0533]

(用以确定背景荧光的对照)	蓝素(APC)、CD4 Alexa Fluor® 700 (AF700)、MsIgG1 mFluor™ Violet 450 (V450)、CD3 Violet 500 (V500)和 CD45RO 生物素-SA BV605
混杂物 #2	CD127 FITC、E-选择素(CD62E) PE、MAC-1 (CD11b) APC、CD4 AF700、CD25 V450、CD3 V500 和 CD45RO 生物素-SA BV605

[0534] 用于流式细胞术测定的所有标记抗体试剂购自Becton Dickinson;E-选择素(CD62E)PE和CD45RO生物素购自Biolegend。

[0535] 研究中使用的其它试剂包括含1％BSA的PBS、基于氯化铵的全血裂解试剂、1％多聚甲醛溶液和Quantum MESF异硫氰酸荧光素(FITC)、藻红素(PE)、别藻蓝素(APC)校准珠。

[0536] 测量LDH水平的测定

[0537] 使用例如Beckman Coulter的化学分析仪采用标准方案测量LDH水平。参见例如2012年3月公布的Lactate OSR6193程序(webcache.googleusercontent.com/search?q＝cache:iyYi7vCetH4J:https://www.beckmancoulter.com/wsrportal/techdocs%3Fdocname%3D/cis/BA OSR6x93/%2525%2525/EN_LACTATE_BAOSR6x93_US.doc+&cd＝2&hl＝en&ct＝clnk&gl＝us),其以引用方式整体并入。

[0538] 数据分析

[0539] 在与Microsoft® Excel 2003或等效软件具有直接数据交换链接的WinList 7.0(Verity Software House,Topsham,Maine)上进行流式细胞术的所有分析。对于图1,对于每一患者将基线值(给药前在第1周期第1天,即C1D1)设置为任意MESF值(例如,100);将获自研究的所有后续值对基线值归一化。图2显示非归一化MESF值。将对于C1D1上的给药前2、4和8小时时间点获得的MESF值进行平均并显示为C1D1的单一值。将对于C1D15上的给药前2和4小时时间点获得的MESF值进行平均并显示为C1D15的单一值。未显示没有可获得的C1D1或C1D15数据的患者。

[0540] 结果

[0541] 如本文所述,在本研究中的所有6名患者中测量CD14+单核细胞上的CD11b水平。图1显示在所指示的时间点对每一患者收集的代表性数据集。所有患者中的CD11b水平到第1周期第15天(C1D15)降低基线值(给药前在第1周期第1天-C1D1)的至少50％。在一个周期(例如,上药段接着是7天离药段的21天)完成时,并且在第二周期(C2D1)开始时,CD11b水平在除了罹患NMC的患者004-001外的所有患者中保持稳定(图1)。此患者中的CD11b水平在离药段过后急剧升高,表明到C2D1,TEN-010在此患者中无效。患者004-001此后不久即死亡。

[0542] 结合CD11b表达水平的测量,也沿类似的时间点测量了乳酸脱氢酶(LDH)水平。LDH是癌症进展的已知临床生物标志物,并且常规是作为癌症诊断和疾病进展的一部分测量的。值得注意的是,如图2C中所示,NMC患者中的CD11b水平顺随LDH水平,验证了CD11b水平为NMC患者中的反应性的标志。相比之下,在非NMC患者中CD11b水平与LDH水平无关。实际上,对于非NMC患者002-021(图2B),LDH水平保持恒定,尽管CD11b水平显著升高。

[0543] 总之,这些结果部分地表明,CD11b水平可用于监测NMC对布罗莫结构域抑制剂疗法的反应性。进一步地,虽然不希望受任何理论的约束,但监测单核细胞上的CD11b水平使得能够追踪NMC疾病活动性。因此,可测量CD11b水平以确定NMC患者在治疗的后续周期中是否将需要更多或更少的布罗莫结构域抑制剂,或者NMC患者是否将需要更早或延迟开始布罗莫结构域抑制剂治疗的后续周期,或其任意组合的情况。

