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(71) **Applicant** *(for all designated States except US)*: **COFERON, INC.** [US/US]; 28 Health Sciences Dr., Mailbox 123, Stony Brook, NY 11790 (US).

(72) **Inventors; and**
(75) **Inventors/Applicants** *(for US only)*: **ARNOLD, Lee, Daniel** [CA/US]; 55 Chestnut Street, Mount Sinai, NY 11766 (US). **FOREMAN, Kenneth, W.** [US/US]; 8 Underhill Avenue, Syosset, NY 11791-5015 (US). **WERNER, Douglas, S.** [US/US]; 35 Cameron Avenue, Babylon, NY 11702 (US).

(74) **Agents**: **KAVANAUGH, Theresa C.** et al.; Goodwin Procter LLP, Exchange Place, Boston, MA 02109 (US).

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(54) **Title**: BIVALENT BROMODOMAIN LIGANDS, AND METHODS OF USING SAME

(57) **Abstract**: Described herein are compounds capable of modulating one or more biomolecules substantially simultaneously, e.g., modulating two or more binding domains (e.g., bromodomains) on a protein or on different proteins.

BIVALENT BROMODOMAIN LIGANDS, AND METHODS OF USING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 61/528,474, filed August 29, 2011, and U.S. Provisional Application No. 61/587,857, filed January 18, 2012, each of which is hereby incorporated by reference in its entirety.

BACKGROUND

[0002] Current drug design and drug therapies have not addressed the urgent need for therapies that interact with extended areas or multiple domains of biomolecules such as proteins. For example, few therapies exist that can modulate protein-protein interactions, e.g., by interacting, simultaneously, with two domains on a single protein or with both a domain on one protein and a domain on another protein. There is also an urgent need for such therapies that modulate fusion proteins, such as those that occur in cancer.

[0003] Signaling pathways are used by cells to generate biological responses to external or internal stimuli. A few thousand gene products control both ontogeny/development of higher organisms and sophisticated behavior by their many different cell types. These gene products can work in different combinations to achieve their goals and often do so through protein-protein interactions. Such proteins possess modular protein domains that recognize, bind, and/or modify certain motifs. For example, some proteins include tandem or repeating domains.

[0004] The BET family of bromodomain containing proteins bind to acetylated histones to influence transcription. Proteins in the BET family are typically characterisized by having tandem bromodomains. Exemplary protein targets having tandem bromodomains include BRD4, a member of the BET family. *BRD4* is also a proto-oncogene that can be mutated via chromosomal translocation in a rare form of squamous cell carcinoma. Further, proteins having tandem bromodomains such as BRD4 may be suitable as a drug target for other indications such as acute myeloid leukemia. Bromodomains are typically small domains having e.g., about 110 amino acids. Bromodomain modulators may be useful for diseases or

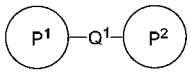
conditions relating to systemic or tissue inflammation, inflammatory response to infection, cell activation and proliferation, lipid metabolism and prevention and treatment of viral infections.

[0005] Current drug design and drug therapy approaches typically focus on modulating one protein domain with limited selectivity and do not address the urgent need to find drugs that are capable of modulating such tandem domains substantially simultaneously in order to further improve on specificity and potency. Although antibodies and other biological therapeutic agents may have sufficient specificity to distinguish among closely related protein surfaces, factors such as their high molecular weight prevent oral administration and cellular uptake of the antibodies. Conversely, orally active pharmaceuticals are generally too small to effectively disrupt protein-protein surface interactions, which can be much larger than the orally active pharmaceuticals.

SUMMARY

[0006] Described herein, for example, are compounds capable of modulating one or more biomolecules substantially simultaneously, e.g., modulate two or more binding domains on a protein or on different proteins.

[0007] For example, in one aspect, a bivalent compound of the formula:



or a pharmaceutically acceptable salt, stereoisomer, metabolite, or hydrate thereof is provided; wherein:

Q^1 is a connecting moiety covalently bound to P^1 and P^2, wherein Q^1 is selected from the group consisting of aliphatic, heteroaliphatic, phenyl, naphthyl, heteroaryl, or a covalently bonded combination thereof; wherein P^1 and P^2 are as defined below.

[0008] In another aspect, a method of treating a disease associated with a protein having tandem bromodomains in a patient in need thereof is provided. The method comprises administering to the patient the bivalent compound as described above.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 shows a screenshot of a protein X-ray crystal structure in which the structures of I-BET762 and an isoxazole pharmacophore are overlaid, according to an embodiment.

[0010] FIG. 2 shows a non-limiting set of pharmacophores (i.e., ligands) with preferred attachment points for connecting the pharmacophores to connecting moieties indicated by arrows, according to an embodiment.

DETAILED DESCRIPTION

[0011] Described herein are compounds capable of modulating one or more biomolecules and, in some cases, modulating two or more binding domains on a protein or on different proteins.

[0012] Advantageously, the bivalent compound may be capable of interacting with a relatively large target site as compared to the individual ligands that form the bivalent compound. For example, a target may comprise, in some embodiments, two protein domains separated by a distance such that a bivalent compound, but not an individual ligand moiety, may be capable of binding to both domains essentially simultaneously. In some embodiments, contemplated bivlalent compounds may bind to a target with greater affinity as compared to an individual ligand moiety binding affinity alone. Also contemplated herein, in some embodiments, is a bivalent compound that, e.g., may be capable of modulating tandem bromo domains.

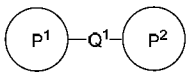
[0013] In an exemplary embodiment, disclosed bivalent compounds may bind to a first target biomolecule domain and a second target biomolecule domain (e.g., protein domains). In one embodiment, the first target binding domain and the second target bidning domain can be tandem domains on the same target, for example, tandem BET bromodomains. In another embodiment, the first target binding domain and the second target binding domain may be located on separate biomolecules. The ligand moiety of a contemplated bivalent compounds, in some cases, may be a pharmacophore or a ligand moiety that is, e.g., capable of binding to and/or modulating a biomolecule, such as, for example, a protein, e.g, a specific protein domain, a component of a biological cell, such as a ribosome (composed of proteins and nucleic acids) or an enzyme active site (e.g., a protease, such as tryptase). The bivalent compound may be used for a variety of purposes. For example, in some instances, the bivalent compound may be used to perturb a biological system. As described in more detail below, in some embodiments, the bivalent compound may bind to or modulate a target biomolecule, such as a protein, nucleic acid, or polysaccharide. In certain embodiments, a contemplated bivalent compound may be used as a pharmaceutical.

[0014] In some embodiments, the first ligand moiety and the second ligand moiety may be capable of binding to a bromodomain. For example, in some embodiments, the first ligand and/or the second ligand may be capable of binding to a bromodomain in a protein selected from the group consisting of BRD2 D2, BRD3 D2, BRD4 D2, BRD-t D2, yBdf1 D2, yBdf2 D2, KIAA2026, yBdf1 D1, yBdf2 D1, TAF1L D1, TAF1 D1, TAF1L D2, TAF1 D2, ZMYND8, ZMYND11, ASH1L, PBRM D3, PBRM D1, PBRM D2, PBRM D4, PBRM D5, SMARCA2, SMARCA4 ySnf2, ySth, PBRM D6, yRsc1 D2, yRsc2 D2, yRsc1 D1, yRsc2 D1, yRsc4 D1, BRWD1 D1, BRWD3 D1, PHIP D1, MLL, MLL4, BRWD2, ATAD2, ATAD2B, BRD1, BRPF1, BRPF3, BRD7, BRD9, BAZ1B, BRWD1 D2, PHIP D2, BRWD3, CREBBP, EP300 BRD8 D1, BRD8 D2, yRsc4 D2, ySpt7, BAZ1A, BAZ2A, BAZ2B, SP140, SP140L, TRIM28, TRIM24, TRIM33, TRIM66, BPTF, GCN5L2, PCAF, yGcn5, BRD2 D1, BRD3 D1, BRD4 D1, BRD-t D1 and CECR2. Reference to protein and domain names used herein are derived from Zhang Q, Chakravarty S, Ghersi D, Zeng L, Plotnikov AN, et al. (2010) Biochemical Profiling of Histone Binding Selectivity of the Yeast Bromodomain Family. PLoS ONE 5(1): e8903. doi:10.1371/journal.pone.0008903. In some embodiments contemplated dimers disclosed herein may be capable of binding to a tandem bromodomain. It will be appreciated that such tandem bromodomains may occur on the same protein or each bromodomain may occur on different proteins. In other embodiments, dimers disclosed herein may be capable of binding to one bromodomain on a first protein and to another bromodomain on a second protein. For example, in some cases, a multimer may be capable of binding to a tandem bromodomain in a protein selected from the group consisting of BRD2, BRD3, BRD4 and BRD-t.

[0015] In some cases, a bivalent compound may bind to a target biomolecule with a dissociation constant of less than 1 mM, in some embodiments less than 500 microM, in some embodiments less than 300 microM, in some embodiments less than 100 microM, in some embodiments less than 10 microM, in some embodiments less than 1 microM, in some embodiments less than 100 nM, in some embodiments less than 10 nM, and in some embodiments less than 1 nM, in some embodiments less than 1 pM, in some embodiments less than 1 fM, in some embodiments less than 1 aM, and in some embodiments less than 1 zM.

Bivalent Compounds

[0016] In certain embodiments, bivalent compounds of formula I are provided:



(I)

and pharmaceutically acceptable salts, stereoisomers, metabolites, and hydrates thereof, wherein:

P^1 is a first ligand capable of modulating a first bromodomain;

P^2 is a second ligand capable of modulating a second bromodomain; and

Q^1 is a connecting moiety covalently bound to P^1 and P^2 that comprises between 3 and 30 atoms, where the atoms are connected to form a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic moiety; substituted or unsubstituted phenyl or naphthyl moiety; substituted or unsubstituted heteroaryl moiety; or a combination thereof.

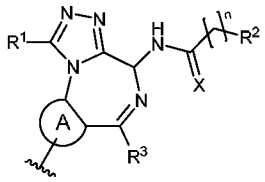
[0017] In some embodiments, the ligand may be a pharmacophore. A pharmacophore is typically an arrangement of the substituents of a moiety that confers biochemical or pharmacological effects (*e.g.*, by targeting a bromodomain). In some embodiments, identification of a pharmacophore may be facilitated by knowing the structure of the ligand in association with a target biomolecule. In some cases, pharmacophores may be moieties derived from molecules previously known to bind to target biomolecules (e.g., proteins), fragments identified, for example, through NMR or crystallographic screening efforts, molecules that have been discovered to bind to target proteins after performing high- throughput screening of natural products libraries, previously synthesized commercial or non-commercial combinatorial compound libraries, or molecules that are discovered to bind to target proteins by screening of newly synthesized combinatorial libraries. Since most pre-existing combinatorial libraries are limited in the structural space and diversity that they encompass, newly synthesized combinatorial libraries may include molecules that are based on a variety of scaffolds.

[0018] In one embodiment, one or more of the ligands in a bivalant compound may be a pharmacophore capable of binding to a bromodomain. The bivalent compound may be capable of binding to tandem bromodomains, *e.g.*, within a BET family of bromodomains that contain tandem bromodomains in close proximity, making them capable of binding two acetylated lysine residues with greater specificity. For example, a "BET bromodomain" may refer to the bromodomains in BRD2, BRD3, BRD4 or BRD-t. One of ordinary skill in the art will

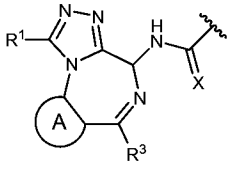
appreciate that additional pharmacophores may be discovered in the future and that the pharmacophores illustrated herein are not intended to be limiting in any way.

[0019] In some embodiments, a ligand (*e.g.*, a pharmacophore) may have one or more preferred attachment points for connecting the pharmacophore to the connecting moiety. In certain embodiments, an attachment point on a pharmacophore may be chosen so as to preserve at least some ability of the pharmacophore to bind to a bromodomain. In one embodiment, preferred attachment points may be identified using X-ray crystallography. The following description of a non-limiting exemplary method illustrates how a preferred attachment point may be identified. For example, as shown in FIG. 1, using the 3P5O structure 100 from the protein databank (PDB), a small molecule 110 (dark gray) labeled "EAM1" in the PDB file [also known as I-BET or IBET762] may be identified. The I-BET triazolo ring (indicated by white circle 120) contains two adjacent nitrogen atoms in the 3 and 4 positions and a methyl group 130 bound to the adjacent carbon at the 5 position. Together, the nitrogen atoms and methyl group constitute an acetyl lysine mimetic. The corresponding acetyl lysine mimetic in the new pharmacophore 140 (light gray) should be aligned to these elements. The final conformation and orientation of the newly aligned pharmacophore 140 in the site may be determined using a variety of approaches known to computational chemists, but can be done as simply as performing an energy minimization using a molecular mechanics forcefield. It should be noted that the alphanumeric identifiers in FIG. 1 (e.g., K141, D144, M149, etc.) correspond to amino acid residues in the 3P5O structure, where the letter of the identifier is the one-letter amino acid symbol and the number of the identifier is the position of the amino acid residue in the primary sequence of the protein. Attachment points 150 on the aligned pharmacophore which permit access to amino acid residues D96, Y139, N140, K141, D144, D145, M149, W81, or Q85 in the 3P5O structure are considered preferred attachment points for connecting moieties. It should be apparent to those skilled in the art that overlays of the I-BET pharmacophore with other alternate pharmacophores can be used to identify potential attachment points.

[0020] FIG. 2 provides a non-limiting set of pharmacophores (i.e., ligands) showing preferred attachment points (indicated by arrows) for connecting the pharmacophore to a connecting moiety. It will be appreciated that the ligands disclosed herein can be attached at any open site to a connector moiety as described herein. Such embodiments described below include specific references to each attachment site. Exemplary bromodomain ligands include quinolines represented by the structure:



Formula F and



Formula G

wherein:

X is O or S;

R^1 is C_{1-6}alkyl, haloC_{1-6}alkyl, -$(CH_2)_nOR^{1a}$, or -$(CH_2)_mNR^{1b}R^{1c}$; wherein R^{1a} is hydrogen, C_{1-6}alkyl or haloC_{1-6}alkyl; R^{1b} and R^{1c}, which may be the same or different, are hydrogen, C_{1-6}alkyl or haloC_{1-6}alkyl; and m and n, which may be the same or different, are 1, 2 or 3;

R^2 is R^{2a}, -OR^{2b}, or -$NR^{2c}R^{2d}$; wherein R^{2a} and R^{2b} are carbocyclyl, carbocyclylC_{1-4}alkyl, heterocyclyl or heterocyclylC_{1-4}alkyl, or R^{2a} is carbocyclylethenyl or heterocyclylethenyl, wherein any of the carbocyclyl or heterocyclyl groups defined for R^{2a} or R^{2b} are optionally substituted by one or more groups independently selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, nitro, cyano, dimethylamino, benzoyl and azido; or two adjacent groups on any of the carbocyclyl or heterocyclyl groups defined for R^{2a} or R^{2b} together with the interconnecting atoms form a 5 or 6-membered ring which ring may contain 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; or

R^{2a} and R^{2b} are C_{1-6}alkyl or haloC_{1-6}alkyl; and R^{2c} and R^{2d}, which may be the same or different, are carbocyclyl, carbocyclylC_{1-4}alkyl, heterocyclyl or heterocyclylC_{1-4}alkyl, wherein any of the carbocyclyl or heterocyclyl groups defined for R^{2c} or R^{2d} are optionally substituted by one or more groups independently selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, nitro, cyano and -CO_2C_{1-4}alkyl; or two adjacent groups on any of the carbocyclyl or heterocyclyl groups defined for R^{2c} and R^{2d} together with the interconnecting atoms form a 5 or 6-membered ring which ring may contain 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; or

R^{2c} and R^{2d} are independently hydrogen, C_{1-6}alkyl or haloC_{1-6}alkyl;

R^3 is C_{1-6}alkyl, phenyl, naphthyl, heteroaryl carbocyclyl or heterocyclyl, optionally substituted independently by one or more substitutents selected from the group consisting of

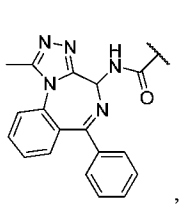
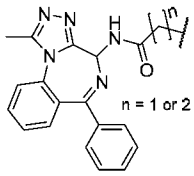
halogen, –SR, -S(O)R', -NHR', -OR', C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, nitro and cyano;

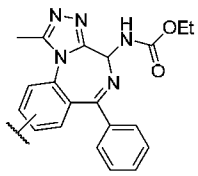
R' is H or C_{1-6}alkyl;

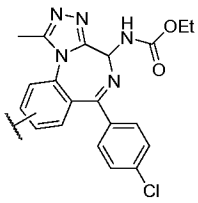
A is a benzene or aromatic heterocyclic ring, each of which is optionally substituted; and

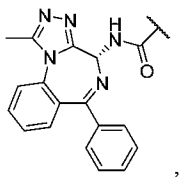
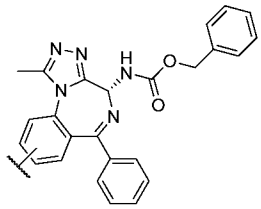
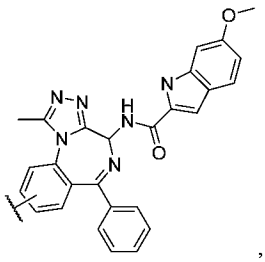
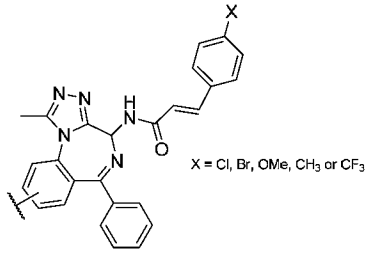
n is 0, 1 or 2.

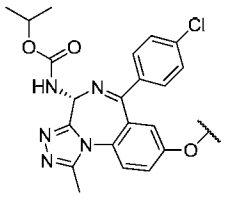
[0021] In some embodiments, compounds of Formula F or Formula G may be selected from the group consisting of:

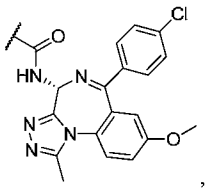

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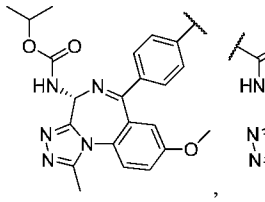
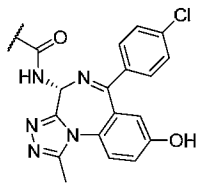
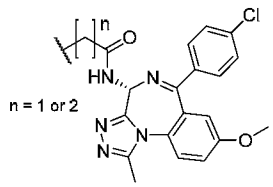
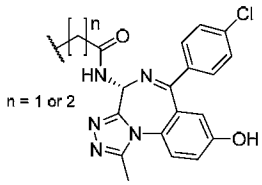
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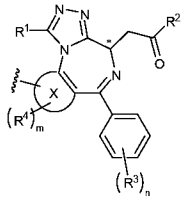
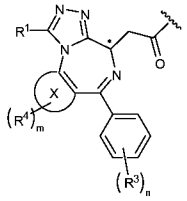
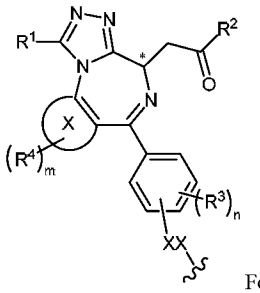
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[0022] In another embodiment, exemplary bromodomain ligands include benzodiazepines represented by the structures:


Formula H and

Formula I and

Formula I'

wherein:

X is phenyl, naphthyl, or heteroaryl;

R^1 is C_{1-3}alkyl, C_{1-3}alkoxy or -S- C_{1-3}alkyl;

R^2 is $-NR^{2a}R^{2a'}$ or $-OR^{2b}$; wherein one of R^{2a} or $R^{2a'}$ is hydrogen, and R^{2b} or the other of R^{2a} or $R^{2a'}$ is selected from the group consisting of C_{1-6}alkyl, haloC_{1-6}alkyl, $R^{2c}R^{2c'}N$-C_{2-6}alkyl, carbocyclyl, carbocyclyloC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, wherein any of the

carbocyclyl or heterocyclyl groups are optionally substituted by one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, carbonyl, -CO-carbocyclyl, azido, amino, hydroxyl, nitro and cyano, wherein the –CO-carbocyclyl group may be optionally substituted by one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, azido, nitro and cyano; or

two adjacent groups on any of the carbocyclyl or heterocyclyl groups together with the interconnecting atoms form a 5- or 6-membered ring which ring may contain 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; or R^{2a} and $R^{2a'}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered ring which optionally contains 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; wherein the 4-, 5-, 6 or 7-membered ring is optionally substituted by C_{1-6}alkyl, hydroxyl or amino;

R^{2c} and $R^{2c'}$ are independently hydrogen or C_{1-6}alkyl;

each R^3 is independently selected from the group consisting of hydrogen, hydroxyl, thiol, sulfinyl, sulfonyl, sulfone, sulfoxide, -OR^t, -NR^tR^{tt}, -$S(O)_2NR^tR^{tt}$, -$S(O)_wR^tR^{tt}$ (where t and tt are independently selected from H, phenyl or C_{1-6}alkyl, and w is 0, 1, or 2), halo, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, nitro, cyano, CF_3, -OCF_3, -$COOR^5$, -C_{1-4}alkylamino , phenoxy, benzoxy, and C_{1-4}alkylOH;

XX is selected from the group consisting of a bond, NR''' (where R''' is H, C_{1-6}alkyl or phenyl), -O-, or $S(O)_w$ wherein w is 0, 1 or 2, and C_{1-6}alkyl; (and wherein in some embodiments XX is in the para position);

each R^4 is hydroxyl, halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -$COOR^5$; -$OS(O)_2C_{1-4}$alkyl, phenyl, naphthyl, phenyloxy, benzyloxy or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, amino, nitro;

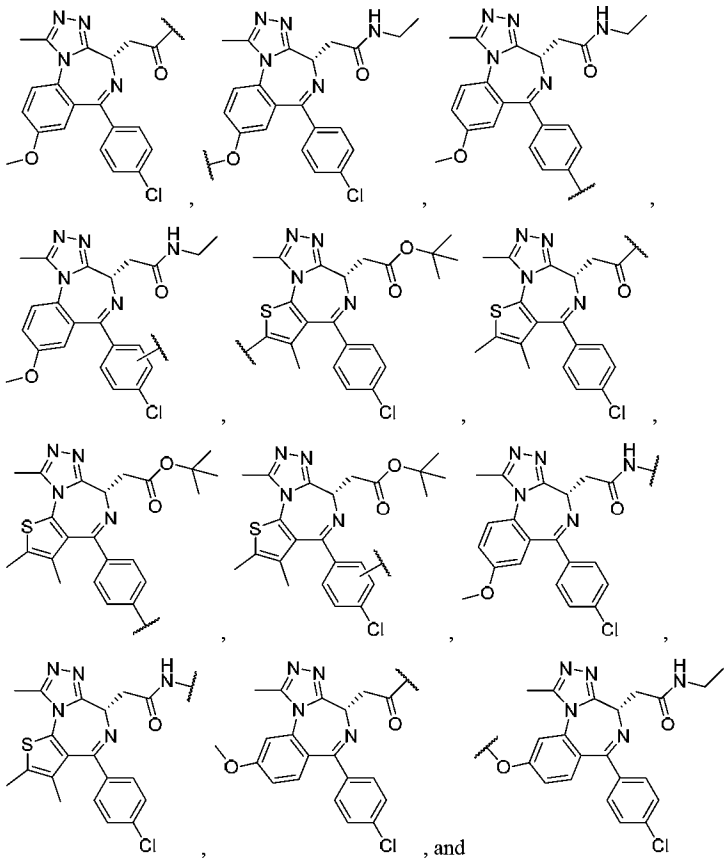
R^5 is C_{1-3}alkyl;

* denotes a chiral center;

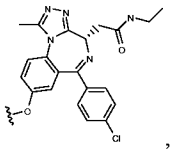
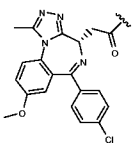
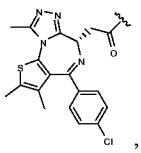
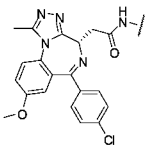
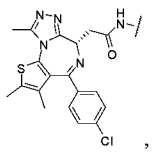
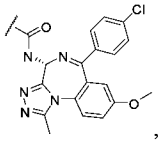
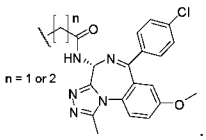
m is an integer 1 to 3; and

n is an integer 1 to 5. In some embodiments, the chiral center has an S configuration.

[0023] In some embodiments, compounds of Formula H or Formula I may be selected from the group consisting of:

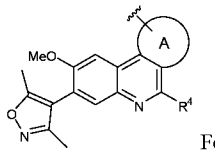


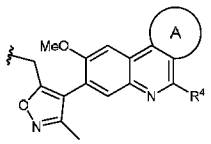
[0024] For example, compounds of Formula F, Formula G, Formula H or Formula I may be selected from the group consisting of:


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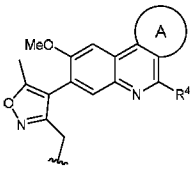
, and .

[0025] In some embodiments, exemplary bromodomain ligands include compounds represented by the structures:



Formula A,


Formula A1, or

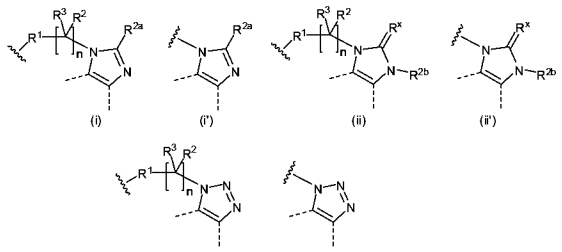


Formula A2,

wherein:

R^4 is hydrogen, cyano or C_{1-6} alkyl;

A is selected from the group consisting of:



;

R^x is O, NR^{2a}, or S;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, a 5 or 6 membered heterocyclyl, an aromatic group or a heteroaromatic group, wherein the aromatic group or the heteroaromatic group is optionally

substituted by one to three groups selected from the group consisting of halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy C_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonyloxy, C_{1-4}alkylsulfonyl C_{1-4}alkyl and C_{1-4}alkylsulfonamido;

R^2 is hydrogen or C_{1-6}alkyl;

R^{2a} is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}haloalkyl, $(CH_2)_m$cyano, $(CH_2)_m$OH, $(CH_2)_mC_{1-6}$alkoxy, $(CH_2)_mC_{1-6}$haloalkoxy, $(CH_2)_mC_{1-6}$haloalkyl, $(CH_2)_mC(O)NR^aR^b$, $(CH_2)_mNR^aR^b$ and $(CH_2)_m$ $C(O)CH_3$, $(CHR^6)_p$phenyl optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo C_{1-4}alkoxy, haloC_{1-4}alkyl, $(CHR^6)_p$heteroaromatic, $(CHR^6)_p$heterocyclyl; wherein R^a is H, C_{1-6}alkyl, or heterocyclyl; wherein R^b is H or C_{1-6}alkyl, or

R^a and R^b together with the N to which they are attached form a 5 or 6 membered heterocyclyl;

R^{2b} is H, C_{1-6}alkyl, $(CH_2)_2C_{1-6}$alkoxy, $(CH_2)_2$cyano, $(CH_2)_m$phenyl or $(CH_2)_2$heterocyclyl;

R^3 is hydrogen;

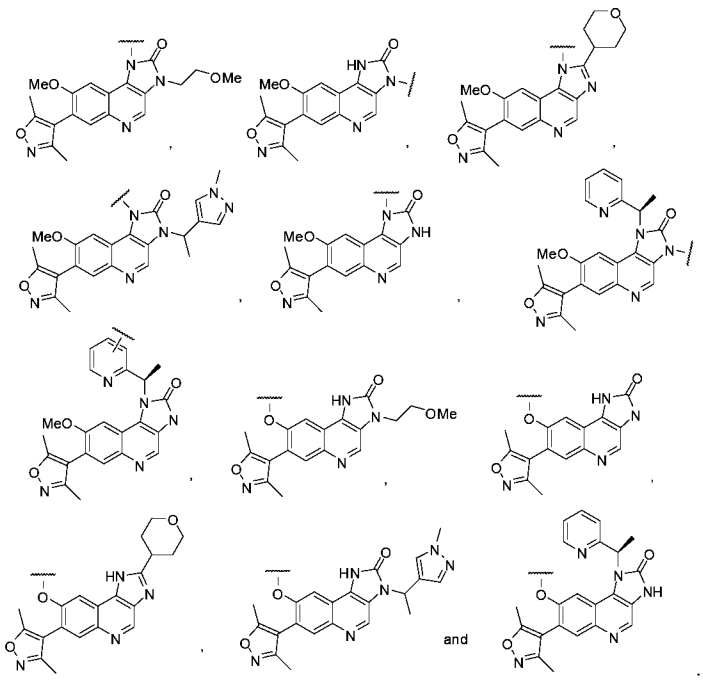
R^6 is hydrogen or C_{1-6}alkyl;

m is 0, 1, 2 or 3;

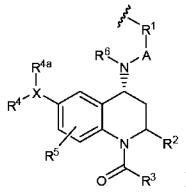
n is 0, 1 or 2; and

p is 0, 1 or 2.

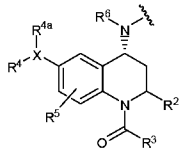
[0026] In some embodiments, compounds of Formulae A, A1, and A2 may be selected from the group consisting of:



[0027] In another embodiment, exemplary bromodomain ligands include tetrahydroquinolines represented by the structures:



Formula B and



Formula C

wherein:

A is a bond, C_{1-4}alkyl or –C(O)-;

X is:

i) a 6 to 10 membered aromatic group, or

ii) a 5 to 10 membered heteroaromatic comprising 1, 2 or 3 heteroatoms selected from the group consisting of O, N and S;

R^1 is:

i) phenyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, -SO_2C_{1-6}alkyl and -COR^7,

ii) a 5 to 10 membered heteroaromatic comprising 1, 2 or 3 heteroatoms selected from the group consisting of O, N and S optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy and -COR^7, or

iii) C_{1-6}alkyl, C_{0-6}alkylcyano, C_{0-6}alkylC_{1-6}alkoxy, C_{0-2}alkyl$C(O)R^7$ or cyclohexyl;

R^2 is C_{1-6}alkyl;

R^3 is C_{1-6}alkyl;

R^4 is:

i) H, halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{0-6}hydroxyalkyl, -SO_2C_{1-6}alkyl, -$C(O)NR^8R^9$, -$C(O)R^{10}$, -C_{0-6}alkyl-$NR^{11}R^{12}$, or

ii) -O_mC_{1-6}alkyl substituted by a 5 or 6 membered heterocyclyl or heteroaromatic each comprising 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S and wherein said hetercyclyl or heteroaromatic is optionally substituted by 1, 2 or 3 groups independently selected from the group consisting of halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl and C_{1-6}alkoxy, wherein m is 0, 1 or 2, wherein when the heterocyclyl or heteroatomic is linked through a heteroatom and m is 1, then the heteroatom and O are not directly linked if the resultant arrangement would be unstable;

R^{4a} is H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy or C_{0-6}hydroxyalkyl;

R^5 is H, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

R^6 is H, C_{1-6}alkyl, C_{0-6}alkylcyano, C_{0-6}alkylC_{1-6}alkoxy or C_{0-2}alkyl$C(O)R^7$;

R^7 is hydroxyl, C_{1-6}alkoxy, -NH_2, -NHC_{1-6}alkyl or $N(C_{1-6}alkyl)_2$;

R^8 and R^9 independently are:

i) H, C_{1-6}alkyl, C_{0-6}alkylphenyl, C_{0-6}alkylheteroaromatic, C_{3-6}cycloalkyl, or

ii) R^8 and R^9 together with the N to which they are attached form a 5 or 6 membered heterocyclyl or heteroaromatic wherein said heterocyclyl or heteroaromatic may comprise 1, 2 or 3 further heteroatoms independently selected from the group consisting of O, N and S;

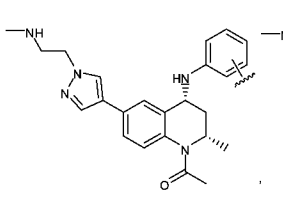
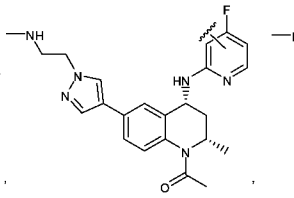
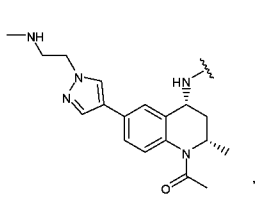
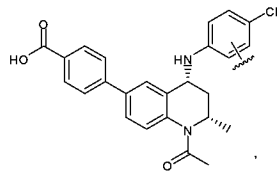
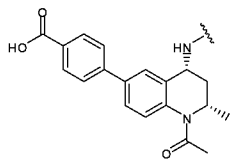
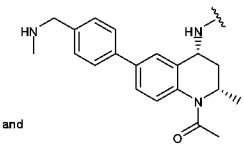
R^{10} is hydroxyl, C_{1-6}alkoxy or a 5 or 6 membered heterocyclyl or heteroaromatic comprising 1, 2, 3 or 4 heteroatoms selected from the group consisting of O, N and S;

$R^{11}$and R^{12} independently are:

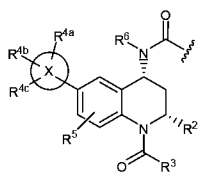
i) H, C_{1-6}alkyl; or

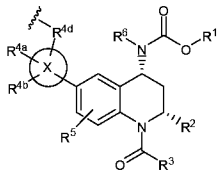
ii) R^{11} and R^{12} together with the N to which they are attached form a 5 or 6 membered heterocyclyl or heteroaromatic wherein said heterocyclyl or heteroaromatic may comprise 1, 2 or 3 further heteroatoms independently selected from the group consisting of O, N and S.

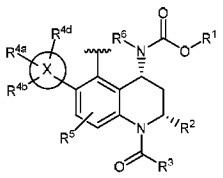
[0028] In certain embodiments, compounds of Formula B or Formula C may be selected from the group consisting of:







and

[0029] In another embodiment, exemplary bromodomain ligands include tetrahydroquinolines represented by the structures:


[0030] Formula D,


Formula E, and


Formula E1

wherein:

R^1 is C_{1-6}alkyl, C_{3-7}cycloalkyl or benzyl;

R^2 is C_{1-4}alkyl;

R^3 is C_{1-4}alkyl;

X is phenyl, naphthyl, or heteroaryl;

R^{4a} is hydrogen, C_{1-4}alkyl or is a group L-Y in which L is a single bond or a C_{1-6}alkylene group and Y is OH, OMe, CO_2H, CO_2C_{1-6}alkyl, CN, or NR^7R^8;

R^7 and R^8 are independently hydrogen, a heterocyclyl ring, C_{1-6}alkyl optionally substituted by hydroxyl, or a heterocyclyl ring; or

R^7 and R^8 combine together to form a heterocyclyl ring optionally substituted by C_{1-6}alkyl, CO_2C_{1-6}alkyl, NH_2, or oxo;

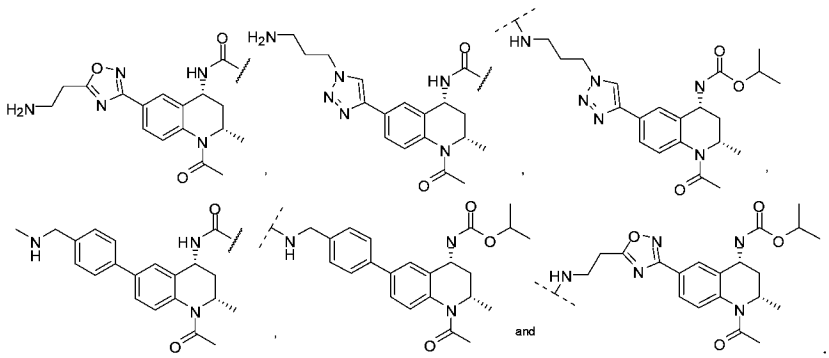
R^{4b} and R^{4c} are independently hydrogen, halogen, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^{4d} is C_{1-4}alkyl or is a group -L-Y- in which L is a single bond or a C_{1-6}alkylene group and Y is -O-, $-OCH_2-$, $-CO_2-$, $-CO_2C_{1-6}$alkyl-, or $-N(R^7)-$;

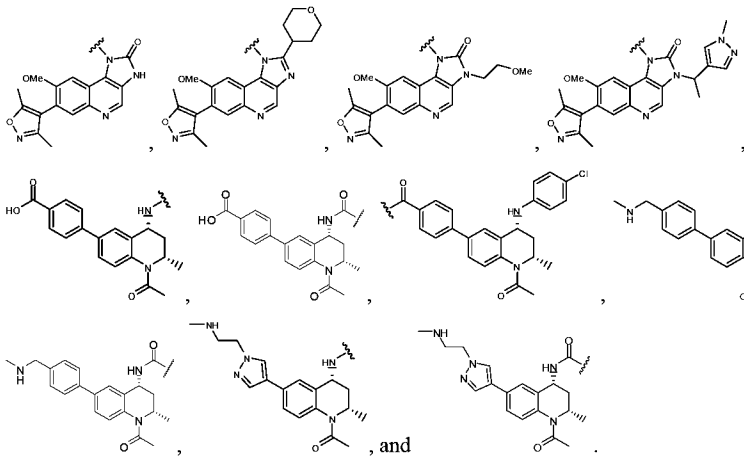
R^5 is hydrogen, halogen, C_{1-6}alkyl, or C_{1-6}alkoxy;

R^6 is hydrogen or C_{1-4}alkyl.

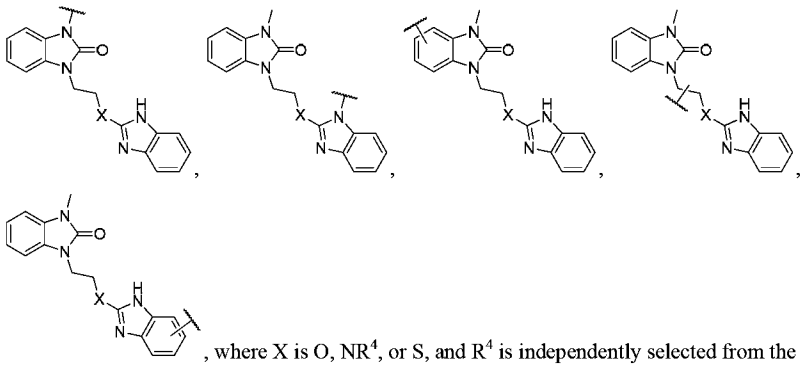
[0031] In some cases, compounds of Formula D or Formula E may be selected from the group consisting of:



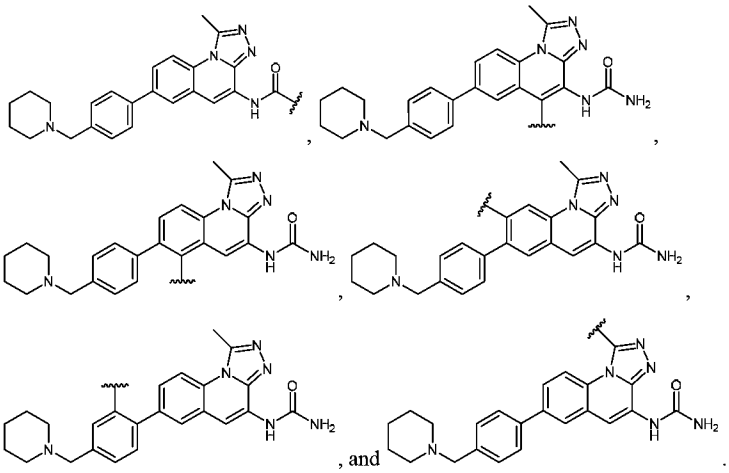
[0032] For example, compounds of Formula A, Formula B, Formula C, Formula D or Formula E may be selected from the group consisting of:



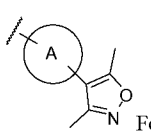
[0033] In another embodiment, exemplary bromodomain ligands are represented by the structures:

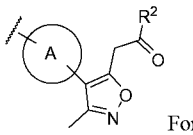


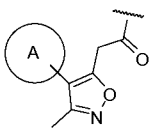
, where X is O, NR^4, or S, and R^4 is independently selected from the group consisting of hydrogen, hydroxyl, halo, amino, thiol, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -S-C_{1-6}alkyl, haloC_{1-6}alkoxy, nitro, cyano, $-CF_3$, $-OCF_3$, -C(O)O-C_{1-6}alkyl, -C_{1-4}alkylamino , phenoxy, benzoxy, and C_{1-4}alkylOH;

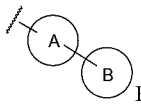


[0034] In another embodiment, exemplary bromodomain ligands include heterocycles represented by the structures:


Formula J,


Formula K,


Formula L, and


Formula M

wherein:

A is independently, for each occurrence, a 4-8 membered cycloalkyl, heterocyclic, phenyl, naphthyl, or heteroaryl moiety, each optionally substituted with one, two, three or more R^1 substituents;

R^1 is selected from the group consisting of hydroxy, halogen, oxo, amino, imino, thiol, sulfanylidene, $C_{1\text{-}6}$alkyl, hydroxy$C_{1\text{-}6}$alkyl, -O-$C_{1\text{-}6}$alkyl, –NH-$C_{1\text{-}6}$alkyl, -CO_2H, -C(O)$C_{1\text{-}6}$alkyl, –C(O)O-$C_{1\text{-}6}$alkyl, amino$C_{1\text{-}6}$alkyl, halo$C_{1\text{-}6}$alkyl, -$C_{1\text{-}6}$alkylC(O)R^2, -O-C(O)R^2, -NH-C(O)R^2, -O-$C_{1\text{-}6}$alkyl-C(O)R^2, -NH$C_{1\text{-}6}$alkyl-C(O)R^2, acylamino$C_{1\text{-}6}$alkyl, nitro, cyano, CF_3, -OCF_3, -OS(O)$_2C_{1\text{-}6}$alkyl, phenyl, naphthyl, phenyloxy, -NH-phenyl, benzyloxy, and phenylmethoxy halogen; wherein $C_{1\text{-}6}$alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, amino,

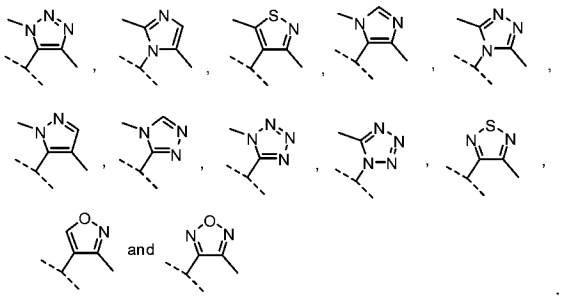
nitro, phenyl and C_{1-6}alkyl; or two R^1 substitutents may be taken together with the atoms to which they are attached to form a fused aliphatic or heterocyclic bicyclic ring system;

R^2 is $-NR^{2a}R^{2a'}$ or $-OR^{2b}$; wherein one of R^{2a} or $R^{2a'}$ is hydrogen, and R^{2b} or the other of R^{2a} or $R^{2a'}$ is selected from the group consisting of C_{1-6}alkyl, haloC_{1-6}alkyl, $R^{2c}R^{2c'}N$-C_{2-6}alkyl, carbocyclyl, carbocyclyloC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, wherein any of the carbocyclyl or heterocyclyl groups are optionally substituted by one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, carbonyl, -CO-carbocyclyl, azido, amino, hydroxyl, nitro and cyano, wherein the –CO-carbocyclyl group may be optionally substituted by one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, azido, nitro and cyano; or

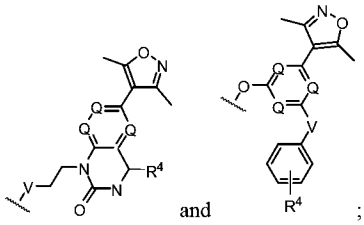
two adjacent groups on any of the carbocyclyl or heterocyclyl groups together with the interconnecting atoms form a 5- or 6-membered ring which ring may contain 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; or R^{2a} and $R^{2a'}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered ring which optionally contains 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; wherein the 4-, 5-, 6 or 7-membered ring is optionally substituted by C_{1-6}alkyl, hydroxyl or amino;

R^{2c} and $R^{2c'}$ are independently hydrogen or C_{1-6}alkyl;

B is selected from the group consisting of:



[0035] In one embodiment, compounds of Formula J may be selected from the group consisting of:



and ;

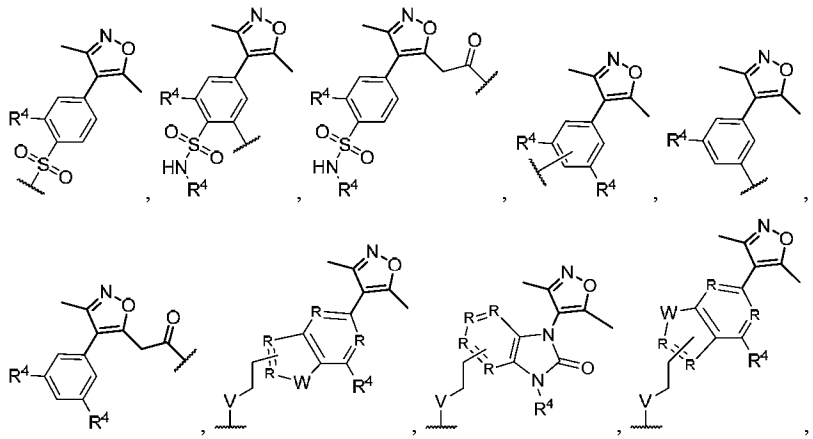
wherein:

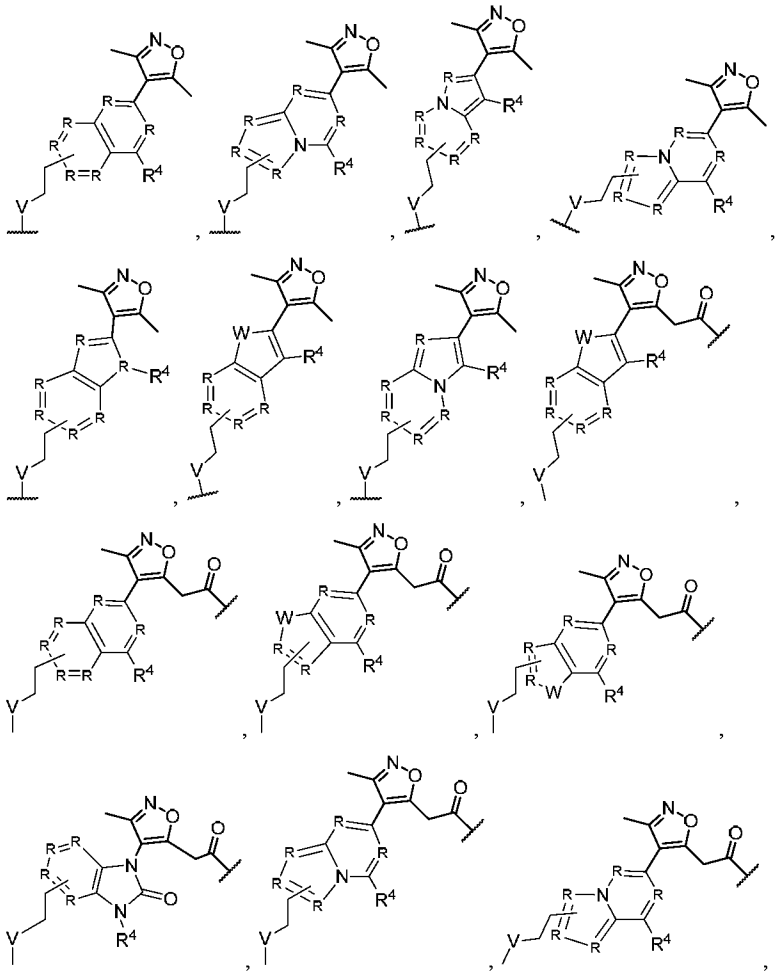
Q is independently, for each occurrence, N or CH;

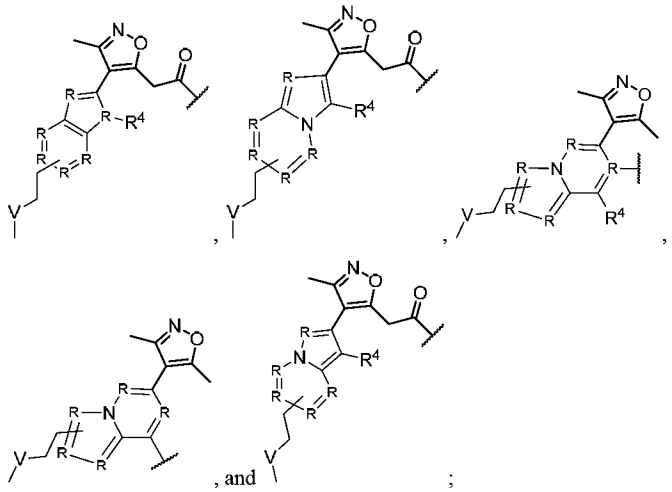
V is independently, for each occurrence, O, S, NH, or a bond; and

R^4 is independently selected from the group consisting of hydrogen, hydroxyl, halo, amino, thiol, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -S-C_{1-6}alkyl, haloC_{1-6}alkoxy, nitro, cyano, $-CF_3$, $-OCF_3$, -C(O)O-C_{1-6}alkyl, -C_{1-4}alkylamino , phenoxy, benzoxy, and C_{1-4}alkylOH.

[0036] For example, compounds of Formula J or Formula L may be selected from the group consisting of:







wherein:

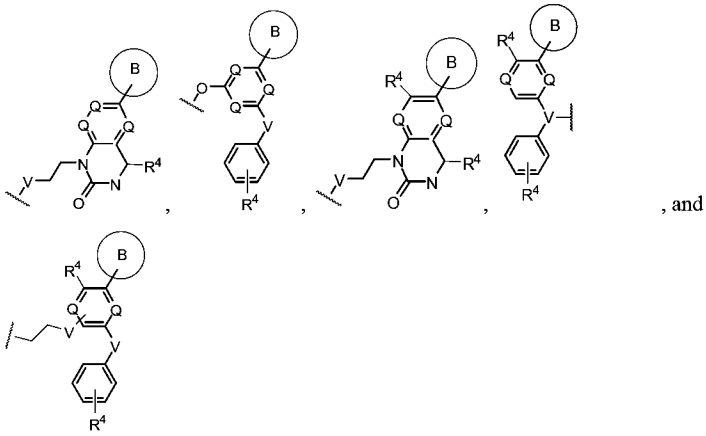
R is independently, for each occurrence, N or CH;

V is independently, for each occurrence, a bond, O or NR^4;

R^4 is independently, for each occurrence, hydrogen, hydroxyl, halo, amino, $-SO_2$, thiol, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -S-C_{1-6}alkyl, haloC_{1-6}alkoxy, nitro, cyano, $-CF_3$, $-OCF_3$, -C(O)O-C_{1-6}alkyl, -C_{1-6}alkylamino , phenoxy, benzoxy, phenyl, naphthyl, heteroaryl and C_{1-4}alkylOH; wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted with 1, 2, 3 or more substituents selected from the group consisting of halogen, hydroxyl, amino and C_{1-6}alkyl; and

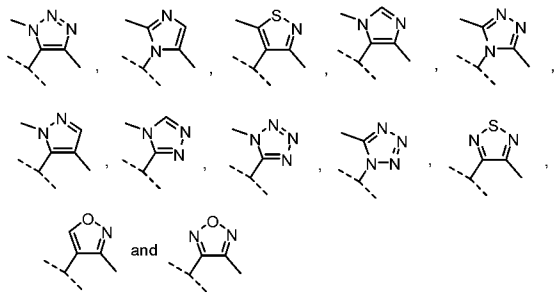
W is independently, for each occurrence, , O, S, or NR^4.

[0037] In another embodiment, compounds of Formula M may be selected from the group consisting of:



wherein:

B is selected from the group consisting of:

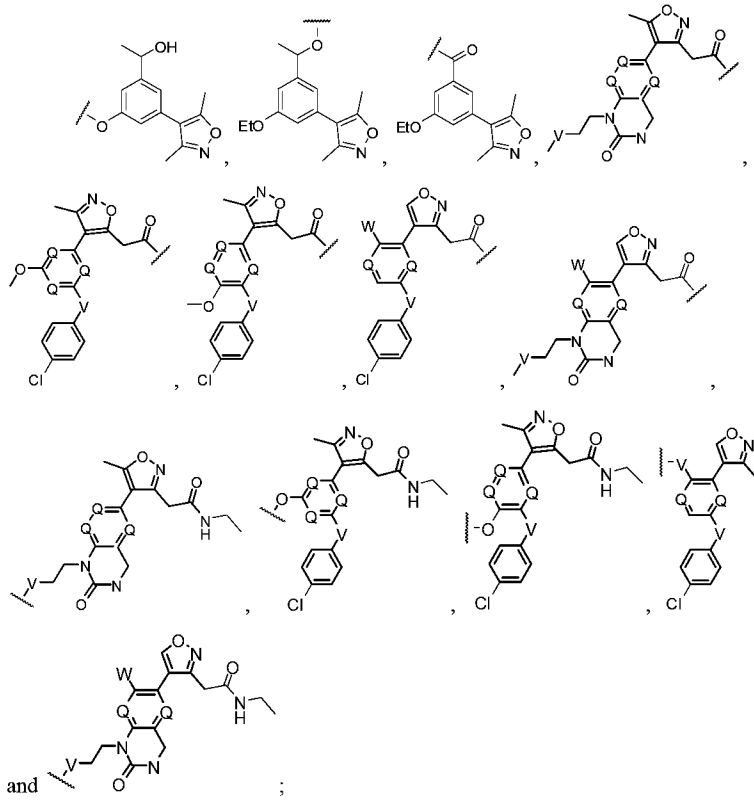


Q is independently, for each occurrence, N or CH;

V is independently, for each occurrence, O, S, NR^4, or a bond; and

R^4 is independently selected from the group consisting of hydrogen, hydroxyl, halo, amino, thiol, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -S-C_{1-6}alkyl, haloC_{1-6}alkoxy, nitro, cyano, $-CF_3$, $-OCF_3$, -C(O)O-C_{1-6}alkyl, -C_{1-4}alkylamino , phenoxy, benzoxy, and C_{1-4}alkylOH.

[0038] For example, compounds of Formula J, Formula K, Formula L or Formula M may be selected from the group consisting of:



and ;

wherein:

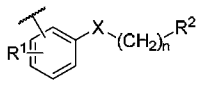
Q is independently, for each occurrence, N or CH;

V is independently, for each occurrence, O, S, NR^4, or a bond;

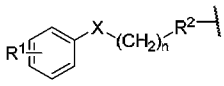
W is independently, for each occurrence, H, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, -NH-C_{1-6}alkyl, or -S-C_{1-6}alkyl; and

R^4 is independently selected from the group consisting of hydrogen, hydroxyl, halo, amino, thiol, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -S-C_{1-6}alkyl, haloC_{1-6}alkoxy, nitro, cyano, $-CF_3$, $-OCF_3$, -C(O)O-C_{1-6}alkyl, -C_{1-4}alkylamino , phenoxy, benzoxy, and C_{1-4}alkylOH.

[0039] In another embodiment, exemplary bromodomain ligands include compounds represented by the structures:



Formula N or



Formula O,

wherein:

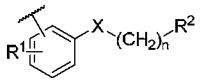
R^1 is selected from the group consisting of hydrogen, lower alkyl, phenyl, naphthyl, aralkyl, heteroalkyl, SO_2, NH_2, NO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, CN, and halogen;

R^2 is selected from the group consisting of hydrogen, lower alkyl, aralkyl, heteroalkyl, phenyl, naphthyl, SO_2, NH_2, NH_3^+, NO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, halogen, carboxy, and alkoxy;

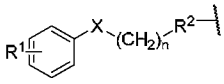
X is selected from the group consisting of lower alkyl, SO_2, NH, NO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, carboxy, and alkoxy; and

n is an integer from 0 to 10.

[0040] For example, compounds of Formula N or Formula O may be selected from the group consisting of:



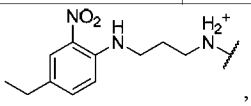
Formula N and

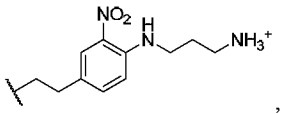
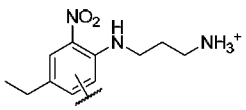


Formula O

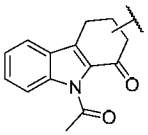
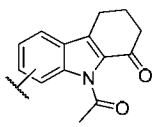
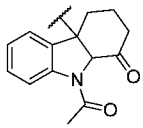
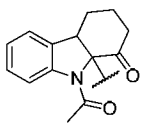
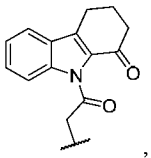
R^1	X	n	R^2
2-NO_2	NH	3	-NH_3^+
2-NO_2, 4-CH_3	NH	3	-NH_3^+
2-NO_2, 4-CH_2-CH_3	NH	3	-NH_3^+
2-NO_2, 3-CH_3	NH	3	-NH_3^+
2-NO_2, 5-CH_3	NH	3	-NH_3^+
2-NO_2, 4-Ph	NH	3	-NH_3^+
2-NO_2, 4-CN	NH	3	-NH_3^+
2-NO_2, 5-CN	NH	3	-NH_3^+
2-CH_3, 5-NO_2	NH	3	-NH_3^+
2-COO^-	NH	3	-NH_3^+
2-$COOCH_3$	NH	3	-NH_3^+
2-NO_2	O	3	-NH_3^+
2-NO_2, 4-CH_3	O	3	-NH_3^+
2-NO_2, 4-CH_3O	O	3	-NH_3^+

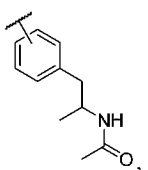
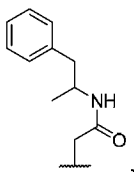
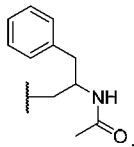
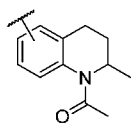
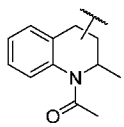
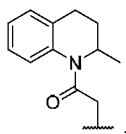
R^1	X	n	R^2
2-NO_2, 4-Cl	O	3	-NH_3^+
2-NO_2, 5-CH_3	O	3	-NH_3^+
2-NO_2, 3-CH_3	O	3	-NH_3^+
2-NO_2	CH_2	3	-NH_3^+
2-NO_2	NH	4	-NH_3^+
4-NO_2	NH	2	-NH_3^+
4-NO_2	NH	4	-NH_3^+
3-NH_2, 4-NO_2	NH	3	-COO^-
2-NO_2, 4-Cl	NH	2	-(OH)CH_3
2-Cl, 4-NO_2	NH	2	-(OH)CH_3

[0041] For example, the compound may be ,

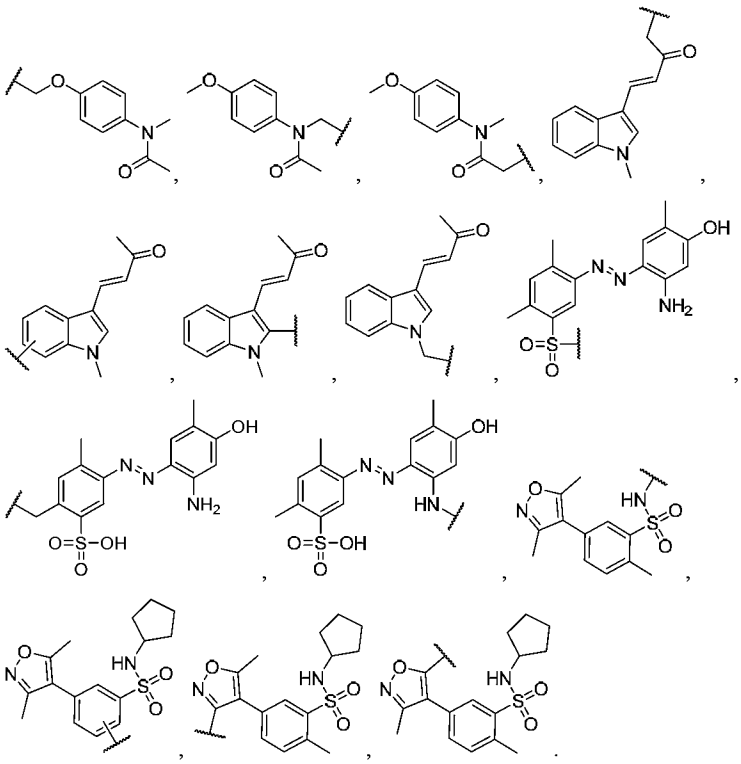
, .

[0042] In some embodiments, a ligand may be selected from the group consisting of:

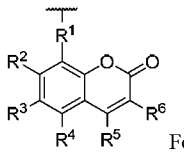
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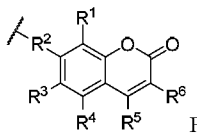
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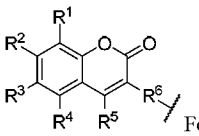
[0043] In yet another embodiment, exemplary bromodomain ligands include compounds represented by the structures:



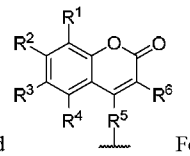
Formula P,



Formula Q,



Formula R, and

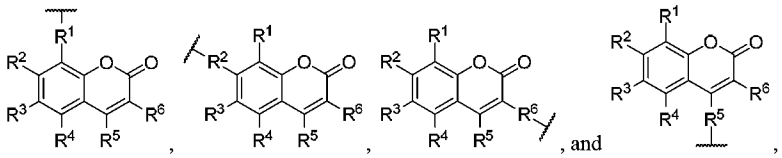


Formula S

wherein:

R^1, R^2, R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, lower alkyl, phenyl, naphthyl, aralkyl, heteroaryl, SO_2, NH_2, NH_3^+, NO^2, SO^2, CH^3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OCH_2CH_3, $OCH(CH_3)_2$, OCH_2COOH, $OCHCH_3COOH$, OCH_2COCH_3, OCH_2CONH_2, $OCOCH(CH_3)_2$, OCH_2CH_2OH, $OCH_2CH_2CH_3$, $O(CH_2)_3CH_3$, $OCHCH_3COOCH_3$, $OCH_2CON(CH_3)_2$, $NH(CH_2)_3N(CH_3)_2$, $NH(CH_2)_2N(CH_3)_2$, $NH(CH_2)_2OH$, $NH(CH_2)_3CH_3$, $NHCH_3$, SH, halogen, carboxy, and alkoxy.

[0044] In some embodiments, compounds of Formula P, Formula Q, Formula R, or Formula S may be selected from the group consisting of:

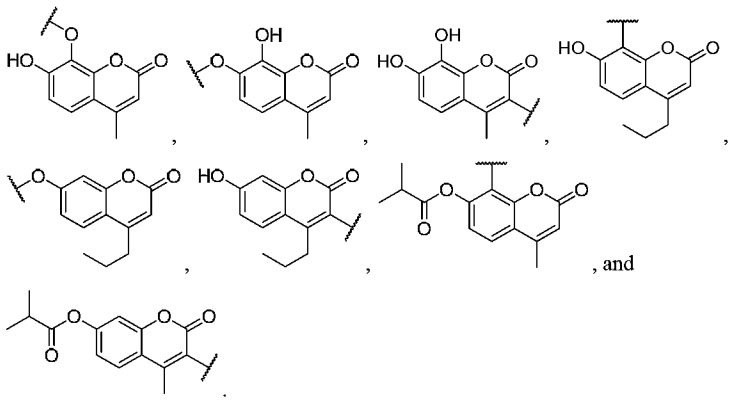


where:

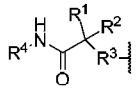
R^1	R^2	R^3	R^4	R^5	R^6
-OH	-OH	H	H	$-CH_3$	H
-OH	-OH	H	H	$-CH_2-CH_2-CH_3$	H
-OH	-OH	H	H	$-(CH_2)_2-CH_3$	H
-OH	-OH	H	H	-Ph	H
-OH	-OH	H	H	-cyclopentane	H
H	-OH	H	H	$-CH_3$	H
H	-OH	H	H	$-CH_2-CH_2-CH_3$	H
H	-OH	H	-OH	$-CH_2-CH_2-CH_3$	H
H	$-CH_3$	H	-OH	$-CH_2-CH_2-CH_3$	H
H	$-CH_3$	H	-OH	$-CH_2-CH_3$	H
H	$-O-CH_3$	H	H	$-CH_2-CH_3$	H
H	$-O-CH_3$	H	H	$-CH_2-CH_2-CH_3$	H
H	$-O-CH_2-CH_3$	H	H	$-CH_2-CH_3$	H
H	$-O-CH_2-CH_3$	H	H	$-CH_2-CH_2-CH_3$	H
H	$-O-CH(CH_3)_2$	H	H	$-CH_3$	H
H	$-O-CO-CH_3$	H	H	$-CH_2-CH_2-CH_3$	H
H	$-O-CH_2-CO-OH$	H	H	$-CH_2-CH_3$	H
H	$-O-CH_2-CO-OH$	H	H	$-(CH_2)_2-CH_3$	H

R^1	R^2	R^3	R^4	R^5	R^6
H	-O-CH(CH_3)-CO-OH	H	H	-$(CH_2)_2$-CH_3	H
H	-O-CH_2-CO-CH_3	H	H	-CH_2-CH_3	H
H	-O-CH_2-CO-NH_2	H	H	-CH_2-CH_3	H
H	-O-CO-CH_3	H	H	-CH_3	H
H	-O-CO-CH(CH_3)$_2$	H	H	-CH_3	H
H	-O-CH_2-CO-CH_3	H	H	-CH_3	H
H	-O-CH_2-CH_2-OH	H	H	-CH_3	H
H	-O-CH_2-CH_2-CH_3	H	H	-CH_3	H
H	-O-CH_2-CH_2-CH_3	H	H	H	H
H	-O-$(CH_2)_3$-CH_3	H	H	H	H
H	-O-CH(CH_3)-CO-OCH_3	H	H	H	H
H	-O-CH_2-CO-N(CH_3)$_2$	H	H	H	H
H	-O-CH(CH_3)$_2$	H	H	-cyclophentane	H
H	-O-CH_2-CH_3	-O-CH_2-CH_3	H	-CH_3	H
H	-CH_3	-NH-CO-CH_3	H	-CH_3	H
H	H	H	H	-NH-$(CH_2)_3$-N(CH_3)$_2$	-NH_2
H	H	H	H	-NH-$(CH_2)_2$-N(CH_3)$_2$	-NH_2
H	H	H	H	-NH-$(CH_2)_2$-OH	-NH_2
H	H	H	H	-NH-$(CH_2)_3$-CH_3	-NH_2
H	H	H	H	-NH-CH_3	-NH_2
H	H	H	H	-NH_2	-NH_2

[0045] For example, the compound may be selected from the group consisting of:



[0046] In still another embodiment, exemplary bromodomain ligands include compounds represented by the structure:

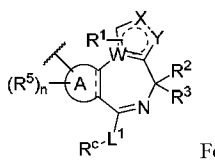


Formula T,

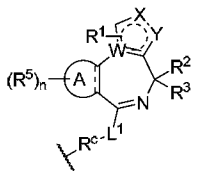
wherein:

R^1, R^2, and R^3 are independently selected from the group consisting of hydrogen, lower alkyl, phenyl, naphthyl, aralkyl, heteroaryl, SO_2, NH_2, NH_3^+, NO_2, SO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, SH, halogen, carboxy, and alkoxy; R^4 is selected from the group consisting of lower alkyl, phenyl, naphthyl, SO_2, NH, NO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, carboxy, and alkoxy.

In yet another embodiment, exemplary bromodomain ligands include compounds represented by the structures:



Formula U and



Formula V,

or a pharmaceutically acceptable salt thereof,

wherein:

X is O or N;

Y is O or N; wherein at least one of X or Y is O;

W is C or N;

R^1 is H, alkyl, alkenyl, alkynyl, aralkyl, phenyl, naphthyl, heteroaryl, halo, CN, OR^A, NR^AR^B, $N(R^A)S(O)_qR^AR^B$, $N(R^A)C(O)R^B$, $N(R^A)C(O)NR^AR^B$, $N(R^A)C(O)OR^A$, $N(R^A)C(S)NR^AR^B$, $S(O)_qR^A$, $C(O)R^A$, $C(O)OR^A$, $OC(O)R^A$, or $C(O)NR^AR^B$;

each R^A is independently alkyl, alkenyl, or alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; phenyl; naphthyl, heteroaryl; heterocyclic; carbocyclic; or hydrogen;

each R^B is independently alkyl, alkenyl, or alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; phenyl; naphthyl; heteroaryl; heterocyclic; carbocyclic; or hydrogen; or

R^A and R^B, together with the atoms to which each is attached, can form a heterocycloalkyl or a heteroaryl; each of which is optionally substituted;

Ring A is cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl;

R^C is alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl, each optionally substituted with 1-5 independently selected R^4, and when L^1 is other than a covalent bond, R^C is additionally selected from H;

R^2 and R^3 are each independently H, halogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, heterocycloalkyl, -OR, -SR, -CN, -N(R')(R''), -C(O)R, -C(S)R, $-CO_2R$, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, $-C(O)CH_2C(O)R$, -C(S)N(R')(R''), -C(S)OR, -S(O)R, $-SO_2R$, $-SO_2N(R')(R'')$, -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R"), $-N(R')SO_2R$, $-N(R')SO_2N(R')(R'')$, -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, -OC(O)N(R')(R''), or $-(CH_2)_pR^x$; or

R_2 and R_3 together with the atoms to which each is attached, form an optionally substituted 3-7 membered saturated or unsaturated spiro-fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^x is independently halogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, heterocycloalkyl, -OR, -SR, -CN, -N(R')(R''), -C(O)R, -C(S)R, $-CO_2R$, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, $-C(O)CH_2C(O)R$, -C(S)N(R')(R''), -C(S)OR, -S(O)R, $-SO_2R$, $-SO_2N(R')(R'')$, -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), $-N(R')SO_2R$, $-N(R')SO_2N(R')(R'')$, -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, -OC(O)N(R')(R'');

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by -NR'-, -N (R')C(O)-, -C(O)N(R')-, -N(R')SO_2-, -SO_2N(R')- -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

each R is independently hydrogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, or heterocycloalkyl;

each R' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R_2), -C(S)N(R_2), -S(O)R, -SO_2R, -SO_2N(R_2), or two R groups on the same nitrogen are taken together with their intervening atoms to form an heteroaryl or heterocycloalkyl group; each R'' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R_2), -C(S)N(R_2), -S(O)R, -SO_2R, -SO_2N(R_2), or two R groups on the same nitrogen are taken together with their intervening atoms to form an heteroaryl or heterocycloalkyl group; or

R' and R'', together with the atoms to which each is attached, can form cycloalkyl, heterocycloalkyl, phenyl, naphthyl, or heteroaryl; each of which is optionally substituted;

each R^4 is independently alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, or heterocycloalkyl, halogen, -OR, -SR, -N(R')(R''), -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R"), -C=NN(R')(R"), -C=NOR, -C(=N(R'))N(R')(R"), -OC(O)R, or -OC(O)N(R')(R'');

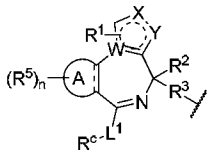
each R^5 is independently -R, halogen, -OR, -SR, -N(R')(R''), -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, or -OC(O)N(R')(R'');

n is 0-5;

each q is independently 0, 1, or 2; and

p is 1-6.

[0047] In still another embodiment, exemplary bromodomain ligands include compounds represented by the structure:



Formula W,

wherein:

X is O or N;

Y is O or N; wherein at least one of X or Y is O;

W is C or N;

R^1 is H, alkyl, alkenyl, alkynyl, aralkyl, phenyl, naphthyl, heteroaryl, halo, CN, OR^A, NR^AR^B, $N(R^A)S(O)_qR^AR^B$, $N(R^A)C(O)R^B$, $N(R^A)C(O)NR^AR^B$, $N(R^A)C(O)OR^A$, $N(R^A)C(S)NR^AR^B$, $S(O)_qR^A$, $C(O)R^A$, $C(O)OR^A$, $OC(O)R^A$, or $C(O)NR^AR^B$;

each R^A is independently optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; phenyl; naphthyl; heteroaryl; heterocyclic; carbocyclic; or hydrogen;

each R^B is independently alkyl, alkenyl, or alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; phenyl; naphthyl; heteroaryl; heterocyclic; carbocyclic; or hydrogen; or

R^A and R^B, together with the atoms to which each is attached, can form a heterocycloalkyl or a heteroaryl; each of which is optionally substituted;

Ring A is cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl;

R^C is alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl, each optionally substituted with 1-5 independently selected R^4, and when L^1 is other than a covalent bond, R^C is additionally selected from H;

R^2 is H, halogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, heterocycloalkyl, -OR, -SR, -CN, -N(R')(R''), -C(O)R, -C(S)R, $-CO_2R$, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, $-C(O)CH_2C(O)R$, -C(S)N(R')(R''), -C(S)OR, -S(O)R, $-SO_2R$, $-SO_2N(R')(R'')$, -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R"), $-N(R')SO_2R$, $-N(R')SO_2N(R')(R'')$, -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, -OC(O)N(R')(R''), or $-(CH_2)_pR^X$;

R^3 is a bond or optionally substituted alkyl; or

R_2 and R_3 together with the atoms to which each is attached, form an optionally substituted 3-7 membered saturated or unsaturated spiro-fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^x is independently halogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, heterocycloalkyl, -OR, -SR, -CN, -N(R')(R''), -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, -OC(O)N(R')(R'');

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by -NR'-, -N (R')C(O)-, -C(O)N(R')-, -N(R')SO_2-, -SO_2N(R')-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, or -SO_2-;

each R is independently hydrogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, or heterocycloalkyl;

each R' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N$(R)_2$, -C(S)N$(R)_2$, -S(O)R, -SO_2R, -SO_2N$(R)_2$, or two R groups on the same nitrogen are taken together with their intervening atoms to form an heteroaryl or heterocycloalkyl group; each R'' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N$(R)_2$, -C(S)N$(R)_2$, -S(O)R, -SO_2R, -SO_2N$(R)_2$, or two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heteroaryl or heterocycloalkyl group; or

R' and R'', together with the atoms to which each is attached, can form cycloalkyl, heterocycloalkyl, phenyl, naphthyl, or heteroaryl; each of which is optionally substituted;

each R^4 is independently alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, or heterocycloalkyl, halogen, -OR, -SR, -N(R')(R''), -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R"), -C=NN(R')(R"), -C=NOR, -C(=N(R'))N(R')(R"), -OC(O)R, or -OC(O)N(R')(R'');

each R^5 is independently -R, halogen, -OR, -SR, -N(R')(R''), -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -

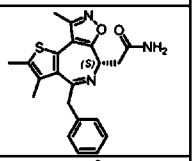
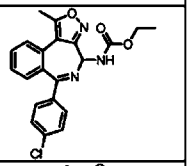
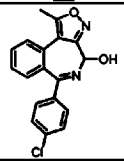
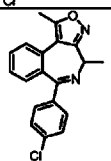
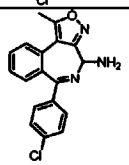
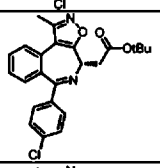
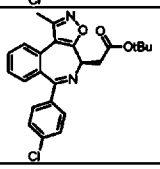
N(R')C(=N(R''))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R''))N(R')(R''), -OC(O)R, or -OC(O)N(R')(R'');

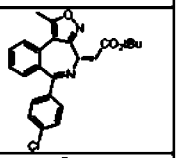
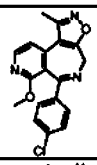
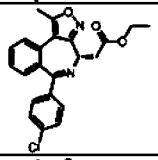
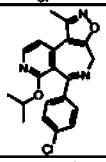
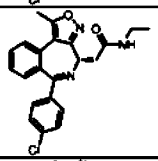
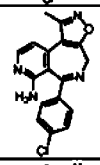
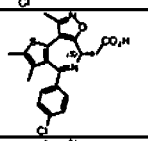
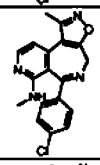
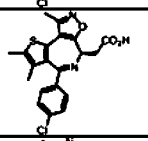
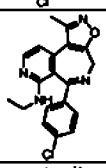
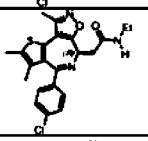
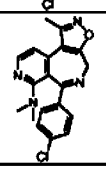
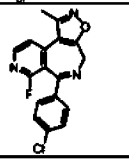
n is 0-5;

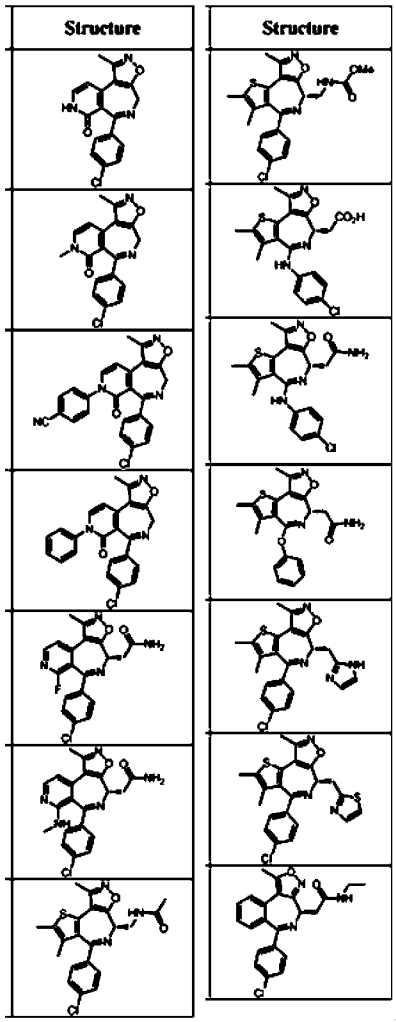
each q is independently 0, 1, or 2; and

p is 1-6.

[0048] In yet another embodiment, compounds of Formula U, Formula V, and Formula W may be selected from the group consisting of:

Structure	Structure
	
	
	
	

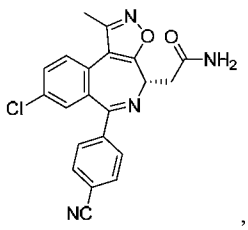
Structure	Structure
	
	
	
	
	
	
	

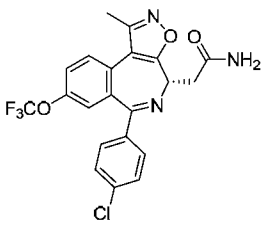


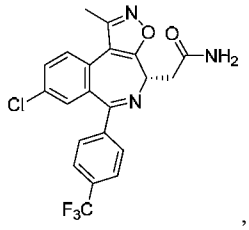
. It will be appreciated that each of these compounds may be connected to a –Y-Z moiety, for example, as illustrated for generic structures Formula U, Formula V, and Formula W above.

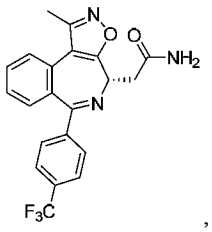
[0049] For example, compounds of Formula U, Formula V, and Formula W may be selected from the group consisting of:

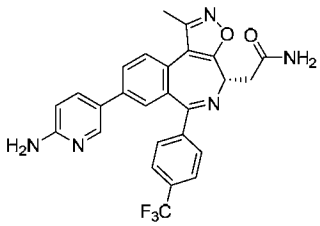
Atty Docket No. COF-018PC

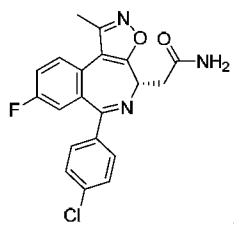


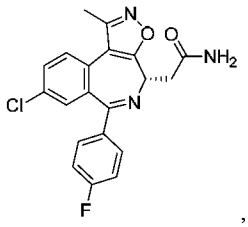
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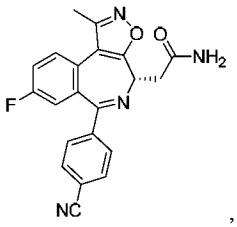
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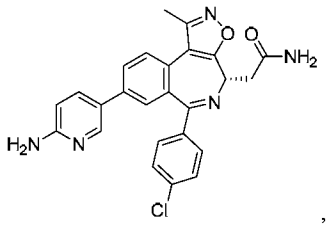
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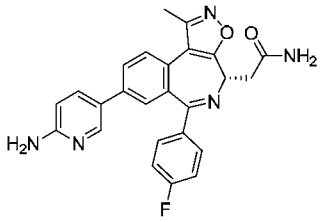
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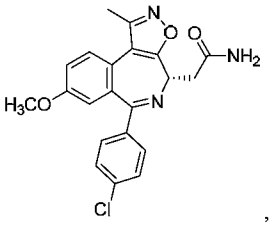
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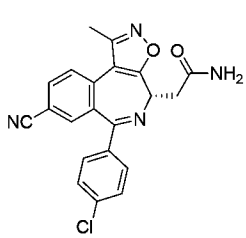
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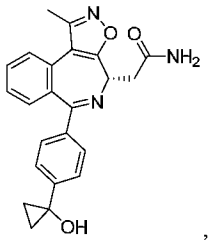
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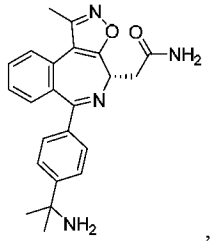
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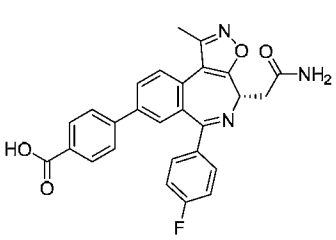
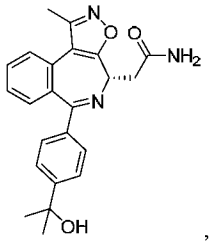
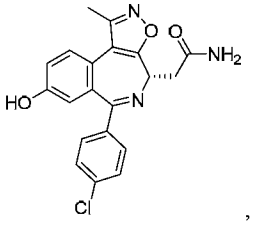
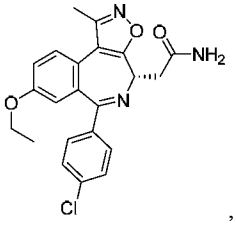
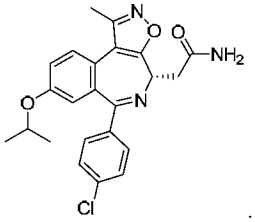
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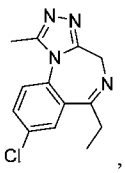
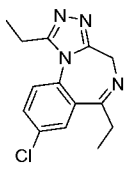
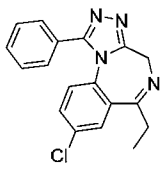
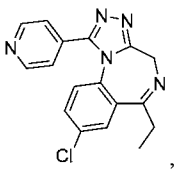
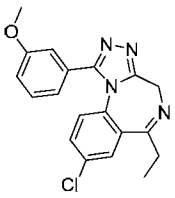
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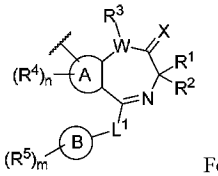
, and . It will be appreciated that each of these compounds may be connected to a –Y-Z moiety, for example, as illustrated for generic structures Formula U, Formula V, and Formula W above.

[0050] In some embodiments, compounds of Formula U, Formula V, and Formula W may be selected from the group consisting of:

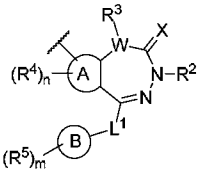






, , , , , and . It will be appreciated that each of these compounds may be connected to a –Y-Z moiety, for example, as illustrated for generic structures Formula U, Formula V, and Formula W above.

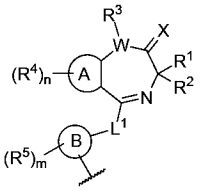
[0051] In some embodiments, exemplary bromodomain ligands include compounds represented by the structures:



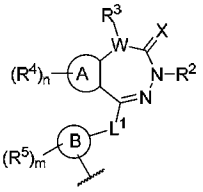
Formula X,



Formula XX,



Formula Y, and



Formula YY,

wherein:

Ring A is benzo, or a 5-6 membered fused heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is a 3-7 membered saturated or partially unsaturated carbocyclic ring, phenyl, an 8-10 membered bicyclic saturated, partially unsaturated, phenyl or naphthyl ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by –NR'-, -N(R')C(O)-, -C(O)N(R'), -N(R')SO_2-, -SO_2N(R'), -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

R^1 is hydrogen, halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$, or -$(CH_2)_pR^x$;

p is 0-3;

R^x is halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -$N(R')_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)$N(R')_2$, -C(O)SR, -C(O)C(O)R, -$C(O)CH_2C(O)R$, -C(S)$N(R')_2$, -C(S)OR, -S(O)R, -SO_2R, -$SO_2N(R')_2$, -N(R')C(O)R, -N(R')C(O)$N(R')_2$, -N(R')C(S)$N(R')_2$, -N(R')SO_2R, -N(R')$SO_2N(R')_2$, -N(R')$N(R')_2$, -N(R')C(=N(R'))$N(R')_2$, -C=NN$(R')_2$, -C=NOR, -C(=N(R'))$N(R')_2$, -OC(O)R, -OC(O)$N(R')_2$;

R^2 is hydrogen, halogen, -CN, -SR, or optionally substituted C_{1-6} aliphatic, or:

R^1 and R^2 are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 7-10 membered bicyclic saturated, partially unsaturated, phenyl or naphthyl ring, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)$N(R)_2$, -C(S)$N(R)_2$, -S(O)R, -SO_2R, -$SO_2N(R)_2$, or two R' on the same nitrogen are taken together with their intervening atoms to form an optionally substituted group selected from a 4-7 membered monocyclic saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 7-12 membered bicyclic saturated, partially unsaturated, or aromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

W is ;

R^3 is optionally substituted C_{1-6} aliphatic;

X is oxygen or sulfur, or:

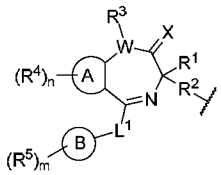
R^3 and X are taken together with their intervening atoms to form an optionally substituted

5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

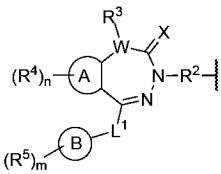
each of m and n is independently 0-4, as valency permits; and

each of R^4 and R^5 is independently -R, halogen, -OR, -SR, -N(R')$_2$, -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, or -OC(O)N(R')$_2$.

[0052] In another embodiment, exemplary bromodomain ligands include compounds represented by the structures:



Formula Z and



Formula ZZ,

wherein:

Ring A is benzo, or a 5-6 membered fused heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is a 3-7 membered saturated or partially unsaturated carbocyclic ring, phenyl, an 8-10 membered bicyclic saturated, partially unsaturated, phenyl or naphthyl ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by –NR'-, -N(R')C(O)-, -C(O)N(R'), -N(R')SO_2-, -SO_2N(R'), -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

R^1 is hydrogen, halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -

$N(R')SO_2R$, $-N(R')SO_2N(R')_2$, $-N(R')N(R')_2$, $-N(R')C(=N(R'))N(R')_2$, $-C=NN(R')_2$, $-C=NOR$, $-C(=N(R'))N(R')_2$, $-OC(O)R$, $-OC(O)N(R')_2$, or $-(CH_2)_pR^x$;

p is 0-3;

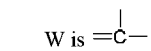
R^x is halogen, optionally substituted C_{1-6} aliphatic, $-OR$, $-SR$, $-CN$, $-N(R')_2$, $-C(O)R$, $-C(S)R$, $-CO_2R$, $-C(O)N(R')_2$, $-C(O)SR$, $-C(O)C(O)R$, $-C(O)CH_2C(O)R$, $-C(S)N(R')_2$, $-C(S)OR$, $-S(O)R$, $-SO_2R$, $-SO_2N(R')_2$, $-N(R')C(O)R$, $-N(R')C(O)N(R')_2$, $-N(R')C(S)N(R')_2$, $-N(R')SO_2R$, $-N(R')SO_2N(R')_2$, $-N(R')N(R')_2$, $-N(R')C(=N(R'))N(R')_2$, $-C=NN(R')_2$, $-C=NOR$, $-C(=N(R'))N(R')_2$, $-OC(O)R$, $-OC(O)N(R')_2$;

R^2 is a bond or optionally substituted C_{1-6} aliphatic, or:

R^1 and R^2 are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 7-10 membered bicyclic saturated, partially unsaturated, phenyl, or naphthyl ring, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R' is independently -R, $-C(O)R$, $-C(S)R$, $-CO_2R$, $-C(O)N(R)_2$, $-C(S)N(R)_2$, $-S(O)R$, $-SO_2R$, $-SO_2N(R)_2$, or two R' on the same nitrogen are taken together with their intervening atoms to form an optionally substituted group selected from a 4-7 membered monocyclic saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 7-12 membered bicyclic saturated, partially unsaturated, or aromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

W is ;

R^3 is optionally substituted C_{1-6} aliphatic;

X is oxygen or sulfur, or:

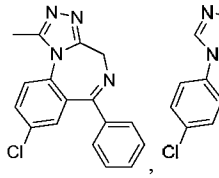
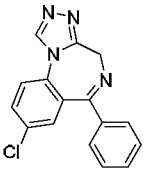
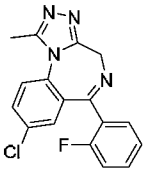
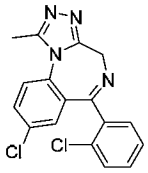
R^3 and X are taken together with their intervening atoms to form an optionally substituted

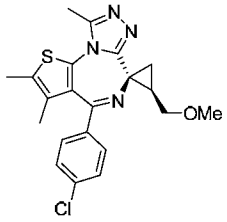
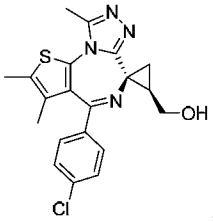
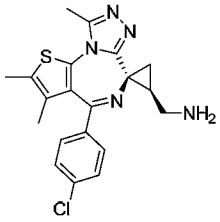
5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

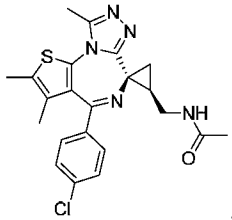
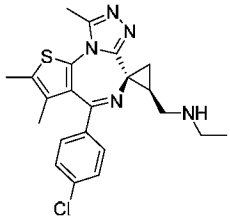
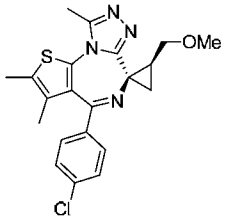
each of m and n is independently 0-4, as valency permits; and

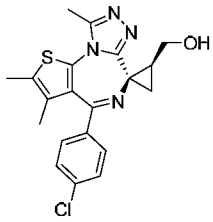
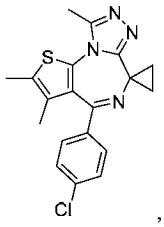
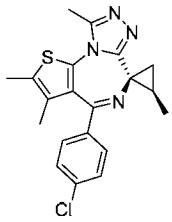
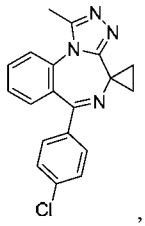
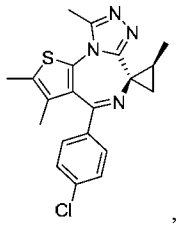
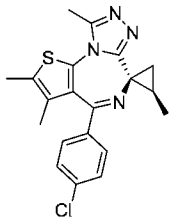
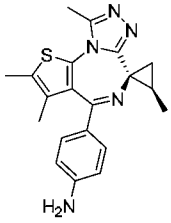
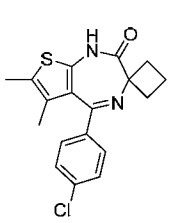
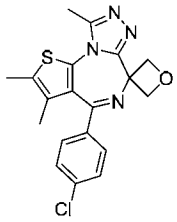
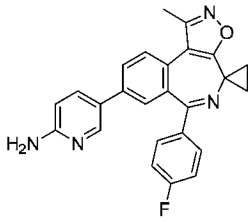
each of R^4 and R^5 is independently –R, halogen, -OR, -SR, -N(R')$_2$, -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, or -OC(O)N(R')$_2$.

[0053] For example, a compound of Formula X, Formula Y, or Formula Z may be selected from the group consisting of:

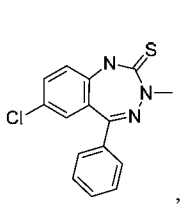
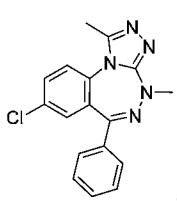
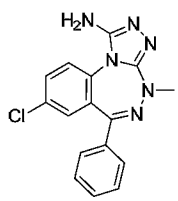
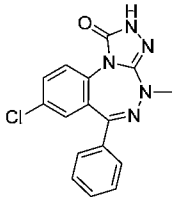





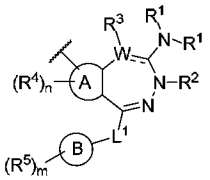





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, and

. It will be appreciated that each of these compounds may be connected to a –Y-Z moiety, for example, as illustrated for generic structures Formula X, Formula Y, and Formula Z above.

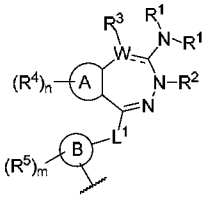
[0054] In some embodiments, a compound of Formula XX, Formula YY, or Formula ZZ may be selected from the group consisting of:


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, and

. It will be appreciated that each of these compounds may be connected to a –Y-Z moiety, for example, as illustrated for generic structures Formula XX, Formula YY, and Formula ZZ above.

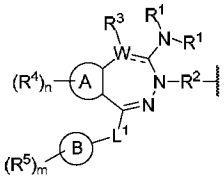
[0055] In another embodiment, exemplary bromodomain ligands include compounds represented by the structures:



Formula XXA,



Formula YYA, and



Formula ZZA,

wherein:

Ring A is benzo, or a 5-6 membered fused heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is a 3-7 membered saturated or partially unsaturated carbocyclic ring, phenyl, an 8-10 membered bicyclic saturated, partially unsaturated, phenyl, or naphthyl ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by –NR'-, -N(R')C(O)-, -C(O)N(R'), -N(R')SO_2-, -SO_2N(R'), -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

R^1 is independently hydrogen, halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$, or -$(CH_2)_pR^x$;

p is 0-3;

R^x is halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$;

R^2 is a bond, hydrogen, or optionally substituted C_{1-6} aliphatic;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 7-10 membered bicyclic saturated, partially unsaturated, phenyl, or naphthyl ring, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R)$_2$, -C(S)N(R)$_2$, -S(O)R, -SO_2R, -SO_2N(R)$_2$, or two R' on the same nitrogen are taken together with their intervening atoms to form an optionally substituted group selected from a 4-7 membered monocyclic saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 7-12 membered bicyclic saturated, partially unsaturated, or aromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

W is C or N;

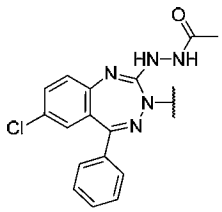
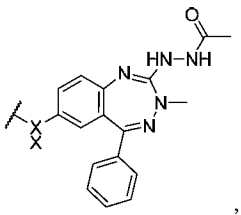
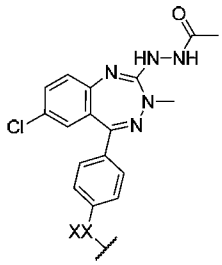
R^3 is optionally substituted C_{1-6} aliphatic;

=== is a single or double bond;

each of m and n is independently 0-4, as valency permits; and

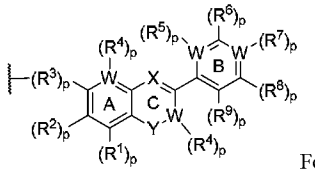
each of R^4 and R^5 is independently –R, halogen, -OR, -SR, -N(R')$_2$, -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, or -OC(O)N(R')$_2$.

[0056] For example, a compound of formula XXA, YYA, or ZZA may be:

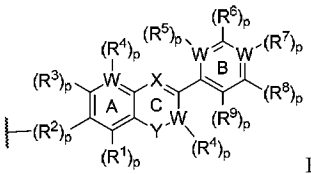




[0057] wherein XX may be a bond, C_{1-6}alkyl, -NR^t- (where t is H, phenyl, or C_{1-6}alkyl), -O-, or -$S(O)_w$- wherein w is 0, 1, or 2;

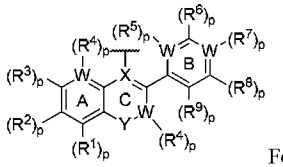
[0058] In yet another embodiment, exemplary bromodomain ligands include compounds represented by the structure:



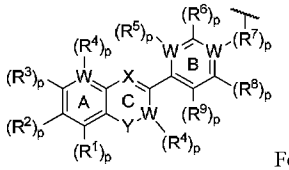
Formula AA,



Formula AA1,



Formula AA2,



Formula AA3,

wherein:

X is selected from N and CH;

Y is CO;

R^1 and R^3 are each independently selected from alkoxy and hydrogen;

R^2 is selected from alkoxy, alkyl, and hydrogen;

R^6 and R^8 are each independently selected from alkyl, alkoxy, chloride, and hydrogen;

R^5 and R^9 are each hydrogen;

R^7 is selected from amino, hydroxyl, alkoxy, and alkyl substituted with a heterocyclyl;

R^{10} is hydrogen; or

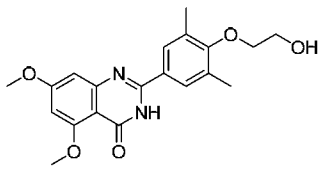
two adjacent substituents selected from R^6, R^7, and R^8 are connected to form a heterocyclyl;

each W is independently selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1;

for W-$(R^{10})_p$, W is N and p is 1; and

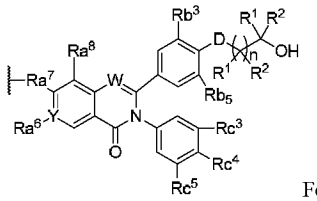
for W-$(R^4)_p$, W is C, p is 1 and R^4 is H, or W is N and p is 0.

[0059] For example, in some embodiments, a compound of Formula AA may be:

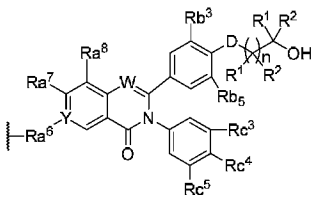


[0060] (2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-5,7-dimethoxyquinazolin-4(3H)-one). It will be appreciated that this compound may be connected to a –Y-Z moiety, for example, as illustrated for generic structures Formula AA, Formula AA1, Formula AA2, and Formula AA3 above.

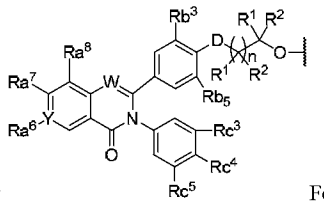
[0061] In still another embodiment, exemplary bromodomain ligands include compounds represented by the structures:



Formula BB,



Formula CC, or



Formula DD,

wherein:

Y and W are each independently selected from carbon and nitrogen;

Ra^6 is selected from fluoride, hydrogen, C_1-C_3 alkoxy, cyclopropyloxy, SO_2R_3, SOR_3, and SR_3, wherein if Y is nitrogen then Ra^6 is absent;

Ra^7 is selected from hydrogen, fluoride, SO_2R_3, SOR_3, and SR_3;

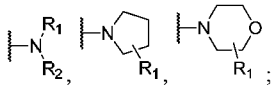
Ra^8 is selected from hydrogen, C_1-C_3 alkoxy, cyclopropyloxy, chloride, and bromide;

n is selected from 1, 2, or 3;

D is selected from O, NH, NR_1, S, or C;

Rb^3 and Rb^5 are independently selected from hydrogen and C_1-C_3 alkyl;

R_C^3 and R_C^5 are independently selected from hydrogen, C_1-C_3 alkyl, and cyclopropyl;

R_C^4 is selected from F, Cl, Br, I, CF_3, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $NHC(O)R^4$, $NHSO_2R^4$, $C(O)OR^4$, and ;

R^1, R'^1, R^2 and R'^2 are independently selected from hydrogen, fluoride, C_1-C_3 alkyl, and cyclopropyl, wherein R^1 and R^2 and/or R'^1 and R'^2 may be connected to form a 3-6 membered ring;

R^3 is selected from C_1-C_3 alkyl and cyclopropyl; and

R^4 is selected from hydrogen, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, phenyl, and naphthyl, provided that if Ra^7 or Ra^6 is fluoride, then R_C^4 is not bromide.