[0544] 本文引用的所有专利、公布的申请和参考文献的教导内容以引用的方式整体并入本文。

[0545] 虽然已经参考本发明的示例实施方案对其进行了具体的说明和描述,但本领域技术人员将会理解的是,在不偏离由所附权利要求涵盖的本发明范围的情况下可在其中进行各种形式和细节方面的改动。

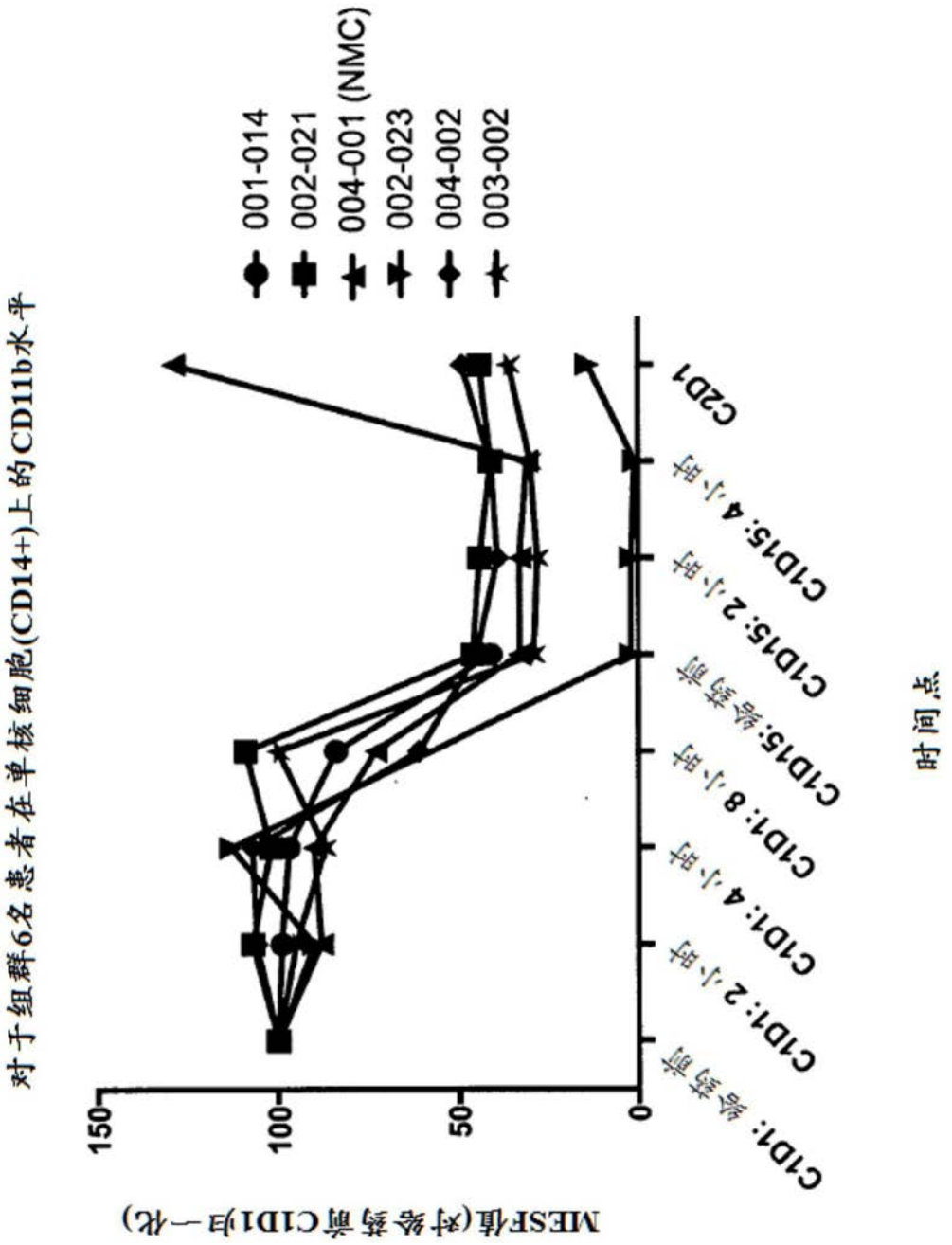

对于组群6名患者在单核细胞(CD14+)上的CD11b水平
001-014
002-021
004-001 (NMC)
002-023
004-002
003-002
MESF值(对给药前C1D1归一化)
150
100
50
0
C1D1: 给药前
C1D1: 2 小时
C1D1: 4 小时
C1D1: 8 小时
C1D15: 给药前
C1D15: 2 小时
C1D15: 4 小时
C2D1
时间点