[0062] In some embodiments, a compound of Formula AA, Formula AA1, Formula AA2, Formula AA3, Formula BB, or Formula CC may be selected from the group consisting of:

3-(4-sec-butylphenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

3-(4-bromophenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin- 4(3H)-one;

3-(4-sec-butylphenyl)-7-fluoro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

3-(4-sec-butylphenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)pyrido[4,3-d]pyrimidin-4(3H)-one;

3-(4-sec-butylphenyl)-2-(4-(2-hydroxyethoxy)phenyl)quinazolin-4(3H)-one;

3-(4-fluorophenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-3-(4-iodophenyl)quinazolin-4(3H)-one;

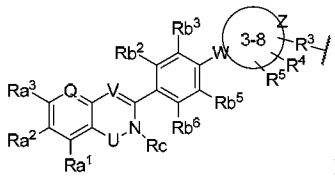
3-(4-sec-butylphenyl)-6-fluoro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-3-(4-(trifluoromethyl)phenyl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-7-(methylsulfonyl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-methoxyquinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-8-methoxyquinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-(methylsulfonyl)quinazolin-4(3H)-one;
3-(4-bromophenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-6-methoxyquinazolin-4(3H)-one;
3-(4-bromophenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-8-methoxyquinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-3-(4-isopropylphenyl)quinazolin-4(3H)-one;
3-(4-bromophenyl)-2-(4-(2-hydroxyethoxy)-3-methyiphenyl)quinazolin-4(3H)-one;
3-(4-bromophenyl)-8-chloro-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-3-(4-morpholinophenyl)quinazolin-4(3H)-one;
3-(4-tert-butylphenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
N-(4-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxoquinazolin-3(4H)-yl)phenyl)acetamide;
N-(4-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxoquinazolin-3(4H)-yl)phenyl)isobutyramide;
methyl 4-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxoquinazolin-3(4H)-yl)benzoate;
3-(4-cyclohexylphenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;
N-(4-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxoquinazolin-3(4H)-yl)phenyl)formamide;
3-(4-aminophenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)quinazolin-4(3H)-one;

N-(4-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxoquinazolin-3(4H)-yl)phenyl)methanesulfonamide;
N-(4-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxoquinazolin-3(4H)-yl)phenyl)benzenesulfonamide;
N-(4-(2-(4-(2-hydroxyethoxy)-3,5-dimethylphenyl)-4-oxoquinazolin-3(4H)-yl)phenyl)propane-2-sulfonamide;
3-(4-(dimethylamino)phenyl)-2-(4-(2-hydroxyethoxy)-3,5-dimethyiphenyl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(4-(2-hydroxyethoxy)-3-methylphenyl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(4-(2-hydroxyethoxy)-3-methylphenyl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(quinolin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(5-fluoropyridin-3-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(6-chloropyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-chloropyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-methoxypyridin-3-yl)quinazolin-4(3H)-one;
2-(6-bromopyridin-3-yl)-3-(4-chlorophenyl)quinazolin-4(3H)-one;
2-(6-bromopyridin-3-yl)-3-(4-sec-butylphenyl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(6-(diethylamino)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-(diethylamino)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(pyrimidin-5-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-methylpyridin-3-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(6-methylpyridin-3-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(6-(piperidin-1-yl)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-(piperidin-1-yl)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(6-phenoxypyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-fluoropyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-phenoxypyridin-3-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(6-(trifluoromethyl)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-(trifluoromethyl)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-phenylpyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(5-phenylpyridin-3-yl)quinazolin-4(3H)-one;
2-(5-bromopyridin-3-yl)-3-(4-sec-butylphenyl)quinazolin-4(3H)-one;

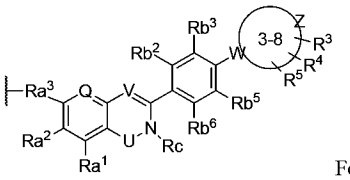
2-(5-bromopyridin-3-yl)-3-(4-chlorophenyl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(5-(diethylamino)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(5-phenylpyridin-3-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(5-(diethylamino)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-cyclopentylphenyl)-2-(6-methylpyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-(hydroxymethyl)pyridin-3-yl)quinazolin-4(3H)-one;
2-(6-methylpyridin-3-yl)-3-(4-(methylthio)phenyl)quinazolin-4(3H)-one;
3-(4-isopropylphenyl)-2-(6-methylpyridin-3-yl)quinazolin-4(3H)-one;
N-(4-(2-(6-methylpyridin-3-yl)-4-oxoquinazolin-3(4H)-yl)phenyl)methanesulfonamide;
3-(4-sec-butylphenyl)-2-(6-(morpholinomethyl)pyridin-3-yl)quinazolin-4(3H)-one;
3-(4-cyclopropylphenyl)-2-(6-methylpyridin-3-yl)quinazolin-4(3H)-one;
3-(4-(dimethylamino)phenyl)-2-(6-methylpyridin-3-yl)quinazolin-4(3H)-one;
2-(6-chloropyridin-3-yl)-3-(4-cyclopropylphenyl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(6-morpholinopyridin-3-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(1H-indazol-5-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(1H-indol-5-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(1H-indol-5-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(2-(hydroxymethyl)-1H-benzo[d]imidazol-6-yl)quinazolin-4(3H)-one;
2-(1H-indol-5-yl)-3-(4-(trifluoromethoxy)phenyl)quinazolin-4(3H)-one;
2-(1H-indol-5-yl)-3-(4-isopropylphenyl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(1-(4-methoxyphenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(1-(4-fluorophenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)quinazolin-4(3H)-one;
3-(4-(dimethylamino)phenyl)-2-(1H-indol-5-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(1-(phenylsulfonyl)-1H-pyrrolo[2,3-b]pyridin-5-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(2-(hydroxymethyl)-1H-indol-5-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(1-methyl-1H-indol-5-yl)quinazolin-4(3H)-one;
3-(4-cyclopentylphenyl)-2-(1H-indol-5-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(1H-indol-6-yl)quinazolin-4(3H)-one;
3-(4-chlorophenyl)-2-(1H-indol-7-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(1H-indol-6-yl)quinazolin-4(3H)-one;
3-(4-sec-butylphenyl)-2-(1H-indol-7-yl)quinazolin-4(3H)-one;

3-(4-chlorophenyl)-2-(1H-indol-4-yl)quinazolin-4(3H)-one; and 3-(4-sec-butylphenyl)-2-(1H-indol-4-yl)quinazolin-4(3H)-one. It will be appreciated that each of these compounds may be connected to a –Y-Z moiety, for example, as illustrated for generic structures Formula AA, Formula AA1, Formula AA2, Formula AA3, Formula BB, Formula CC, and Formula DD.

[0063] In yet another embodiment, exemplary bromodomain ligands include compounds represented by the structure:



Formula DD or



Formula EE,

wherein:

Q and V are independently selected from CH and nitrogen;

U is selected from C=O, C=S, SO_2, S=O, SR^1, CR^1R^2, CR^1OR^2, CR^1SR^2;

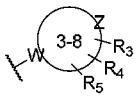
R^1 and R^2 are independently selected from hydrogen and C_1-C_6 alkyl;

Rc is selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

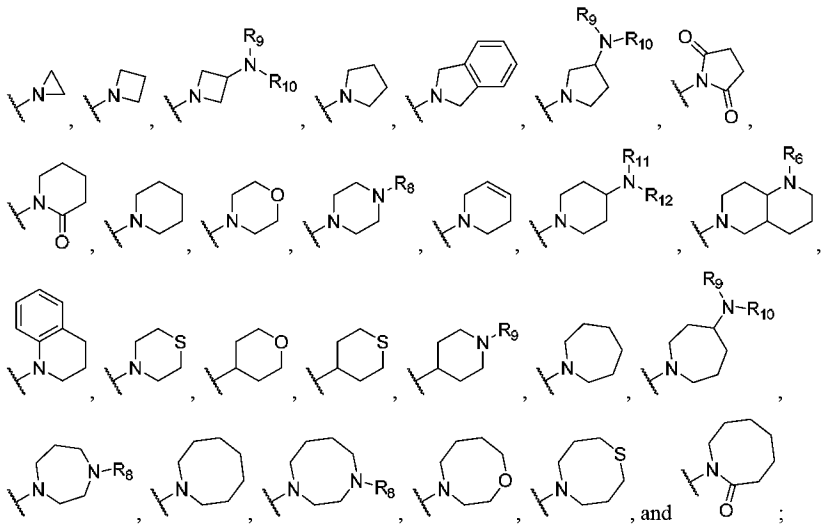
Ra^1, Ra^2, and Ra^3 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 alkoxy, halogen, amino, amide, hydroxyl, heterocycle, and C_3-C_6 cycloalkyl, wherein Ra^1 and Ra^2 and/or Ra^2 and Ra^3 may be connected to form a cycloalkyl or a heterocycle;

Rb^2 and Rb^6 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_6 cycloalkyl, hydroxyl, and amino;

Rb^3 and Rb^5 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, hydroxyl, and amino, wherein Rb^2 and Rb^3 and/or Rb^5 and Rb^6 may be connected to form a cycloalkyl or a heterocycle;



represents a 3-8 membered ring system wherein: W is selected from carbon and nitrogen; Z is selected from CR^6R^7, NR^8, oxygen, sulfur, -S(O)-, and -SO_2-; said ring system being optionally fused to another ring selected from cycloalkyl, heterocycle, and phenyl, and wherein said ring system is optionally selected from rings having the structures:



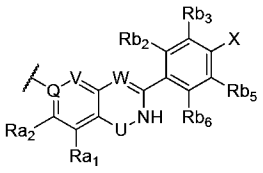
R^3, R^4, and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, phenyl, naphthyl, aryloxy, hydroxy1, amino, amide, oxo, -CN, and sulfonamide;

R^6 and R^7 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, naphthyl, halogen, hydroxyl, -CN, amino, and amido; and

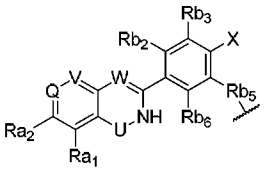
R^8 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, acyl, and C_3-C_6 cycloalkyl; and

R^9, R^{10}, R^{11}, and R^{12} are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, naphthyl, heterocycle, hydroxyl, sulfonyl, and acyl.

[0064] In still another embodiment, exemplary bromodomain ligands include compounds represented by the structure:



Formula FF and



Formula GG,

wherein:

Q is selected from N and CRa^3;

V is selected from N and CRa^4;

W is selected from N and CH;

U is selected from C=O, C=S, SO_2, S=O, and SR^1;

X is selected from OH, SH, NH_2, S(O)H, $S(O)_2H$, $S(O)_2NH_2$, $S(O)NH_2$, NHAc, and $NHSO_2Me$;

Ra^1, Ra^3, and Ra^3 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, and halogen;

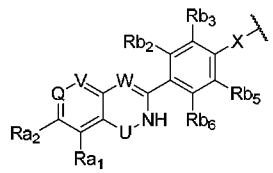
Ra^2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, amino, amide, and halogen;

Rb^2 and Rb^6 are independently selected from hydrogen, methyl and fluorine;

Rb^3 and Rb^5 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy; and

Rb^2 and Rb^3 and/or Rb^5 and Rb^6 may be connected to form a cycloalkyl or a heterocycle, provided that at least one of Ra^1, Ra^2, Ra^3, and Ra^4 is not hydrogen.

[0065] In yet another embodiment, exemplary bromodomain ligands include compounds represented by the structure:



Formula HH,

wherein:

Q is selected from N and CRa^3;

V is selected from N and CRa^4;

W is selected from N and CH;

U is selected from C=O, C=S, SO_2, S=O, and SR^1;

X is selected from OH, SH, NH_2, S(O)H, $S(O)_2H$, $S(O)_2NH_2$, $S(O)NH_2$, NHAc, and $NHSO_2Me$;

Ra^1, Ra^3, and Ra^3 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, and halogen;

Ra^2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, amino, amide, and halogen;

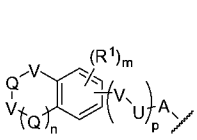
Rb^2 and Rb^6 are independently selected from hydrogen, methyl and fluorine;

Rb^3 and Rb^5 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy; and

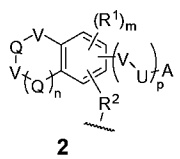
Rb^2 and Rb^3 and/or Rb^5 and Rb^6 may be connected to form a cycloalkyl or a heterocycle, provided that at least one of Ra^1, Ra^2, Ra^3, and Ra^4 is not hydrogen.

[0066] The following are hereby incorporated by reference in their entirety: Zeng *et al.* J. Am. Chem. Soc. (2005) *127*, 2376-2377; Chung *et al.* J. Med. Chem. (2012) *55*, 576-586; Filippakopoulos *et al.* Bioorg. Med. Chem. (2012) *20*, 1878-1886; U.S. Patent No. 8,053,440, by Hansen; U.S. Patent Publication No. 2008/0188467, by Wong *et al.*; U.S. Patent Publication No. 2012/0028912; International Patent Publication Nos. WO/2010/123975, WO/2010/106436, WO/2010/079431, WO/2009/158404, and WO/2008/092231, by Hansen *et al.*; International Patent Publication Nos. WO/2012/075456 and WO/2012/075383, by Albrecht *et al.*; International Patent Publication Nos. WO/2007/084625 and WO/2006/083692, by Zhou *et al.*

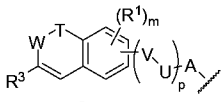
[0067] In another aspect, exemplary bromodomain ligands include fused heterocyclic systems represented by the structures:



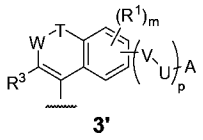
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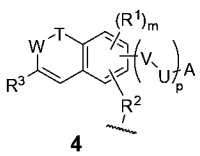
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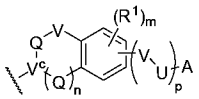


3'



4

and



5

;

wherein:

V is independently selected, for each occurrence, from the group consisting of NH, S, $N(C_{1-6}alkyl)$, O, or CR^4R^4;

Q is independently selected, for each occurrence, from the group consisting of C(O), C(S), C(N), SO_2, or CR^4R^4;

U is independently selected from the group consisting of a bond, C(O), C(S), C(N), SO_2, or CR^4R^4

W and T are independently selected from the group consisting of NH, $N(C_{1-6}alkyl)$, O, or Q;

V^C is selected from the group consisting of N, SH or CR^4;

A is selected from the group consisting of aliphatic, cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl or bicyclic moiety, wherein the cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl, or bicyclic moiety is optionally substituted with one, two, three, four or more groups represented by R^4;

R^1 is independently selected, for each occurrence, from the group consisting of hydroxyl, halo, $C_{1-6}alkyl$, $hydroxyC_{1-6}alkyl$, $aminoC_{1-6}alkyl$, $haloC_{1-6}alkyl$, $C_{1-6}alkoxy$, $haloC_{1-6}alkoxy$, $acylaminoC_{1-6}alkyl$, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}alkyl$, $-OS(O)_2C_{1-4}alkyl$, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein $C_{1-6}alkyl$, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1-6}alkyl$, amino, or nitro;

R^2 is selected from the group consisting of -O-, amino, $C_{1-6}alkyl$, $-O-C_{1-6}alkyl-$, $hydroxylC_{1-6}alkyl$, $aminoC_{1-6}alkyl$, $haloC_{1-6}alkyl$, $haloC_{1-6}alkoxy$, $acylaminoC_{1-6}alkyl$, -C(O)-, -C(O)O-, $-C(O)NC_{1-6}alkyl-$, $-OS(O)_2C_{1-4}alkyl-$, $-OS(O)_2-$, $-S-C_{1-6}alkyl-$, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein $C_{1-6}alkyl$, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1-6}alkyl$, amino, or nitro;

R^3 is selected from the group consisting of hydrogen or $C_{1-6}alkyl$;

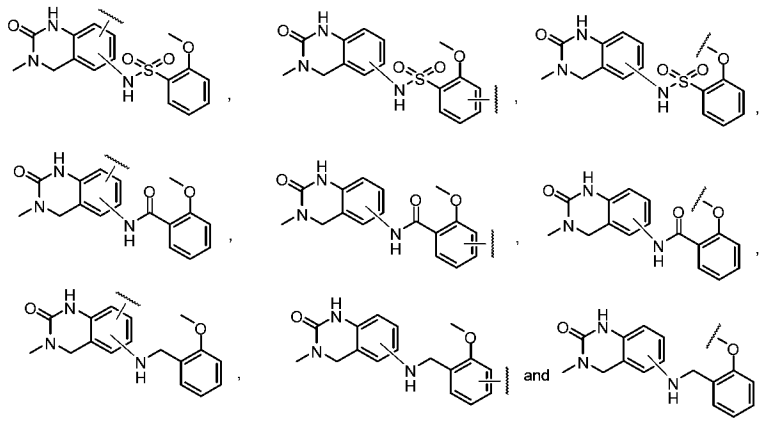
R^4 is independently selected, for each occurrence, from the group consisting of hydrogen, hydroxyl, oxo, imino, amino, halo, $C_{1-6}alkyl$, cycloalkyl, phenyl, naphthyl, heterocyclyl, $-O-C_{1-6}alkyl$, $-NH-C_{1-6}alkyl$, $-N(C_{1-6}alkyl)C_{1-6}alkyl$, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}alkyl$, $-C(O)NHC_{1-6}alkyl$, $-C(O)NH_2$ or $-OS(O)_2C_{1-4}alkyl$;

m is selected from the group consisting of 0, 1, 2, or 3;

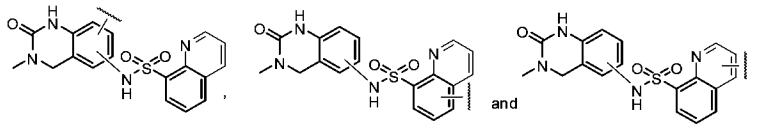
n is selected from the group consisting of 0, 1, or 2; and

p is selected from the group consisting of 0 or 1.

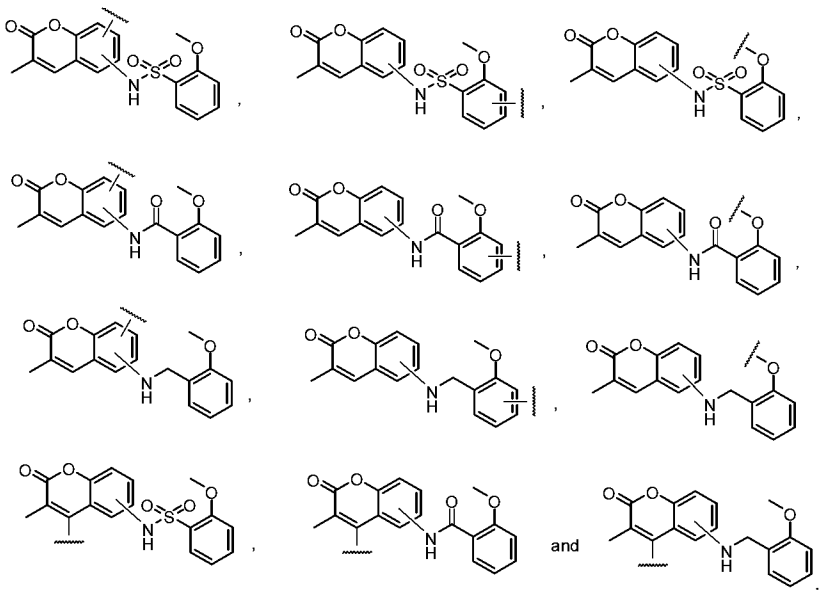
[0068] For example, compounds of Formula **1**, Formula **2** or Formula **5** may be selected from the group consisting of:



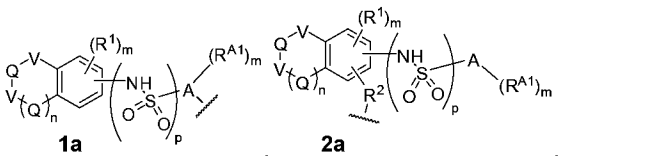
[0069] In a further example, compounds of Formula **1**, Formula **2** or Formula **5** may be selected from the group consisting of:



[0070] For example, compounds of Formula **3,** Formula **3'** or Formula **4** may be selected from the group consisting of:

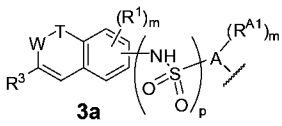


[0071] In another embodiment, bromodomain ligands include fused heterocyclic systems represented by the structures:

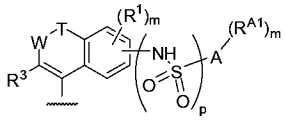


1a

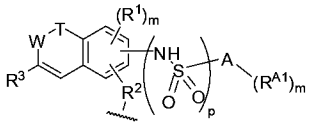
2a



3a

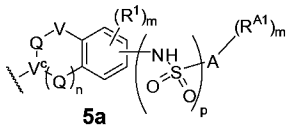


3a'



4a

and



5a

;

wherein:

V is independently selected, for each occurrence, from the group consisting of NH, S, $N(C_{1-6}alkyl)$, O, or CR^4R^4;

Q is independently selected, for each occurrence, from the group consisting of C(O), C(S), C(N), SO_2, or CR^4R^4;

W and T are independently selected from the group consisting of NH, $N(C_{1-6}alkyl)$, O, or Q;

V^C is selected from the group consisting of N, SH or CR^4;

A is a ring selected from the group consisting of: phenyl, a 5-6 membered cycloalkyl, a 5-6 membered heteroaryl having 1, 2 or 3 heteroatoms each selected from S, N or O, and a 4-7 membered heterocycle having 1, 2 or 3 heteroatoms each selected from N or O;

R^{A1} is R^1; or two R^{A1} substituents may be taken together with the atoms to which they are attached to form phenyl, a 5-6 membered heteroaryl having 1, 2 or 3 heteroatoms each selected from S, N or O, and a 4-7 membered heterocycle having 1, 2 or 3 heteroatoms each selected from N or O;

R^1 is independently selected, for each occurrence, from the group consisting of hydroxyl, halo, $C_{1-6}alkyl$, $hydroxyC_{1-6}alkyl$, $aminoC_{1-6}alkyl$, $haloC_{1-6}alkyl$, $C_{1-6}alkoxy$, $haloC_{1-6}alkoxy$, $acylaminoC_{1-6}alkyl$, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}alkyl$, $-OS(O)_2C_{1-4}alkyl$, phenyl, naphthyl, phenyloxy, benzyloxy or phenylmethoxy, wherein $C_{1-6}alkyl$, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1-6}alkyl$, amino, or nitro;

R^2 is selected from the group consisting of -O-, amino, $C_{1-6}alkyl$, $-O-C_{1-6}alkyl-$, $hydroxylC_{1-6}alkyl$, $aminoC_{1-6}alkyl$, $haloC_{1-6}alkyl$, $haloC_{1-6}alkoxy$, $acylaminoC_{1-6}alkyl$, -C(O)-, -C(O)O-, $-C(O)NC_{1-6}alkyl-$, $-OS(O)_2C_{1-4}alkyl-$, $-OS(O)_2-$, $-S-C_{1-6}alkyl-$, phenyl, naphthyl, phenyloxy, benzyloxy or phenylmethoxy, wherein $C_{1-6}alkyl$ phenyl, and naphthylare optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1-6}alkyl$, amino, or nitro;

R^3 is selected from the group consisting of hydrogen or $C_{1-6}alkyl$;

R^4 is independently selected, for each occurrence, selected from the group consisting of hydrogen, hydroxyl, oxo, imino, amino, halo, $C_{1-6}alkyl$, cycloalkyl, phenyl, naphthyl, heterocyclyl, $-O-C_{1-6}alkyl$, $-NH-C_{1-6}alkyl$, $-N(C_{1-6}alkyl)C_{1-6}alkyl$, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}alkyl$, $-C(O)NHC_{1-6}alkyl$, $-C(O)NH_2$ or $-OS(O)_2C_{1-4}alkyl$;

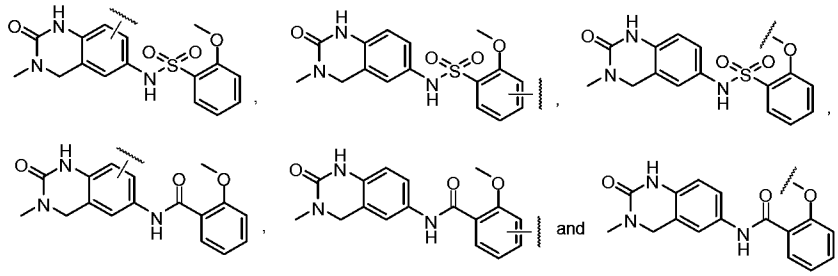
m is independently selected, for each occurrence, selected from the group consisting of 0, 1, 2, or 3;

n is selected from the group consisting of 0, 1, or 2; and

p is selected from the group consisting of 0 or 1.

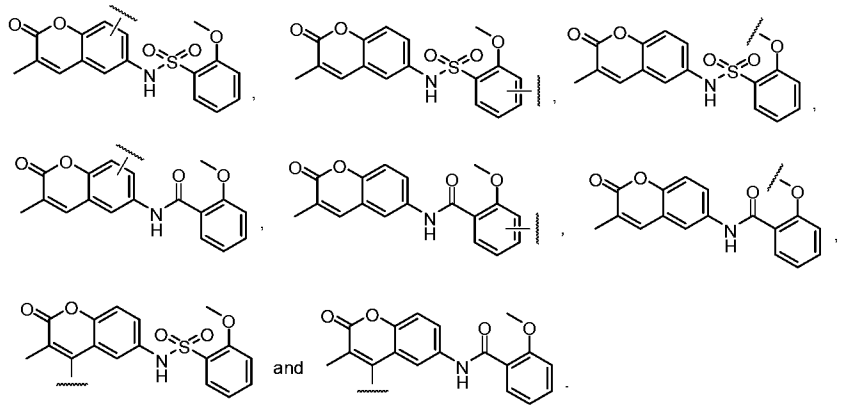
A person of skill in the art appreciates that certain substituents may, in some embodiments, result in compounds that may have some instability and hence would be less preferred.

[0072] For example, compounds of Formula **1a**, Formula **2a** or Formula **5a** may be selected from the group consisting of:

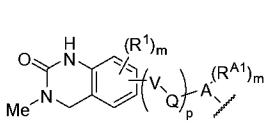


.

[0073] For example, compounds of Formula **3a** or Formula **4a** may be selected from the group consisting of:

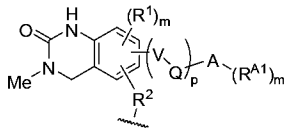


[0074] In a further embodiment, bromodomain ligands include fused heterocyclic systems represented by the structures:



1b

and



2b ;

wherein:

V is selected from the group consisting of a NH, S, N(C_{1-6}alkyl), O, or CR^4R^4;

Q is selected from the group consisting of a bond, C(O), C(S), C(N), SO_2, or CR^4R^4;

A is a ring selected from the group consisting of: phenyl, a 5-6 membered cycloalkyl, a 5-6 membered heteroaryl having 1, 2 or 3 heteroatoms each selected from S, N or O, and a 4-7 membered heterocycle having 1, 2 or 3 heteroatoms each selected from N or O;

R^{A1} is R^1; or two R^{A1} substituents may be taken together with the atoms to which they are attached to form phenyl, a 5-6 membered heteroaryl having 1, 2 or 3 heteroatoms each selected from S, N or O, and a 4-7 membered heterocycle having 1, 2 or 3 heteroatoms each selected from N or O;

R^1 is independently selected, for each occurrence, from the group consisting of hydroxyl, halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}$alkyl, $-OS(O)_2C_{1-4}$alkyl, $-S(C_{1-4}$alkyl$)C(O)R'$, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and napththyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^2 is selected from the group consisting of -O-, amino, C_{1-6}alkyl, $-O-C_{1-6}$alkyl-, hydroxylC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, -C(O)-, -C(O)O-, $-C(O)NC_{1-6}$alkyl-, $-OS(O)_2C_{1-4}$alkyl-, $-OS(O)_2$--$S(C_{1-4}$alkyl$)C(O)R''$-, $-S-C_{1-6}$alkyl-, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^3 is selected from the group consisting of hydrogen or C_{1-6}alkyl;

R^4 is independently selected, for each occurrence, from the group consisting of hydrogen, hydroxyl, oxo, imino, amino, halo, C_{1-6}alkyl, cycloalkyl, phenyl, naphthyl, heterocyclyl, $-O-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}$alkyl$)C_{1-6}$alkyl, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}$alkyl, $-C(O)NHC_{1-6}$alkyl, $-C(O)NH_2$ or $-OS(O)_2C_{1-4}$alkyl;

R' is independently selected, for each occurrence, from the group consisting of hydroxyl, amino, thio, phenyl, naphthyl, or C_{1-6}alkyl, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

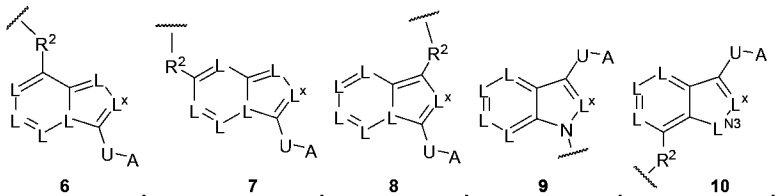
R'' is independently selected, for each occurrence, from the group consisting of –O-, amino, thio, phenyl, naphthyl, or C_{1-6}alkyl, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

m is independently selected, for each occurrence, from the group consisting of 0, 1, 2, or 3;

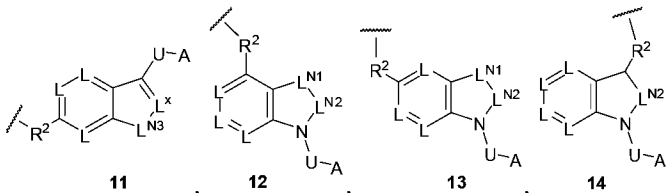
n is selected from the group consisting of 0, 1, or 2; and

p is selected from the group consisting of 0 or 1.

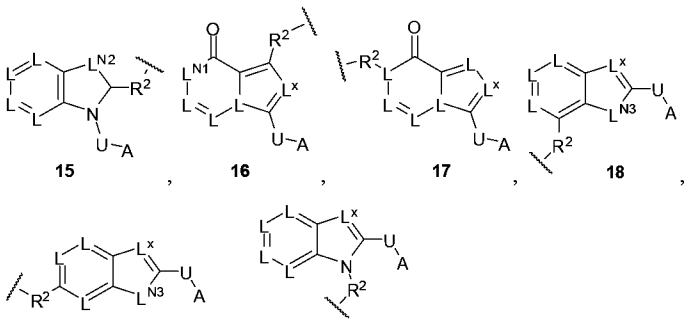
[0075] Exemplary bromodomain ligands include fused heterocyclic systems represented by the structures:



6, **7**, **8**, **9**, **10**,



11, **12**, **13**, **14**,



15 , 16 , 17 , 18 ,

19 , and 20 ;

wherein:

L and L^X are independently selected, for each occurrence, from the group consisting of N, CH, and CR^1;

L^{N1} and L^{N2} are independently selected from the group consisting of CH_2, CHR^1, CR^1R^1, NH, and $N(C_{1-6}alkyl)$; wherein $C_{1-6}alkyl$ is optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1-6}alkyl$, amino, or nitro;

L^{N3} is selected from the group consisting of O, S, NH, and $N(C_{1-6}alkyl)$; wherein $C_{1-6}alkyl$ is optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1-6}alkyl$, amino, or nitro;

U is independently selected from the group consisting of a bond, C(O), C(S), C(N), SO_2, or CR^4R^4;

A is selected from the group consisting of aliphatic, cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl, or bicyclic moiety, wherein the cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl, or bicyclic moiety is optionally substituted with one, two, three, four or more groups represented by R^4;

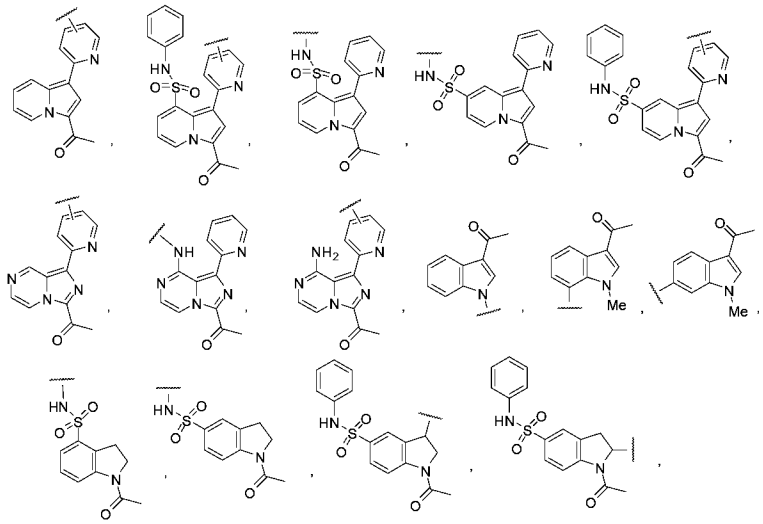
R^1 is independently selected, for each occurrence, from the group consisting of hydroxyl, halo, $C_{1-6}alkyl$, $hydroxyC_{1-6}alkyl$, $aminoC_{1-6}alkyl$, $haloC_{1-6}alkyl$, $C_{1-6}alkoxy$, $haloC_{1-6}alkoxy$, $acylaminoC_{1-6}alkyl$, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}alkyl$, $-OS(O)_2C_{1-4}alkyl$, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein $C_{1-6}alkyl$, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1-6}alkyl$, amino, or nitro;

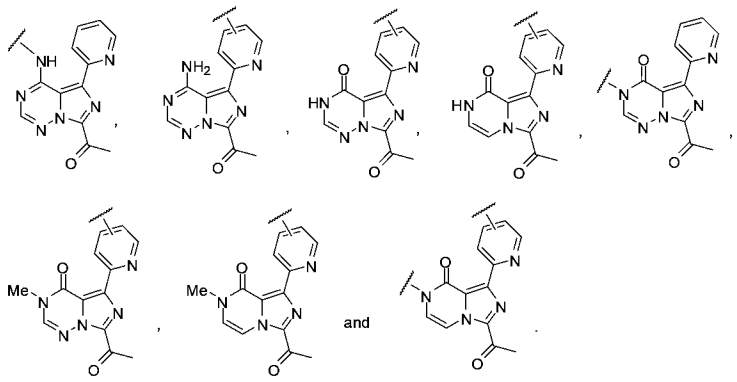
R^2 is selected from the group consisting of -O-, amino, C_{1-6}alkyl, -O-C_{1-6}alkyl-, hydroxylC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, -C(O)-, -C(O)O-, -C(O)NC_{1-6}alkyl-, -OS(O)$_2$C$_{1-4}$alkyl-, -OS(O)$_2$-, -S-C_{1-6}alkyl-, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^3 is selected from the group consisting of hydrogen or C_{1-6}alkyl; and

R^4 is independently selected, for each occurrence, from the group consisting of hydrogen, hydroxyl, oxo, imino, amino, halo, C_{1-6}alkyl, cycloalkyl, phenyl, naphthyl, heterocyclyl, -O-C_{1-6}alkyl, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)C_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -C(O)OC_{1-6}alkyl, -C(O)NHC_{1-6}alkyl, -C(O)NH_2 or -OS(O)$_2$C$_{1-4}$alkyl.

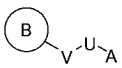
[0076] For example, compounds of Formula **6**, **7**, **8**, **9**, **10**, **11**, **12**, **13**, **14**, **15**, **16** and **17** may be selected from the group consisting of:

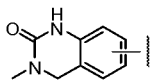
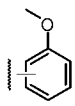
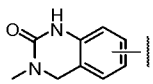
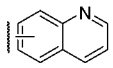
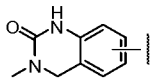
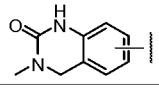
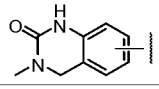


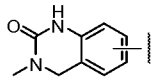
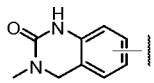
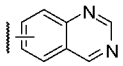
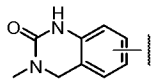
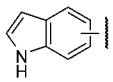
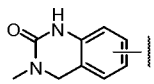
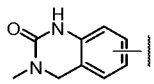
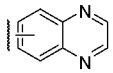
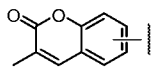
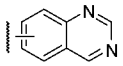
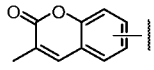
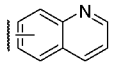
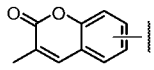
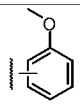
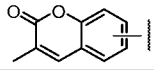
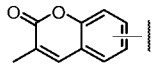
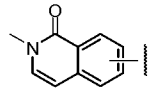
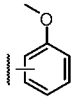
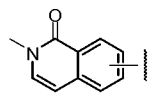
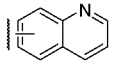


[0077] In certain other embodiments, the ligand is one of the compounds listed in Table 1 below or a pharmaceutically acceptable salt thereof, wherein the connector attachment point may be understood to be on (B) or A.

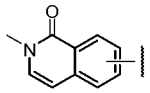
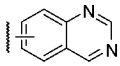
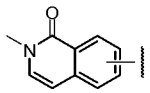
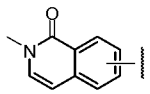
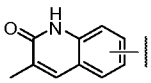
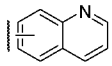
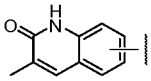
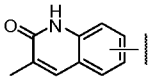
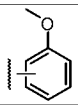
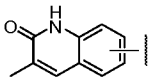
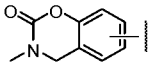
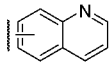
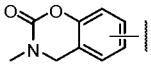
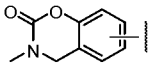
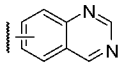
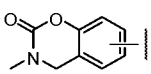
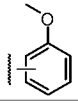
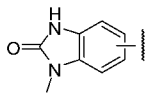
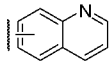
TABLE 1



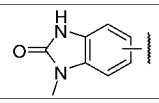
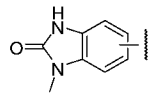
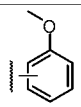
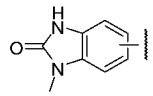
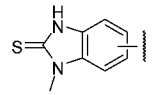
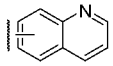
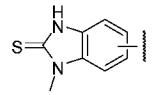
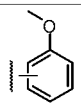
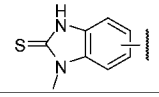
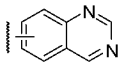
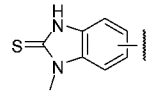
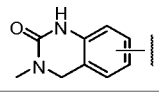
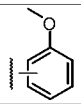
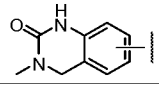
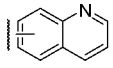
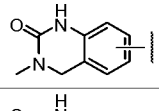
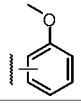
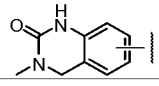
Compound No.	B	V	U	A
I-1		NH	SO_2	
I-2		NH	SO_2	
I-3		NH	SO_2	
I-4		NH	SO_2	
I-5		NH	SO_2	

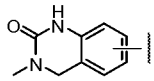
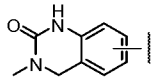
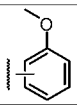
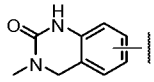
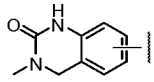
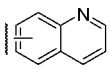
Compound No.	B	V	U	A
I-6		NH	SO_2	
I-7		NH	SO_2	
I-8		NH	SO_2	
I-9		NH	SO_2	
I-10		NH	SO_2	
I-11		NH	SO_2	
I-12		NH	C(O)	
I-13		O	C(O)	
I-14		CH_2	CH_2	
I-15		O	CH_2	
I-16		NH	CH_2	
I-17		NH	C(O)	

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Compound No.	B	V	U	A
I-18		NH	SO_2	
I-19		NH	SO_2	
I-20		NH	C(O)	
I-21		CH_2	CH_2	
I-22		O	C(O)	
I-23		NH	SO_2	
I-24		NH	CH_2	
I-25		NH	SO_2	
I-26		CH_2	CH_2	
I-27		NH	C(O)	
I-28		NH	SO_2	
I-29		NH	SO_2	

Atty Docket No. COF-018PC

Compound No.	B	V	U	A
I-30		NH	C(O)	
I-31		NH	CH_2	
I-32		CH_2	CH_2	
I-33		O	C(O)	
I-34		NH	SO_2	
I-35		NH	C(O)	
I-36		CH_2	CH_2	
I-37		NH	C(O)	
I-38		SO_2	NH	
I-39		O	C(O)	
I-40		C(O)	NH	

Compound No.	B	V	U	A
I-41		CH_2	CH_2	
I-42		NH	CH_2	
I-43		CH_2	NH	
I-44		O	CH_2	

[0078] One of ordinary skill in the art will appreciate that certain substituents may, in some embodiments, result in compounds that may have some instability and hence would be less preferred.

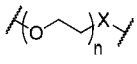
Connectors

[0079] As discussed above, certain compounds contemplated herein comprise a first ligand and a second ligand covalently joined by a connector moiety. In some instances, such connector moieties do not have significant binding or other affinity towards an intended target. However, in certain embodiments, a connector may contribute to the affinity of a ligand moiety to a target.

[0080] In some instances, the connector moiety may be varied to control the spacing between two ligands. For example, in some cases, it may be desirable to adjust the spacing between two ligands so as, for instance, to achieve optimal binding of the bivalent compound to a target. In some cases, the connector moiety may be used to adjust the orientation of the ligands. In certain embodiments, the spacing and/or orientation the connector moiety relative to the ligand moiety can affect the binding affinity of the ligand moiety (*e.g.*, a pharmacophore) to a target. In some cases, connector moities with restricted degrees of freedom are preferred to reduce the entropic losses incurred upon the binding of a bivalent compound to its target biomolecule. In some embodiments, connector moieties with restricted degrees of freedom are preferred to promote cellular permeability of the bivalent compound.

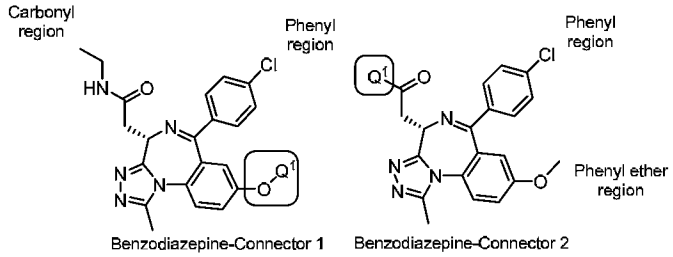
[0081] In some embodiments, the connector moiety may be used for modular assembly of ligands. For example, in some instances, a connector moiety may comprise a functional group formed from reaction of a first and second molecule. In some cases, a series of ligand moieties may be provided, where each ligand moiety comprises a common functional group that can participate in a reaction with a compatible functional group on a connector moiety. In some embodiments, the connector moiety may comprise a spacer having a first functional group that forms a bond with a first ligand moiety and a second functional group that forms a bond with a second ligand moiety.

[0082] Contemplated connecter moieties may be any acceptable (*e.g.*, pharmaceutically and/or chemically acceptable) bivalent linker. For instance, such connecter moieties may comprise 3 to 30 atoms, 3 to 20 atoms, 3 to 15 atoms, 3 to 10 atoms, 5 to 15 atoms, 10 to 20 atoms, 15 to 25 atoms, 20 to 30 atoms, or 10 to 30 atoms. The atoms may be connected in any suitable arrangement. For example, the atoms may be connected to form a cyclic or acyclic, substituted or unsubstituted, branched or unbranched aliphatic moiety; cyclic or acyclic, substituted or unsubstituted, branched or unbranched heteroaliphatic moiety; substituted or unsubstituted phenyl or naphthyl moiety; substituted or unsubstituted heteroaryl moiety; or a combination thereof. In some instances, a connector moiety may include a substituted or unsubstituted C_1-C_{10} alkylene, substituted or unsubstituted cycloalkylene, acyl, sulfone, phosphate, ester, carbamate, or amide.

[0083] In some instances, contemplated connecter moieties may include polymeric connectors, such a polyethylene glycol (e.g., , where n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20, and X is O, S, NH, or -C(O)-) or other pharmaceutically acceptable polymers. For example, contemplated connecter moieties may be a covalent bond or a bivalent C_{1-40}, C_{1-30}, C_{1-20}, C_{1-10}, C_{10-40}, or C_{20-40}, saturated or unsaturated, branched or unbranched, hydrocarbon chain, wherein one, two, or three or four methylene units of the hydrocarbon chain are optionally and independently replaced by cyclopropylene, -NR-, -N(R)C(O)-, -C(O)N(R)-, -N(R)SO_2-, -SO_2N(R)-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO_2-, -C(=S)-, -C(=NR)-, phenyl, or a mono or bicyclic heterocycle ring, where R is hydrogen or any suitable substituent. In some embodiments, a connector may be from about 7 atoms to about 13 atoms in length, or about 8 atoms to about 12 atoms, or about 9 atoms to about 11 atoms in length.

[0084] In another embodiment, a connecter moiety may maximally span from about 5Å to about 50Å, in some embodiments about 5Å to about 25Å, in some embodiments about 20Å to about 50Å, and in some embodiments about 6Å to about 15Å in length.

[0085] In one embodiment, for the benzodiazepine compounds disclosed herein, there are several possible connection regions that can contain an attachment point for the connector element: the carbonyl region, the phenyl ether region, and the chlorophenyl region. Of course, other attachments points may also be envisioned by one of ordinary skill in the art using the present disclosure. As seen below, the connector moiety may be identified as a Q^1 group in benzodiazepine-connector 1 **A**, benzodiazepine-connector 2 **B**, benzodiazepine-connector 3 **C**, and dimethyl isoxazole-connector 4 **D**:



Benzodiazepine-Connector 1

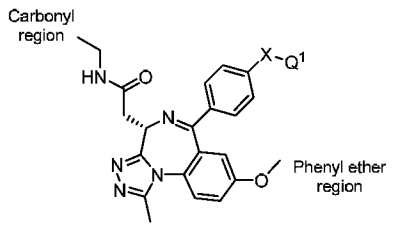
A

,

Benzodiazepine-Connector 2

B

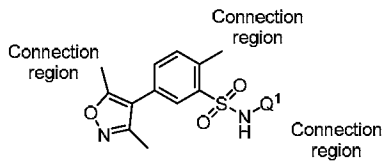
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Benzodiazepine-Connector 3

C

, and



Dimethyl isoxazole-Connector 1

D

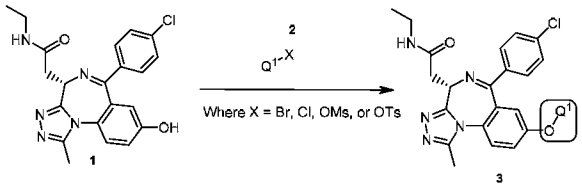
,

where X = CH_2, S, O, or NH and Q^1 = connector moiety as described herein.

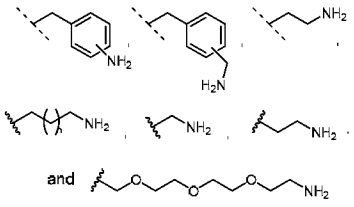
[0086] The synthetic route in Scheme Xa illustrates a general method for preparing benzodiazepine-connector 1 derivatives. The method involves attaching the desired substituents to the phenol core. Benzodiazepine **1** can be prepared following procedures described below. The desired Q^1 group attached at the 4-position of the phenol can be installed by reacting benzodiazepine **1** with the appropriate electrophile **2** to provide **3** (benzodiazepine-

connector 1 derivative). For example, Scheme Xa provides for a connector Q^1, which may then be used to connect to a second ligand, thus forming a contemplated bivalent compound. It should be understood that the synthetic routes described herein are not limited to the depicted schemes, but rather may be applied, as one of ordinary skill in the art would understand, to any suitable ligand-connector pair contemplated herein.

SCHEME Xa



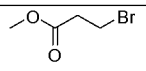
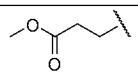
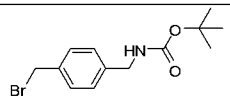
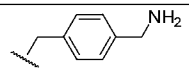
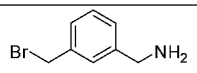
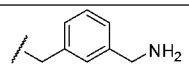
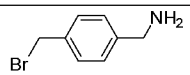
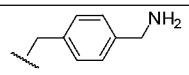
[0087] For example, Q^1 may be selected from the group consisting of:

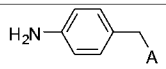
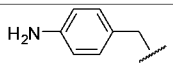
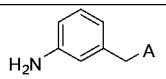
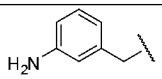
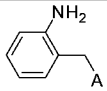
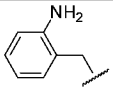
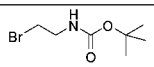
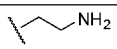
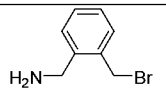
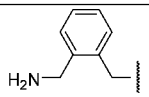
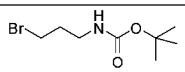
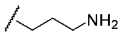
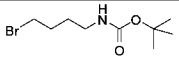
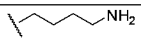


, wherein n is 0, 1, 2, 3, 4 or 5.