图1

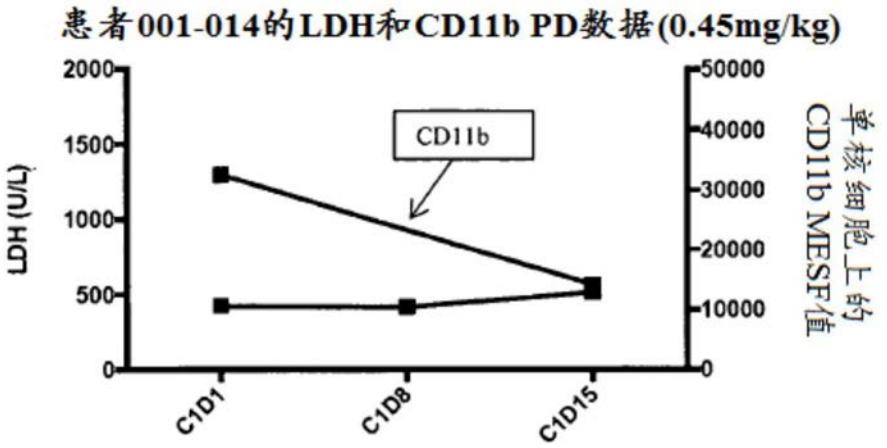

患者001-014的LDH和CD11b PD数据(0.45mg/kg)
LDH (U/L)
2000
1500
1000
500
0
CD11b
50000
40000
30000
20000
10000
0
单核细胞上的CD11b MESF值
C1D1
C1D8
C1D15

图2A

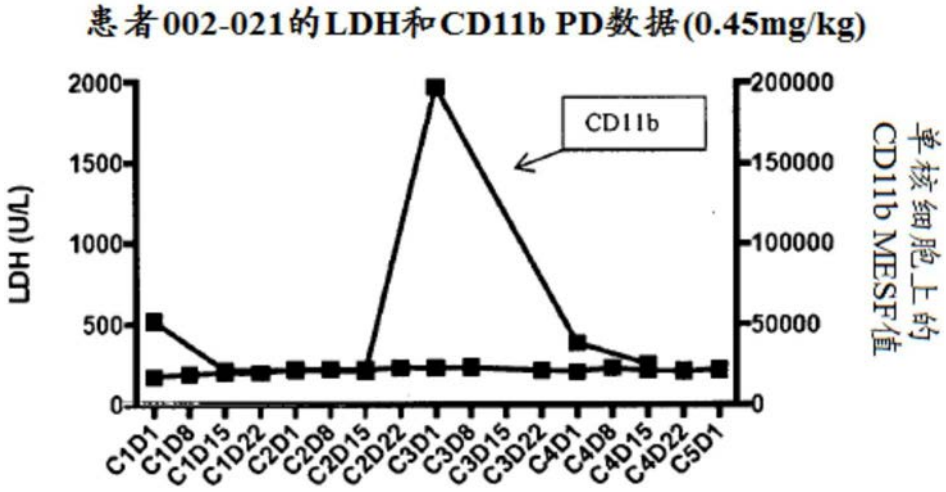

患者002-021的LDH和CD11b PD数据(0.45mg/kg)
LDH (U/L)
2000
1500
1000
500
0
CD11b
200000
150000
100000
50000
0
单核细胞上的CD11b MESF值
C1D1
C1D8
C1D15
C1D22
C2D1
C2D8
C2D15
C2D22
C3D1
C3D8
C3D15
C3D22
C4D1
C4D8
C4D15
C4D22
C5D1