[0088] Additional examples for **2** and Q^1 can be found in Table A, seen below:

Table A

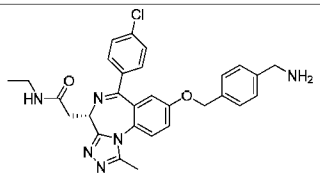
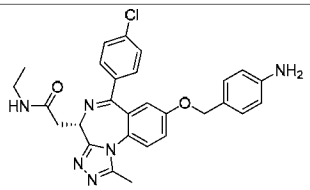
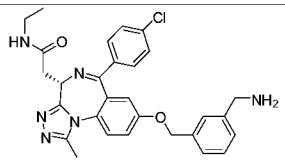
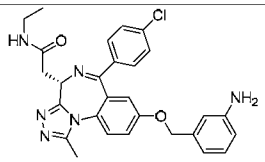
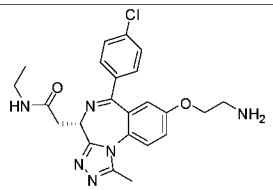
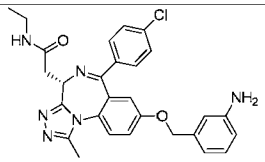
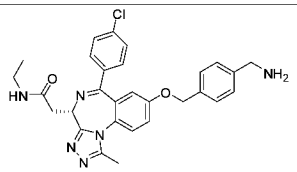
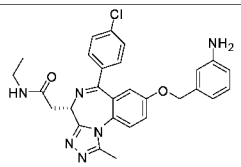
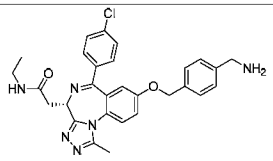
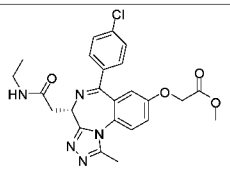
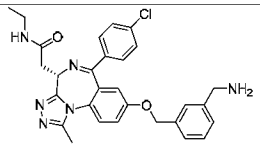
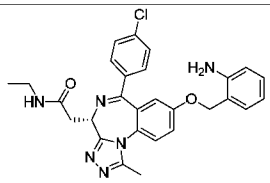
No.	2	- Q^1
1		
2		
3		
4		

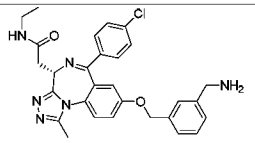
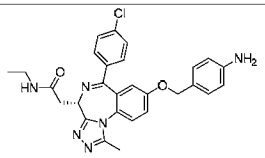
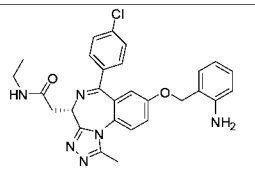
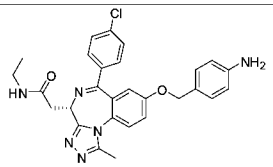
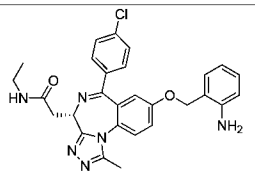
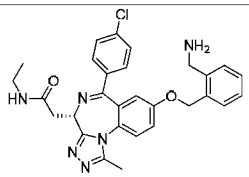
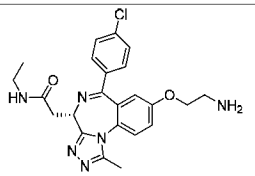
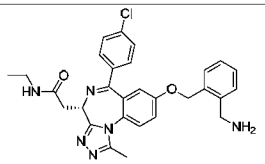
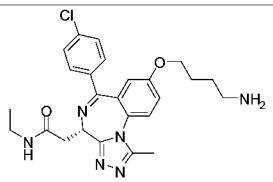
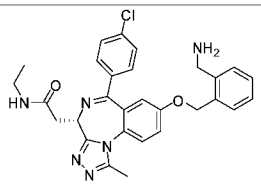
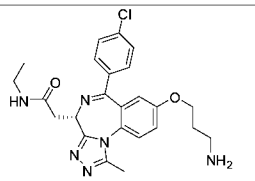
5	 A=Cl, Br, I or OH	
6	 A=Cl, Br, I or OH	
7	 A=Cl, Br, I or OH	
8		
9		
10		
11		
12		

[0089] The following table (Table U) indicates exemplary benzodiazepine-connector **1** derivatives (*e.g.*, **3** of Scheme Xa) that include a ligand moiety (e.g., P^1) and a connector (Q^1). It is understood that such derivatives can be modified to include a second ligand moiety such as provided for herein.

Table U

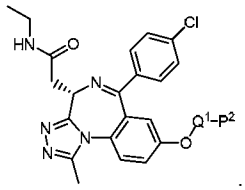
No.	Compound Structure (P^1-Q^1)	No.	Compound Structure (P^1-Q^1)

1		13	
2		14	
3		15	
4		16	
5		17	
6		18	

7		19	
8		20	
9		21	
10		22	
11		23	
12			

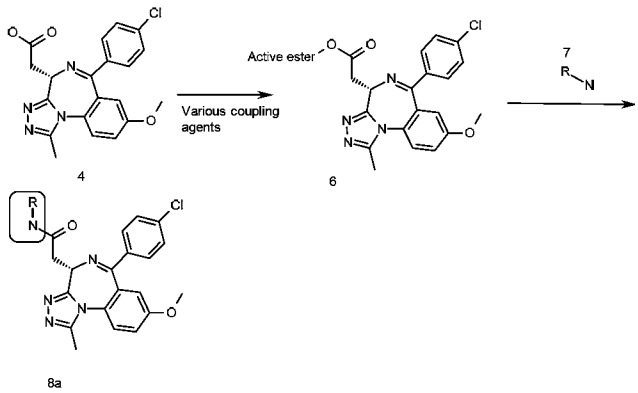
[0090] Any free amino group seen in the Q^1 examples of Table A above may be functionalized further to include additional functional groups, e.g., a benzoyl moiety.

[0091] In another embodiment, the attachment point identified in **A** (benzodiazepine-connector **1**) may be further elaborated to incorporate not only the connector moiety (Q^1), but also a second ligand (P^2), as represented by:

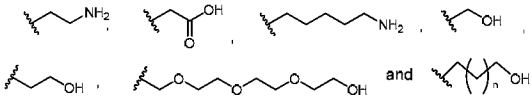


[0092] . The Q^1-P^2 moiety may be formed from direct attachment of Q^1-P^2 to the phenyl ether, or the Q^1-P^2 moiety may be formed from the further functionalization of any free amino group seen in the Q^1 examples of Table A above to include the second ligand (P^2). The synthetic route in Scheme Xb illustrates a general method for preparing benzodiazepine-connector **2** derivatives. The method involves attaching the desired substituents to the carbonyl substituent. The desired R group attached at the carbonyl substituent can be installed by reacting carboxylic acid **4** with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC) and hydroxybenzotriazole (HOBt) then further reacting the activated ester **6** with the appropriate nucleophile, for example, amine **7**, to provide **8a** (benzodiazepine-connector 2 derivative). For example, Scheme Xb provides for a connector Q^1, wherein Q^1 is –NH-R (e.g., -NH-R of **8a**).

SCHEME Xb

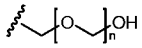


[0093] For example, R may be selected from the group consisting of:



, where n may be 0, 1, 2, 3,4 or 5.

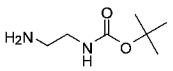
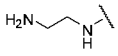
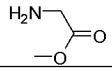
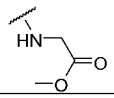
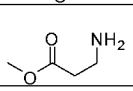
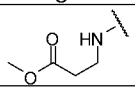
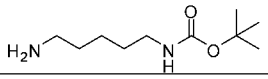
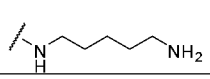
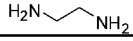
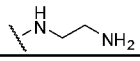
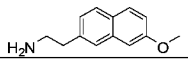
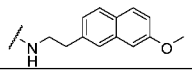
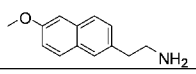
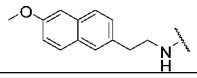
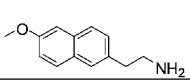
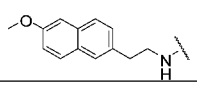
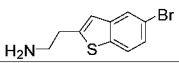
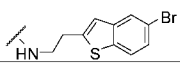
[0094] In some embodiments, R may generally be represented for example, by:



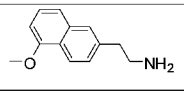
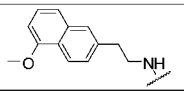
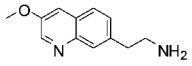
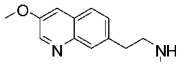
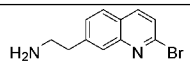
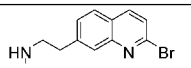
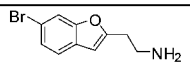
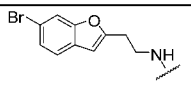
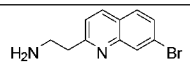
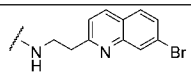
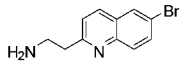
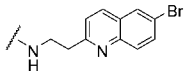
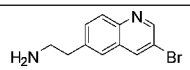
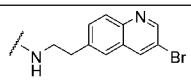
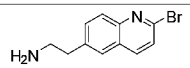
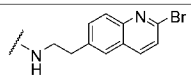
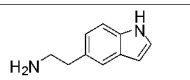
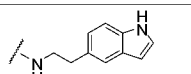
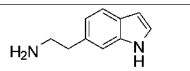
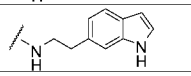
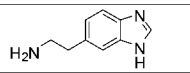
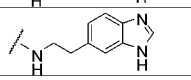
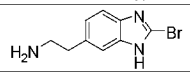
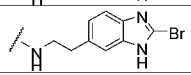
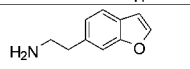
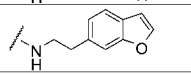
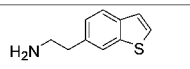
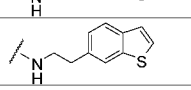
where n may be 0, 1, 2, 3, 4, 5, or 6.

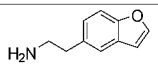
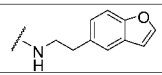
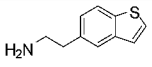
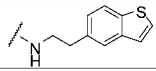
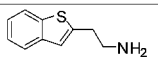
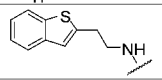
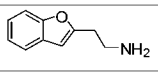
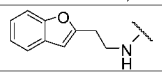
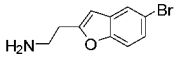
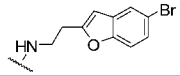
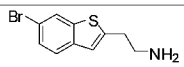
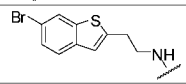
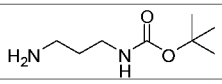
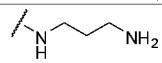
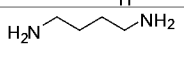
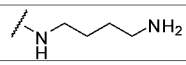
[0095] Additional examples for **7** and –NH-R (e.g., Q^1) can be found in Table B, seen below:

Table B

No.	7	-NH-R (e.g., -Q^1)
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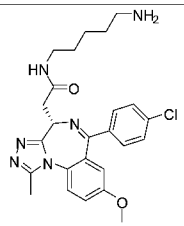
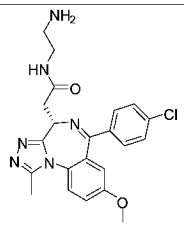
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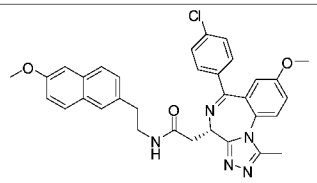
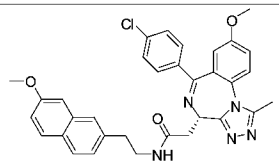
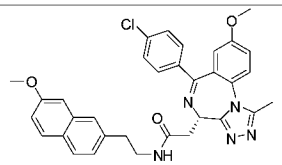
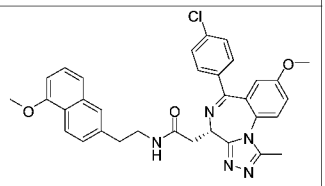
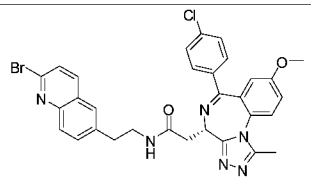
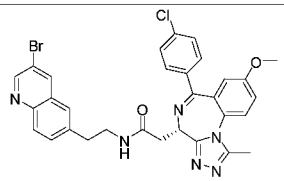
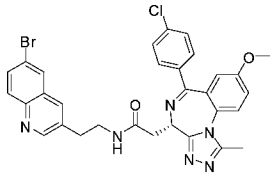
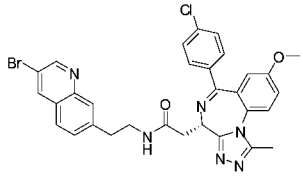
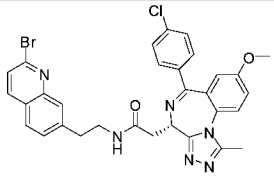
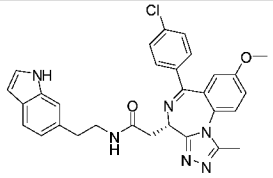
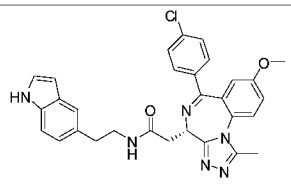
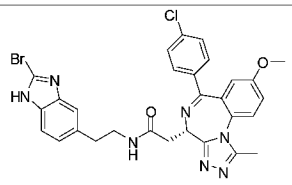
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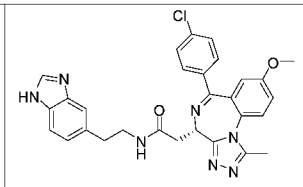
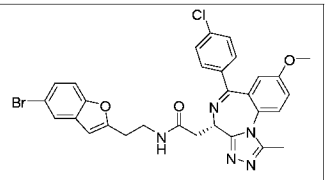
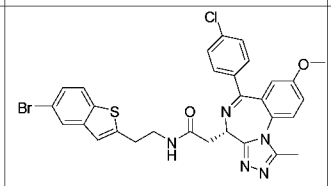
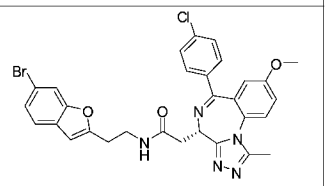
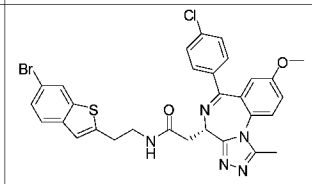
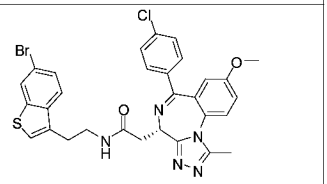
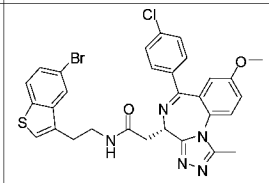
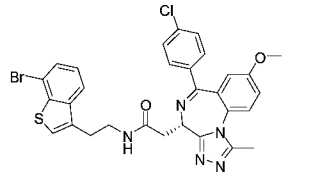
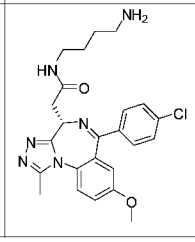
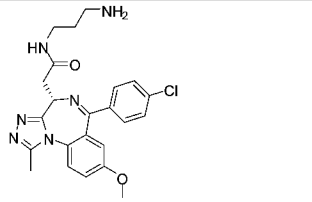
[0096] The following table (Table V) contains exemplary benzodiazepine-connector **2** derivatives (e.g., **8a** of Scheme Xb) that include a ligand moiety (e.g., P^1) and a connector (Q^1).

Table V

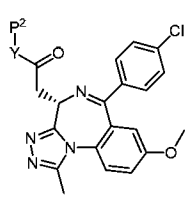
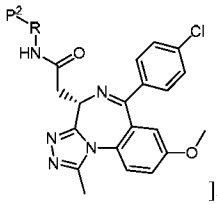
No.	Compound Structure (i.e., P^1-Q^1)	No.	Compound Structure (i.e., P^1-Q^1)
1		26	

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2		31	
3		33	
4		34	
5		35	
6		36	
7		37	

8		39	
9		43	
10		44	
11		45	
12		46	

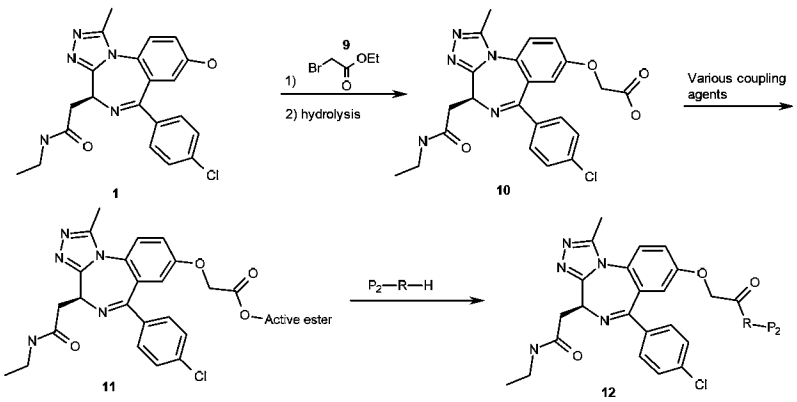
[0097] In another embodiment, the attachment point identified in **B** may be further elaborated to incorporate not only a connector moiety, but also a second ligand, as e.g.,

represented by:  [e.g., ]. The Q^1-P^2 moiety may be formed from direct attachment of Q^1-P^2 to the carbonyl, or the Q^1-P^2 moiety may be formed from the further functionalization of any free amino group seen in the –NH-R examples (i.e., Q^1 examples) of Table B above to include the second ligand moiety (P^2).

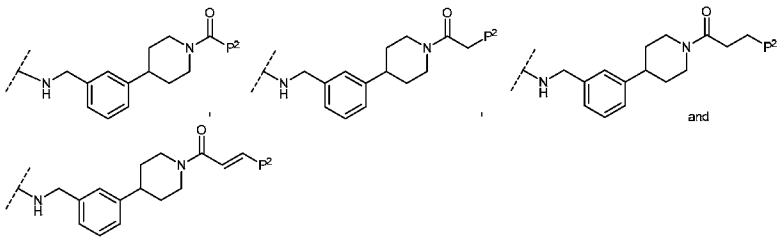
[0098] In another embodiment, the two attachment points identified in **A** and **B** may be further elaborated to incorporate not only a connector moiety, but also a second ligand moiety.

[0099] Scheme Xc provides a synthetic procedure for making **A** derivatives having various connectors attached to both the benzodiazepine compound and to any of the above-identified ligands. In the scheme below, the second ligand moiety is designated by P^2. Phenol **1** is converted to carboxylic acid **10** using ethyl-2-bromoacetate, followed by hydrolysis. Following formation of **10**, the general procedure outlined in Scheme Xb can be utilized in the synthesis of the benzodiazepine-connector **1** derivative **12**. For example, Scheme Xc provides for a connector Q^1 attached to a second ligand moiety (P^2), wherein Q^1 is $–CH_2$-C(O)-R- (e.g., $–CH_2$-C(O)-R- of **12**).

SCHEME Xc

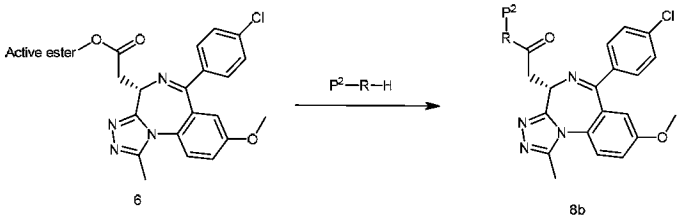


[00100] For example, R-P^2 may be selected from the group consisting of:

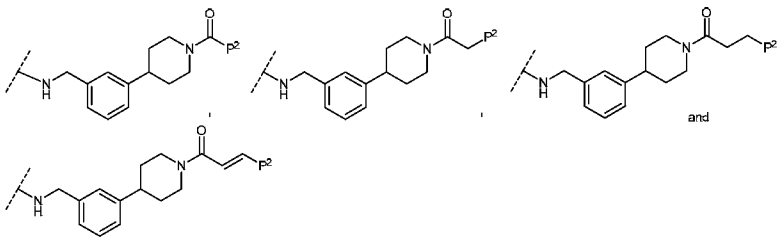


[00101] Scheme Xd provides an exemplary synthetic procedure for making **B** derivatives having various connectors attached to both the benzodiazepine compound and to any of the above-identified ligands. In the scheme below, the second ligand moiety is designated by P^2. Activated ester **6** is reacted with various nucleophiles to provide benzodiazepine-connector **2** derivative **8b**. For example, Scheme Xd provides for a connector Q^1 attached to a second ligand moiety (P^2), wherein Q^1 is -R- (e.g., -R- of **8b**).

SCHEME Xd



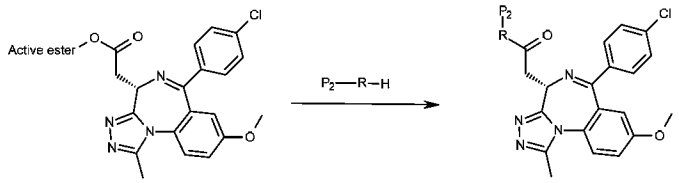
[00102] For example, R-P^2 (i.e., Q^1-P^2) may be selected from the group consisting of:



[00103] Similar to Scheme Xd, Scheme Xe provides a synthetic procedure for making **B** derivatives having various connectors of shorter length attached to both the benzodiazepine compound and to any of the above-identified ligands. In the scheme below, the second ligand moiety is designated by P^2. Activated ester **6** is reacted with various nucleophiles to provide

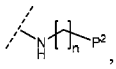
benzodiazepine-connector 2 derivative **8c**. For example, Scheme Xe provides for a connector Q^1 attached to a ligand moiety (P^2), wherein Q^1 is -R- (*e.g.*, -R- of **8c**).

SCHEME Xe



6 8c

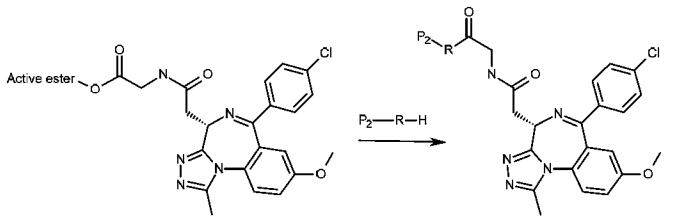
[00104] For example, R-P^2 (*i.e.*, Q^1-P^2) may be represented by the structure:



, wherein n is 0, 1, 2, 3, 4, or 5, e.g. n is 1 to 5. For example, Scheme Xe provides for a connector moiety Q^1.

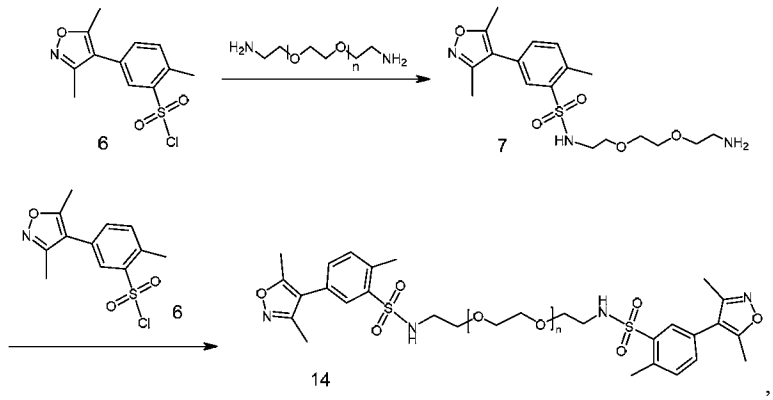
[00105] Scheme Xf provides an additional exemplary synthetic procedure for making **B** derivatives having various connector moieties attached to both the benzodiazepine compound and to any of the above-identified ligands. In the scheme below, the second ligand moiety is designated by P^2. Activated ester **6a** is reacted with various nucleophiles to provide benzodiazepine-connector 2 derivative **8d**. For example, Scheme Xf provides for a connector Q^1 attached to a second ligand moiety (P^2), wherein Q^1 is $-NHCH_2-C(O)-R-$ (*e.g.*, $-NHCH_2-C(O)-R-$ of **8d**).

SCHEME Xf



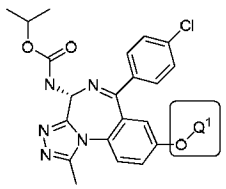
6a 8d

[00106] For example, R-P^2 may be represented by the structure:



wherein n is 0, 1, 2, 3, 4 or 5, e.g. n is 1 to 5.

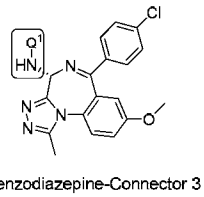
[00107] The above-identified benzodiazepine compounds may for example, attach to a connector element at one of at least two possible attachment points: e.g., the phenyl ether or the amino group. As seen below, a connector element may be identified as a Q^1 group in benzodiazepine-connector 1' **A'** and benzodiazepine-connector 3 **C**:



Benzodiazepine-Connector 1'

A'

and



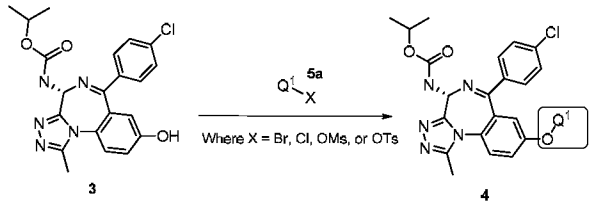
Benzodiazepine-Connector 3

C

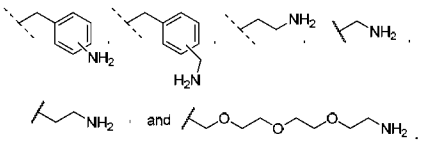
.

[00108] In correlation to Scheme Xa, the synthetic route in Scheme Xa' illustrates a general method for preparing benzodiazepine-connector 1' derivatives. The method involves attaching the desired substituents to the phenol core. The desired Q^1 group attached at the 4-position of the phenol can be installed by reacting benzodiazepine **3** (see Scheme Xa'') with the appropriate electrophile **5a** to provide **4** (benzodiazepine-connector 1' derivative). For example, Scheme Xa' provides for a connector Q^1.

SCHEME Xa'

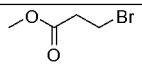
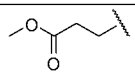
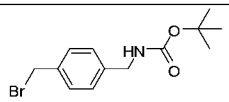
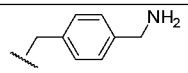
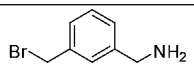
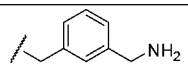
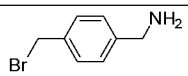
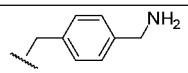
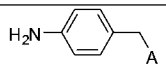
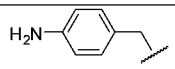
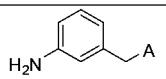
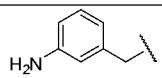
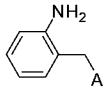
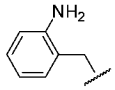


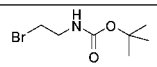
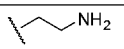
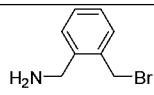
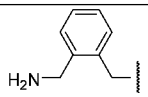
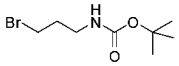
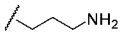
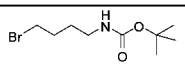
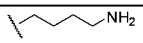
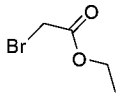
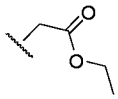
[00109] For example, Q^1 may be selected from the group consisting of:



[00110] Additional examples for **5a** and Q^1 can be found in Table F, seen below:

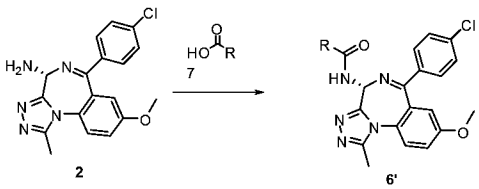
Table F

No.	5a	$-Q^1$
1		
2		
3		
4		
5	 A=Cl, Br, I or OH	
6	 A=Cl, Br, I or OH	
7		

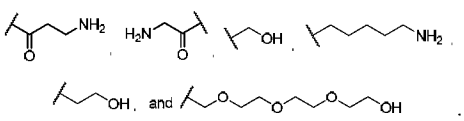
	A=Cl, Br, I or OH	
8		
9		
10		
11		
12		
13		

[00111] The synthetic route in Scheme Xb' illustrates a general method for preparing benzodiazepine-connector 3 derivatives. The method involves attaching the desired carbonyl substituents to the free amine. The carbonyl group can be installed by reacting amine **2** (see Scheme Xa'') with carboxylic acid **7** to provide **6'** (benzodiazepine-connector 3 derivative). For example, Scheme Xb' provides for a connector Q^1, wherein Q^1 is –C(O)R (e.g., –C(O)R of **6'**).

SCHEME Xb'

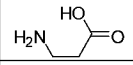
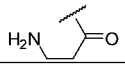
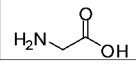
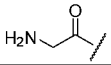


[00112] For example, -C(O)R (i.e., Q^1) may be selected from the group consisting of:



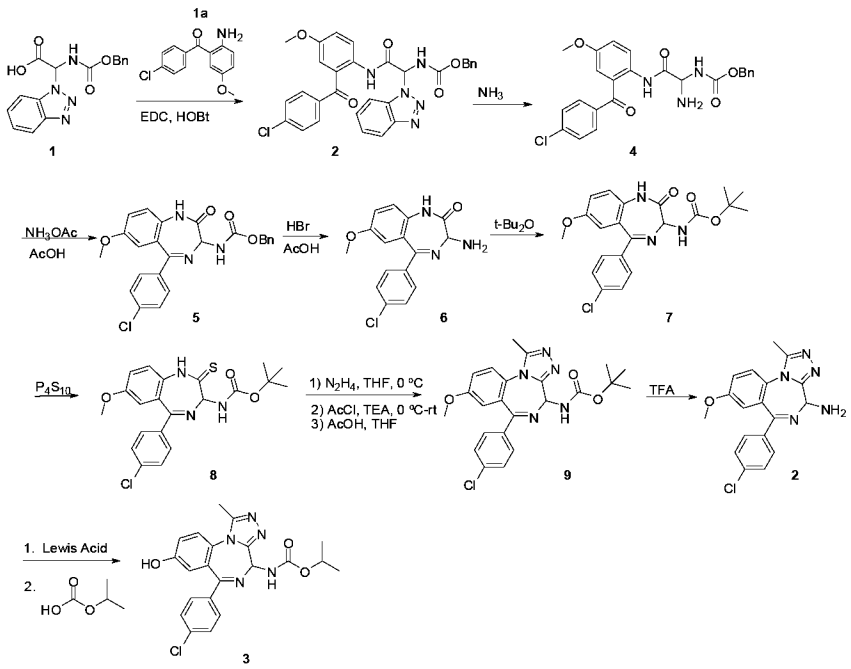
[00113] Additional examples for **7** and –C(O)R (i.e., -Q^1) can be found in Table G, seen below:

Table G

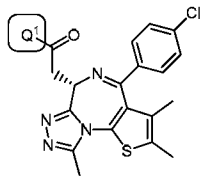
Example No.	7	-C(O)R (i.e., -Q^1)
1		
10		

[00114] The synthetic route in Scheme Xa'' illustrates a general method for preparing benzodiazepine derivatives, for example, benzodiazepine **3**, as seen in Scheme Xa' or , benzodiazepine **2**, as seen in Scheme Xb'. The starting material, benzotriazole **1**, may be purchased from commercial sources or can be prepared by one of skill in the art, for example, following procedures described in *J. Org. Chem.* v. 55, p. 2206, 1990. Following the amide coupling of **1** with **1a** (to provide **2**), ammonia is used to prepare amino-substituted **4**. Acid-promoted cyclization (condensation) of **4** affords benzodiazepine carbamate **5**. A three step procedure is used to prepare thioamide **8**: cleavage of the carbamate **5**, Boc-protection of amine **6**, and thiolation, utilizing P_4S_{10} as the sulfur source. The fused triazole **9** is formed from **8** following a three step procedure: hydrazone formation, acylation and cyclization. Boc-group removal from the reaction of **9** with trifluoroacetic acid (TFA) affords the key intermediate **2**, which is used to prepare benzodiazepine-connector 3 derivatives. Intermediate **2** is reacted further to prepare phenol **3**, which is a key intermediate in the formation of benzodiazepine-connector 1' derivatives. To this end, cleavage of methyl ether **2** and selective coupling of the free amine affords phenol **3**.

SCHEME Xa''



[00115] In a certain embodiment, for the above-identified benzodiazepine compounds, the attachment point for a connector element of benzodiazepine-connector 2 **B** is utilized in benzodiazepine-connector 2'' **B''**:

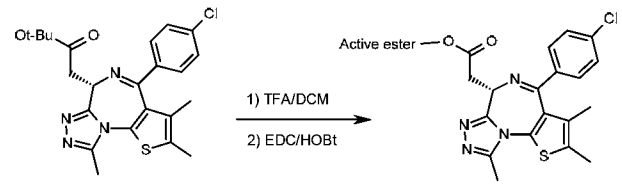


Benzodiazepine-Connector 2"

B"

[00116] Scheme Xb'' provides a synthetic procedure for making key intermediate **6b.** The intermediate (+)-JQ1 may be prepared, for example, by known methods. The activated ester **6b** can be prepared by reacting (+)-JQ1, e.g., with *N*-hydroxysuccinimide and a coupling agent such as EDC, or e.g., with EDC and HOBt.

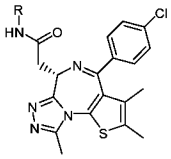
SCHEME Xb''



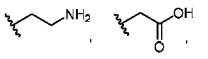
(+)-JQ1 6b

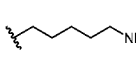
[00117] It is contemplated herein that the general methods seen above in Scheme Xb and Schemes Xd-Xg can also utilize intermediate **6b**, in place of intermediate **6** or **6a**, in the preparation of **B'** derivatives.

[00118] In one embodiment, an exemplary **B'** derivative is represented by the structure:



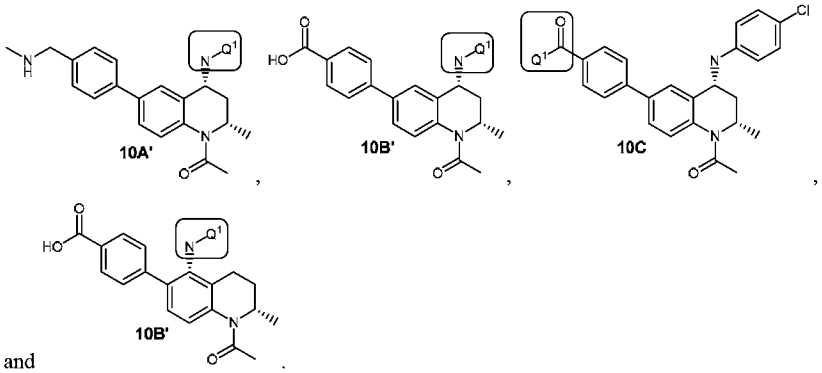
8h
(see Scheme Xb) ,wherein R is, for example, selected from the group consisting of:



and 

. For example, **8h** provides for a connector Q^1 wherein Q^1 is –NH-R.

[00119] It will be appreciated that for tetrahydroquinoline compounds, the connector element may attach at one of at least two possible attachment points for example, via a terminal amino group or via a carbonyl substituent. As seen below, a connector element may be identified as a Q^1 group in tetrahydoquinoline-connector 1 **10A'**, tetrahydoquinoline-connector 1 **10B'**, tetrahydroquinoline-connector 2 **10C**, and tetrahydroquinoline-connector **10D**:

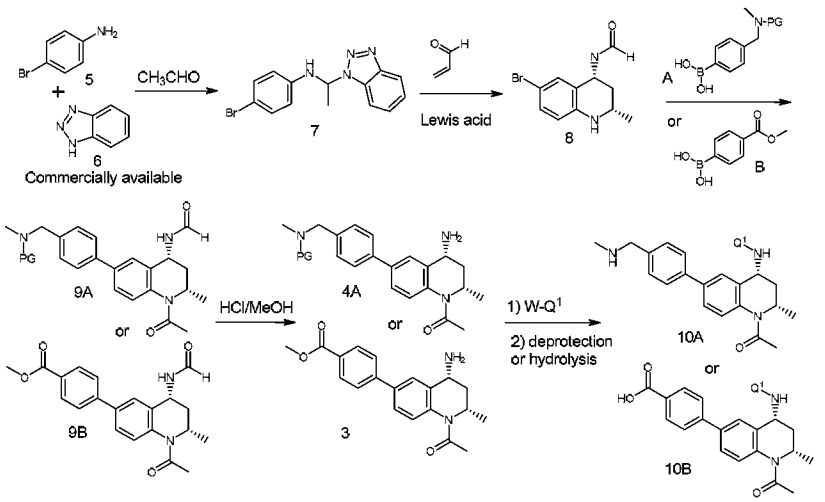


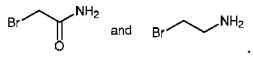
and .

[00120] For example, Q^1 may be as described above in connector 1 **10A'** connector 1 **10B'** or connector 2 **10C**.

[00121] The synthetic route in Scheme Xh illustrates a divergent procedure for preparing tetrahydroquinoline-connector 1 derivatives. The tetrahydroquinoline core is formed in a two step-process beginning with the condensation of **5**, **6** and acetaldehyde to form **7** and followed by conjugate addition to acrylaldehyde to afford **8**. Tetrahydroquinoline **8** is utilized in a divergent step to install varying phenyl substituents via reaction with the bromo-group to provide **9A** and **9B**. Following hydrolysis of the amide group, the desired Q^1 group is attached at the terminal amino group by reacting the unsubstituted amines of **4A** or **3** with the appropriate electrophile to provide **10A** or **10B** (tetrahydroquinoline-connector 1 derivative). For example, Scheme Xh provides for a connector Q^1.

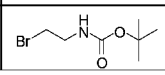
SCHEME Xh



For example, W-Q^1 may be selected from the group consisting of:  and .

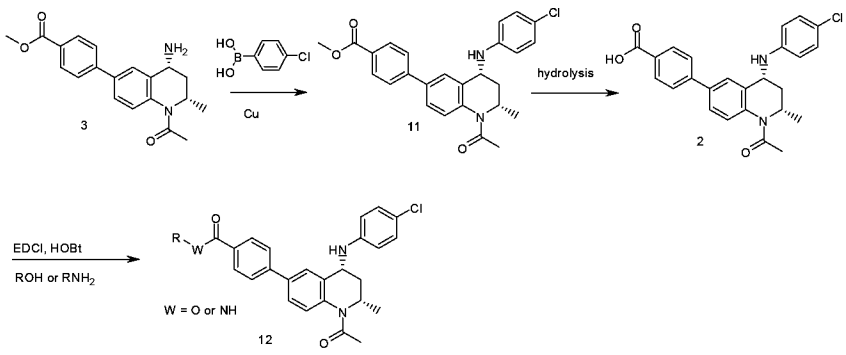
[00122] Additional examples for W-Q^1 and -Q^1 can be found in Table J, seen below:

Table J

Example No.	W-Q^1	-Q^1
3		

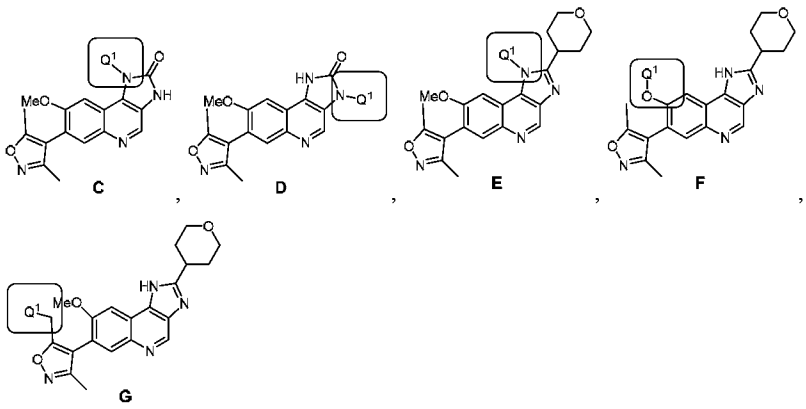
[00123] The synthetic route in Scheme Xi illustrates a general method for preparing tetrahydroquinoline-connector 2 derivatives. Tetrahydroquinoline **3** is converted to phenyl-substituted **11** utilizing a Suzuki coupling, and the ester of **11** is hydrolyzed to afford carboxylic acid **2**. The connecter moieties can be installed via a peptide coupling of the carboxylic acid **2** to prepare **12** (tetrahydroquinoline-connector 2 derivatives **10C**). For example, Scheme Xi provides for a connector Q^1, wherein Q^1 is -W-R (e.g., -W-R of **12**).

SCHEME Xi



[00124] For example, R may be .

[00125] The above-identified imidazoquinoline compounds may have an attachment point for a connector element via the imidazole group. As seen below, a connector element may be identified as a Q^1 group in imidazoquinoline-connector 1 **C**, imidazoquinoline-connector 1 **D**, imidazoquinoline-connector 1 **E**, imidazoquinoline-connector 1 **F**, and imidazoquinoline-connector 1 **G**:

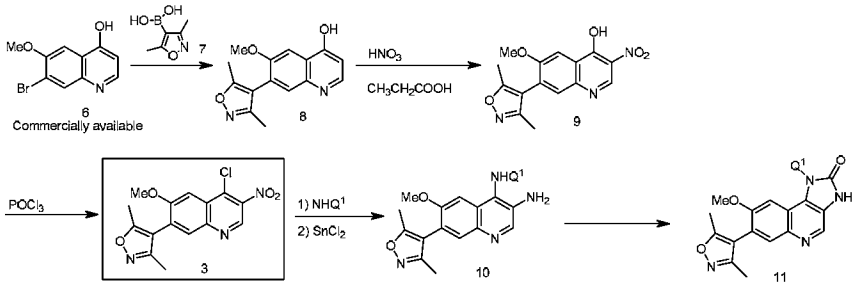


[00126] The synthetic routes in Scheme Xm and Scheme Xn provide two complementary methods for preparing imidazoquinoline-connector 1 derivatives. In Scheme Xm, commercially available **6** is reacted with isoxazole **7** under Suzuki coupling conditions to prepare quinoline intermediate **8**. The amine intermediate **9** is formed via nitration of quinoline

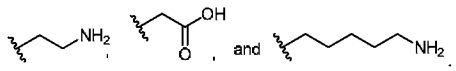
8 and is followed by chlorination to afford key intermediate **3**. Nucleophilic aromatic substitution to install the desired Q^1 group and reduction of the nitro group provides **10**. In the final step, the fused imidazolidinone ring is is formed to afford **11** (imidazoquinoline-connector 1 derivative). For example, Scheme Xm provides for a connector Q^1.

[00127] In Scheme Xn, commercially available diester **12** and aniline **13** are reacted to prepare the quinoline core intermediate **14**. The isoxazole of **15** is installed via a Suzuki coupling. A three step procedure: hydrolysis, chlorination and amidation, provides carboxamide **4**. Nucleophilic aromatic substitution is utilized to install the desired Q^1 group, and formation of the imidazolidinone ring is the final step in the preparation of **18** (imidazoquinoline-connector 1 derivative). For example, Scheme Xn provides for a connector moiety Q^1.

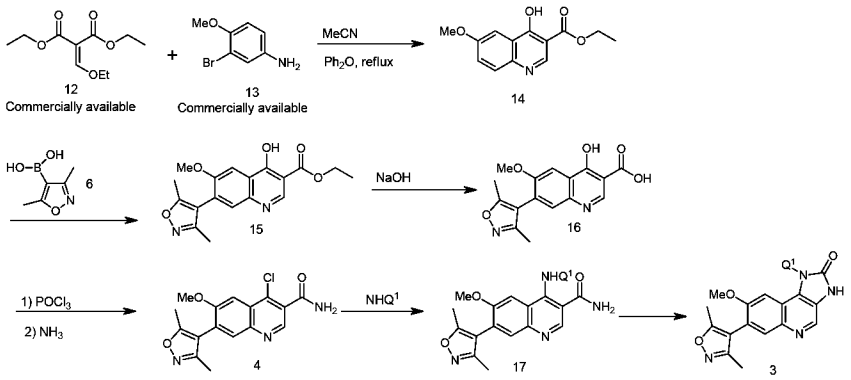
SCHEME Xm



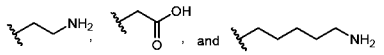
[00128] For example, Q^1 may be selected from the group consisting of:



SCHEME Xn

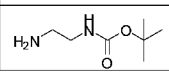
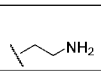


[00129] For example, Q^1 may be selected from the group consisting of:

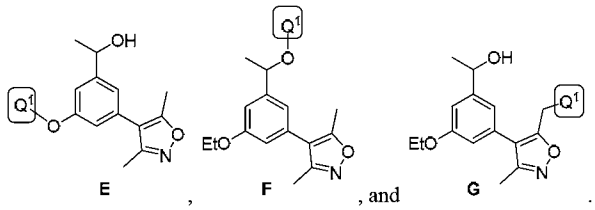


[00130] Additional examples for NHQ^1 and $-Q^1$ that can be utilized in Scheme Xm and Scheme Xn can be found in Table M, seen below:

Table M

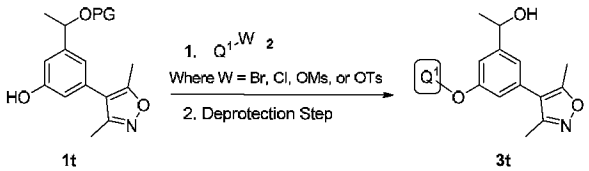
Example No.	NH-Q^1	-Q^1
3		

[00131] The above-identified isoxazole compounds may have one of *e.g.*, two possible attachment points for a connector element: the phenyl ether and the benzylic ether. As seen below, a connector element may be identified as a Q^1 group in isoxazole-connector 1 **E** and isoxazole-connector 2 **F**:



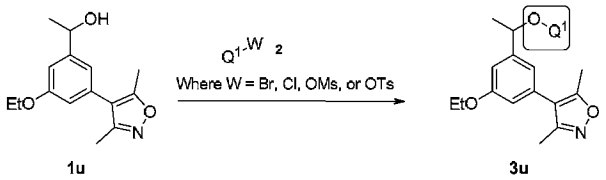
[00132] The synthetic route in Scheme Xt illustrates a general method for preparing isoxazole-connector 1 derivatives. The method involves attaching the desired substituents to the phenol core. The desired Q^1 group attached at the meta-position of the phenol can be installed by reacting isoxazole **1t** with the appropriate electrophile **2** to provide **3t** (isoxazole-connector 1 derivative). For example, Scheme Xt provides for a connector moiety Q^1.

SCHEME Xt



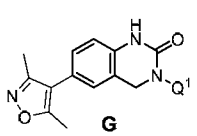
[00133] Similar to Scheme Xt, Scheme Xu provides a synthetic route for preparing isoxazole-connector 2 derivatives. The method involves attaching the desired substituents to the phenol core. The desired Q^1 group attached at the benzylic alcohol can be installed by reacting isoxazole **1u** with the appropriate electrophile **2** to provide **3u** (isoxazole-connector 2 derivative). For example, Scheme Xu provides for a connector moiety Q^1.

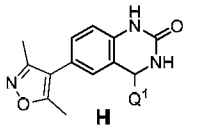
SCHME Xu

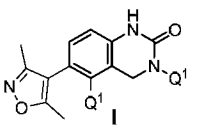


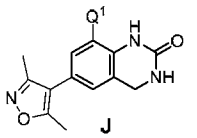
[00134] For Scheme Xt and Scheme Xu, additional examples for **2** and Q^1 can be found in Table A.

[00135] Isoxazole compounds may be attached to a connector through a different attachment point, e.g., the amino group of the quinazolone core. As seen below, a connector element may be identified, e.g., as a Q^1 group in isoxazole-connector **G**, isoxazole-connector **H**, isoxazole-connector **I**, isoxazole-connector **J**, isoxazole-connector **K**,:

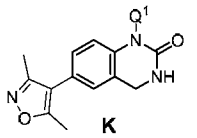

G


H


I


J

, and

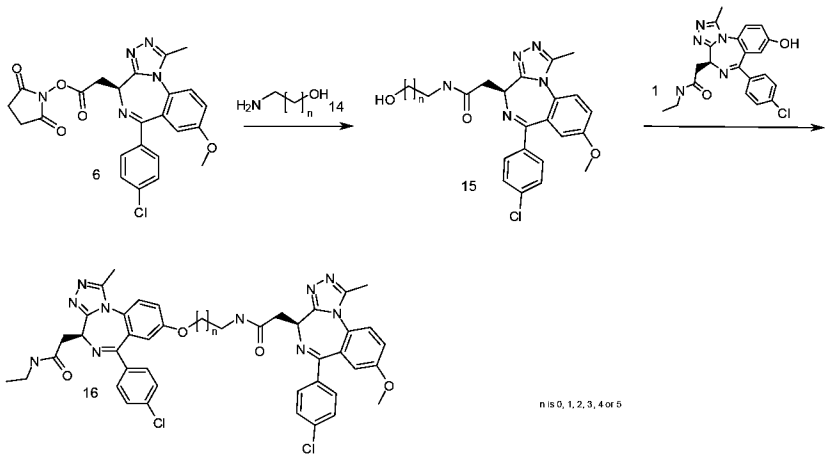

K

.