图2B

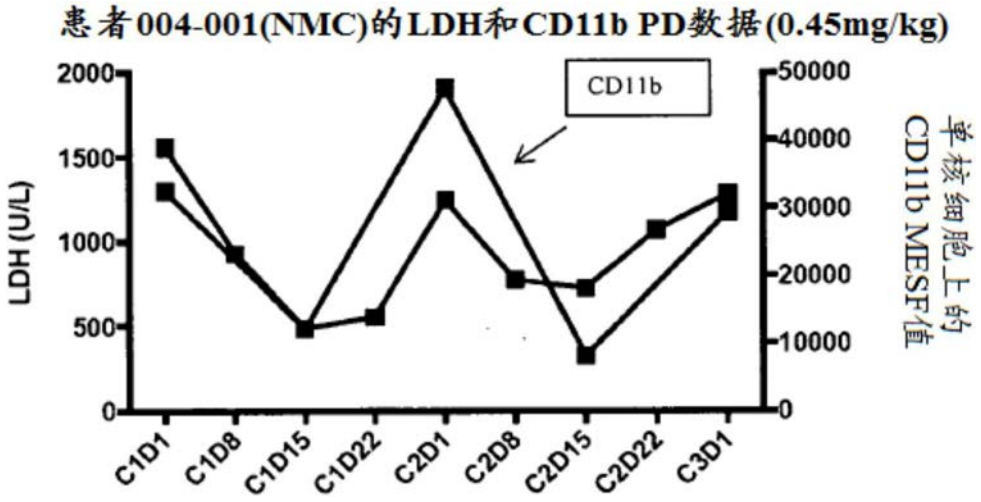

患者004-001(NMC)的LDH和CD11b PD数据(0.45mg/kg)
LDH (U/L)
2000
1500
1000
500
0
CD11b
50000
40000
30000
20000
10000
0
单核细胞上的CD11b MESF值
C1D1
C1D8
C1D15
C1D22
C2D1
C2D8
C2D15
C2D22
C3D1

图2C

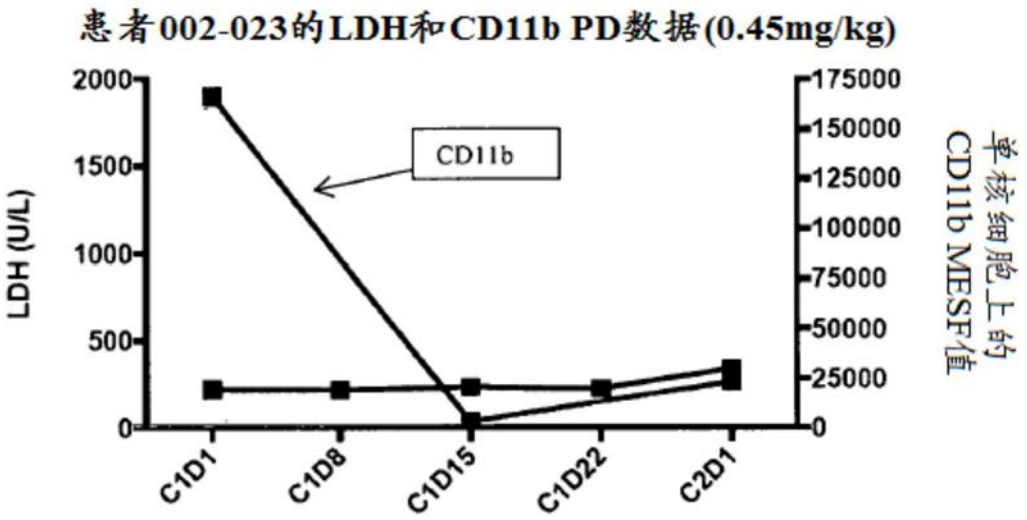

患者002-023的LDH和CD11b PD数据(0.45mg/kg)
LDH (U/L)
2000
1500
1000
500
0
CD11b
175000
150000
125000
100000
75000
50000
25000
0
单核细胞上的CD11b MESF值
C1D1
C1D8
C1D15
C1D22
C2D1