A) Carbonyl Region-to-Phenyl Ether Region Connections

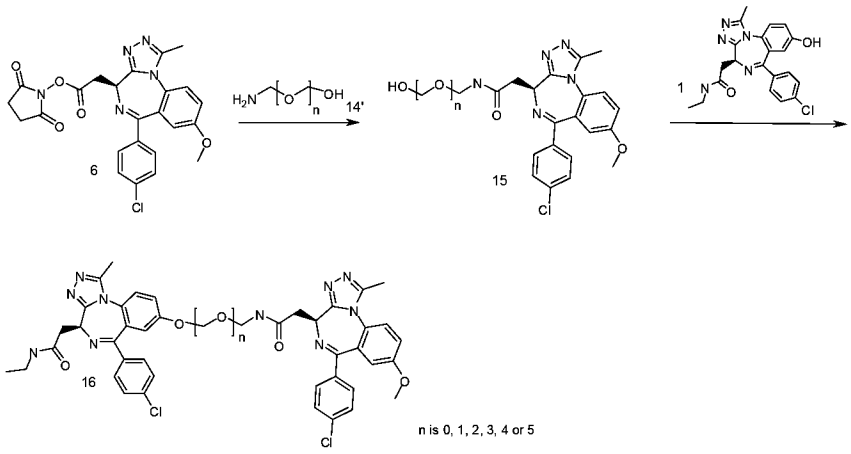
[00136] Scheme Xr and Scheme Xr' provide exemplary synthetic procedures for making bivalent molecules with a carbonyl region-to-phenyl ether region orientations, having a connecting moiety between the two attachment points of the **A** and **B** derivatives, **1** and **15**, respectively. Intermediate **6** is converted to alcohol **15** via reaction with amine **14**. The dimerization of **15** and **1** affords the bivalent molecule **16**.

SCHEME Xr



[00137] The bivalent molecule **16'** of Scheme Xr' can be prepared following the general procedure outlined for **16** of Scheme Xr.

SCHEME Xr'

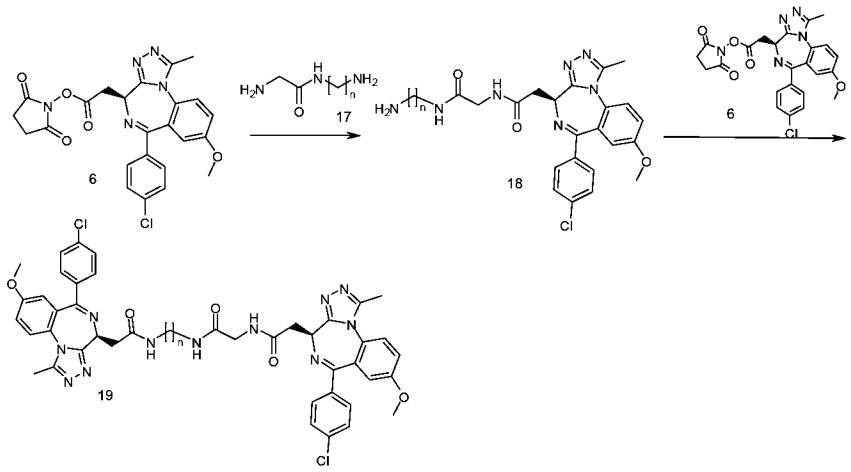


[00138] In one embodiment, the bivalent molecules **16** or **16'** may be capable of binding to a bromodomain or to tandem bromodomains.

B) Carbonyl Region-to-Carbonyl Region Connections

[00139] Scheme Xs provides a synthetic procedure for making bivalent molecules with a carbonyl region-to-carbonyl region orientation, having a connecting moiety between the two attachment points of the **B** derivatives, **18** and **6**. Intermediate **6** is converted to amine **18** via reaction with linear amine **17**. The dimerization of **18** and **6** affords the bivalent molecule **19**.

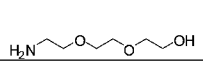
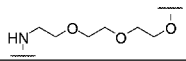
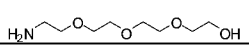
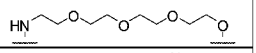
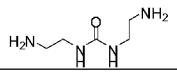
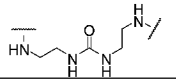
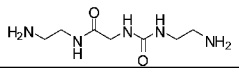
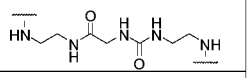
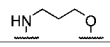
SCHEME Xs

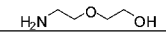
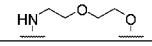
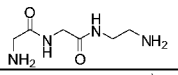
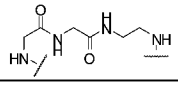
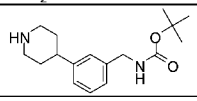
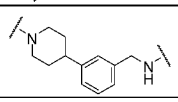
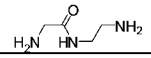
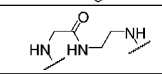
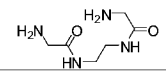
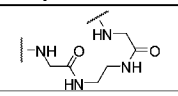


[00140] In one embodiment, the bivalent molecule **19** may be capable of binding to a bromodomain or to tandem bromodomains.

[00141] Additional examples of connecting moieties that can be utilized in Scheme Xr, Scheme Xr' and Scheme Xs can be found in Table P', seen below:

Table P'

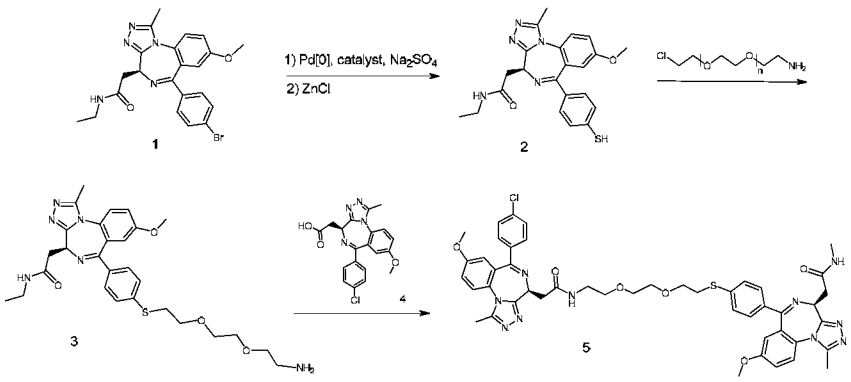
Example No.	HW-R-WH (e.g. 14, 14' or 17)	-W-R-W-
1		
2		
3		
4		
5		
6		

7		
8		
9		
10		
11		

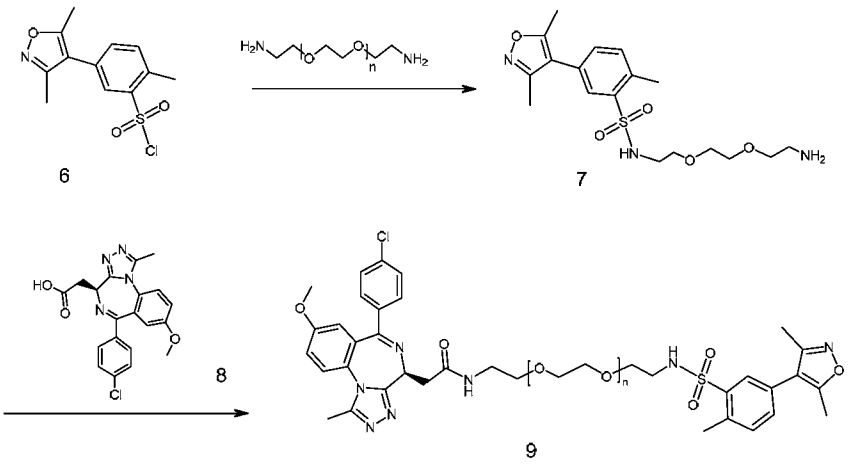
C) Phenyl Region-to-Carbonyl Region Connections

[00142] Schemes Xt and Xu provide synthetic procedures for making bivalent molecules with a phenyl region-to-carbonyl region orientation.

SCHEME Xt



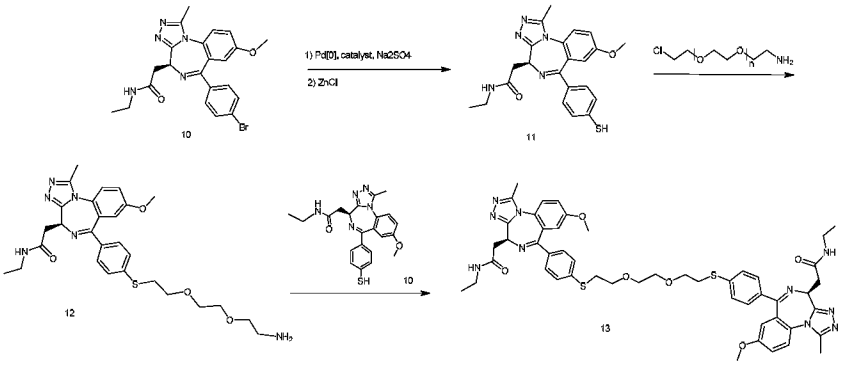
SCHEME Xu



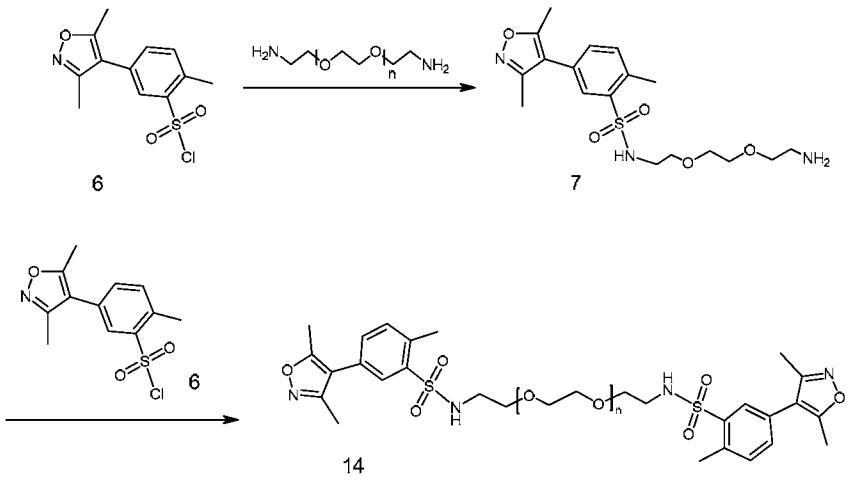
D) Phenyl Region-to-Phenyl Region Connections

[00143] Schemes Xv and Xw provide synthetic procedures for making bivalent molecules with a phenyl region-to-phenyl region orientation.

SCHEME Xv



SCHEME Xw



Methods

[00144] In some embodiments, contemplated bivalent compounds may be administered to a patient in need therof. In some embodiments, a method of administering a pharmaceutically effective amount of a compound to a patient in need thereof is provided. In some instances, a method of modulating two or more target biomolecule domains is provided. In some embodiments, the target biomolecule may be a protein. In other embodiments, the target biomolecule may be nucleic acid.

[00145] In some instances, a method of modulating two or more target biomolecule domains is provided, e.g., two bromodomains. In some embodiments, a compound may be used to inhibit or facilitate protein-protein interactions. For example, in some cases, a compound may be capable of activating or inactivating a signaling pathway. Without wishing to be bound by any theory, a compound may bind to a target protein and affect the conformation of the target protein such that the target protein is more biologically active as compared to when the compound does not bind the target protein. In some embodiments, the compound may bind to one region (e.g., domain) of a target molecule. In some embodiments, the compound may bind to two regions of a target molecule. In some embodiments, the compound may bind to a first region of a first target molecule and a second region of a second target molecule.

[00146] For example, in some embodiments, P^1 and P^2 of Formula I may each be capable of binding to a bromodomain in a protein selected from the group consisting of BRD2 D2, BRD3 D2, BRD4 D2, BRD-t D2, yBdf1 D2, yBdf2 D2, KIAA2026, yBdf1 D1, yBdf2 D1, TAF1L D1, TAF1 D1, TAF1L D2, TAF1 D2, ZMYND8, ZMYND11, ASH1L, PBRM D3, PBRM D1, PBRM D2, PBRM D4, PBRM D5, SMARCA2, SMARCA4 ySnf2, ySth, PBRM D6, yRsc1 D2, yRsc2 D2, yRsc1 D1, yRsc2 D1, yRsc4 D1, BRWD1 D1, BRWD3 D1, PHIP D1, MLL, MLL4, BRWD2, ATAD2, ATAD2B, BRD1, BRPF1, BRPF3, BRD7, BRD9, BAZ1B, BRWD1 D2, PHIP D2, BRWD3, CREBBP, EP300 BRD8 D1, BRD8 D2, yRsc4 D2, ySpt7, BAZ1A, BAZ2A, BAZ2B, SP140, SP140L, TRIM28, TRIM24, TRIM33, TRIM66, BPTF, GCN5L2, PCAF, yGcn5, BRD2 D1, BRD3 D1, BRD4 D1, BRD-t D1 and CECR2. Reference to protein and domain names used herein are derived from Zhang Q, Chakravarty S, Ghersi D, Zeng L, Plotnikov AN, et al. (2010) Biochemical Profiling of Histone Binding Selectivity of the Yeast Bromodomain Family. PLoS ONE 5(1): e8903. doi:10.1371/journal.pone.0008903.

[00147] In one embodiment, compounds contemplated herein may be capable of binding to a protein having a bromodomain, wherein the protein is independently selected from the group consisting of BRD2, BRD3, BRD4 and BRD-t. In another embodiment, compounds contemplated herein may be capable of binding to a tandem bromodomain in a protein selected from the group consisting of BRD2, BRD3, BRD4 and BRD-t. For example, a contemplated bivalent compound may be capable of binding to a tandem bromodomain in a protein selected from the group consisting of BRD2, BRD3, BRD4 and BRD-t.

[00148] In one embodiment, a contemplated bivalent compound may be capable of binding to a bromodomain and a second protein domain, wherein the protein domain is within, *e.g.*, about 40 Å, or about 50 Å, of the bromodomain.

[00149] In one embodiment, bivalent compounds contemplated herein may be capable of modulating oncology fusion proteins. For example, a bivalent compound may be capable of modulating oncology fusion proteins. Methods of modulating oncology fusion proteins include methods of modulating, e.g., BRD-NUT. In some embodiments, the oncology fusion protein (e.g., fusion gene product) is a BRD fusion product, for example, BRD3-NUT and BRD4-NUT. For example, a method of modulating a fusion protein provided, wherein the fusion protein is selected from the group consisting of BRD3-NUT and BRD4-NUT.

[00150] In an embodiment, the compounds contemplated herein may be used in a method for treating diseases or conditions for which a bromodomain inhibitor is indicated, for

example, a compound may be used for treating a chronic autoimmune and/or inflammatory condition in a patient in need thereof. In another embodiment, the compounds contemplated herein may be used in a method for treating cancer, such as midline carcinoma. For example, provided herein is a method of treating a disease associated with a protein having tandem bromodomains in a patient in need.

[00151] Provided herein, for example, is a use of a compound in the manufacture of a medicament for the treatment of diseases or conditions for which a bromodomain inhibitor is indicated. In another embodiment, provided herein is a use of a compound or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a chronic autoimmune and/or inflammatory condition. In a further embodiment, provided herein is a use of a compound or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of cancer, such as midline carcinoma or acute myeloid leukemia.

[00152] Provided herein is a method of treating a disease or condition such as systemic or tissue inflammation, inflammatory responses to infection or hypoxia, cellular activation and proliferation, lipid metabolism, fibrosis, or the prevention and treatment of viral infections in a patient in need thereof comprising administering a pharmaceutically effective amount of a contemplated bivalent compound.

[00153] For example, methods of treating chronic autoimmune and inflammatory conditions such as rheumatoid arthritis, osteoarthritis, acute gout, psoriasis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease (Crohn's disease and Ulcerative colitis), asthma, chronic obstructive airways disease, pneumonitis, myocarditis, pericarditis, myositis, eczema, dermatitis, alopecia, vitiligo, bullous skin diseases, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, depression, retinitis, uveitis, scleritis, hepatitis, pancreatitis, primary biliary cirrhosis, sclerosing cholangitis, Addison's disease, hypophysitis, thyroiditis, type II diabetes, acute rejection of transplanted organs in a patient in need thereof are contemplated, comprising administering a contemplated bivalent compound.

[00154] Also contemplated herein are methods of treating acute inflammatory conditions in a patient in need thereof such as acute gout, giant cell arteritis, nephritis including lupus nephritis, vasculitis with organ involvement such as glomerulonephritis, vasculitis including giant cell arteritis, Wegener's granulomatosis, Polyarteritis nodosa, Behcet's disease, Kawasaki disease, Takayasu's Arteritis, or vasculitis with organ involvement, comprising administering a contemplated bivalent compound.

[00155] Methods of treating disorders relating to inflammatory responses to infections with bacteria, viruses, fungi, parasites or their toxins, in a patient in need thereof is contemplated, such as sepsis, sepsis syndrome, septic shock, endotoxaemia, systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute lung injury, ARDS (adult respiratory distress syndrome), acute renal failure, fulminant hepatitis, burns, acute pancreatitis, post-surgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, meningitis, malaria, SIRS associated with viral infections such as influenza, herpes zoster, herpes simplex, coronavirus, cold sores, chickenpox, shingles, human papilloma virus, cervical neoplasia, adenovirus infections, including acute respiratory disease, poxvirus infections such as cowpox and smallpox and African swine fever virus comprising administering administering a contemplated bivalent compound.

[00156] Contemplated bivalent compounds may be useful, when administered to a patient in need thereof, in the prevention or treatment of conditions associated with ischaemia-reperfusion injury in a patient need thereof such as myocardial infarction, cerebrovascular ischaemia (stroke), acute coronary syndromes, renal reperfusion injury, organ transplantation, coronary artery bypass grafting, cardio-pulmonary bypass procedures, pulmonary, renal, hepatic, gastro-intestinal or peripheral limb embolism.

[00157] Other contemplated methods of treatment that include administering disclosed compounds include treatment of disorders of lipid metabolism via the regulation of APO-A1 such as hypercholesterolemia, atherosclerosis and Alzheimer's disease, treatment of fibrotic conditions such as idiopathic pulmonary fibrosis, renal fibrosis, post-operative stricture, keloid formation, scleroderma, cardiac fibrosis, and the prevention and treatment of viral infections such as herpes virus, human papilloma virus, adenovirus and poxvirus and other DNA viruses.

[00158] Contemplated herein are methods of treating cancers, e.g., cancers such as including hematological, epithelial including lung, breast and colon carcinomas, mesenchymal, hepatic, renal and neurological tumors, comprising administering a disclosed compound to a patient in need thereof. For example, contemplated herein is a method of treating squamous cell carcinoma, midline carcinoma or leukemia such as acute myeloid leukemia in a patient in need thereof comprising administering a bivalent compound.

[00159] In an embodiment, a bivalent compound may be administered at the point of diagnosis to reduce the incidence of: SIRS, the onset of shock, multi-organ dysfunction syndrome, which includes the onset of acute lung injury, ARDS, acute renal, hepatic, and cardiac and gastro-intestinal injury.

[00160] Also contemplated herein are methods of providing contraceptive agents, or a method of providing contraception, to a male patient, comprising administering a bivalent compound.

[00161] In some embodiments, a ligand moiety (e.g., a pharmacophore) may have a molecular weight between 50 Da and 2000 Da, in some embodiments between 50 Da and 1500 Da, in some embodiments, between 50 Da and 1000 Da, and in some embodiments, between 50 Da and 500 Da. In certain embodiments, a ligand moiety may have a molecular weight of less than 2000 Da, in some embodiments, less than 1000 Da, and in some embodiments less than 500 Da.

[00162] In certain embodiments, the compound utilized by one or more of the foregoing methods is one of the generic, subgeneric, or specific compounds described herein.

[00163] Disclosed compositions may be administered to patients (animals and humans) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. It will be appreciated that the dose required for use in any particular application will vary from patient to patient, not only with the particular compound or composition selected, but also with the route of administration, the nature of the condition being treated, the age and condition of the patient, concurrent medication or special diets then being followed by the patient, and other factors which those skilled in the art will recognize, with the appropriate dosage ultimately being at the discretion of the attendant physician. For treating clinical conditions and diseases noted above, a compound may be administered orally, subcutaneously, topically, parenterally, by inhalation spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants, and vehicles. Parenteral administration may include subcutaneous injections, intravenous or intramuscular injections, or infusion techniques.

[00164] Treatment can be continued for as long or as short a period as desired. The compositions may be administered on a regimen of, for example, one to four or more times per day. A suitable treatment period can be, for example, at least about one week, at least about two weeks, at least about one month, at least about six months, at least about 1 year, or indefinitely. A treatment period can terminate when a desired result, for example a partial or total alleviation of symptoms, is achieved.

[00165] In another aspect, pharmaceutical compositions comprising bivalent compounds as disclosed herein formulated together with a pharmaceutically acceptable carrier provided. In particular, the present disclosure provides pharmaceutical compositions bivalent compounds as

disclosed herein formulated together with one or more pharmaceutically acceptable carriers. These formulations include those suitable for oral, rectal, topical, buccal, parenteral (e.g., subcutaneous, intramuscular, intradermal, or intravenous) rectal, vaginal, or aerosol administration, although the most suitable form of administration in any given case will depend on the degree and severity of the condition being treated and on the nature of the particular compound being used. For example, disclosed compositions may be formulated as a unit dose, and/or may be formulated for oral or subcutaneous administration.

[00166] Exemplary pharmaceutical compositions may be used in the form of a pharmaceutical preparation, for example, in solid, semisolid, or liquid form, which contains one or more of the compounds, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, solutions, emulsions, suspensions, and any other form suitable for use. The active object compound is included in the pharmaceutical composition in an amount sufficient to produce the desired effect upon the process or condition of the disease.

[00167] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical carrier, *e.g.,* conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, *e.g.,* water, to form a solid preformulation composition containing a homogeneous mixture of a compound, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[00168] In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the subject composition is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6)

absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets and pills, the compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

[00169] A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the subject composition moistened with an inert liquid diluent. Tablets, and other solid dosage forms, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art.

[00170] Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the subject composition, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, cyclodextrins and mixtures thereof.

[00171] Suspensions, in addition to the subject composition, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

[00172] Formulations for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing a subject composition with one or more suitable

non-irritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the body cavity and release the active agent.

[00173] Dosage forms for transdermal administration of a subject composition includes powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required.

[00174] The ointments, pastes, creams and gels may contain, in addition to a subject composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

[00175] Powders and sprays may contain, in addition to a subject composition, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays may additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

[00176] Compositions and compounds may alternatively be administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation or solid particles containing the compound. A non-aqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers may be used because they minimize exposing the agent to shear, which may result in degradation of the compounds contained in the subject compositions. Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of a subject composition together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular subject composition, but typically include non-ionic surfactants (Tweens, Pluronics, or polyethylene glycol), innocuous proteins like serum albumin, sorbitan esters, oleic acid, lecithin, amino acids such as glycine, buffers, salts, sugars, or sugar alcohols. Aerosols generally are prepared from isotonic solutions.

[00177] Pharmaceutical compositions suitable for parenteral administration comprise a subject composition in combination with one or more pharmaceutically-acceptable sterile isotonic aqueous or non-aqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the

formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

[00178] Examples of suitable aqueous and non-aqueous carriers which may be employed in the pharmaceutical compositions include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate and cyclodextrins. Proper fluidity may be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants

[00179] In another aspect, enteral pharmaceutical formulations including a disclosed pharmaceutical composition comprising bivalent compounds, an enteric material; and a pharmaceutically acceptable carrier or excipient thereof are provided. Enteric materials refer to polymers that are substantially insoluble in the acidic environment of the stomach, and that are predominantly soluble in intestinal fluids at specific pHs. The small intestine is the part of the gastrointestinal tract (gut) between the stomach and the large intestine, and includes the duodenum, jejunum, and ileum. The pH of the duodenum is about 5.5, the pH of the jejunum is about 6.5 and the pH of the distal ileum is about 7.5. Accordingly, enteric materials are not soluble, for example, until a pH of about 5.0, of about 5.2, of about 5.4, of about 5.6, of about 5.8, of about 6.0, of about 6.2, of about 6.4, of about 6.6, of about 6.8, of about 7.0, of about 7.2, of about 7.4, of about 7.6, of about 7.8, of about 8.0, of about 8.2, of about 8.4, of about 8.6, of about 8.8, of about 9.0, of about 9.2, of about 9.4, of about 9.6, of about 9.8, or of about 10.0. Exemplary enteric materials include cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HPMCP), polyvinyl acetate phthalate (PVAP), hydroxypropyl methylcellulose acetate succinate (HPMCAS), cellulose acetate trimellitate, hydroxypropyl methylcellulose succinate, cellulose acetate succinate, cellulose acetate hexahydrophthalate, cellulose propionate phthalate, cellulose acetate maleat, cellulose acetate butyrate, cellulose acetate propionate, copolymer of methylmethacrylic acid and methyl methacrylate, copolymer of methyl acrylate, methylmethacrylate and methacrylic acid, copolymer of methylvinyl ether and maleic anhydride (Gantrez ES series), ethyl methyacrylate-methylmethacrylate-chlorotrimethylammonium ethyl acrylate copolymer, natural resins such as zein, shellac and copal collophorium, and several commercially available enteric dispersion systems (e. g. , Eudragit L30D55, Eudragit FS30D, Eudragit L100, Eudragit S100, Kollicoat EMM30D, Estacryl 30D, Coateric, and Aquateric). The solubility of each of the above materials is either

known or is readily determinable *in vitro*. The foregoing is a list of possible materials, but one of skill in the art with the benefit of the disclosure would recognize that it is not comprehensive and that there are other enteric materials that may be used.

[00180] Advantageously, kits are provided containing one or more compositions. Such kits include a suitable dosage form such as those described above and instructions describing the method of using such dosage form to treat a disease or condition. The instructions would direct the consumer or medical personnel to administer the dosage form according to administration modes known to those skilled in the art. Such kits could advantageously be packaged and sold in single or multiple kit units. An example of such a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process recesses are formed in the plastic foil. The recesses have the size and shape of the tablets or capsules to be packed. Next, the tablets or capsules are placed in the recesses and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are sealed in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

[00181] It may be desirable to provide a memory aid on the kit, *e.g.,* in the form of numbers next to the tablets or capsules whereby the numbers correspond with the days of the regimen which the tablets or capsules so specified should be ingested. Another example of such a memory aid is a calendar printed on the card, *e.g.,* as follows "First Week, Monday, Tuesday, . . . etc. . . . Second Week, Monday, Tuesday, . . . " etc. Other variations of memory aids will be readily apparent. A "daily dose" can be a single tablet or capsule or several pills or capsules to be taken on a given day. Also, a daily dose of a first compound can consist of one tablet or capsule while a daily dose of the second compound can consist of several tablets or capsules and vice versa. The memory aid should reflect this.

[00182] Also contemplated herein are methods and compositions that include a second active agent, or administering a second active agent.

[00183] Certain terms employed in the specification, examples, and appended claims are collected here. These definitions should be read in light of the entirety of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

DEFINITIONS

[00184] In some embodiments, the compounds, as described herein, may be substituted with any number of substituents or functional moieties. In general, the term "substituted" whether preceded by the term "optionally" or not, and substituents contained in formulas, refer to the replacement of hydrogen radicals in a given structure with the radical of a specified substituent.

[00185] In some instances, when more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position.

[00186] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic and inorganic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds. In some embodiments, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms. Non-limiting examples of substituents include acyl; aliphatic; heteroaliphatic; phenyl; naphthyl; heteroaryl; arylalkyl; heteroarylalkyl; alkoxy; cycloalkoxy; heterocyclylalkoxy; heterocyclyloxy; heterocyclyloxyalkyl; alkenyloxy; alkynyloxy; phenoxy; heteroalkoxy; heteroaryloxy; alkylthio; phenylthio; heteroalkylthio; heteroarylthio; oxo; -F; -Cl; -Br; -I; -OH; $-NO_2$; -CN; -SCN; $-SR_x$; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-OR_x$, $-C(O)R_x$; $-CO_2(R_x)$; $-C(O)N(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OC(O)N(R_x)_2$; $-N(R_x)_2$; $-SOR_x$; $-S(O)_2R_x$; $-NR_xC(O)R_x$; or $-C(R_x)_3$; wherein each occurrence of R_x independently is hydrogen, aliphatic, heteroaliphatic, phenyl, naphthyl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the phenyl, naphthyl, or heteroaryl substituents described above and herein may be substituted or unsubstituted. Furthermore, the

compounds described herein are not intended to be limited in any manner by the permissible substituents of organic compounds. In some embodiments, combinations of substituents and variables described herein may be preferably those that result in the formation of stable compounds. The term "stable," as used herein, refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

[00187] The term "acyl," as used herein, refers to a moiety that includes a carbonyl group. In some embodiments, an acyl group may have a general formula selected from -$C(O)R_x$; -$CO_2(R_x)$; -$C(O)N(R_x)_2$; -$OC(O)R_x$; -OCO_2R_x; and -$OC(O)N(R_x)_2$; wherein each occurrence of R_x independently includes, but is not limited to, hydrogen, aliphatic, heteroaliphatic, phenyl, naphthyl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein any of the aliphatic, heteroaliphatic, arylalkyl, or heteroarylalkyl substituents described above and herein may be substituted or unsubstituted, branched or unbranched, cyclic or acyclic, and wherein any of the phenyl, naphthyl, or heteroaryl substituents described above and herein may be substituted or unsubstituted.

[00188] The term "aliphatic," as used herein, includes both saturated and unsaturated, straight chain (i.e., unbranched), branched, acyclic, cyclic, or polycyclic aliphatic hydrocarbons, which are optionally substituted with one or more functional groups. As will be appreciated by one of ordinary skill in the art, "aliphatic" is intended herein to include, but is not limited to, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, and cycloalkynyl moieties. The term "heteroaliphatic," as used herein, refers to aliphatic moieties that contain one or more oxygen, sulfur, nitrogen, phosphorus, or silicon atoms, e.g., in place of carbon atoms. Heteroaliphatic moieties may be branched, unbranched, cyclic or acyclic and include saturated and unsaturated heterocycles such as morpholino, pyrrolidinyl, etc.

[00189] In general, the terms "aryl," "aromatic," "heteroaryl," and "heteroaromtic" as used herein, refer to stable mono- or polycyclic, heterocyclic, polycyclic, and polyheterocyclic unsaturated moieties having preferably 3-14 carbon atoms, each of which may be substituted or unsubstituted. Substituents include, but are not limited to, any of the previously mentioned substituents, i.e., the substituents recited for aliphatic moieties, or for other moieties as disclosed herein, resulting in the formation of a stable compound. In certain embodiments, aryl or aromatic refers to a mono- or bicyclic carbocyclic ring system having one or two aromatic rings selected from phenyl, naphthyl, tetrahydronaphthyl, indanyl, and indenyl. In certain

embodiments, the term heteroaryl, as used herein, refers to a cyclic aromatic radical having from five to ten ring atoms of which one ring atom is selected from the group consisting of S, O, and N; zero, one, or two ring atoms are additional heteroatoms independently selected from the group consisting of S, O, and N; and the remaining ring atoms are carbon, the radical being joined to the rest of the molecule via any of the ring atoms. Heteroaryl moieties may be selected from: pyridyl, pyrazinyl, pyrimidinyl, pyrrolyl, pyrazolyl, imidazolyl, thiazolyl, oxazolyl, isooxazolyl, thiadiazolyl,oxadiazolyl, thiophenyl, furanyl, quinolinyl, isoquinolinyl, and the like.

[00190] It will be appreciated that aryl, aromatic, heteroaryl, and heteroaromatic groups described herein can be unsubstituted or substituted, wherein substitution includes replacement of one, two, three, or more of the hydrogen atoms thereon independently with a group selected from: C_{1-6}alkyl; phenyl; heteroaryl; benzyl; heteroarylalkyl; C_{1-6}alkoxy; C_{1-6}cycloalkoxy; C_{1-6}heterocyclylalkoxy; C_{1-6}heterocyclyloxy; heterocyclyloxyalkyl; C_{2-6}alkenyloxy; C_{2-6}alkynyloxy; phenoxy; heteroalkoxy; heteroaryloxy; C_{1-6}alkylthio; phenylthio; heteroalkylthio; heteroarylthio; oxo; -F; -Cl; -Br; -I; -OH; $-NO_2$; -CN; $-CF_3$; $-CH_2CF_3$; $-CHCl_2$; $-CH_2OH$; $-CH_2CH_2OH$; $-CH_2NH_2$; $-CH_2SO_2CH_3$; $-C(O)R_x$; $-CO_2(R_x)$; $-CON(R_x)_2$; $-OC(O)R_x$; $-OCO_2R_x$; $-OCON(R_x)_2$; $-N(R_x)_2$; $-S(O)_2R_x$; $-NR_x(CO)R_x$, wherein each occurrence of R_x is selected from hydrogen, C_{1-6}alkyl, aliphatic, heteroaliphatic, phenyl, or heteroaryl. Additional examples of generally applicable substituents are illustrated by the specific embodiments shown in the Examples that are described herein.

[00191] The term "heterocyclic," as used herein, refers to an aromatic or non-aromatic, partially unsaturated or fully saturated, 3- to 10-membered ring system, which includes single rings of 3 to 8 atoms in size and bi- and tri-cyclic ring systems which may include aromatic five- or six-membered aryl or aromatic heterocyclic groups fused to a non-aromatic ring. These heterocyclic rings include those having from one to three heteroatoms independently selected from the group consisting of oxygen, sulfur, and nitrogen, in which the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. In certain embodiments, the term heterocyclic refers to a non-aromatic 5-, 6-, or 7-membered ring or a polycyclic group wherein at least one ring atom is a heteroatom selected from the group consisting of O, S, and N (wherein the nitrogen and sulfur heteroatoms may be optionally oxidized), including, but not limited to, a bi- or tri-cyclic group, comprising fused six-membered rings having between one and three heteroatoms independently selected from the group consisting of the oxygen, sulfur, and nitrogen, wherein (i) each 5-membered ring has 0 to

2 double bonds, each 6-membered ring has 0 to 2 double bonds, and each 7-membered ring has 0 to 3 double bonds, (ii) the nitrogen and sulfur heteroatoms may be optionally oxidized, (iii) the nitrogen heteroatom may optionally be quaternized, and (iv) any of the above heterocyclic rings may be fused to an aryl or heteroaryl ring.

[00192] The term "alkenyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon double bond, such as a straight or branched group of 2-6 or 3-4 carbon atoms, referred to herein for example as C_{2-6}alkenyl, and C_{3-4}alkenyl, respectively. Exemplary alkenyl groups include, but are not limited to, vinyl, allyl, butenyl, pentenyl, etc.

[00193] The term "alkenyloxy" used herein refers to a straight or branched alkenyl group attached to an oxygen (alkenyl-O). Exemplary alkenoxy groups include, but are not limited to, groups with an alkenyl group of 3-6 carbon atoms referred to herein as C_{3-6}alkenyloxy. Exemplary "alkenyloxy" groups include, but are not limited to allyloxy, butenyloxy, etc.

[00194] The term "alkoxy" as used herein refers to a straight or branched alkyl group attached to an oxygen (alkyl-O-). Exemplary alkoxy groups include, but are not limited to, groups with an alkyl group of 1-6 or 2-6 carbon atoms, referred to herein as C_{1-6}alkoxy, and C_2-C_6alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

[00195] The term "alkoxycarbonyl" as used herein refers to a straight or branched alkyl group attached to oxygen, attached to a carbonyl group (alkyl-O-C(O)-). Exemplary alkoxycarbonyl groups include, but are not limited to, alkoxycarbonyl groups of 1-6 carbon atoms, referred to herein as C_{1-6}alkoxycarbonyl. Exemplary alkoxycarbonyl groups include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, etc.

[00196] The term "alkynyloxy" used herein refers to a straight or branched alkynyl group attached to an oxygen (alkynyl-O)). Exemplary alkynyloxy groups include, but are not limited to, propynyloxy.

[00197] The term "alkyl" as used herein refers to a saturated straight or branched hydrocarbon, for example, such as a straight or branched group of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as C_{1-6}alkyl, C_{1-4}alkyl, and C_{1-3}alkyl, respectively. Exemplary alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 3-methyl-2-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-

pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, neopentyl, hexyl, etc.

[00198] The term "alkylene" as used herein refers to a bivalent saturated straight or branched hydrocarbon, for example, such as a straight or branched group of 1-6, 1-4, or 1-3 carbon atoms, referred to herein as -C_{1-6}alkylene-, -C_{1-4}alkylene-, and -C_{1-3}alkylene-, respectively, where the alkylene has two open valences. Exemplary alkyl groups include, but are not limited to, methylene, ethylene, propylene, isopropylene, 2-methyl-1-propylene, 2-methyl-2-propylene, 2-methyl-1-butylene, 3-methyl-1-butylene, 3-methyl-2-butylene, 2,2-dimethyl-1-propylene, 2-methyl-1-pentylene, 3-methyl-1-pentylene, 4-methyl-1-pentylene, 2-methyl-2-pentylene, 3-methyl-2-pentylene, 4-methyl-2-pentylene, 2,2-dimethyl-1-butylene, 3,3-dimethyl-1-butylene, 2-ethyl-1-butylene, butylene, isobutylene, t-butylene, pentylene, isopentylene, neopentylene, hexylene, etc.

[00199] The term "alkylcarbonyl" as used herein refers to a straight or branched alkyl group attached to a carbonyl group (alkyl-C(O)-). Exemplary alkylcarbonyl groups include, but are not limited to, alkylcarbonyl groups of 1-6 atoms, referred to herein as C_{1-6}alkylcarbonyl groups. Exemplary alkylcarbonyl groups include, but are not limited to, acetyl, propanoyl, isopropanoyl, butanoyl, etc.

[00200] The term "alkynyl" as used herein refers to an unsaturated straight or branched hydrocarbon having at least one carbon-carbon triple bond, such as a straight or branched group of 2-6, or 3-6 carbon atoms, referred to herein as C_{2-6}alkynyl, and C_{3-6}alkynyl, respectively. Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, etc.

[00201] The term "carbonyl" as used herein refers to the radical -C(O)-.

[00202] The term "carboxylic acid" as used herein refers to a group of formula -CO_2H.

[00203] The term "cyano" as used herein refers to the radical -CN.

[00204] The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to an oxygen (cycloalkyl-O-).

[00205] The term "cycloalkyl" as used herein refers to a monocyclic saturated or partially unsaturated hydrocarbon group of for example 3-6, or 4-6 carbons, referred to herein, e.g., as C_{3-6}cycloalkyl or C_{4-6}cycloalkyl and derived from a cycloalkane. Exemplary cycloalkyl groups include, but are not limited to, cyclohexyl, cyclohexenyl, cyclopentyl, cyclobutyl or, cyclopropyl.

[00206] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

[00207] The term "heterocyclylalkoxy" as used herein refers to a heterocyclyl- alkyl-O- group.

[00208] The term "heterocyclyloxyalkyl" refers to a heterocyclyl-O-alkyl- group.

[00209] The term "heterocyclyloxy" refers to a heterocyclyl-O- group.

[00210] The term "heteroaryloxy" refers to a heteroaryl-O- group.

[00211] The terms "hydroxy" and "hydroxyl" as used herein refers to the radical -OH.

[00212] The term "oxo" as used herein refers to the radical =O.

[00213] The term "connector" as used herein to refers to an atom or a collection of atoms optionally used to link interconnecting moieties, such as a disclosed connecting moiety and a pharmacophore. Contemplated connectors are generally hydrolytically stable.

[00214] "Treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[00215] "Pharmaceutically or pharmacologically acceptable" include molecular entities and compositions that do not produce an adverse, allergic, or other untoward reaction when administered to an animal, or a human, as appropriate. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by FDA Office of Biologics standards.

[00216] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" as used herein refers to any and all solvents, dispersion media, coatings, isotonic and absorption delaying agents, and the like, that are compatible with pharmaceutical administration. The use of such media and agents for pharmaceutically active substances is well known in the art. The compositions may also contain other active compounds providing supplemental, additional, or enhanced therapeutic functions.

[00217] The term "pharmaceutical composition" as used herein refers to a composition comprising at least one compound as disclosed herein formulated together with one or more pharmaceutically acceptable carriers.

[00218] "Individual," "patient," or "subject" are used interchangeably and include any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans. The compounds can be administered to a mammal, such as a human, but can also be administered to other mammals such as an animal in need of veterinary treatment, *e.g.,* domestic 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). The mammal treated is desirably a mammal in

which treatment of obesity, or weight loss is desired. "Modulation" includes antagonism (*e.g.*, inhibition), agonism, partial antagonism and/or partial agonism.

[00219] In the present specification, the term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by the researcher, veterinarian, medical doctor, or other clinician. The compounds are administered in therapeutically effective amounts to treat a disease. Alternatively, a therapeutically effective amount of a compound is the quantity required to achieve a desired therapeutic and/or prophylactic effect, such as an amount which results in weight loss.

[00220] The term "pharmaceutically acceptable salt(s)" as used herein refers to salts of acidic or basic groups that may be present in compounds used in the present compositions. Compounds included in the present compositions that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, including but not limited to malate, oxalate, chloride, bromide, iodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, *p*-toluenesulfonate and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds included in the present compositions that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium, lithium, zinc, potassium, and iron salts. Compounds included in the present compositions that include a basic or acidic moiety may also form pharmaceutically acceptable salts with various amino acids. The compounds of the disclosure may contain both acidic and basic groups; for example, one amino and one carboxylic acid group. In such a case, the compound can exist as an acid addition salt, a zwitterion, or a base salt.

[00221] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as geometric isomers, enantiomers or diastereomers. The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. These compounds may be designated by the symbols "*R*" or "*S*," depending on the configuration of substituents around the stereogenic carbon atom.

Various stereoisomers of these compounds and mixtures thereof are encompassed by this disclosure. Stereoisomers include enantiomers and diastereomers. Mixtures of enantiomers or diastereomers may be designated "(±)" in nomenclature, but the skilled artisan will recognize that a structure may denote a chiral center implicitly.

[00222] The compounds of the disclosure may contain one or more chiral centers and/or double bonds and, therefore, exist as geometric isomers, enantiomers or diastereomers. The enantiomers and diastereomers may be designated by the symbols "(+)," "(-)." "*R*" or "*S*," depending on the configuration of substituents around the stereogenic carbon atom, but the skilled artisan will recognize that a structure may denote a chiral center implicitly. Geometric isomers, resulting from the arrangement of substituents around a carbon-carbon double bond or arrangement of substituents around a cycloalkyl or heterocyclic ring, can also exist in the compounds. The symbol ═ denotes a bond that may be a single, double or triple bond as described herein. Substituents around a carbon-carbon double bond are designated as being in the "*Z*" or "*E*" configuration wherein the terms "*Z*" and "*E*" are used in accordance with IUPAC standards. Unless otherwise specified, structures depicting double bonds encompass both the "*E*" and "*Z*" isomers. Substituents around a carbon-carbon double bond alternatively can be referred to as "cis" or "trans," where "cis" represents substituents on the same side of the double bond and "trans" represents substituents on opposite sides of the double bond. The arrangement of substituents around a carbocyclic ring can also be designated as "cis" or "trans." The term "cis" represents substituents on the same side of the plane of the ring and the term "trans" represents substituents on opposite sides of the plane of the ring. Mixtures of compounds wherein the substituents are disposed on both the same and opposite sides of plane of the ring are designated "cis/trans."

[00223] The term "stereoisomers" when used herein consist of all geometric isomers, enantiomers or diastereomers. Various stereoisomers of these compounds and mixtures thereof are encompassed by this disclosure.

[00224] Individual enantiomers and diastereomers of the compounds can be prepared synthetically from commercially available starting materials that contain asymmetric or stereogenic centers, or by preparation of racemic mixtures followed by resolution methods well known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary, (2) salt formation employing an optically active resolving agent, (3)

direct separation of the mixture of optical enantiomers on chiral liquid chromatographic columns or (4) kinetic resolution using stereoselective chemical or enzymatic reagents. Racemic mixtures can also be resolved into their component enantiomers by well known methods, such as chiral-phase gas chromatography or crystallizing the compound in a chiral solvent. Stereoselective syntheses, a chemical or enzymatic reaction in which a single reactant forms an unequal mixture of stereoisomers during the creation of a new stereocenter or during the transformation of a pre-existing one, are well known in the art. Stereoselective syntheses encompass both enantio- and diastereoselective transformations. For examples, see Carreira and Kvaerno, *Classics in Stereoselective Synthesis*, Wiley-VCH: Weinheim, 2009.

[00225] The compounds disclosed herein can exist in solvated as well as unsolvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In one embodiment, the compound is amorphous. In one embodiment, the compound is a polymorph. In another embodiment, the compound is in a crystalline form.

[00226] Also embraced are isotopically labeled compounds which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluorine and chlorine, such as ^{10}B, ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. For example, a compound may have one or more H atom replaced with deuterium.

[00227] Certain isotopically-labeled disclosed compounds (*e.g.*, those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (*i.e.*, ^{3}H) and carbon-14 (*i.e.*, ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (*i.e.*, ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (*e.g.*, increased *in vivo* half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labeled compounds can generally be prepared by following procedures analogous to those disclosed in the Examples herein by substituting an isotopically labeled reagent for a non-isotopically labeled reagent.

[00228] The term "prodrug" refers to compounds that are transformed *in vivo* to yield a disclosed compound or a pharmaceutically acceptable salt, hydrate or solvate of the compound. The transformation may occur by various mechanisms (such as by esterase, amidase, phosphatase, oxidative and or reductive metabolism) in various locations (such as in the

intestinal lumen or upon transit of the intestine, blood, or liver). Prodrugs are well known in the art (for example, see Rautio, Kumpulainen, *et al,* Nature Reviews Drug Discovery 2008, 7, 255). For example, if a compound or a pharmaceutically acceptable salt, hydrate, or solvate of the compound contains a carboxylic acid functional group, a prodrug can comprise an ester formed by the replacement of the hydrogen atom of the acid group with a group such as (C_{1-8})alkyl, (C_{2-12})alkanoyloxymethyl, 1-(alkanoyloxy)ethyl having from 4 to 9 carbon atoms, 1-methyl-1-(alkanoyloxy)-ethyl having from 5 to 10 carbon atoms, alkoxycarbonyloxymethyl having from 3 to 6 carbon atoms, 1-(alkoxycarbonyloxy)ethyl having from 4 to 7 carbon atoms, 1-methyl-1-(alkoxycarbonyloxy)ethyl having from 5 to 8 carbon atoms, N-(alkoxycarbonyl)aminomethyl having from 3 to 9 carbon atoms, 1-(N-(alkoxycarbonyl)amino)ethyl having from 4 to 10 carbon atoms, 3-phthalidyl, 4-crotonolactonyl, gamma-butyrolacton-4-yl, di-N,N-$(C_1$-$C_2)$alkylamino$(C_2$-$C_3)$alkyl (such as β-dimethylaminoethyl), carbamoyl-$(C_1$-$C_2)$alkyl, N,N-di$(C_1$-$C_2)$alkylcarbamoyl-$(C_1$-$C_2)$alkyl and piperidino-, pyrrolidino- or morpholino$(C_2$-$C_3)$alkyl.

[00229] Similarly, if a compound contains an alcohol functional group, a prodrug can be formed by the replacement of the hydrogen atom of the alcohol group with a group such as (C_{1-6})alkanoyloxymethyl, 1-$((C_{1-6})$alkanoyloxy)ethyl, 1-methyl-1-$((C_{1-6})$alkanoyloxy)ethyl (C_{1-6})alkoxycarbonyloxymethyl, N-(C_{1-6})alkoxycarbonylaminomethyl, succinoyl, (C_{1-6})alkanoyl, α-amino(C_{1-4})alkanoyl, arylacyl and α-aminoacyl, or α-aminoacyl-α-aminoacyl, where each α-aminoacyl group is independently selected from the naturally occurring L-amino acids, $P(O)(OH)_2$, $-P(O)(O(C_1$-$C_6)$alkyl$)_2$ or glycosyl (the radical resulting from the removal of a hydroxyl group of the hemiacetal form of a carbohydrate).

[00230] If a compound incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-acyloxyakyl derivative, an (oxodioxolenyl)methyl derivative, an N-Mannich base, imine, or enamine. In addition, a secondary amine can be metabolically cleaved to generate a bioactive primary amine, or a tertiary amine can be metabolically cleaved to generate a bioactive primary or secondary amine. For examples, see Simplício, *et al., Molecules* 2008, *13,* 519 and references therein.

INCORPORATION BY REFERENCE

[00231] All publications and patents mentioned herein, including those items listed below, are hereby incorporated by reference in their entirety for all purposes as if each

individual publication or patent was specifically and individually incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

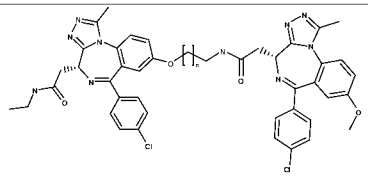
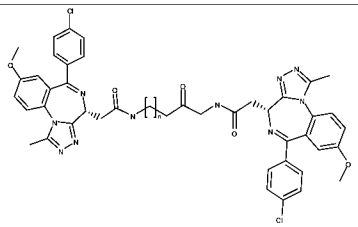
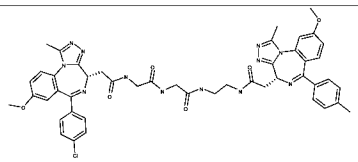
EXAMPLES

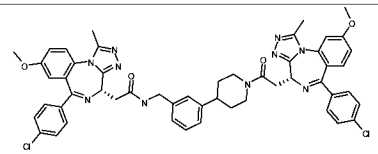
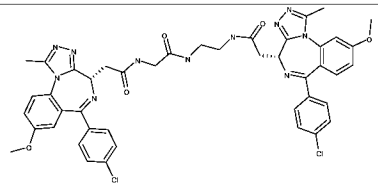
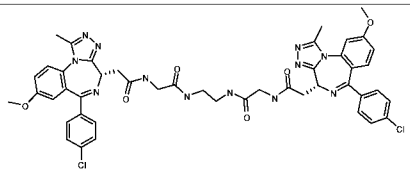
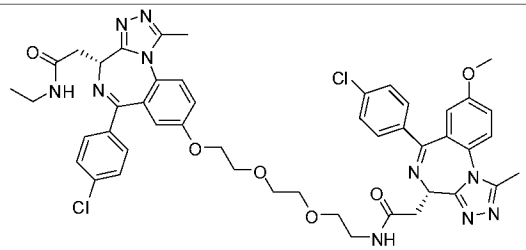
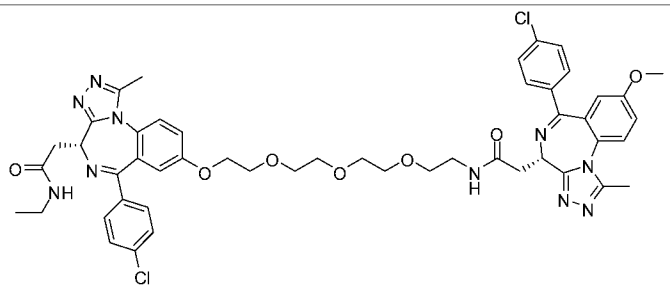
[00232] The compounds described herein can be prepared in a number of ways based on the teachings contained herein and synthetic procedures known in the art.

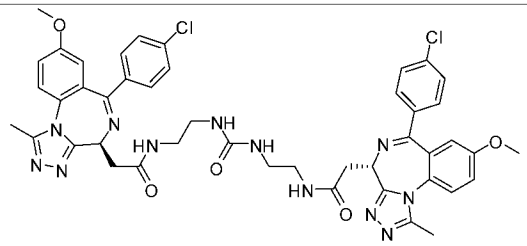
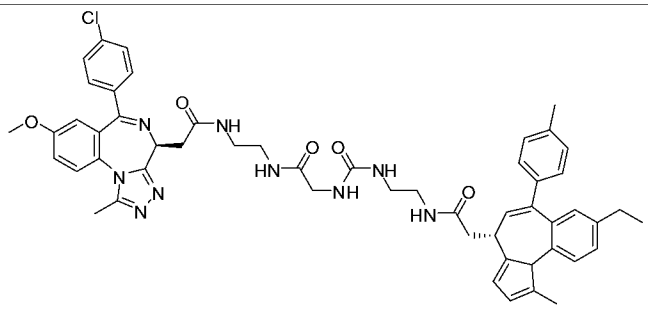
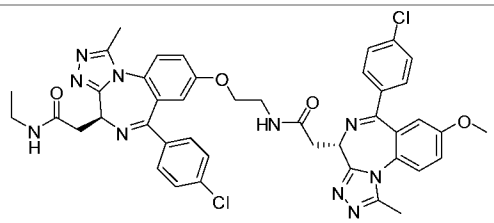
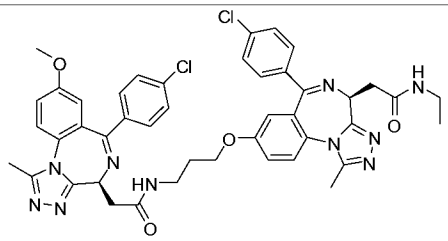
EXAMPLES 1-106:

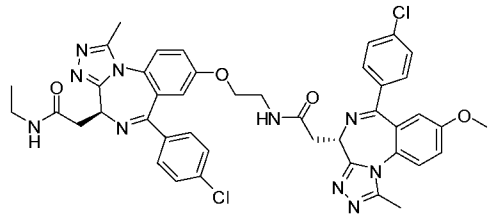
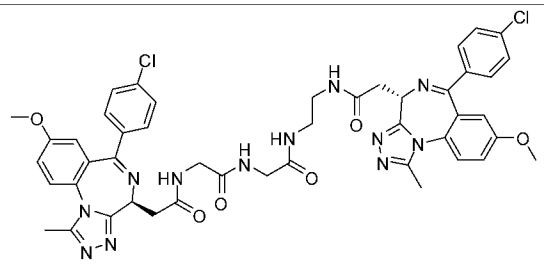
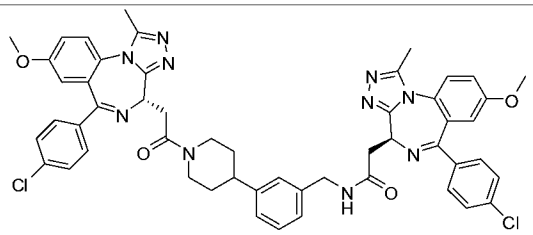
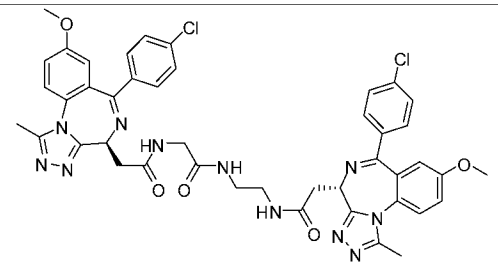
[00233] The following table (Table Q) contains examples 1-106. Examples 1-106 are bivalent molecules that can be obtained from disclosed compounds.

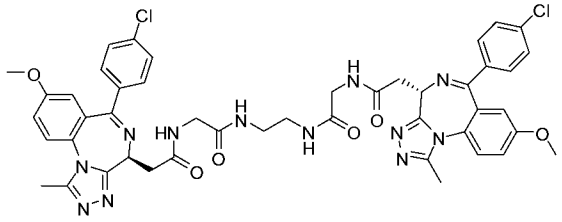
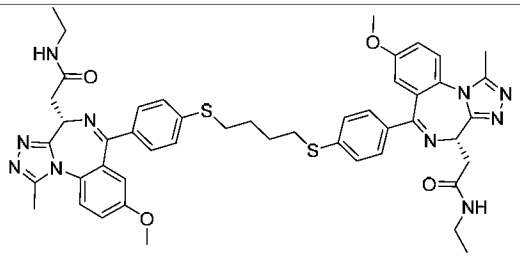
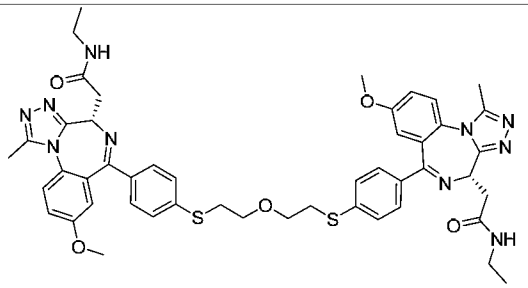
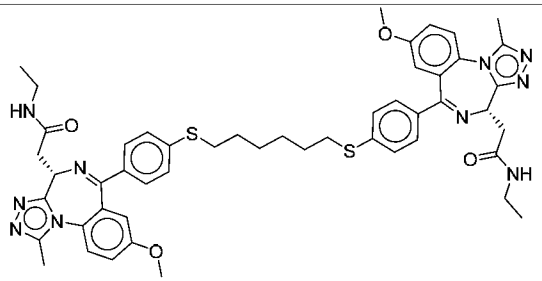
TABLE Q

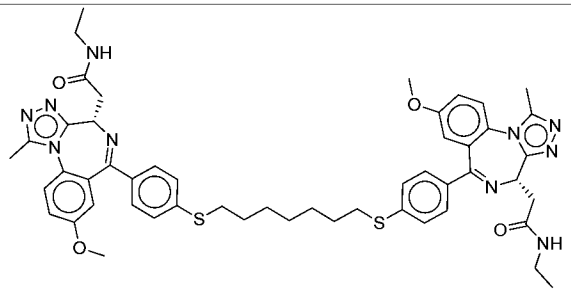
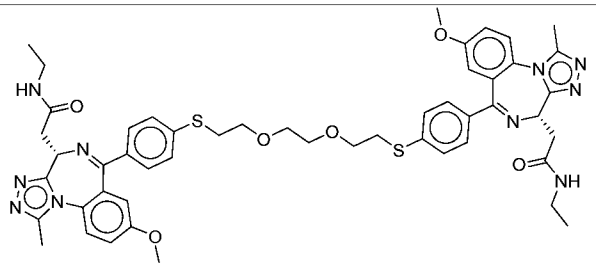
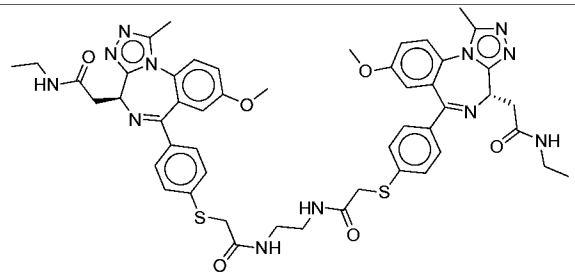
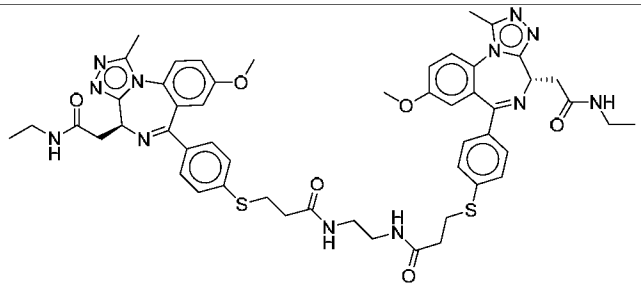
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2	 n is 0, 1, 2, 3, 4 or 5	
3		

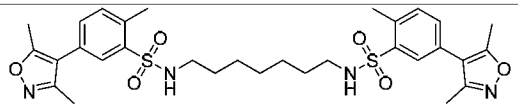
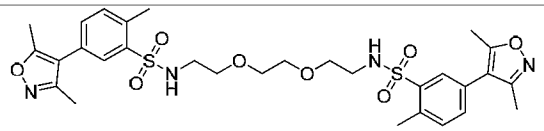
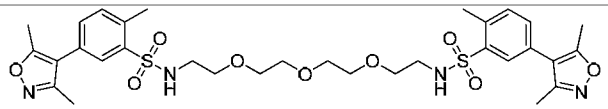
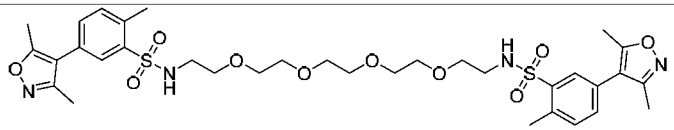
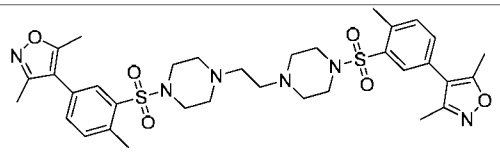
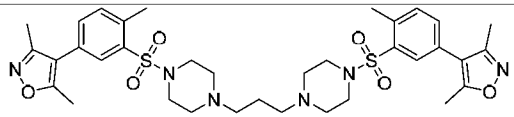
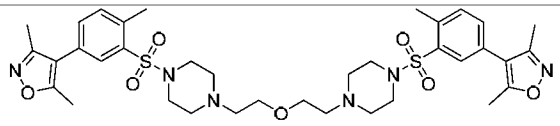
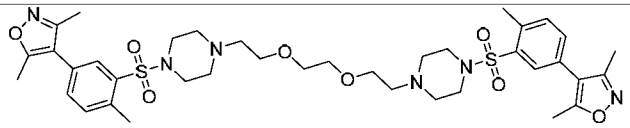
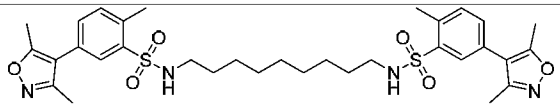
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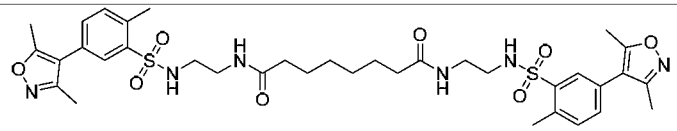
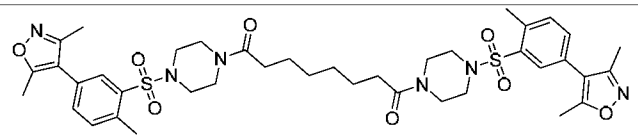
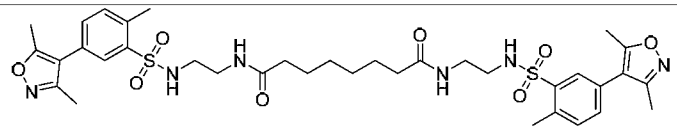
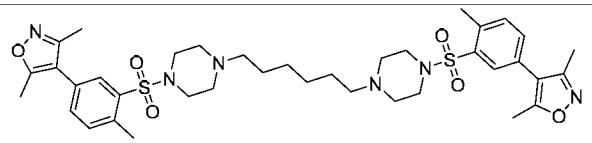
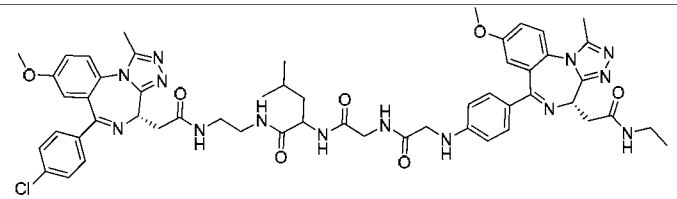
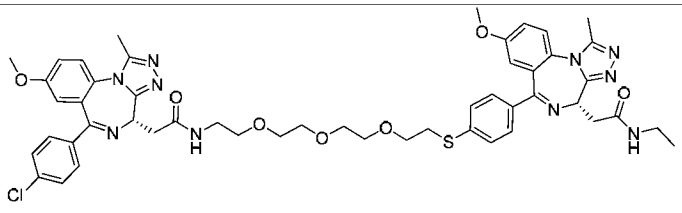
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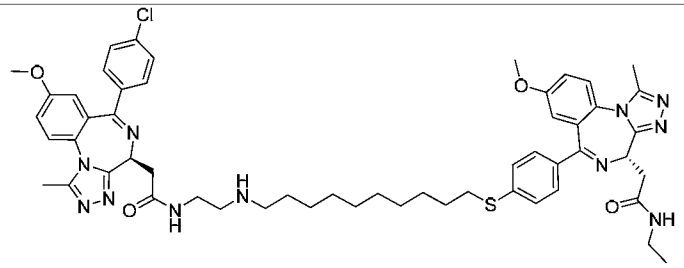
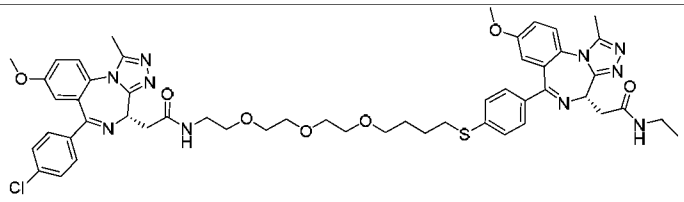
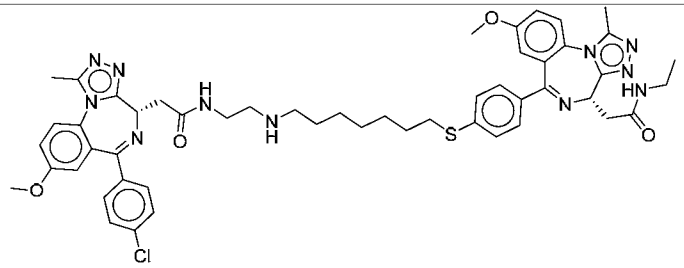
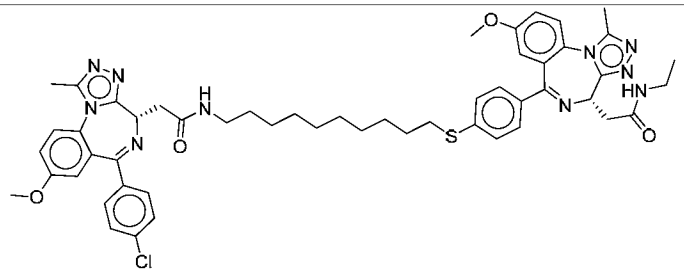
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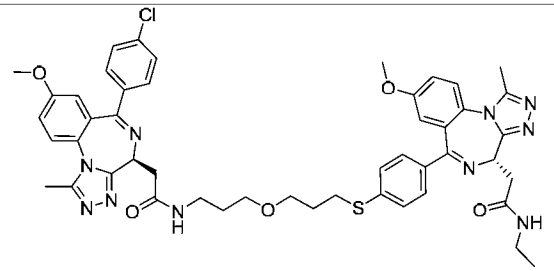
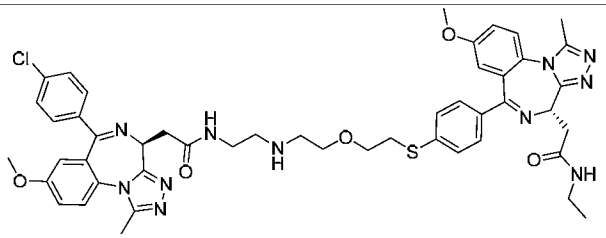
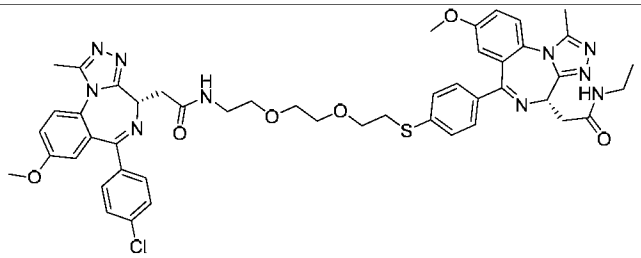
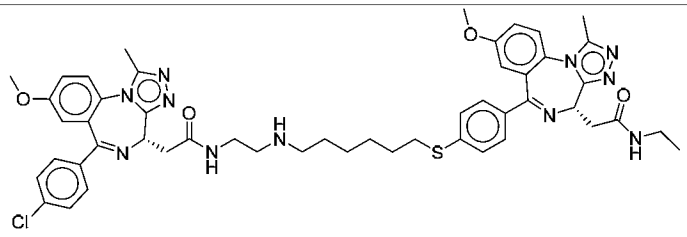
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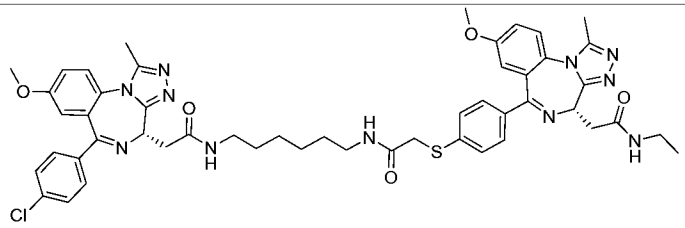
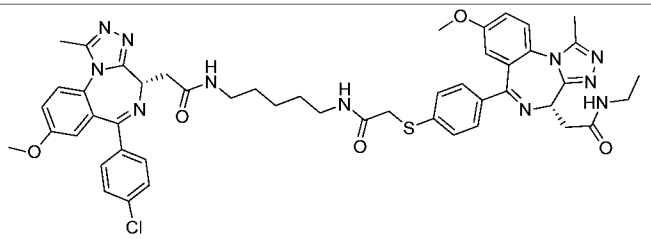
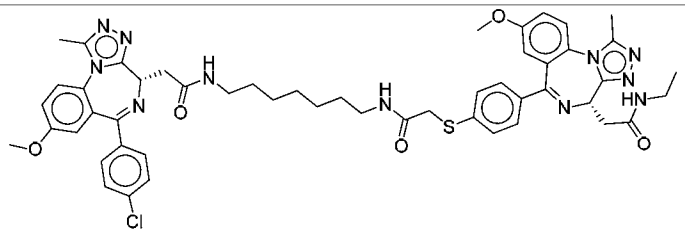
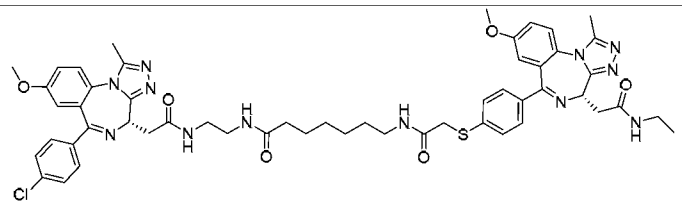
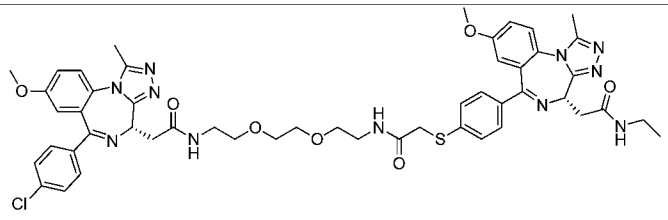
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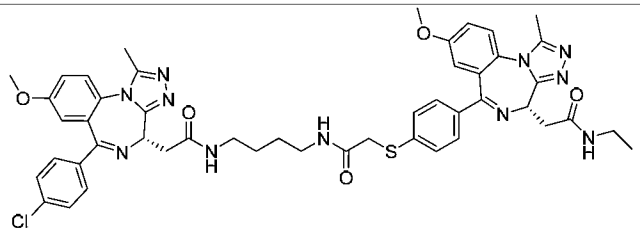
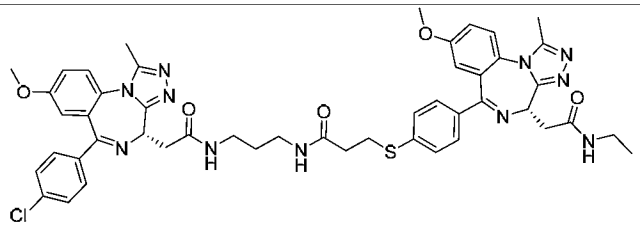
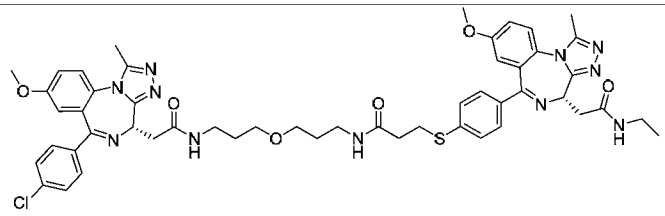
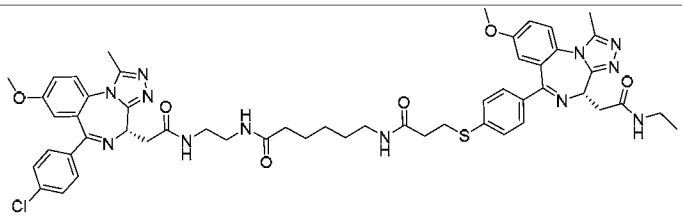
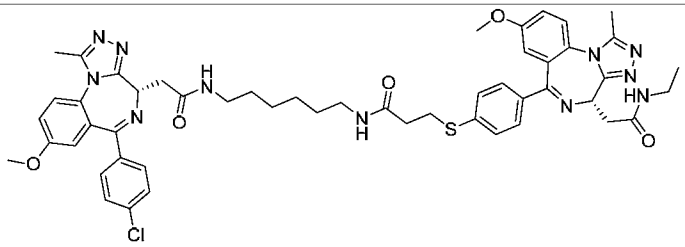
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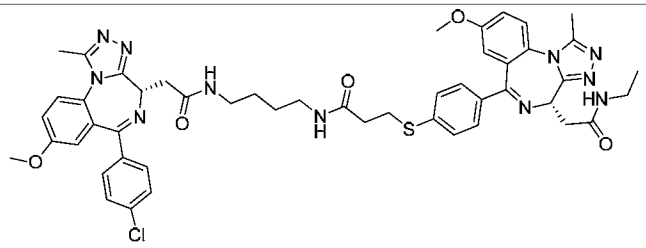
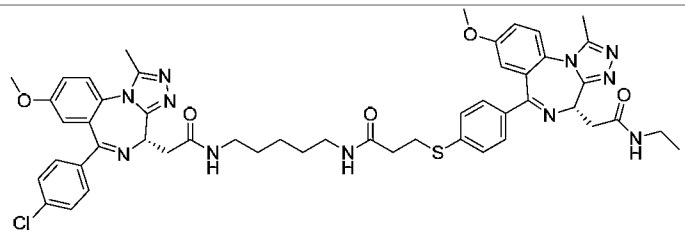
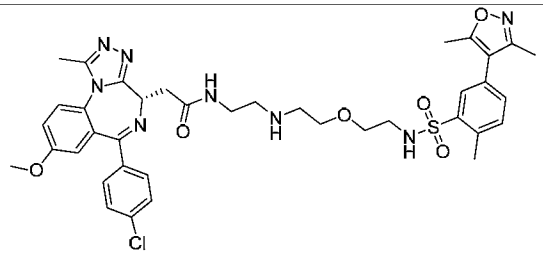
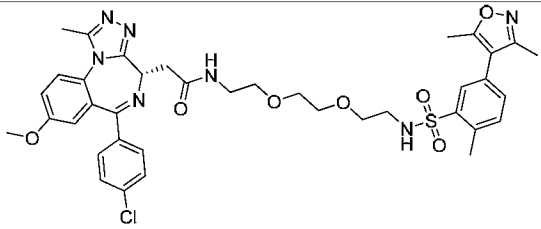
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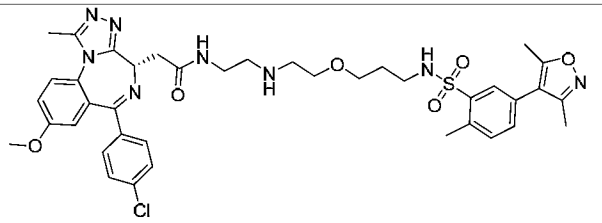
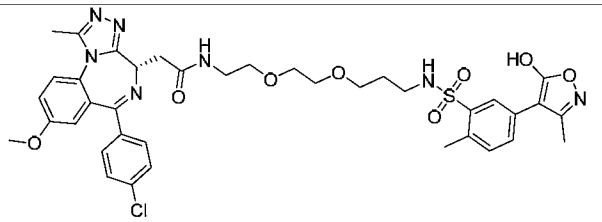
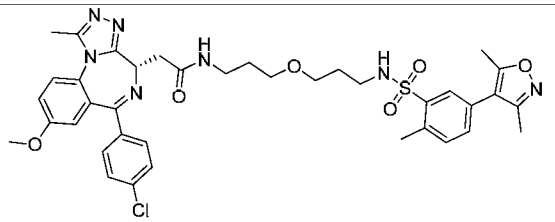
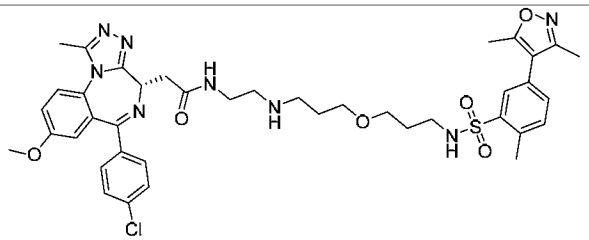
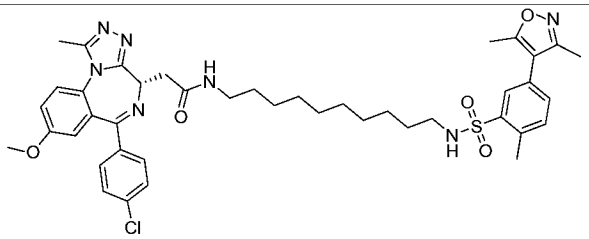
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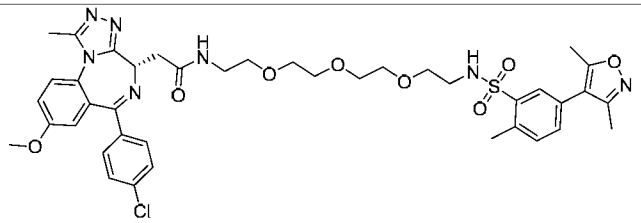
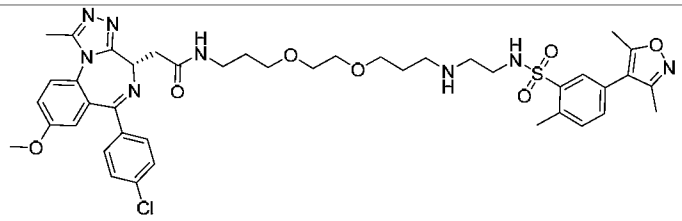
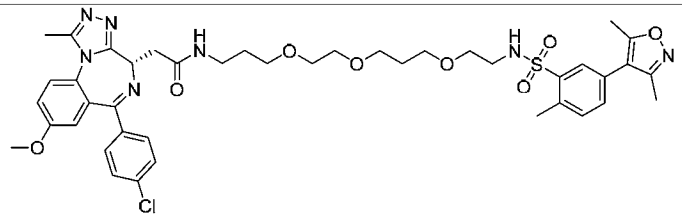
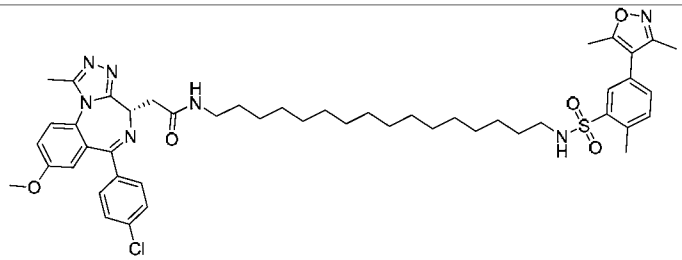
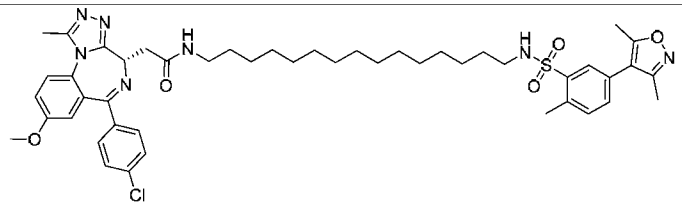
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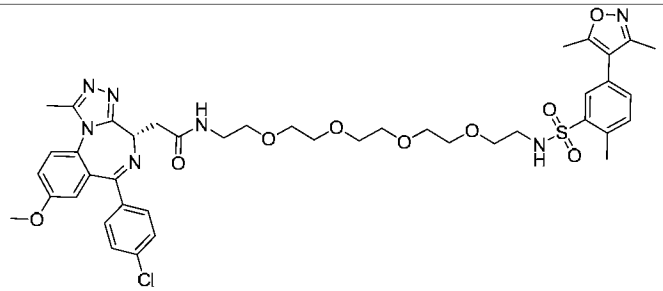
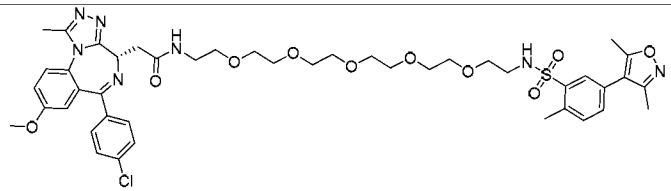
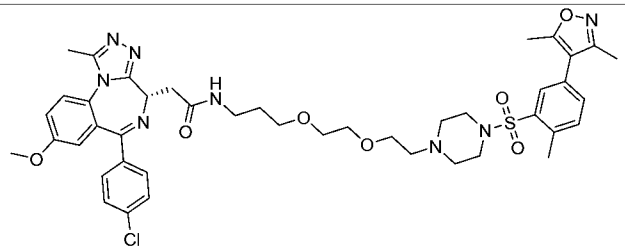
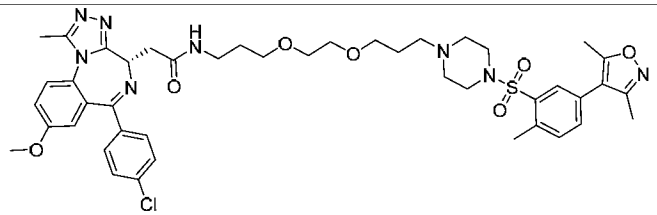
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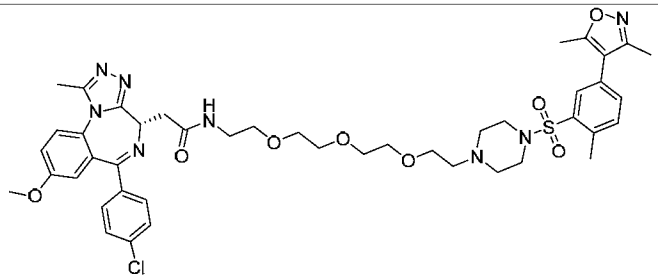
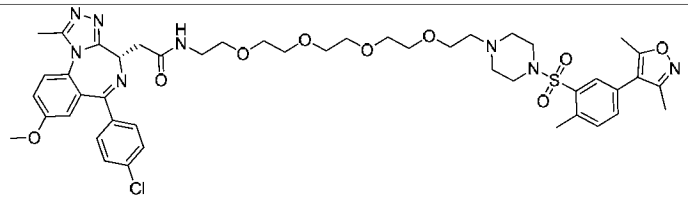
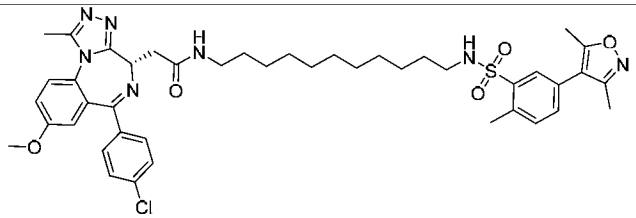
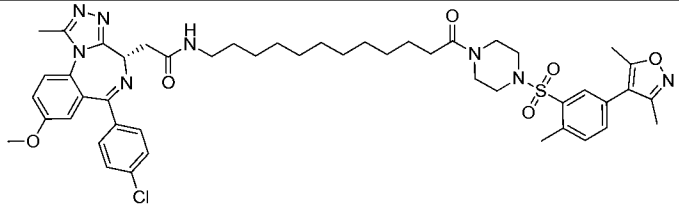
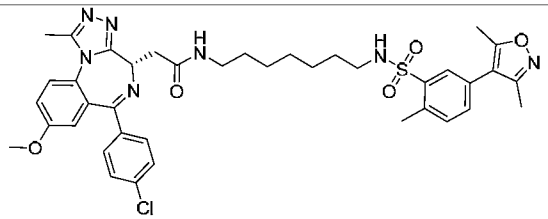
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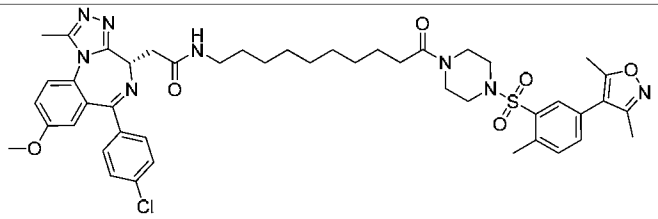
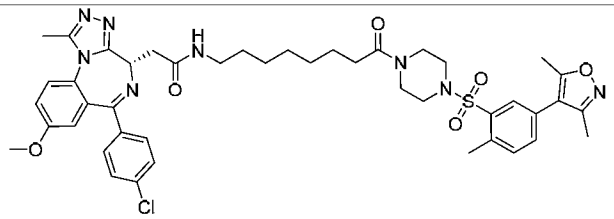
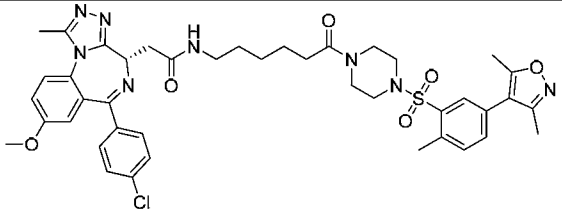
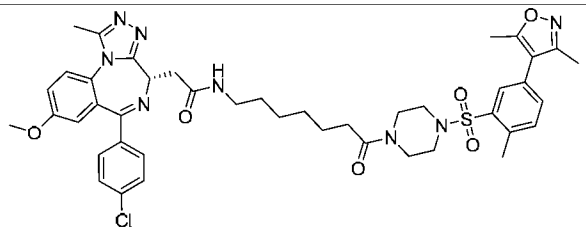
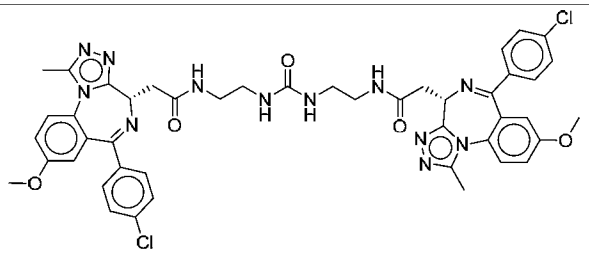
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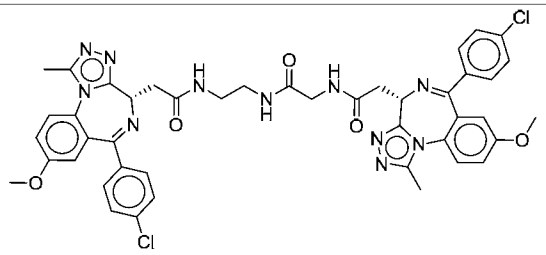
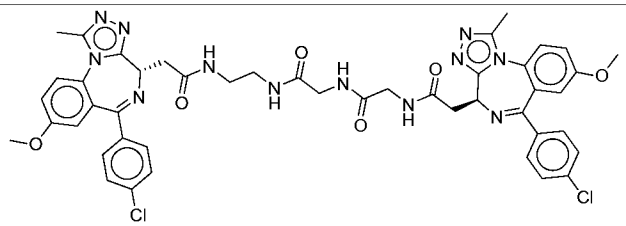
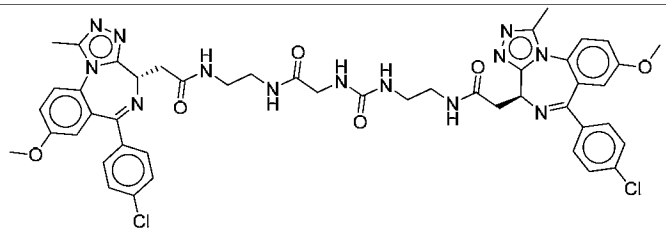
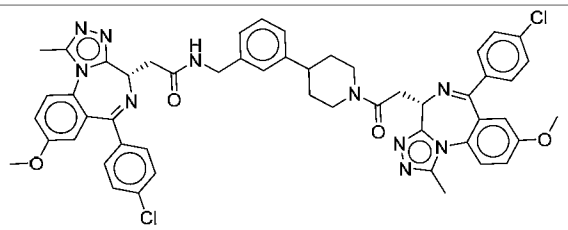
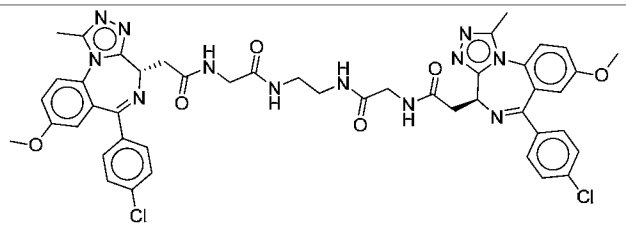
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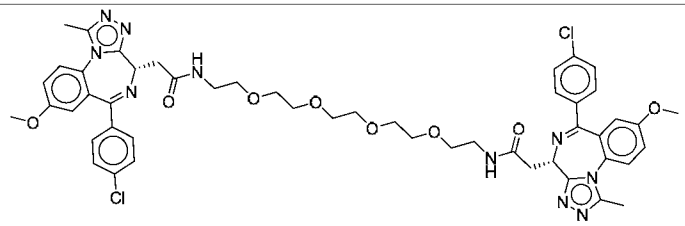
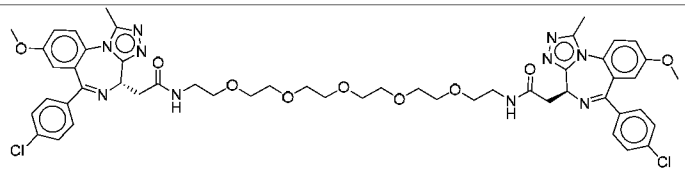
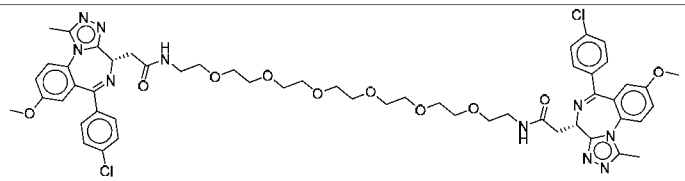
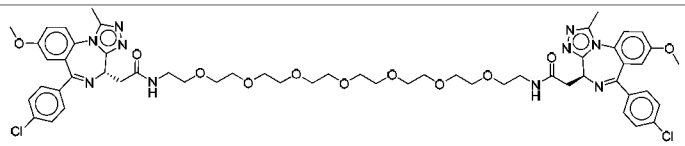
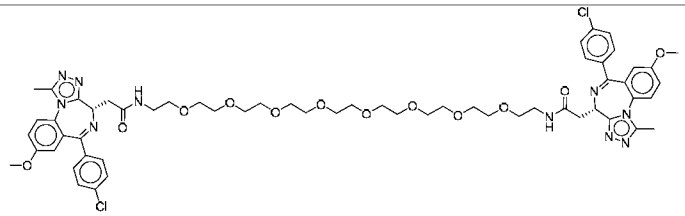
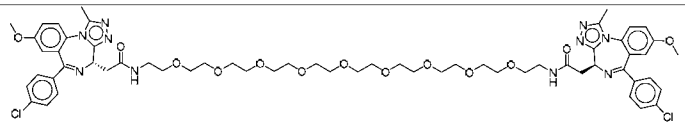
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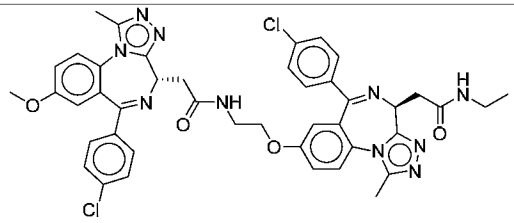
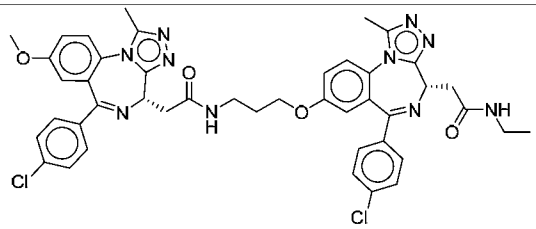
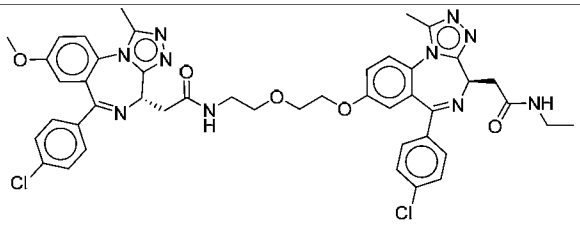
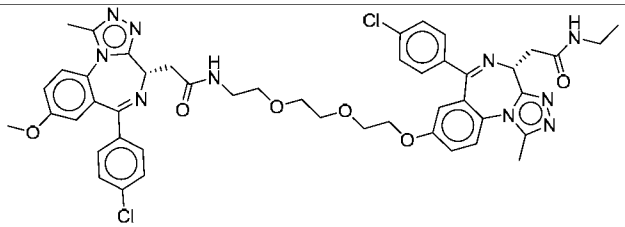
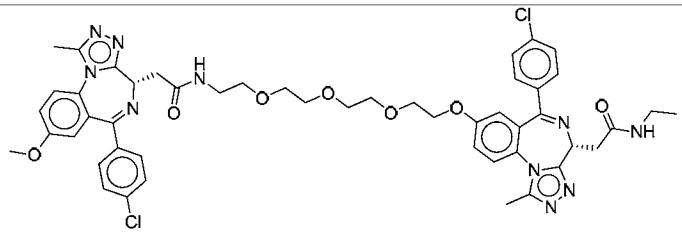
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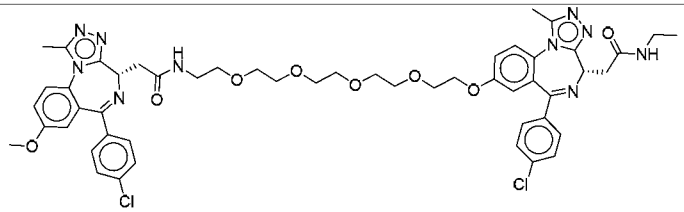
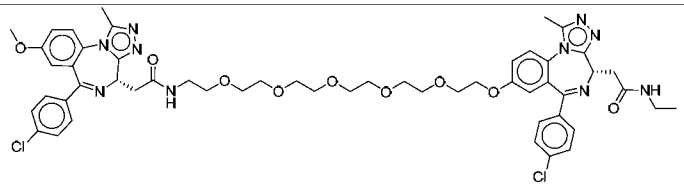
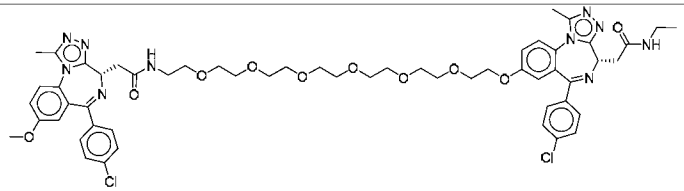
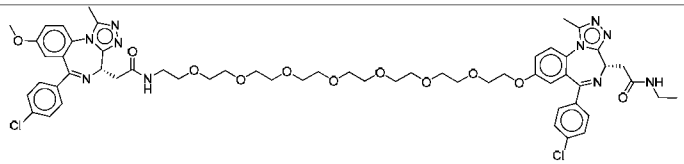
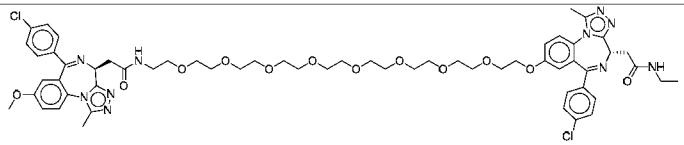
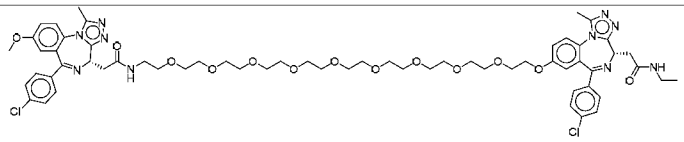
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84		BRD-B-06

85		BRD-B-07
86		BRD-B-08
87		BRD-B-09
88		BRD-B-10
89		BRD-B-11

90		BRD-B-16
91		BRD-B-17
92		BRD-B-18
93		BRD-B-19
94		BRD-B-22
95		BRD-B-23

96		BRD-B-01
97		BRD-B-02
98		BRD-B-03
99		BRD-B-04
100		BRD-B-05

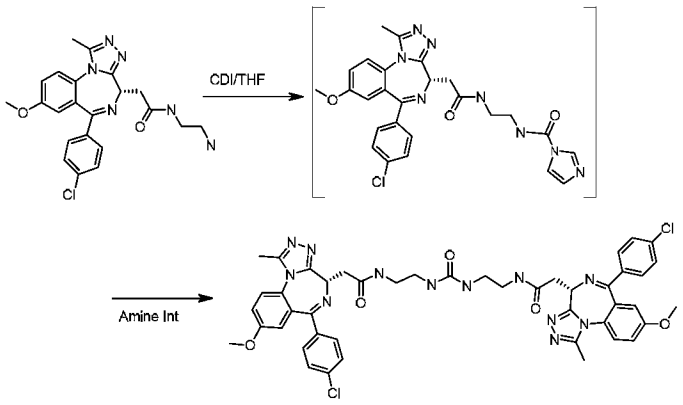
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103		BRD-B-14
104		BRD-B-15
105		BRD-B-20
106		BRD-B-21

EXAMPLE 107:

[00234] Bivalent compounds were synthesized according to the procedures described below.

[00235] **Synthesis of (*S*)-*N*,*N*'-((carbonylbis(azanediyl))bis(ethane-2,1-diyl))bis(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide) (BRD-B-06):**

Scheme 1. Reaction scheme for synthesis of (*S*)-*N*,*N*'-((carbonylbis(azanediyl))bis(ethane-2,1-diyl))bis(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide).

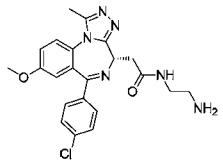


[00236] A solution of (*S*)-*N*-(2-aminoethyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (100 mg,0.227 mmol) in THF (1 mL) was charged with CDI (48 mg,0.296 mmol) and resulting solution was stirred at room temperature for 2 h. To this solution (*S*)-*N*-(2-aminoethyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (100 mg,0.227 mmol) was added and the reaction mixture was heated to 61°C for 2 hr. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC resulting in 40 mg of title pure compound, yield 20% as a white solid.

[00237] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (t, J = 5.4 Hz, 1H), 7.50-7.39 (m, 7H), 7.35 – 7.25 (m, 4H), 7.21 (dd, J = 8.9, 2.9 Hz, 1H), 6.84 (d, J = 2.8 Hz, 1H), 4.76 – 4.64 (m, 2H), 3.80 (s, 6H), 3.70 – 3.55 (m, 4H), 3.42 – 3.19 (m, 4H), 3.15-3.09 (m, 4H), 2.61 (s, 6H). Mol

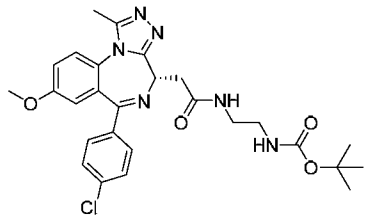
Wt:-903.81, MS (ES+): *m/z* 903.53 (100) [MH^+].(basic +ve mode), HPLC purity:-98.20% (Max plot).

[00238] ***((S)-N-(2-aminoethyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide:***



[00239] A solution of (*S*)-*tert*-butyl(2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)ethyl)carbamate (2.8 g, 0.52mmol) in DCM (50 mL) was charged with TFA (5 mL) and stirred for at rt for 12 h. The reaction mixture was then evaporated *in vacuo* to obtain a residue which was redissolved in DCM (10 mL) and powdered KOH was added to bring solution to pH ~8-9 and filtered through a pad of celite and the filtrate was concentrated *in vacuo* resulting in a crude product which was purified by column chromatography on silica gel (100-200 mesh), eluting with 4% methanol in chloroform to afford pure product 1.7 g, yield 74.59 % as a yellow solid.Mol Wt:-438.09, MS (ES+): *m/z* 439.15 (100) [MH^+]. (LCMS: 439.15 (M+1).