图2D

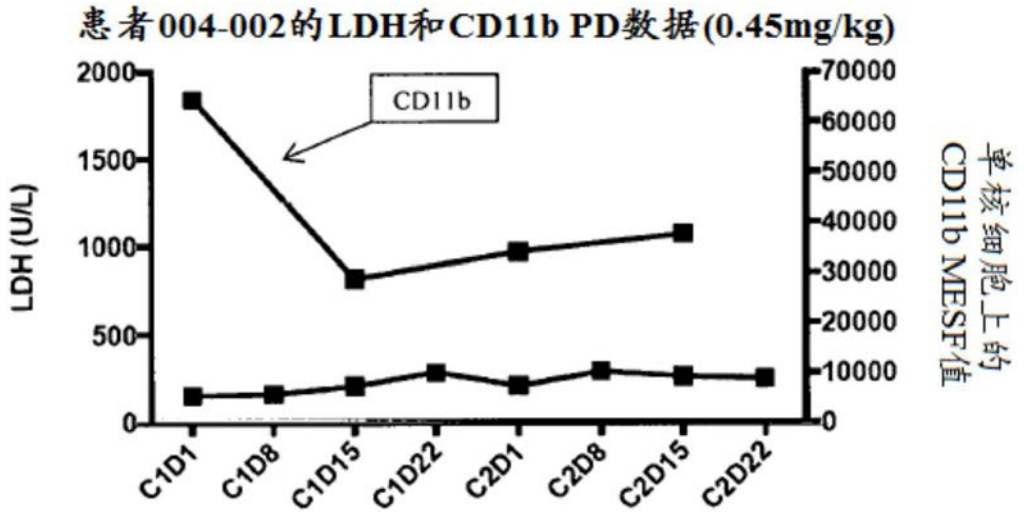

患者004-002的LDH和CD11b PD数据(0.45mg/kg)
LDH (U/L)
2000
1500
1000
500
0
CD11b
70000
60000
50000
40000
30000
20000
10000
0
单核细胞上的CD11b MESF值
C1D1
C1D8
C1D15
C1D22
C2D1
C2D8
C2D15
C2D22

图2E

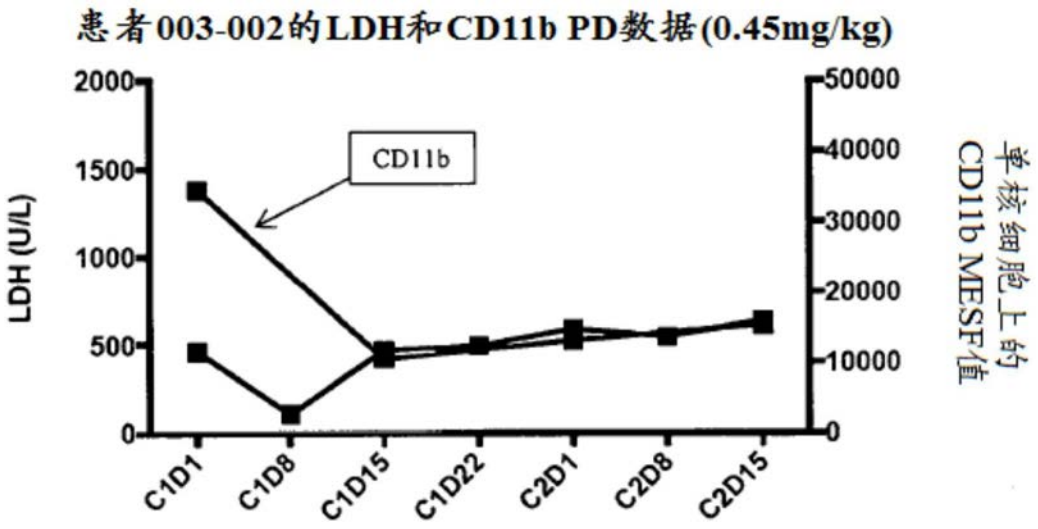

患者003-002的LDH和CD11b PD数据(0.45mg/kg)
LDH (U/L)
2000
1500
1000
500
0
CD11b
50000
40000
30000
20000
10000
0
单核细胞上的CD11b MESF值
C1D1
C1D8
C1D15
C1D22
C2D1
C2D8
C2D15

图2F