[00240] ***(S)-tert-butyl(2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)ethyl)carbamate:***

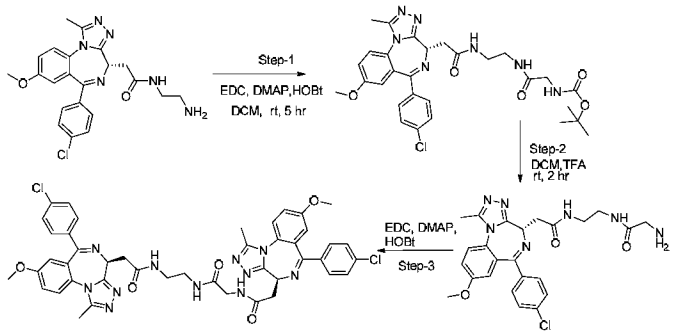


[00241] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (2.5 g, 6.3 mmol) in DCM (6 mL) was charged with EDCI (1.79 g, 9.4 mmol), 4-DMAP (1.1 g, 9.4 mmol), HOBt (1.2g, 9.4 mmol) and stirred at rt for 10 minutes. To this solution *tert*-butyl (2-aminoethyl) carbamate (1.5 g, 9.4 mmol) was added and the resulting solution was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were dried over

anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by column chromatography on silica gel (100-200 mesh), eluting with 1 % methanol in chloroform to afford pure product 3.3 g, yield 85.5 % as an off white solid. Mol Wt: 539.03, MS (ES+): *m/z* 539.15 (100) [MH^+].

[00242] Synthesis of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(2-(2-(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetamido)ethyl)acetamide (BRD-B-07):

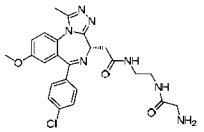
Scheme 2. Reaction scheme for synthesis of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(2-(2-(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetamido)ethyl)acetamide.



[00243] A solution of (*S*)-2-amino-*N*-(2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)ethyl)acetamide (70 mg, 0.14mmol.) in DCM (40 mL) was charged with EDCI (42 mg, 0.22 mmol.) and stirred at rt for 10 minutes. To this solution, (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetic acid (55 mg, 0.14 mmol), HOBt (26 mg, 0.22 mmol) and DMAP (42 mg, 0.22 mmol.) were added and the resulting solution was stirred at room temperature for 5 hr. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were washed with 2N acetic acid solution (2 x 5mL) and then with H_2O (2 x 10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC to afford the title compound, 30mg, 25% yield as an off white solid.

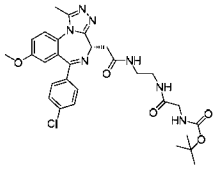
[00244] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 – 8.62 (m, 1H), 7.86 (t, *J* = 5.9 Hz, 1H), 7.50 – 7.33 (m, 4H), 7.32 – 7.16 (m, 6H), 6.84 (dd, *J* = 5.8, 2.9 Hz, 2H), 4.77 (m, 2H), 4.48 (dd, *J* = 17.2, 8.6 Hz, 1H), 4.10 (dd, *J* = 15.2, 11.6 Hz, 1H), 4.03 – 3.85 (m, 2H), 3.80 (s, 6H), 3.65 (dt, *J* = 10.3, 6.0 Hz, 1H), 3.56 – 3.46 (m, 2H), 3.32 – 3.12 (m, 3H), 3.03 (s, 1H), 2.63 (s, 6H). Mol. Wt: 874.77; MS (ES+): *m/z* 874.35 (100) [MH^+].(basic +ve mode). HPLC purity: 94.14% (Max plot).

[00245] ***(S)-2-amino-N-(2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)ethyl)acetamide:***



[00246] A solution of (*S*)-*tert*-butyl 3-(1-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetyl)piperidin-4-yl)benzylcarbamate (183 mg, 0.30 mmol) in DCM (20 mL) and TFA (1.83ml) and was stirred at rt for 2 hr. The reaction mixture was concentrated to dryness and was dissolved in DCM (5 mL) and pH was adjusted to ~8-9 by using KOH. The reaction mixture was filtered through a pad of celite and concentrated *in vacuo* resulting in a crude product which was used in the next reaction without further purification. Amount: 144mg, 95% yield of the title compound. Mol. Wt: 495.18; MS (ES+): *m/z* 496.20 (100) [MH^+].

[00247] ***(S)-tert-butyl (2-((2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)ethyl)amino)-2-oxoethyl)carbamate:***

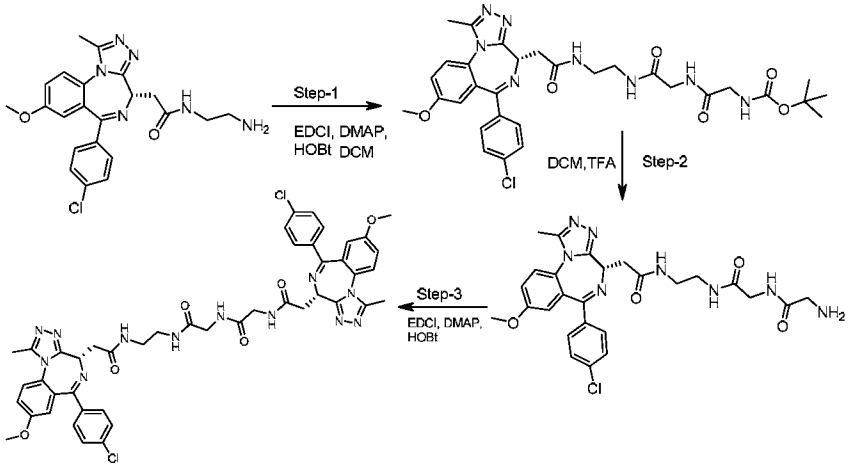


[00248] A solution of (*S*)-*N*-(2-aminoethyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (150 mg, 0.34mmol) in DCM (40mL) was charged with EDCI (98 mg, 051mmol) and stirred at rt for 10 minutes. To this solution, *N*-boc glycine (59 mg, 0.34 mmol), HOBt (68 mg, 0.51 mmol) and DMAP (62mg, 0.51mmol.) were added and the resulting solution was stirred at room temperature for 5 hr. The

reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were washed with 2N acetic acid solution (2 x 5mL) and then with H_2O (2 x 10 mL). The combined fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was used in the next step without further purification. Amount:183 mg, 90% yield of the title compound. Mol. Wt: 596.08; MS (ES+): *m/z* 596.25 (100) [MH^+].

[00249] Synthesis of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(2-(2-(2-(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetamido)acetamido)ethyl)acetamide (BRD-B-08):

Scheme 3. Reaction scheme for synthesis of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(2-(2-(2-(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetamido)acetamido)ethyl)acetamide:

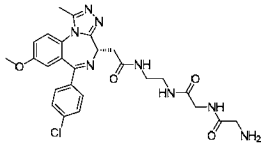


[00250] A solution of (*S*)-2-amino-*N*-(2-((2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)ethyl)amino)-2-oxoethyl)acetamide (60 mg, 0.10 mmol) in DCM (40 mL) was charged with EDCI (31 mg, 0.16 mmol) and stirred at rt for 10 minutes. To this solution, (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (43 mg, 0.10 mmol), HOBt (22 mg, 016 mmol) and DMAP (19 mg, 0.16 mmol) were added. The resulting

solution was stirred at room temperature for 5 hr. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were washed with 2N acetic acid solution (2 x 5mL) and then with H_2O (2 x 10 mL). The combined fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC to afford 30 mg, 25% yield of the title compound as and off white solid.

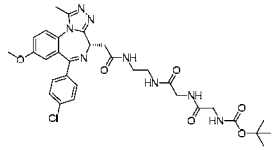
[00251] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (s, 2H), 8.26 (d, J = 8.1Hz, 2H), 8.17 (dd, J = 7.8, 2.9 Hz, 2H), 7.82 – 7.73 (m, 6H), 7.51 (dd, J = 27.4, 14.0 Hz, 2H), 7.35- 6.85 (m, 2H), 4.48 (d, J = 10.5 Hz, 2H), 3.22 (s, 6H), 3.13-3.05 (m, 12H), 2.18 (s, 6H). Mol. Wt: 931.82; MS (ES+): *m/z* 931.35 (100) [MH$^+$], ESMS: 931.82(basic +ve mode), HPLC purity: 98.07% (Max plot).

[00252] ***(S)-2-amino-N-(2-((2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)ethyl)amino)-2-oxoethyl)acetamide:***



[00253] A solution of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(3-(1-(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetyl)piperidin-4-yl)benzyl)acetamide (80 mg, 0.12 mmol) in DCM (20 mL) and TFA (0.08ml) and was stirred at rt for 2 hr. The reaction mixture was concentrated to dryness and dissolved in DCM (5 mL) and pH was adjusted to ~8-9 using KOH. The reaction mixture was filtered through a pad of celite and concentrated *in vacuo* resulting in 60 mg, 90% yield of a crude product which was used in the next step without further purification. Mol. Wt: 553.01; MS (ES+): *m/z* 553.30 (100) [MH$^+$].

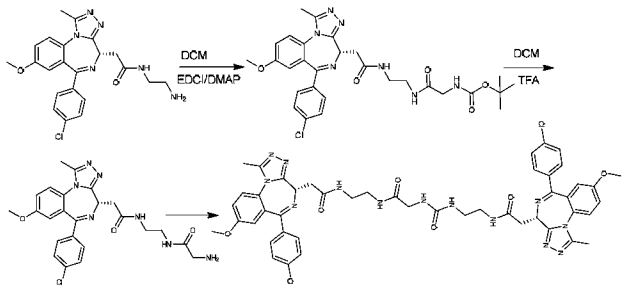
[00254] ***tert-butyl N-[2-[[2-[2-[[2-[(4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-[1,2,4]triazolo[4,3-a][1,4]benzodiazepin-4-yl]acetyl]amino]ethylamino]-2-oxo-ethyl]amino]-2-oxo-ethyl]carbamate:***



[00255] A solution of (*S*)-*N*-(2-aminoethyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (70 mg, 0.15mmol.) in DCM (40mL/g) was charged with EDCI (46 mg, 0.23mmol.) and stirred at rt for 10 minutes. This solution was charged with, 2-(2-((*tert*-butoxycarbonyl) amino) acetamido) acetic acid (37 mg, 0.15 mmol), HOBt (31 mg, 0.23 mmol) and DMAP (28 mg, 0.23 mmol.) and stirred at room temperature for 5 hr. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were washed with 2N acetic acid solution (2 x 5mL) and then with H_2O (2 x 10 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 83 mg, 80%yield of the crude product which was used in the next step without further purification. Mol. Wt: 653.13; MS (ES+): *m/z* 653.13 (100) [MH^+].

[00256] Synthesis of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(13-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-4,7,12-trioxo-3,5,8,11-tetraazatridecyl)acetamide (BRD-B-09):

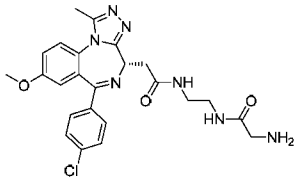
Scheme 4. Reaction scheme for synthesis of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(13-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-4,7,12-trioxo-3,5,8,11-tetraazatridecyl)acetamide:



[00257] A solution of (*S*)-*N*-(2-aminoethyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (50 mg, 0.113 mmol) in THF (1

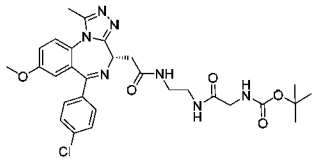
mL) was charged with CDI (22 mg, 0.136 mmol) and resulting solution was stirred at room temperature for 2 h. This solution was charged with (*S*)-2-amino-*N*-(2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)ethyl)acetamide (56.5 mg, 0.113 mmol) and the reaction mixture was heated to 61°C for 2 hr. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC to afford 20 mg, 18.69 % yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 7.80 Hz, 1H), 7.90-7.70 (m, 2H), 7.56 – 7.44 (m, 8H), 7.39 (dd, J = 9.0, 2.9 Hz, 2H), 6.87 (s, 1H), 4.52 (dd, J = 8.2, 5.8 Hz, 2H), 3.87 (d, J = 6.7 Hz, 1H), 3.79 (s, 6H), 3.32–2.91 (m, 13H), 2.50 (s, 6H). Mol Wt:-960.87, MS (ES+): *m/z* 960.71 (100) [MH^+] (basic +ve mode), HPLC purity: 93.05% (254 nm).

[00258] ***(S)-2-amino-N-(2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)ethyl)acetamide:***



[00259] A solution of (*S*)-*tert*-butyl (2-((2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)ethyl)amino)-2-oxoethyl)carbamate (160 mg, 0.268 mmol) in DCM (3.2 mL) was charged with TFA (1.6 mL) and stirred at rt for 2 h. The reaction mixture was then evaporated *in vacuo* to obtain a residue which was redissolved in DCM (10 mL) and charged with powdered KOH to adjust to pH~8-9 and filtered through a pad of celite and the filtrate was concentrated *in vacuo* resulting in a crude product which was purified by column chromatography using 10 % DCM in MeoH to afford 120 mg, 91 % yield as a colorless oil. Mol Wt: 496.00, MS (ES+): *m/z* 497.20 (100) [MH^+].

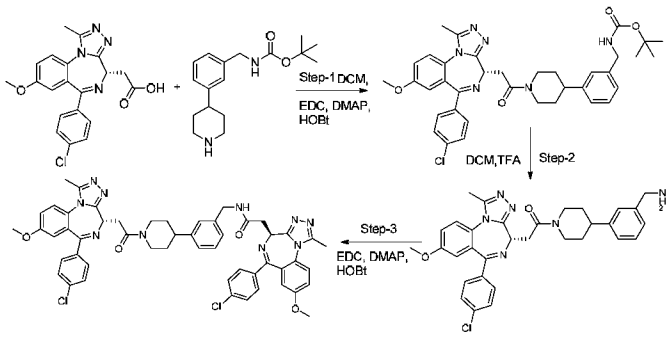
[00260] ***(S)-tert-butyl (2-((2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)ethyl)amino)-2-oxoethyl)carbamate:***



[00261] A suspension of 2-((*tert*-butoxycarbonyl)amino)acetic acid (77.8 mg, 0.44 mmol) in DCM (3mL) was charged with EDCI (98.4 mg, 0.51 mmol), 4-DMAP(83 mg, 0.68 mmol), HOBt (69.4 mg, 0.0.51 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-*N*-(2-aminoethyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (150 mg, 0.34 mmol) and the resulting solution was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by column chromatography to afford 162.9 mg, 80% yield of the title compound as a white solid. Mol Wt: 596.08; MS (ES+): *m/z* 597.20 (100) [MH^+].

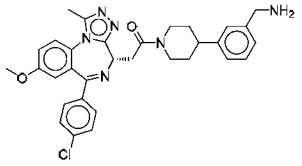
[00262] **Synthesis of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(3-(1-(2-((S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetyl)piperidin-4-yl)benzyl)acetamide (BRD-B-10):**

Scheme 5. Reaction scheme for synthesis of 2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(3-(1-(2-((S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetyl)piperidin-4-yl)benzyl)acetamide:



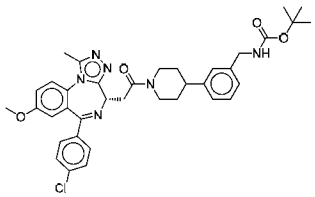
[00263] A solution of (*S*)-1-(4-(3-(aminomethyl)phenyl)piperidin-1-yl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)ethanone (50 mg, 0.08 mmol.) in DCM (40 mL) was charged with EDCI (25 mg, 0.13mmol.) and stirred at rt for 10 minutes. This solution was charged with, (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (35 mg, 0.08 mmol), HOBt (17 mg, 0.13mmol) and DMAP (16 mg, 0.13mmol.) and the resulting solution was stirred at room temperature for 5 hr. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were washed with 2N acetic acid solution (2 x 5mL) and then with H_2O (2 x 10 mL). The organic fractions were combined and dried over anhydrous Na_2SO_4 filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC to afford 21 mg, 25% yield of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 – 7.76 (m, 2H), 7.57 – 7.35 (m, 10H), 7.29 (td, J = 7.7, 2.9 Hz, 1H), 7.23 – 7.12 (m, 3H), 6.91 – 6.82 (m, 2H), 4.65 – 4.47 (m, 3H), 4.37-4.22 (m, 3H), 3.84 (s, 6H), 3.60 (dd, J = 16.7, 7.3 Hz, 1H), 3.40 – 3.18 (m, 3H), 2.87 – 2.76 (m, 1H), 2.54 (s, 6H), 1.91 – 1.62 (m, 5H), 1.49 – 1.38 (m, 1H). Mol Wt: 947.90, MS (ES+): *m/z* 947.89 (100) [MH^+].(basic +ve mode), HPLC purity: 92.32% (254 nm).

[00264] ***1-(4-(3-(aminomethyl)phenyl)piperidin-1-yl)-2-((4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)ethanone (BRD-B-10-Int.-2):***



[00265] A solution of *tert*-butyl-3-(1-(2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetyl)piperidin-4-yl)benzylcarbamate (70 mg, 0.10 mmol) in DCM (15 mL) was charged with TFA (35 mg, 0.31 mmol) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo* to obtain 60 mg of crude product which was purified by preparative HPLC to afford corresponding 35 mg, 59% yield of the title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (s, 1H), 8.19 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.58 – 7.21 (m, 7H), 6.92 – 6.84 (m, 2H), 4.60 – 4.47 (m, 1H), 4.31 – 4.22 (m, 1H), 4.11 (t, J = 6.2 Hz, 2H), 3.80 (s, 3H), 3.68 – 3.55 (m, 4H), 3.43 – 2.91 (m, 3H), 2.80 (d, J = 12.7 Hz, 1H), 2.55 (s, 3H), 1.88 (d, J = 13.7 Hz, 1H), 1.76 (d, J = 12.8 Hz, 1H). Mol. Wt: 569.10; MS (ES+): *m/z* 569.20 (100) [MH$^+$], HPLC purity: 94.84% (254 nm).

[00266] ***tert-butyl-3-(1-(2-((4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetyl)piperidin-4-yl)benzylcarbamate (BRD-B-10-Int.-1):***

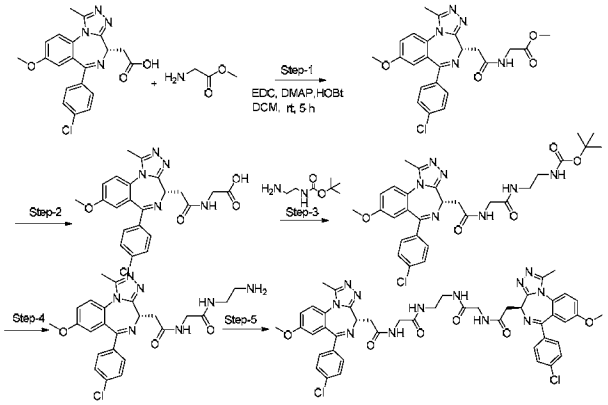


[00267] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (50 mg, 0.12 mmol) in DCM (15 mL) was charged with EDCI (35 mg, 0.18 mmol) and stirred at 0 ^{0}C for 10 minutes. This solution was charged with *tert*-butyl 3-(piperidin-4-yl)benzylcarbamate (36.6 mg, 0.12 mmol) and DMAP (18 mg, 0.15 mmol) and stirred at room temperature overnight. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 15 mL) and the combined organic fractions were washed with 1N HCl (10 mL) and brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 80 mg, 88% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (dd, J = 8.5, 4.5 Hz, 1H), 7.60-7.05 (m, 6H), 7.12 (dd, J =

21.2, 12.7 Hz, 2H), 6.87 (s, 1H), 4.60 – 4.47 (m, 1H), 4.31 – 4.22 (m, 1H), 4.11 (t, *J* = 6.2 Hz, 2H), 3.80 (s, 3H), 3.68 – 3.55 (m, 4H), 3.43 – 2.91 (m, 3H), 2.80 (d, *J* = 12.7 Hz, 1H), 2.55 (s, 6H), 1.88 (d, *J* = 13.7 Hz, 1H), 1.76 (d, *J* = 12.8 Hz, 1H), 1.39 (s, 9H). Mol. Wt: 669.21; MS (ES+): 669.25 *m/z* (100) [MH^+], HPLC purity: 96.93% (254 nm).

[00268] **Synthesis of (*S*)-*N*,*N*'-(ethane-1,2-diyl)bis(2-(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetamide) (BRD-B-11)**:

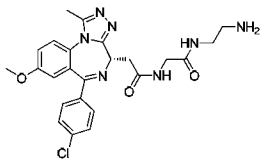
[00269] **Scheme 6.** Reaction scheme for synthesis of (*S*)-*N*,*N*'-(ethane-1,2-diyl)bis(2-(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetamide):



[00270] A solution of (*S*)-*N*-(2-aminoethyl)-2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetamide (40 mg, 0.08 mmol.) in DCM (40 mL) was charged with EDCI (23 mg, 0.12 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)acetic acid (44 mg, 0.097 mmol), HOBt (16 mg, 0.12 mmol) and DMAP (14 mg, 0.12 mmol.) and stirred at room temperature for 5 hr. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were washed with 2N acetic acid solution (2 x 5mL) and then with H_2O (2 x 10 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC to afford 13.5 mg, 15% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.53 (s, 2H), 7.91 (s,

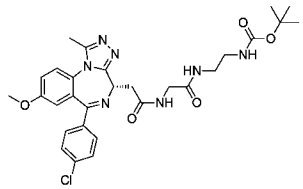
2H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.9 Hz, 2H), 6.80-6.70 (m, 6H), 4.51 – 4.43 (m, 4H), 3.76 (s, 6H), 3.80-3.15 (m, 16H).Mol. Wt: 931.82; MS (ES+): 931.61 *m/z* (100) [MH^+] (basic +ve mode), LCMS (m/z): 466.35 [M/2].HPLC purity: 97.61% (254 nm).

[00271] ***(S)-N-(2-aminoethyl)-2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)acetamide:***



[00272] A solution of (*S*)-*tert*-butyl(2-(2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetamido)ethyl)carbamate (50 mg, 0.084mmol) in DCM (20 mL) and TFA (0.05ml) and was stirred at rt for 2 hr. The reaction mixture was concentrated to dryness and dissolved in DCM (5 mL) and pH was adjusted to ~8-9 by using KOH. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo* resulting in 40mg, 98% yield of the title compound and taken on to the next step without further purification Mol. Wt: 495.96; MS (ES+): 496.20 *m/z* (100) [MH^+].

[00273] ***(S)-tert-butyl(2-(2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)acetamido)ethyl)carbamate:***

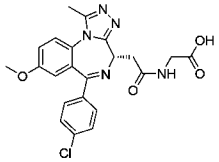


[00274]

[00275] A solution of (*S*)-2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetic acid (40 mg, 0.088 mmol.) in DCM (40mL) was charged with EDCI (25 mg, 0.13 mmol) and stirred at rt for 10 minutes. To this solution, monoboc ethylene diamine (16 mg, 0.10 mmol), HOBt (17 mg, 0.0.13 mmol) and DMAP (16 mg, 0.13 mmol.) were added. The resulting solution was stirred at room temperature for 5 hr and the reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were washed with 2N acetic acid solution (2 x 5mL) and then with H_2O (2 x

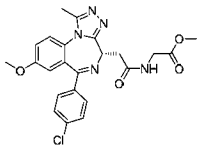
10 mL). The organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 52 mg, 100% yield of the title compound and crude was taken on to the next step without further purification. Mol. Wt: 596.08; MS (ES+): 596.25 *m/z* (100) [MH^+].

[00276] ***(S)-2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)acetic acid:***



[00277] A solution of (*S*)-methyl 2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamido)acetate (107 mg, 0.22 mmol) in ethanol:water (40:40mL) and potassium hydroxide (64 mg, 0.011mmol) and was stirred at rt for 2 hr. The reaction mixture was concentrated to dryness and dissolved in water (50mL) and the pH was adjusted to ~2-3 by using dilute HCl. The solid formed was then filtered resulting in 93mg, 90% yield of the title compound which was used in the next step without further purification. Mol. Wt: 453.88; MS (ES+): 454.15*m/z* (100) [MH^+].

[00278] ***(S)-methyl 2-(2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamido)acetate:***

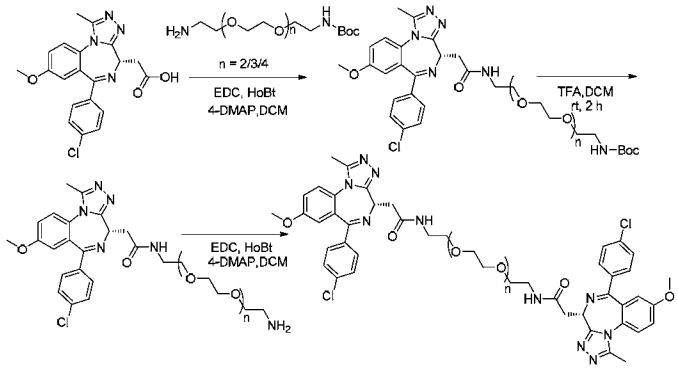


[00279] A solution of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (100 mg ,0.25 mmol.) in DCM (40mL) was charged with EDCI (73 mg, 0.37mmol.) and stirred at rt for 10 minutes. This solution was charged with glycine methyl ester HCl (37 mg, 0.30mmol), HOBt (51mg, 0.37mmol) and DMAP (46 mg, 0.37 mmol.) and stirred at room temperature for 5 hr. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were washed with 2N acetic acid solution (2 x 5mL) and then with H_2O (2 x 10 mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 107 mg,

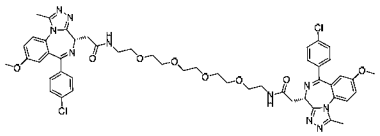
90% yield of the title compound as a crude product which was purified by preparative HPLC. Mol. Wt: 467.90; MS (ES+): 467.40 *m/z* (100) [MH].

[00280] Synthesis of bivalent compounds connected by polyethylene glycol.

Scheme 7. Reaction scheme for synthesis of bivalent compounds connected by polyethylene glycol.



[00281] Synthesis of (*S*)-N,N'-(3,6,9,12-tetraoxatetradecane-1,14-diyl)bis(2-((S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide) (BRD-B-16):

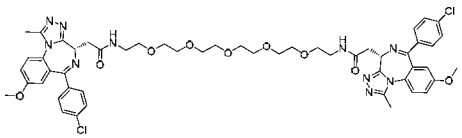


[00282] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (64 mg, 0.162 mmol) in DCM (3 mL) was charged with EDCI (37 mg, 0.194 mmol), 4-DMAP (23.7 mg, 0.194 mmol), HoBt (26 mg, 0.194 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-*N*-(14-amino-3,6,9,12-tetraoxatetradecyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide (100 mg, 0.604 mmol) and was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by column chromatography on silica gel (100-200 mesh), eluting with 3% methanol in chloroform to afford 125 mg, 77.63% yield of the

corresponding the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 4H), 7.42 – 7.25 (m, 6H), 7.18 (dt, *J* = 9.0, 3.3 Hz, 2H), 6.85 (d, *J* = 2.9 Hz, 2H), 4.65 (t, *J* = 6.9 Hz, 2H), 3.79 (s, 6H), 3.73 – 3.40 (m, 24H), 2.61 (s, 6H). Mol. Wt: 993.93; MS (ES+): 993.90 *m/z* (100) [MH^+].(basic +ve mode), HPLC purity: 96.80% (Max plot).

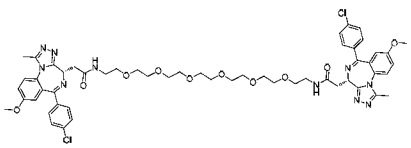
[00283] Following the general procedure for synthesis of (*S*)-N,N'-(3,6,9,12-tetraoxatetradecane-1,14-diyl)bis(2-((S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide), the below compounds were synthesized and characterized.

[00284] **Synthesis of (*S*)-*N*,*N*'-(3,6,9,12,15-pentaoxaheptadecane-1,17-diyl)bis(2-((S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide) (BRD-B-17):**



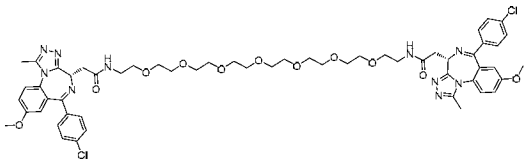
[00285] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (60 mg, 0.151 mmol) in DCM (3 mL) was charged with EDCI (34.9 mg, 0.181 mmol) ,4-DMAP (22.1 mg ,0.151 mmol), HoBt (24.6 mg, 0.151 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-*N*-(17-amino-3,6,9,12,15-pentaoxaheptadecyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (100 mg, 0.151 mmol). Title compound weight: 100 mg, 64.1 % yield as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 4H), 7.41 – 7.28 (m, 4H), 7.22 – 7.05 (m, 4H), 6.85 (d, *J* = 2.9 Hz, 2H), 4.65 (t, *J* = 7.0 Hz, 2H), 3.79 (s, 6H), 3.71 – 3.38 (m, 28H), 2.61 (s, 6H). Mol Wt: 1037.98, MS (ES+): 1037.90 *m/z* (100) [MH^+]. (basic +ve mode. HPLC purity: 97.10% (Max plot).

[00286] **Synthesis of (*S*)-*N*,*N*'-(3,6,9,12,15,18-hexaoxaicosane-1,20-diyl)bis(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide) (BRD-B-18):**



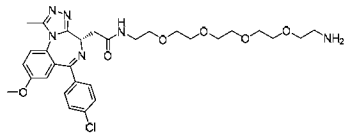
[00287] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (56.4 mg, 0.142 mmol) in DCM (3 mL) was charged with EDCI (32.8 mg, 0.170 mmol), 4-DMAP (20.7 mg, 0.170 mmol), HOBt (23.17 mg, 0.170 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-*N*-(20-amino-3,6,9,12,15,18-hexaoxaicosyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (100 mg, 0.142 mmol). Title compound weight: 90 mg, 58.8 % yield as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.2 Hz, 4H), 7.35 (dd, *J* = 19.4, 8.5 Hz, 4H), 7.19 (dd, *J* = 9.1, 2.9 Hz, 2H), 6.98 (t, *J* = 5.8 Hz, 2H), 6.85 (d, *J* = 2.9 Hz, 2H), 4.64 (t, *J* = 7.0 Hz, 2H), 3.79 (s, 6H), 3.70 – 3.54 (m, 26H), 3.58 – 3.35 (m, 8H), 2.61 (s, 6H). Mol Wt: 1082.04, MS (ES+): 1082.04 *m/z* (100) [MH^+] (basic +ve mode), HPLC purity: 97.23% (Max plot).

[00288] **Synthesis of (*S*)-*N*,*N*'-(3,6,9,12,15,18,21-heptaoxatricosane-1,23-diyl)bis(2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide) (BRD-B-19):**



[00289] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (46 mg, 0.118 mmol) in DCM (3 mL) was charged with EDCI (19.2 mg, 0.141 mmol), 4-DMAP (17 mg, 0.141 mmol), HoBt (19.2 mg, 0.141 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-*N*-(2,3-amino-3,6,9,12,15,18,21-heptaoxatricosyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (100 mg, 0.118 mmol) was added. Title compound weight: 79 mg, 60 % yield as white Solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.43 (m, 4H), 7.41 – 7.28 (m, 4H), 7.19 (dd, *J* = 8.9, 2.9 Hz, 2H), 6.88 (dd, *J* = 24.7, 4.2 Hz, 4H), 4.64 (dd, *J* = 7.7, 6.1 Hz, 2H), 3.79 (s, 6H), 3.73 – 3.54 (m, 29H), 3.57 – 3.31 (m, 7H), 2.61 (s, 6H). Mol Wt: 1126.09, MS (ES+): 1126.09 *m/z* (100) [MH^+] (basic +ve mode). HPLC purity: 95.81% (Max plot).

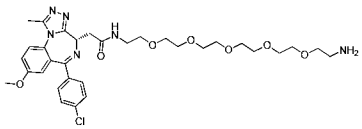
[00290] ***(S)-N-(14-amino-3,6,9,12-tetraoxatetradecyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide (BRD-C-89):***



[00291] A solution of boc-amide (250 mg, 0.349 mmol) in DCM (2.5 mL) was charged with TFA (2.5 mL) and stirred at rt for 2 h. The reaction mixture was then evaporated under reduced pressure to obtain a residue which was redissolved in DCM (10 mL) and powdered KOH was added to adjust pH~8-9 and filtered through a pad of celite. The filtrate was concentrated *in vacuo* resulting in a crude product which was purified by column chromatography on silica gel (100-200 mesh), eluting with 2% methanol in chloroform to afford 180 mg, 83.7% yield of the corresponding title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.55 – 7.46 (m, 2H), 7.41 – 7.29 (m, 3H), 7.19 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.86 (d, *J* = 2.9 Hz, 1H), 4.68 (t, *J* = 7.3 Hz, 1H), 3.80 (s, 3H), 3.76 – 3.31 (m, 20H), 2.91 – 2.72 (m, 2H), 2.59 (s, 3H).Mol Wt:-615.12, MS (ES+): 847.50 *m/z* (100) [MH^+].

[00292] Following the general procedure for synthesis of (*S*)-N-(14-amino-3,6,9,12-tetraoxatetradecyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide, the below compounds were synthesized and characterized.

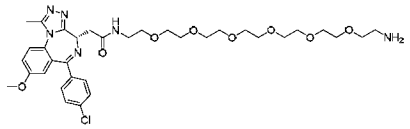
[00293] ***(S)-N-(17-amino-3,6,9,12,15-pentaoxaheptadecyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide (BRD-C-90):***



[00294]

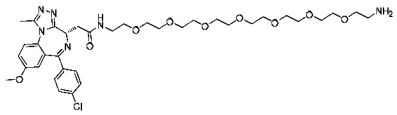
[00295] A solution of boc-amide (250 mg, 0.349 mmol) in DCM (2.5 mL) was charged with TFA (2.5 mL) and obtained title compound, weight: 190 mg, 87.55 % yield as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.41 – 7.27 (m, 2H), 7.19 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.86 (d, *J* = 2.9 Hz, 1H), 4.68 (t, *J* = 7.2 Hz, 1H), 3.79 (s, 3H), 3.74 – 3.29 (m, 24H), 2.87 (q, *J* = 5.1 Hz, 2H), 2.58 (s, 3H). Mol Wt:-659.17, MS (ES+): 659.30 *m/z* (100) [MH^+].

[00296] ***(S)-N-(20-amino-3,6,9,12,15,18-hexaoxaicosyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide (BRD-C-91):***



[00297] A solution of boc-amide (250 mg, 0.349 mmol) in DCM (2.5 mL) was charged with TFA (2.5 mL) and obtained title compound, weight: 196 mg, 90 % yield as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.54 – 7.46 (m, 2H), 7.41 – 7.29 (m, 3H), 7.19 (dd, J = 8.9, 2.9 Hz, 1H), 6.85 (d, J = 2.9 Hz, 1H), 4.66 (t, J = 7.2 Hz, 1H), 3.79 (s, 3H), 3.71 – 3.30 (m, 28H), 2.84 (t, J = 5.2 Hz, 2H), 2.59 (s, 3H). Mol Wt: 703.23, MS (ES+): 703.35 *m/z* (100) [MH^+].

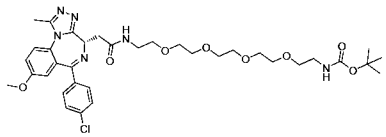
[00298] ***(S)-N-(23-amino-3,6,9,12,15,18,21-heptaoxatricosyl)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide (BRD-C-92):***



[00299]

[00300] A solution of boc-amide (250 mg, 0.349 mmol) in DCM (2.5 mL) was charged with TFA (2.5 mL) and obtained title compound, weight:187 mg, 85 % yield as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H), 7.41 – 7.22 (m, 3H), 7.20-7.17 (m, 1H), 6.85-6.80 (m, 1H), 4.77 – 4.60 (m, 2H), 3.89 (s, 3H), 3.74 – 3.34 (m, 28H), 2.89 – 2.79 (m, 2H), 2.59 (s, 3H). Mol Wt: 747.28, MS (ES+): 747.40 *m/z* (100) [MH^+].

[00301] ***(S)-tert-butyl (1-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-2-oxo-6,9,12,15-tetraoxa-3-azaheptadecan-17-yl)carbamate (BRD-C-85):***

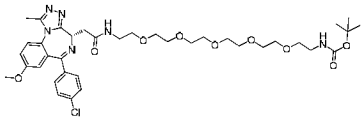


[00302] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (200 mg, 0.503 mmol) in DCM (6 mL) was charged with EDCI (74 mg, 0.755 mmol), 4-DMAP (73.8 mg, 0.604 mmol), HOBt (82 mg, 0.604 mmol) and stirred at rt for 10 minutes. This solution was charged with, *tert*-butyl (14-amino-3,6,9,12-tetraoxatetradecyl)carbamate (203 mg, 0.604mmol) and the resulting

solution was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 10 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by column chromatography on silica gel (100-200 mesh), eluting with 3% methanol in chloroform to afford 280 mg, 77.9% yield of the title compound, as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.2 Hz, 2H), 7.35 (dd, J = 16.5, 8.5 Hz, 2H), 7.19 (dd, J = 8.9, 2.9 Hz, 1H), 6.85 (d, J = 2.5 Hz, 2H), 5.16 (s, 1H), 4.64 (dd, J = 7.7, 6.2 Hz, 1H), 3.80 (s, 3H), 3.71 – 3.31 (m, 22H), 2.61 (s, 3H), 1.44 (s, 9H). Mol Wt: 715.24, MS (ES+): 715.30 *m/z* (100) [MH^+].

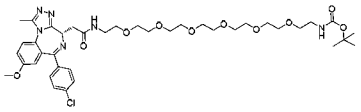
[00303] Following the general procedure for synthesis of (*S*)-tert-butyl (1-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-2-oxo-6,9,12,15-tetraoxa-3-azaheptadecan-17-yl)carbamate, the below compounds were synthesized and characterized.

[00304] ***(S)-tert-butyl (1-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-2-oxo-6,9,12,15,18-pentaoxa-3-azaicosan-20-yl)carbamate (BRD-C-86):***



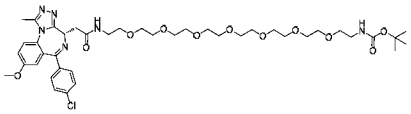
[00305] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (200 mg,0.503 mmol) in DCM (6 mL) was charged with EDCI (74 mg, 0.755 mmol), 4-DMAP (73.8 mg, 0.604 mmol), HOBt (82 mg, 0.604 mmol) and stirred at rt for 10 minutes. This solution was charged with *tert*-butyl (17-amino-3,6,9,12,15-pentaoxaheptadecyl)carbamate (229 mg,0.604 mmol) and obtained 280 mg, 73.4% yield of the title compound as a colorless oil. 1H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H), 7.40 – 7.29 (m, 2H), 7.19 (dd, J = 8.9, 2.9 Hz, 1H), 6.88 – 6.76 (m, 2H), 4.64 (dd, J = 7.7, 6.1 Hz, 1H), 3.79 (s, 3H), 3.71 – 3.54 (m, 18H), 3.57 – 3.36 (m, 6H), 3.30 (q, J = 5.3 Hz, 2H), 2.60 (s, 3H), 1.43 (s, 9H). Mol Wt: 759.29, MS (ES+): 759.40 *m/z* (100) [MH^+].

[00306] ***(S)-tert-butyl (1-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-2-oxo-6,9,12,15,18,21-hexaoxa-3-azatricosan-23-yl)carbamate (BRD-C-87):***



[00307] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (200 mg, 0.503 mmol) in DCM (6 mL) was charged with EDCI (74 mg, 0.755 mmol), 4-DMAP (73.8 mg, 0.604 mmol), HOBt (82 mg, 0.604 mmol) and stirred at rt for 10 minutes. This solution was charged with *tert*-butyl (20-amino-3,6,9,12,15,18-hexaoxaicosyl)carbamate (256 mg, 0.604 mmol) and obtained 300 mg, 74.25% yield of the title compound as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.44 (m, 2H), 7.41 – 7.29 (m, 2H), 7.19 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.88 – 6.78 (m, 2H), 4.64 (dd, *J* = 7.7, 6.1 Hz, 1H), 3.80 (s, 3H), 3.71 – 3.36 (m, 28H), 3.30 (q, *J* = 5.4 Hz, 2H), 2.61 (s, 3H), 1.44 (s, 9H). Mol Wt: 803.34, MS (ES+): 803.45 *m/z* (100) [MH^+].

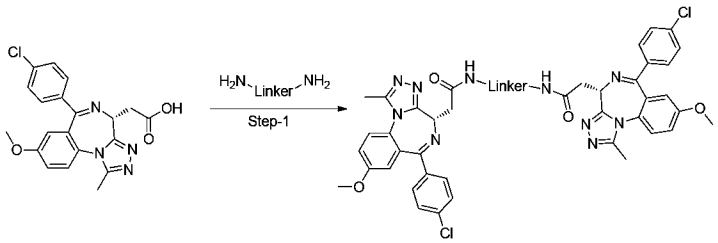
[00308] ***(S)-tert-butyl (1-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-2-oxo-6,9,12,15,18,21,24-heptaoxa-3-azahexacosan-26-yl)carbamate (BRD-C-88):***



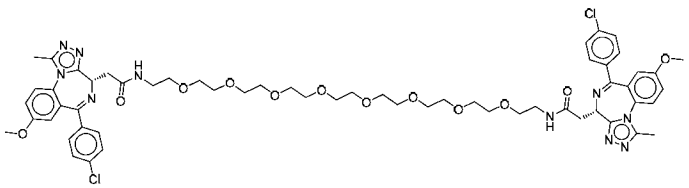
[00309] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (200 mg, 0.503 mmol) in DCM (6 mL) was charged with EDCI (74 mg, 0.755 mmol), 4-DMAP (73.8 mg, 0.604 mmol), HOBt (82 mg, 0.604 mmol) and stirred at rt for 10 minutes. This solution was charged with *tert*-butyl (23-amino-3,6,9,12,15,18,21-heptaoxatricosyl)carbamate (283 mg, 0.604 mmol) and obtained 320 mg, 74.94% yield of the title compound as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 2H), 7.40 – 7.28 (m, 3H), 7.19 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.85-6.50 (m, 1H), 4.65-4.62 (m, 1H), 3.79 (s, 3H), 3.71 – 3.35 (m, 32H), 3.30 (q, *J* = 5.4 Hz, 2H), 2.60 (s, 3H), 1.43 (s, 9H). Mol Wt: 847.39, MS (ES+): 847.50 *m/z* (100) [MH^+].

[00310] **Synthesis of bivalent compounds connected by polyethylene glycol:**

Scheme 8. Reaction scheme for synthesis of bivalent compounds connected by polyethylene glycol:



[00311] Synthesis of (*S*)-*N*,*N*'-(3,6,9,12,15,18,21,24-octaoxahexacosane-1,26-diyl)bis(2-((4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide) (BRD-B-22):

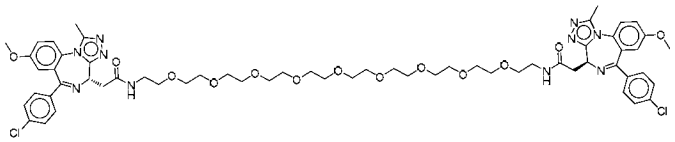


[00312] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (150 mg, 0.37 mmol) in DCM (15 mL) was charged with EDCI (179 mg, 0.94 mmol) and stirred at 0 ^{0}C for 10 minutes. This solution was charged with 3,6,9,12,15,18,21,24-octaoxahexacosane-1,26-diamine (78 mg, 0.18 mmol) and DMAP (101 mg, 0.83 mmol) and the resulting solution was stirred at room temperature overnight. The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 15 mL) and the combined organic fractions were washed with 1N HCl (10 mL), brine solution (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC to afford 20 mg, 9% yield of the corresponding title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (m, 4H), 7.78 (d, J = 9.0 Hz, 2H), 7.53-7.46 (m, 4H), 7.38 (dd, J = 9.0, 2.9 Hz, 2H), 6.86 (d, J = 2.9 Hz, 2H), 4.48 (dd, J = 8.5, 5.5 Hz, 2H), 3.78 (s, 6H), 3.56 – 3.41 (m, 34H), 3.31-3.11(m, 6H), 2.53 (s, 6H). Mol. Wt: 1170.14; MS (ES+): 1170.31 *m/z* (100) [MH^+] (basic +ve mode. HPLC purity: 98.90% (Max plot).

[00313] (*S*)-N,N'-(3,6,9,12,15,18,21,24,27-nonaoxanonacosane-1,29-diyl)bis(2-((4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide) was synthesized and characterized following the general procedure for synthesis

of (*S*)-*N*,*N*'-(3,6,9,12,15,18,21,24-octaoxahexacosane-1,26-diyl)bis(2-((4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide).

[00314] Synthesis of (*S*)-N,N'-(3,6,9,12,15,18,21,24,27-nonaoxanonacosane-1,29-diyl)bis(2-((4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)acetamide) (BRD-B-23):

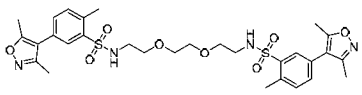


[00315] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (33 mg, 0.25 mmol) in DCM (15 mL) was charged with EDCI (119 mg, 0.63 mmol) and stirred at 0 ^{0}C for 10 minutes. This solution was charged with 3,6,9,12,15,18,21,24,27-nonaoxanonacosane-1,29-diamine (57 mg,0.12 mmol) and DMAP (67 mg,0.55 mmol) and obtained 10 mg, 6.6% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 2H), 8.27 (t, J = 5.6 Hz, 2H), 7.78 (d, J = 8.9 Hz, 2H), 7.56 – 7.43 (m, 6H), 7.37 (dd, J = 9.0, 2.9 Hz, 2H), 6.86 (d, J = 2.9 Hz, 2H), 4.48 (dd, J = 8.5, 5.5 Hz, 2H), 3.79 (s, 6H), 3.56 – 3.41 (m, 36H), 3.36 – 3.09 (m, 8H), 2.53 (s, 6H). Mol. Wt: 1214.19; MS (ES+): 1214.09 *m/z* (100) [MH^{+}] (basic +ve mode). HPLC purity: 93.20% (Max plot).

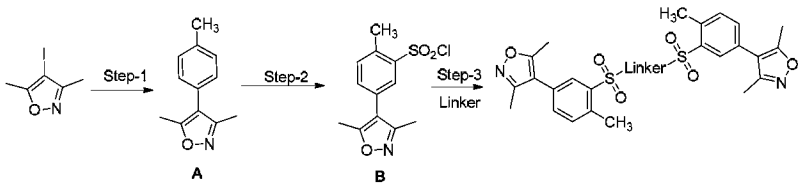
EXAMPLE 108:

[00316] Bivalent compounds were synthesized according to the procedures described below.

[00317] Synthesis of *N*,*N*'-((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide) (BRD-B-76):



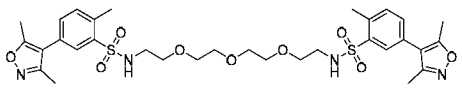
Scheme 9. Reaction scheme for synthesis of bivalent compounds connected by polyethylene glycol:



[00318] A solution of 5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzene-1-sulfonyl chloride (**B**) (200 mg, 0.70 mmol) and 2,2'-(ethane-1,2-diylbis(oxy))diethanamine (51.9 mg, 0.35 mmol) in pyridine (10 mL) was stirred at room temperature for 3 hr. The solvent was concentrated under reduced pressure and water (50 mL) was added and the aqueous was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with dil HCl solution (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* resulting crude product which was purified by column chromatography eluting with 5-10% methanol in DCM to afford 80 mg, 17% yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (t, J = 5.8 Hz, 1H), 7.72-7.65 (m, 1H), 7.53-7.47 (m, 4H), 3.40-3.29 (m, 10H), 2.99-2.94 (m 2H), 2.59 (s, 6H), 2.39 (s, 6H), 2.21 (s, 6H). Mol. Wt: 646.77; MS (ES+): *m/z* 647.20 [MH^+], HPLC purity: 94.79 % (Max plot).

[00319] *N,N'*-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide) was synthesized following the general procedure for synthesis of *N,N'*-((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide).

[00320] **Synthesis of *N,N'*-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide) (BRD-B-77):**

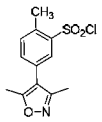


[00321] A solution of 5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzene-1-sulfonyl chloride (200 mg, 0.70 mmol) and 2,2'-((oxybis(ethane-2,1-diyl))bis(oxy))diethanamine (67.4 mg, 0.35 mmol) in pyridine (10 mL) was stirred at room temperature for 2 h. After similar work up procedure as above resulted in a crude product which was purified by column chromatography eluting with 5-10% methanol in DCM to afford 50 mg, 10.3 % yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (t, J = 5.8 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.57 – 7.45 (m, 4H), 3.43 – 3.31 (m, 12H), 2.99 (q, J = 5.8 Hz, 4H), 2.60

(s, 6H), 2.40 (s, 6H), 2.22 (s, 6H). Mol. Wt: 690.83; MS (ES+): *m/z* 713.25 [M+Na], HPLC purity: 95.59 % (Max plot).

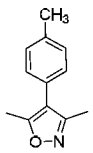
[00322] Intermediates A and B were synthesized as described in Bamborough et al., J. Med. Chem (2012) *55*, 587-596, which is hereby incorporated by reference in its entirety.

[00323] ***5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzene-1-sulfonyl chloride (BRD-C-97):***



[00324] A cold solution of 3, 5-dimethyl-4-(*p*-tolyl) isoxazole (5g, 26.70 mmol), chloro sulphonic acid (16.39 mL, 32.04 mmol), and PCl_5 (7.70 g, 26.70 mmol) in DCM (20 mL) at 0 °C under an atomosphere of nitrogen was stirred at 0 °C for 15 min then reaction mixture was heated to 70 °C for 4hr. The reaction mixture was allow cooling to rt and then poured into ice cold water with stirring. The resulting suspension was filtered through a pad of celite and the filtrate was extracted with DCM (3 x 100 mL). The combined organic extract were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* resulting 6.0 g, 80% yield of the title compound as brown oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 2.55 (s, 3H), 2.36 (s, 3H), 2.18 (s, 3H). Mol. Wt: 285.75; MS (ES+): *m/z* 286.80 [MH^+].

[00325] ***3,5-dimethyl-4-(p-tolyl) isoxazole:***



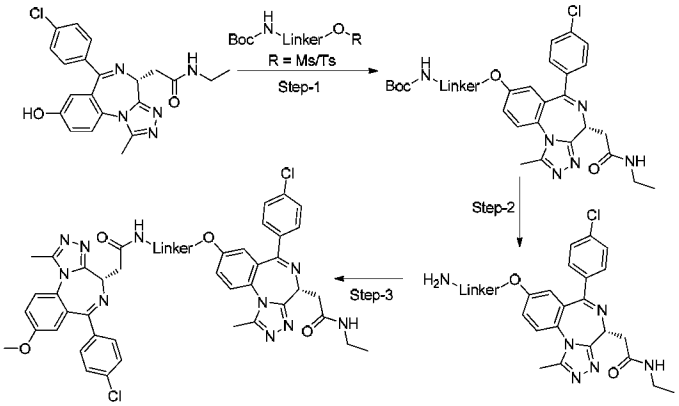
[00326] A solution of 4-tolylboronic acid (5 g, 36.77 mmol.) in 1,4-dioxane (20mL) was charged with 4-iodo 3,5 dimethylisooxazole (8.14 g, 36.77 mmol.), aq. sodium carbonate solution 5 mL (2M) and was degassed for 15 min and charged with $Pd(PPh_3)_4$ (1.18 g, 1.0 mmol). The reaction mixture was stirred at 85 °C for 12hr. The reaction mixture was partitioned in between ethyl acetate (70 mL) and H_2O (20 mL) and separated. The aqueous layer was re-extracted with ethyl acetate (3 x 10 mL) and combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by column chromatography (100-200 mesh silica gel) to afford 5g, 72%

yield of the title compound as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 7.6 Hz, 2H), 2.39 (s, 6H), 2.26 (s, 3H). Mol. Wt; 187.24; MS (ES+): *m/z* 187.95 [MH^+].

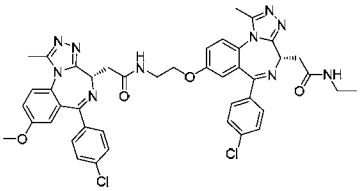
EXAMPLE 109:

[00327] Bivalent compounds were synthesized according to the procedures described below.

Scheme 10. Reaction scheme for synthesis of bivalent compounds:



[00328] **Synthesis of *N*-(2-(((*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)ethyl)-2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-01):**

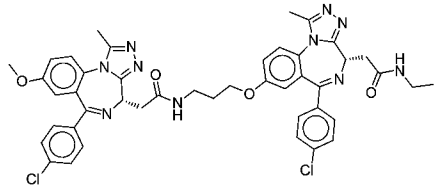


[00329] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (75 mg, 0.188 mmol) in DCM (2.25 mL) was charged with EDCI (54 mg, 0.282 mmol), DMAP (46 mg, 0.376 mmol), and HOBt (38 mg, 0.282 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-2-(8-

(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (102 mg, 0.225 mmol) and stirred at room temperature overnight. The reaction mixture was partitioned between DCM (20 mL) and H_2O (10 mL) and separated. The aqueous layer was re-extracted with DCM (3 x 15 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC to afford 90 mg, 57.32 % yield of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.3, 5.7 Hz, 2H), 7.41 – 7.10 (m, 8H), 6.84 (dd, *J* = 8.2, 2.9 Hz, 2H), 6.50 (t, *J* = 5.9 Hz, 2H), 4.58 (td, *J* = 7.2, 3.8 Hz, 2H), 4.03 (t, *J* = 5.5 Hz, 2H), 3.80 (s, 3H), 3.69 – 3.45 (m, 4H), 3.31-3.40 (m, 4H), 2.60 (s, 6H), 1.17 (t, *J* = 7.2 Hz, 3H). Mol Wt: 830.26, MS (ES+): *m/z* 831.39 [MH^+] *m/z* 416.30 [$MH^+/2$] (basic +ve mode). HPLC purity: 94.31% (Max plot).

[00330] Following the general procedure for synthesis of *N*-(2-(((*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)ethyl)-2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide, the below compounds were synthesized and characterized.

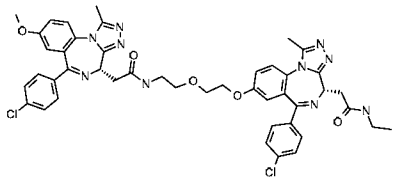
[00331] **Synthesis of *N*-(3-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)propyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-02):**



[00332] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (80 mg, 0.20 mmol) in DCM (15 mL) was charged with EDCI (57.5 mg, 0.30 mmol), DMAP (24 mg, 0.20 mmol) and HOBt (27 mg, 0.20 mmol) and stirred at rt for 10 minutes. The solution was charged with 2-((4*S*)-8-(3-aminopropoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (93.9 mg, 0.20 mmol) and purified using the same conditions as above general procedure resulting in 26 mg, 15.4% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.74 – 7.64 (m, 2H), 7.55 – 7.46 (m, 4H), 7.38 – 7.24 (m, 6H), 6.78 (d, *J* = 2.8 Hz, 1H), 6.60 (d, *J* = 3.0 Hz, 1H), 4.84 (d, *J* = 16.0 Hz, 4H), 4.61-4.50 (m,

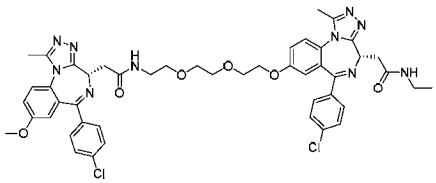
3H), 4.15 (dt, *J* = 9.3, 6.3 Hz, 1H), 3.99 (dt, *J* = 9.4, 6.2 Hz, 1H), 3.72 (s, 3H), 3.55 (dt, *J* = 13.1, 6.7 Hz, 1H), 3.47 – 3.10 (m, 4H), 2.62 (s, 6H), 1.18 (t, *J* = 6.2 Hz, 3H). Mol. Wt: 845.77; MS (ES+): *m/z* 845.2 9 [MH^+], HPLC purity:-98.41% (220 nm).

[00333] Synthesis of *N*-(2-(2-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethoxy)ethyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-03):



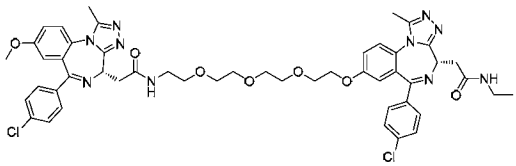
[00334] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (70 mg, 0.17 mmol) in DCM (15 mL) was charged with EDCI (49 mg, 0.18 mmol), DMAP (20 mg, 0.17 mmol) and HOBt (23 mg, 0.17 mmol) and stirred at rt for 10 minutes. This solution was charged with solution,2-((4*S*)-8-(2-(2-aminoethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (85 mg, 0.10 mmol) and purified using the same conditions as above general procedure resulting in 10 mg, 6.4% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 – 8.27 (m, 1H), 8.25 – 8.16 (m, 1H), 7.81 – 7.68 (m, 2H), 7.55 – 7.33 (m, 8H), 6.89 – 6.78 (m, 2H), 4.47 (t, *J* = 6.8 Hz, 2H), 4.20 (dd, *J* = 15.7, 9.7 Hz, 1H), 4.15-4.10 (m, 1H), 3.82 – 3.72 (m, 8H), 3.76 (s, 3H), 3.59 – 3.47 (m, 5H), 2.55 (s, 6H), 1.17 (t, *J* = 6.2 Hz, 3H). Mol. Wt: 875.80; MS (ES+): *m/z* 875.6 [MH^+], HPLC purity: 92.92% (Max plot).

[00335] Synthesis of *N*-(2-(2-(2-(((*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethoxy)ethoxy)ethyl)-2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-04):



[00336] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (54 mg, 0.138 mmol) in DCM (2.25 mL) was charged with EDCI (40 mg, 0.207 mmol), DMAP (25 mg, 0.207 mmol), and HOBt (28 mg, 0.207 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-2-(8-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl purified using the same conditions as above general procedure)-*N*-ethylacetamide (75 mg, 0.138mmol) and purified using the same conditions as above general procedure resulting in 50 mg, 39.2 % yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73 (t, J = 9.3 Hz, 2H), 7.52 – 7.31 (m, 10H), 6.84 – 6.77 (m, 2H), 4.49 – 4.41 (m, 2H), 4.17– 4.00 (m, 2H), 3.72(s, 3H), 3.80-3.51 (m,14H), 3.43 (t, J = 5.9 Hz, 2H), 3.35 – 3.00 (m, 6H), 1.04 (t, J = 7.1 Hz, 3H). Mol Wt: 919.85, MS (ES+): *m/z* 919.51 [MH$^+$] (basic +ve mode), HPLC purity: 99.83% (Max plot).

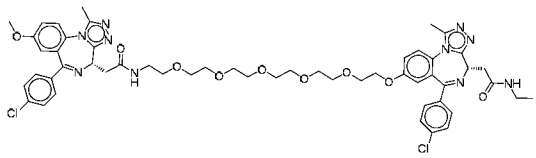
[00337] **Synthesis of *N*-(2-(2-(2-(2-(((*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)-2-((*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-05):**



[00338] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (50 mg, 0.128 mmol) in DCM (2.25 mL) was charged with EDCI (37 mg, 0.192 mmol), DMAP(23.4 mg, 0.192 mmol), and HOBt (26 mg, 0.192 mmol) and stirred at rt for 10 minutes. This solution was charged with (*S*)-2-(8-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (75 mg, 0.128 mmol) and purified using the same conditions as above general procedure resulting in 50 mg, 40.65 %

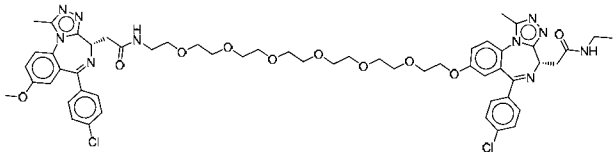
yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.21 (t, J = 5.6 Hz, 1H), 7.77 (t, J = 8.1 Hz, 2H), 7.55 – 7.43 (m, 7H), 7.38 (dd, J = 7.7, 4.4 Hz, 2H), 6.86 (dd, J = 7.8, 2.9 Hz, 2H), 4.51 – 4.43 (m, 2H), 4.21 – 4.02 (m, 2H), 3.77 (s, 3H), 3.72 (d, J = 4.8 Hz, 2H), 3.60- 3.50 (m, 10H), 3.44 (t, J = 5.9 Hz, 2H), 3.35-3.07 (m, 6H), 1.06 (t, J = 7.3 Hz, 3H). Mol Wt: 963.91, MS (ES+): *m/z* 963.83 [MH$^+$] (basic +ve mode). HPLC purity: 99.56% (Max plot).

[00339] Synthesis of *N*-(17-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15-pentaoxaheptadecyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-13):



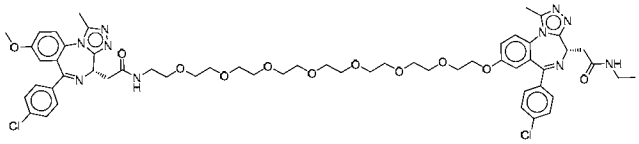
[00340] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (44 mg, 0.11 mmol) in DCM (15 mL) was charged with EDCI (42 mg, 0.22 mmol) and stirred at 0^{0}C for 10 minutes. This solution was charged with 2-((4*S*)-8-((17-amino-3,6,9,12,15-pentaoxaheptadecyl)oxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (100 mg, 0.14 mmol) and DMAP (21 mg, 0.17 mmol) and purified using the same conditions as above general procedure to obtain 25 mg, 21.5 % yield of the title compound as a white Solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.74 (dd, J = 8.7, 4.8 Hz, 2H), 7.50 – 7.30 (m, 10H), 6.88 – 6.80 (m, 2H), 4.50 – 4.42 (m, 2H), 4.17-4.03 (m, 2H), 3.76 (s, 3H), 3.70 (s, 3H), 3.55-3.42 (m, 23H), 3.23-3.05 (m, 8H), 1.05 (t, J = 7.2 Hz, 3H). Mol. Wt: 1052.01; MS (ES+): *m/z* 1051.3 [MH$^+$], HPLC purity: 99.43% (Max plot).

[00341] Synthesis of *N*-(20-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18-hexaoxaicosyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-14):



[00342] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (33 mg, 0.083 mmol) in DCM (15 mL) was charged with EDCI (31 mg, 0.15 mmol) and stirred at 0 ^{0}C for 10 minutes. This solution was charged with 2-((4*S*)-8-((20-amino-3,6,9,12,15,18-hexaoxaicosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (80 mg, 0.11 mmol) and DMAP (16 mg, 0.13 mmol) and purified using the same conditions as above general procedure resulting in 25 mg, 27.4% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.29 (d, J = 9.9 Hz, 2H), 8.19 (s, 1H), 7.77 (dd, J = 8.6, 5.0 Hz, 2H), 7.49 (m, 6H), 7.37 (d, J = 8.6 Hz, 2H), 6.90 – 6.82 (m, 2H), 4.51 – 4.43 (m, 2H), 4.14-4.08 (m, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 3.49 - 3.24 (m, 31H), 3.28-3.10 (m, 4H), 1.05 (t, J = 7.0 Hz, 3H). Mol. Wt: 1096.06; MS (ES+): *m/z* 1095.40 [MH$^+$], HPLC purity: 99.50% (Max plot).

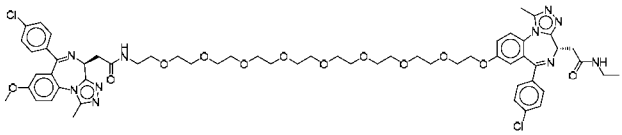
[00343] **Synthesis of *N*-(23-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18,21-heptaoxatricosyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-15):**



[00344] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (39 mg, 0.098 mmol) in DCM (15 mL) was charged with EDCI (41 mg, 0.21 mmol) and stirred at 0 ^{0}C for 10 minutes. This solution was charged with 2-((4*S*)-8-((23-amino-3,6,9,12,15,18,21-heptaoxatricosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (110 mg, 0.14 mmol) and DMAP (19 mg, 0.15 mmol) and purified using the same conditions as above general procedure resulting in 28 mg, 25% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 8.32 – 8.23 (m, 1H), 8.18 (d, J = 6.3 Hz, 1H), 7.77 (t,

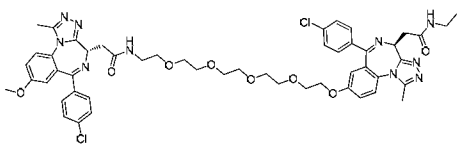
J = 7.0 Hz, 2H), 7.55 – 7.43 (m, 6H), 7.37 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 7.5 Hz, 2H), 4.47 (t, J = 6.8 Hz, 2H), 4.16 (d, J = 10.5 Hz, 1H), 4.08 (d, J = 6.9 Hz, 1H), 3.78 (s, 3H), 3.71 (s, 3H), 3.60-3.10 (m, 38H), 1.07 (t, J = 7.4 Hz, 3H). Mol. Wt: 1140.12; MS (ES+): *m/z* 1139.30 [MH^+], HPLC purity: 99.59% (Max plot).

[00345] Synthesis of *N*-(26-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18,21,24-octaoxahexacosyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-20):



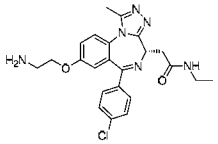
[00346] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (31 mg, 0.078 mmol) in DCM (15 mL) was charged with EDCI (30 mg, 0.15 mmol) and stirred at 0 ^{0}C for 10 min. This solution was charged with 2-((4*S*)-8-((26-amino-3,6,9,12,15,18,21,24-octaoxahexacosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (85 mg, 0.10 mmol) and DMAP (15 mg, 0.12 mmol) and purified using the same conditions as above general procedure resulting in 20 mg, 22.4% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 – 8.24 (m, 1H), 8.19 (d, J = 6.0 Hz, 1H), 7.77 (dd, J = 9.1, 5.1 Hz, 2H), 7.55 – 7.43 (m, 6H), 7.42 – 7.33 (m, 2H), 6.90 – 6.83 (m, 2H), 4.48 (d, J = 7.3 Hz, 2H), 4.08 (d, J = 10.9 Hz, 1H), 3.78 (s, 3H), 3.71 (d, J = 5.0 Hz, 2H), 3.50-3.45 (m, 32H), 3.40-3.10 (m, 7H), 2.98 (s, 3H), 1.05 (t, J = 7.0 Hz, 3H). Mol. Wt: 1184.17; MS (ES+): *m/z* 592.85 [MH^+/2], HPLC purity: 99.69% (Max plot).

[00347] Synthesis of *N*-(14-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12-tetraoxatetradecyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-12):



[00348] A solution of (*S*)-2-(6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (150 mg, 0.23 mmol) in DCM (20 mL) was cooled to 0 ^{0}C then charged with HOBt (37 mg, 0. 28 mmol), DMAP (34 mg, 0.28 mmol) and (*S*)-2-(8-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (94 mg, 0.23 mmol) and stirred for 30 min then portion wise charged with EDCI.HCl (93 mg, 0.38 mmol) and stirred at 0 ^{0}C for 1hr and at room temperature for an additional 12 hr. The reaction mixture was partioned in between 1N $KHSO_4$ (10 mL) and DCM (10 mL) and separated. The aqueous was re-extracted with DCM (2x10 mL) and the combined organic fractions were washed with 10 % $NaHCO_3$ (10 mL), brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC resulting in 10 mg, 4.16 % yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77 (dd, J = 8.9, 5.5 Hz, 2H), 7.53 – 7.34 (m, 8H), 6.84 (d, J = 8.7 Hz, 4H), 4.54 – 4.46 (m, 2H), 4.17 – 4.02 (m, 2H), 3.76 (s, 6H), 3.69 (t, J = 4.5 Hz, 2H), 3.56 – 3.39 (m, 10H), 3.34 – 3.02 (m, 12H), 2.57 (s, 6H), 1.04 (t, J = 7.0 Hz, 3H). Mol. Wt:;1007.96, MS (ES+): *m/z* 1007.55 [MH$^+$], HPLC purity: 96.72 % (Max plot).

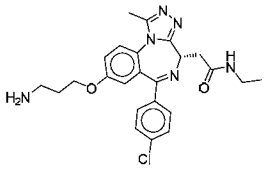
[00349] ***(S)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide (BRD-C-27):***



[00350] A solution of (*S*)-*tert*-butyl (2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate (250 mg, 0.452 mmol) in DCM (5 mL) was charged with TFA (2.5 mL) and stirred at rt for 24 h. The reaction mixture was concentrated *in vacuo* to obtain a residue which was triturated with diethyl ether to afford 162 mg, 79.41% yield of the title compound as an oil. Mol Wt:-452.94, MS (ES+): *m/z* 453.90 [MH$^+$].

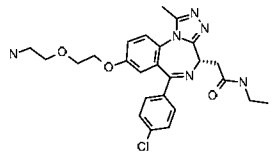
[00351] Following the general procedure for synthesis of (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide, the below compounds were synthesized and characterized.

[00352] ***2-((4S)-8-(3-aminopropoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide (BRD-C-30 or BRC-C-42):***



[00353] The procedure for the preparation of (2-((4*S*)-8-(3-aminopropoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide is the same as for (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using 2-[(4*S*)-8-(3-aminopropoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-4-yl]-*N*-ethyl-acetamide in place of (*S*)-*tert*-butyl (2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate affording 120 mg, 77 % yield of the title compound as a light yellow solid. Mol. Wt: 466.96; MS (ES+): *m/z* 467.15 [MH^+].

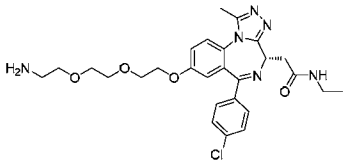
[00354] ***2-((4S)-8-(2-(2-aminoethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide (BRD-C-38):***



[00355] The procedure for the preparation of 2-((4S)-8-(2-(2-aminoethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide is the same as (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using *tert*-butyl (2-(2-(((4S)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethoxy)ethyl)carbamate in place of (*S*)-*tert*-butyl (2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate affording 10 mg, 20.4 % yield of the title compound as a light yellow solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.53 (s,

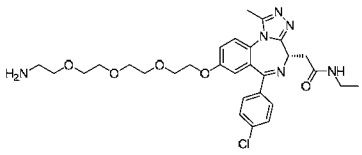
1H), 7.73 (d, J = 8.9 Hz, 1H), 7.53 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.5 Hz, 3H), 6.94 (s, 1H), 4.62 (dd, J = 9.1, 5.1 Hz, 1H), 4.19 (tq, J = 10.1, 4.7, 4.2 Hz, 2H), 3.88 (d, J = 4.6 Hz, 2H), 3.79 – 3.72 (m, 2H), 3.46 – 3.18 (m, 4H), 3.16 – 3.08 (m, 2H), 2.64 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H). Mol. Wt: 496.99; MS (ES+): *m/z* 497.25 [MH^+].

[00356] ***(S)-2-(8-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide (BRD-C-39):***



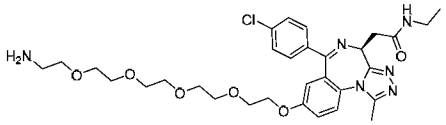
[00357] The procedure for the preparation of (*S*)-2-(8-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide is the same as (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using (*S*)-*tert*-butyl (2-(2-(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8yl)oxy)ethoxy)ethoxy)ethyl)carbamate except using (*S*)-*tert*-butyl (2-(2-(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethoxy)ethoxy)ethyl)carbamate in place of (*S*)-*tert*-butyl(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H* benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate resulting in 151 mg, 90 % yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 (s, 2H), 8.25 – 8.18 (m, 1H), 7.77 (d, J = 8.7 Hz, 1H), 7.53-7.38 (m, 4H), 7.39 (d, J = 9.1 Hz, 1H), 6.88 (s, 1H), 4.51 – 4.39 (m, 2H), 4.24 – 4.02 (m, 4H), 3.76 (s, 3H), 3.60 – 3.45 (m, 6H), 3.26-3.03(m, 4H), 2.85 – 2.78 (m, 2H), 1.06 (t, J = 7.0 Hz, 3H). Mol Wt:-541.04, MS (ES+): *m/z* 541.25 [MH^+].

[00358] ***(S)-2-(8-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide (BRD-C-40):***



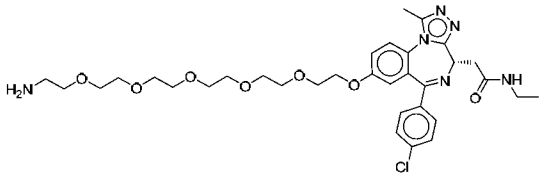
[00359] The procedure for the preparation of ((*S*)-2-(8-(2-(2-(2-(2-aminoethoxy)ethoxy)ethoxy)ethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide is the same as (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using (*S*)-*tert*-butyl (2-(2-(2-(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)carbamate in place of (*S*)-*tert*-butyl(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate resulting in 191 mg,, 80 % yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 8.26 – 8.19 (m, 1H), 7.77 (d, J = 8.9 Hz, 1H), 7.55 – 7.45 (m, 3H), 7.39 (dd, J = 8.9, 3.0 Hz, 1H), 6.90 – 6.85 (m, 1H), 4.47 (dd, J = 8.2, 5.3 Hz, 1H), 4.21 – 4.04 (m, 2H), 3.87-3.71 (m, 2H), 3.59 – 3.43 (m, 15H), 3.28 – 3.05 (m, 4H), 2.80 (q, J = 8.0, 6.7 Hz, 2H), 1.06 (t, J = 7.1 Hz, 3H). Mol Wt: 585.09. MS (ES+): *m/z* 585.25 [MH$^+$].

[00360] ***2-((4S)-8-((14-amino-3,6,9,12-tetraoxatetradecyl)oxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide (BRD-C-82):***



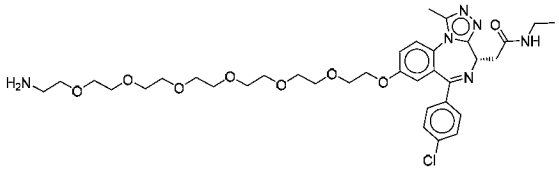
[00361] The procedure for the preparation of 2-((4*S*)-8-((14-amino-3,6,9,12-tetraoxatetradecyl)oxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide is the same as (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using *tert*-butyl (14-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12-tetraoxatetradecyl)carbamate in place of (*S*)-*tert*-butyl(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate resulting in 160 mg, 84.6 % yield of the title compound as a light yellow oil. Mol. Wt:629.15, MS (ES+): *m/z* 629.20 [MH$^+$].

[00362] ***(S)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetaminde (BRD-C-83):***



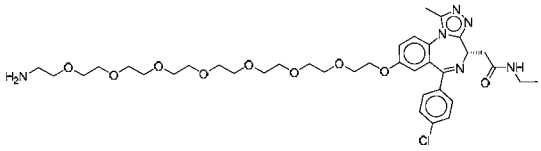
[00363] The procedure for the preparation of (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetaminde is the same as (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using *tert*-butyl (17-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15-pentaoxaheptadecyl)carbamate in place of (*S*)-*tert*-butyl(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate resulting in 100 mg, 57 % yield of the title compound as a light yellow oil. Mol. Wt: 673.20; MS (ES+): *m/z* 673.25 [MH^+].

[00364] ***2-((4S)-8-((20-amino-3,6,9,12,15,18-hexaoxaicosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide.***



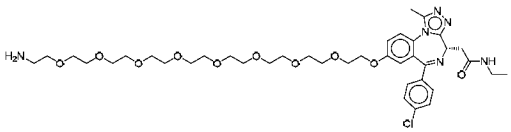
[00365] The procedure for the preparation of 2-((4*S*)-8-((20-amino-3,6,9,12,15,18-hexaoxaicosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide is the same as (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using *tert*-butyl (20-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[f][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18-hexaoxaicosyl)carbamate in place of (*S*)-*tert*-butyl(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate resulting in 88 mg, 61% yield of the title compound as a light yellow semi solid. Mol. Wt: 717.25; MS (ES+): *m/z* 717.40 [MH^+].

[00366] ***2-((4S)-8-((23-amino-3,6,9,12,15,18,21-heptaoxatricosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide (BRD-C-84):***



[00367] The procedure for the preparation of 2-((4*S*)-8-((23-amino-3,6,9,12,15,18,21-heptaoxatricosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide is the same as (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using *tert*-butyl (23-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18,21-heptaoxatricosyl)carbamate in place of (*S*)-*tert*-butyl(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate resulting in 110 mg, 59% yield of the title compound as a light yellow semi solid. Mol. Wt: 760.36; MS (ES+): *m/z* 783.35 [M+Na].

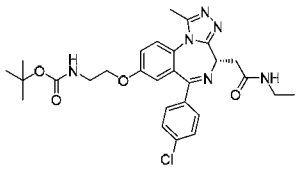
[00368] ***2-((4S)-8-((26-amino-3,6,9,12,15,18,21,24-octaoxahexacosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-ethylacetamide:***



[00369] The procedure for the preparation of 2-((4*S*)-8-((26-amino-3,6,9,12,15,18,21,24-octaoxahexacosyl)oxy)-6-(4-chlorophenyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide is the same as (*S*)-2-(8-(2-aminoethoxy)-6-(4-chlorophenyl)-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide except for using *tert*-butyl (26-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18,21,24-octaoxahexacosyl)carbamate in place of (*S*)-*tert*-butyl(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-

yl)oxy)ethyl)carbamate resulting in 85 mg, 56% yield of the title compound as a light yellow solid. Mol. Wt: 804.38; MS (ES+): *m/z* 805.55 [MH^+].

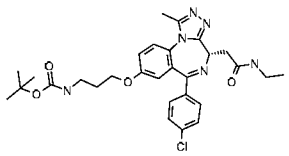
[00370] ***(S)-tert-butyl (2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)ethyl)carbamate:***



[00371] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (250 mg, 0.609 mmol) in acetonitrile (6 mL) was charged with potassium carbonate (134 mg, 0.947 mmol) and stirred at 81 °C for 10 minutes. This solution was charged with 2-((*tert*-butoxycarbonyl)amino)ethyl methanesulfonate (218 mg, 0.914 mmol) and the resulting solution was heated at 80 °C for 6-10 h. The reaction mixture was cooled to room temperature, diluted with water (25 mL) and extracted with ethyl acetate (3 x 20mL). The combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by column chromatography on silica gel (230-400 mesh), eluting with 5 % methanol in chloroform to afford 252 mg, 73% yield of the title compound as a white solid. Mol Wt: 553.05 MS (ES+): *m/z* 554.10 [MH^+].

[00372] Following the general procedure for synthesis of *(S)-tert*-butyl (2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)ethyl)carbamate, the below compounds were synthesized and characterized.

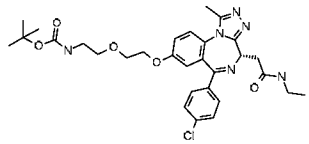
[00373] ***tert-butyl (3-(((4S)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)propyl)carbamate.***



[00374] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (200 mg, 0.48 mmol) in acetonitrile (5 mL) was charged with potassium carbonate (132 mg, 96 mmol) and 3-((*tert*-

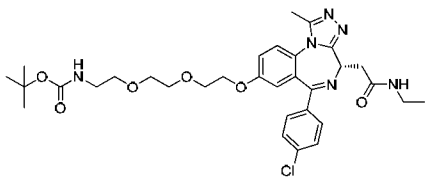
butoxycarbonyl)amino)propyl 4-methylbenzenesulfonate (185 mg, 0.73 mmol) under nitrogen atmosphere and purified using the same conditions which were used for. (*S*)-tert-butyl (2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate resulting in 170 mg, 78% yield of the title compound as an off white semi solid. Mol. Wt: 567.08, MS (ES+): *m/z* 567.25 [MH^+].

[00375] ***tert-butyl (2-(2-(((4S)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)ethoxy)ethyl)carbamate:***



[00376] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (150 mg, 0.37 mmol) in DMF (5 mL) was charged with potassium carbonate (61 mg, 44mmol) and 2-(2-((*tert*-butoxycarbonyl)amino)ethoxy)ethyl 4-methylbenzenesulfonate (208 mg, 0.35 mmol) under nitrogen atmosphere and purified using the same conditions which were used for. (*S*)-tert-butyl(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)ethyl)carbamate resulting in 65 mg, 89.5% yield of the title compound as an off white semi solid. Mol. Wt: 597.10; MS (ES+): *m/z* 597.20 [MH^+].

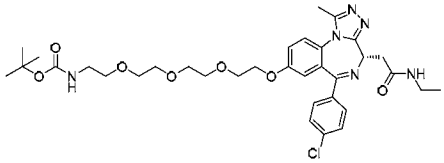
[00377] ***(S)-tert-butyl(2-(2-(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)ethoxy)ethoxy)ethyl)-carbamate.***



[00378] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (200 mg, 0.487 mmol) in acetonitrile (6 mL) was charged with potassium carbonate (134 mg, 0.947 mmol) and stirred at 81°C for 10 minutes. This solution was charged with 2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl methanesulfonate (239 mg, 0.731mmol) and purified using the same

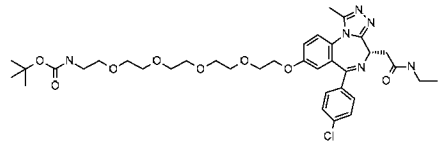
conditions as above general procedure resulting in 250 mg, 80 % yield of the title compound as a white solid. Mol Wt:-641.16; MS (ES+): *m/z* 642.20 [MH^+].

[00379] ***(S)-tert-butyl(2-(2-(2-(2-((6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)ethoxy)ethoxy)ethoxy)ethyl)-carbamate.***



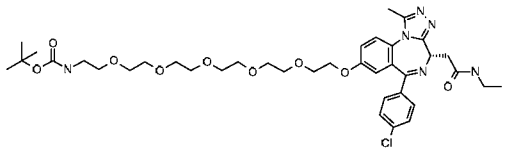
[00380] A suspension of (*S*)-2-(6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (200 mg, 0.487 mmol) in acetonitrile (6 mL) was charged with potassium carbonate (134 mg, 0.947 mmol) and stirred at 81^0C for 10 minutes. This solution was charged with 2,2-dimethyl-4-oxo-3,8,11-trioxa-5-azatridecan-13-yl methanesulfonate (271 mg, 0.730mmol) and purified using the same conditions as above general procedure resulting in 300 mg, 80 % yield of the title compound as a white solid.Mol Wt: 685.21, MS (ES+): *m/z* 686.100 [MH^+].

[00381] ***tert-butyl (14-(((4S)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)-3,6,9,12-tetraoxatetradecyl)-carbamate.***



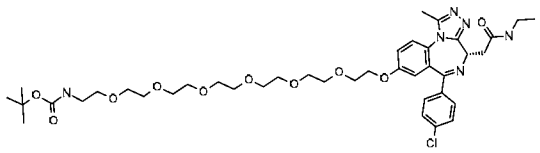
[00382] A solution of 2,2-dimethyl-4-oxo-3,8,11,14,17-pentaoxa-5-azanonadecan-19-yl 4-methylbenzenesulfonate (270 mg, 0.54 mmol) in acetonitrile (20 mL) was charged with potassium carbonate (151 mg, 1.00 mmol) and 2-((4*S*)-6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (225 mg, 0.54 mmol) under nitrogen atmosphere purified using the same conditions as above general procedure resulting in 220 mg, 55 % yield of the title compound as an off white semi solid. Mol. Wt: 729.26; MS (ES+): *m/z* 731.40 [MH+2].

[00383] ***tert-butyl(17-(((4S)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)-3,6,9,12,15-pentaoxaheptadecyl)-carbamate:***



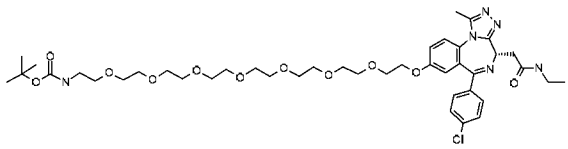
[00384] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (89 mg, 0.21 mmol) in aceotonitrile (20 mL) was charged with potassium carbonate (180 mg, 1.30 mmol) and 2,2-dimethyl-4-oxo-3,8,11,14,17,20-hexaoxa-5-azadocosan-22-yl methanesulfonate (200 mg, 0.43 mmol) under nitrogen atmosphere and purified using the same conditions as above general procedure resulting in 205 mg, 61% yield of the title compound as a white solid. Mol. Wt: 772.36, MS (ES+): *m/z* 773.20 [MH^+].

[00385] ***tert-butyl(20-(((4S)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18-hexaoxaicosyl)carbamate:***



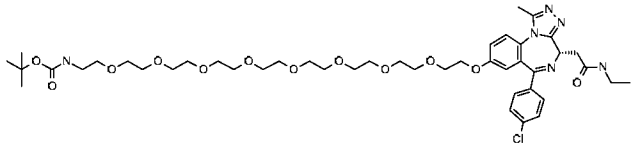
[00386] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (83.5 mg, 0.20 mmol) in aceotonitrile (20 mL) was charged with potassium carbonate (168.7 mg, 1.20 mmol) and 2,2-dimethyl-4-oxo-3,8,11,14,17,20,23-heptaoxa-5-azapentacosan-25-yl methanesulfonate (205 mg, 0.40 mmol) under nitrogen atmosphere and purified using the same conditions as above general procedure resulting in 150 mg, 45% yield of the title compound as an off white semi solid. Mol. Wt: 816.38; MS (ES+): *m/z* 839.30 [M+Na].

[00387] ***tert-butyl(23-(((4S)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18,21-heptaoxatricosyl)carbamate:***



[00388] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-hydroxy-1-methyl-4H-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (74 mg, 0.18 mmol) in aceotonitrile (20 mL) was charged with potassium carbonate (151 mg, 1.00 mmol) and 2,2-dimethyl-4-oxo-3,8,11,14,17,20,23,26-octaoxa-5-azaoctacosan-28-yl methanesulfonate (200 mg, 0.36 mmol) under nitrogen atmosphere and purified using the same conditions as above general procedure resulting in 210 mg, 67% yield of the title compound as an off white semi solid. Mol. Wt: 860.41; MS (ES+): *m/z* 861.00 [MH^+].

[00389] ***tert-butyl(26-(((4S)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18,21,24-octaoxahexacosyl)carbamate.***

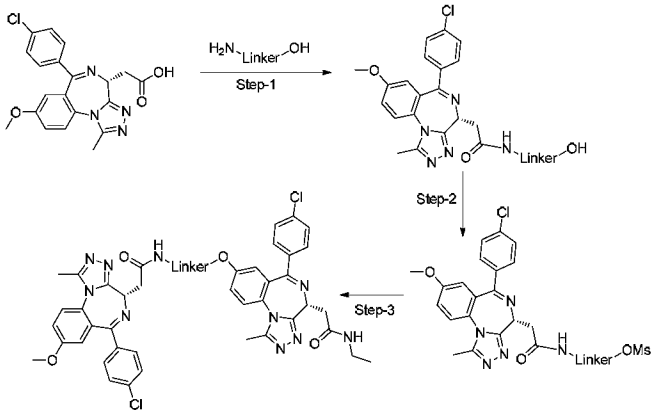


[00390] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (72 mg, 0.17 mmol) in aceotonitrile (20 mL) was charged with potassium carbonate (145 mg, 1.0 mmol) and 2,2-dimethyl-4-oxo-3,8,11,14,17,20,23,26,29-nonaoxa-5-azahentriacontan-31-yl methanesulfonate (208 mg, 0.35 mmol) under nitrogen atmosphere and purified using the same conditions as above general procedure resulting in 170 mg, 60% yield of the title compound as an off white semi solid. Mol. Wt: 904.43, MS (ES+): *m/z* 927.45 [M+Na].

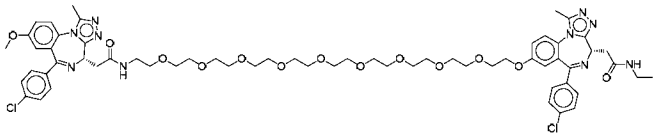
EXAMPLE 110:

[00391] Bivalent compounds were synthesized according to the procedures described below.

Scheme 11. Reaction scheme for synthesis of bivalent compounds:



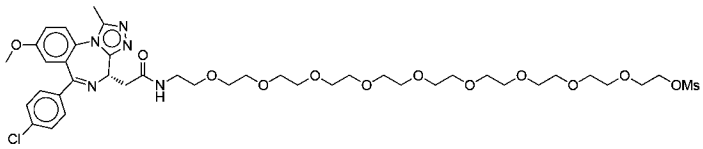
[00392] Synthesis of *N*-(29-(((4*S*)-6-(4-chlorophenyl)-4-(2-(ethylamino)-2-oxoethyl)-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-8-yl)oxy)-3,6,9,12,15,18,21,24,27-nonaoxanonacosyl)-2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetamide (BRD-B-21):



[00393] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-hydroxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-ethylacetamide (33 mg, 0.08 mmol) in aceotonitrile (20 mL) was charged with potassium carbonate (45 mg, 0.32 mmol) and 1-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-2-oxo-6,9,12,15,18,21,24,27,30-nonaoxa-3-azadotriacontan-32-yl methanesulfonate (100 mg, 0.10 mmol) under nitrogen atmosphere. The resulting solution was heated at 80 °C for 6-10 h. The reaction mixture was cooled to room temperature, diluted with water (25 mL) and extracted with ethyl acetate (3 x 20 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by preparative HPLC to afford 12 mg, 9% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (t, *J* = 7.5 Hz, 1H), 8.21 (t, *J* = 6.5 Hz, 1H), 7.77 (dd, *J* = 8.9, 5.1 Hz, 2H), 7.54-7.44 (m, 6H), 7.40-7.36 (m, 2H), 6.86 (dd, *J* = 7.1, 2.9 Hz, 2H), 4.47 (dd, *J* = 8.4, 5.6 Hz, 2H), 3.78 (s, 3H), 3.71 (t, *J* = 4.6 Hz, 2H), 3.57 – 3.41 (m, 37H), 3.31 –

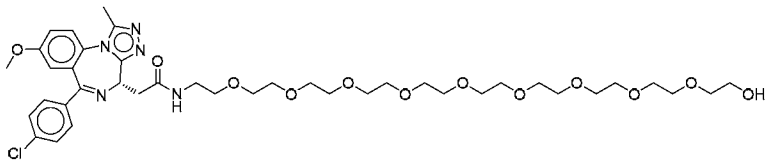
3.04 (m, 7H), 2.52 (s, 6H), 1.05 (t, J = 7.2 Hz, 3H). Mol. Wt: 1228.50; MS (ES+): *m/z* 615.00 [MH^+/2]. HPLC purity: 95.67% (Max plot).

[00394] ***1-((4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-2-oxo-6,9,12,15,18,21,24,27,30-nonaoxa-3-azadotriacontan-32-yl methanesulfonate:***



[00395] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)-*N*-(29-hydroxy-3,6,9,12,15,18,21,24,27-nonaoxanonacosyl)acetamide (100 mg, 0.11 mmol) in anhydrous DCM (15 mL) was cooled to 0°C and charged with triethylamine (36 mg, 0.35 mmol) and stirred at 0°C for 10 min. This solution was charged wiht methane sulfonyl chloride (27 mg, 0.23 mmol) and stirred at room temperature for 4 h. The reaction mixture was partitioned between DCM (20 mL) and water (10 mL) and separated. The aqueous was re-extracted with DCM (3x20 mL) and the combined organic fractions were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude product which was purified by column chromatography on silica gel (100-200 mesh), eluting with 5% methanol in chloroform to afford 100 mg, 91% yield of the title compound as an oil. Mol. Wt: 913.35; MS (ES+): *m/z* 936.00 [M+Na].

[00396] ***2-((4S)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4H-benzo[f][1,2,4]triazolo[4,3-a][1,4]diazepin-4-yl)-N-(29-hydroxy-3,6,9,12,15,18,21,24,27-nonaoxanonacosyl)acetamide:***



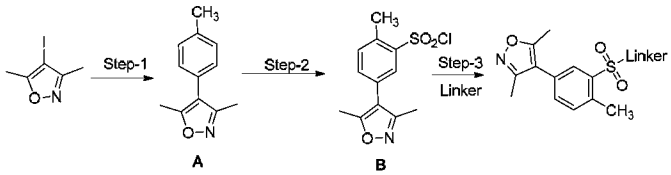
[00397] A solution of 2-((4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-benzo[*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-4-yl)acetic acid (100 mg, 0.25 mmol) in DCM (15 mL) was charged with EDCI (71 mg, 0.37 mmol) and stirred at 0^0C for 10 minutes The reaction was charged with 29-amino-3,6,9,12,15,18,21,24,27-nonaoxanonacosan-1-ol (115 mg, 0.25 mmol) and DMAP (36 mg, 0.30 mmol) and stirred at room temperature for overnight.

The reaction mixture was partitioned between DCM and H_2O and separated. The aqueous layer was re-extracted with DCM (3 x 15 mL) and the combined organic fractions were washed with 1 N HCl (10 mL), and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a 100 mg, 47% yield of the title compound as crude oil which was used in the next step without further purification. Mol. Wt: 835.38; MS (ES+): *m/z* 857.95 [M+Na].

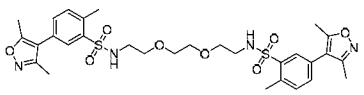
EXAMPLE 111:

[00398] This example describes the preparation of bivalent compounds.

Scheme 12.



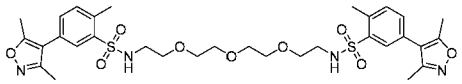
[00399] **Synthesis of *N,N'*-((ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide) (BRD-B-76):**



[00400] A solution of 5-(3, 5-dimethylisoxazol-4-yl)-2-methylbenzene-1-sulfonyl chloride (200 mg, 0.70 mmol) and 2,2'-(ethane-1,2-diylbis(oxy))diethanamine (51.9 mg, 0.35 mmol) in pyridine (10 mL) was stirred at room temperature for 3 hr. The solvent was concentrated under reduced pressure and water (50 mL) was added and the aqueous was extracted with ethyl acetate (2 x 50 mL). The combined organic extracts were washed with dil HCl solution (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* resulting crude product which was purified by column chromatography eluting with 5-10% methanol in DCM to afford 80 mg, 17% yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (t, J = 5.8 Hz, 1H), 7.72-7.65 (m, 1H), 7.53-7.47 (m, 4H), 3.40-3.29 (m, 10H), 2.99-2.94 (m 2H), 2.59 (s, 6H), 2.39 (s, 6H), 2.21 (s, 6H). Mol. Wt: 646.77; MS (ES+): *m/z* 647.20 [MH^+], HPLC purity: 94.79 % (Max plot).

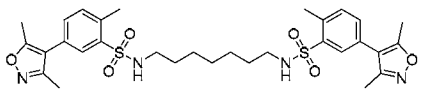
[00401] Following a general procedure, all below compounds have been synthesized and characterized.

[00402] Synthesis of *N,N'*-(((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide) (BRD-B-77):



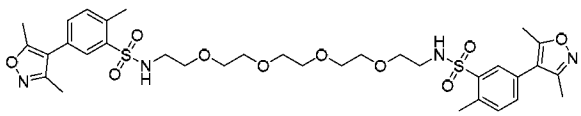
[00403] A solution of 5-(3, 5-dimethylisoxazol-4-yl)-2-methylbenzene-1-sulfonyl chloride (200 mg, 0.70 mmol) and 2,2'-((oxybis(ethane-2,1-diyl))bis(oxy))diethanamine (67.4 mg, 0.35 mmol) in pyridine (10 mL) was stirred at room temperature for 2 h. After similar work up procedure as above resulted in a crude product which was purified by column chromatography eluting with 5-10% methanol in DCM to afford 50 mg, 10.3 % yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (t, J = 5.8 Hz, 1H), 7.76 – 7.68 (m, 1H), 7.57 – 7.45 (m, 4H), 3.43 – 3.31 (m, 12H), 2.99 (q, J = 5.8 Hz, 4H), 2.60 (s, 6H), 2.40 (s, 6H), 2.22 (s, 6H). Mol. Wt: 690.83; MS (ES+): *m/z* 713.25 [M+Na], HPLC purity: 95.59 % (Max plot).

[00404] Synthesis of *N,N'*-(heptane-1,7-diyl)bis(5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide) (BRD-B-75):



[00405] A solution of 5-(3, 5-dimethylisoxazol-4-yl)-2-methylbenzene-1-sulfonyl chloride (200 mg, 0.70 mmol) in pyridine (10 mL) was charged with heptane-1,7-diamine (45.6 mg, 0.35 mmol) and stirred at rt for 3h. After similar work up procedure as in **BRD-B-76** above resulted in a product which was purified by column chromatography eluting with 5-10% methanol in DCM to afford 15 mg ,3.40% yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 1.9 Hz, 2H), 7.44 – 7.32 (m, 4H), 3.03-2.93 (m, 4H), 2.68 (s, 6H), 2.42 (s, 6H), 2.28 (s, 6H), 1.49-1.43 (m, 4H), 1.29-1.23 (m, 6H). Mol. Wt: 628.80; MS (ES+): *m/z* 628.95 [MH^+], HPLC purity: 98.49 % (Max plot).

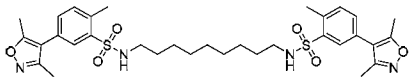
[00406] Synthesis of *N, N'*-(3, 6, 9, 12-tetraoxatetradecane-1, 14-diyl) bis (5-(3, 5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide) (BRD-B-78):



[00407] A solution of 5-(3, 5-dimethylisoxazol-4-yl)-2-methylbenzene-1-sulfonyl chloride (200 mg, 0.70 mmol) in pyridine (10 mL) was charged with 3,6,9,12-

tetraoxatetradecane-1,14-diamine (82.8 mg, 0.35 mmol) and stirred at rt for 6 h. After similar work up procedure as in **BRD-B-76** resulted in crude product which was purified by preparative HPLC to afford 20 mg, 3.88% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 1.9 Hz, 2H), 7.42 – 7.29 (m, 4H), 6.00 (s, 2H), 3.68 – 3.49 (m, 16H), 3.15 (t, J = 5.1 Hz, 4H), 2.68 (s, 6H), 2.41 (s, 6H), 2.28 (s, 6H). Mol. Wt: 734.88; MS (ES+): *m/z* 735.80 [MH^+], HPLC purity: 99.81 % (Max plot).

[00408] Synthesis of *N, N'*-(nonane-1, 9-diyl) bis (5-(3, 5-dimethylisoxazol-4-yl)-2-methylbenzenesulfonamide) (BRD-B-83):



[00409] A solution of 5-(3,5-dimethylisoxazol-4-yl)-2-methylbenzene-1-sulfonyl chloride (200 mg, 0.70 mmol) in pyridine (10 mL) and nonane-1,9-diamine (55.4 mg, 0.35 mmol) at rt for 1 h. After a similar work up procedure to **BRD-B-76** resulted in a crude product which was purified by column chromatography on silica gel eluting with 5-10% methanol in DCM to afford 15 mg, 3.26 % yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76 – 7.68 (m, 3H), 7.57 – 7.45 (m, 3H), 2.79 (q, J = 6.6 Hz, 4H), 2.60 (s, 6H), 2.39 (s, 6H), 2.21 (s, 6H), 1.35-1.26 (m, 4H), 1.10-1.05 (m, 10H). Mol. Wt: 656.86; MS (ES+): *m/z* 657.00 [MH^+], HPLC purity: 98.87 % (Max plot).

Intermediate Synthesis:

[00410] Intermediates A and B shown in Scheme 12 were prepared as described in *J. Med. Chem*, 2012, vol 55 pg 587-596.

EXAMPLE 112:

[00411] Monomers were synthesized according to the procedures described below.

[00412] List of abbreviations:

HPLC : High performance liquid chromatography

LCMS : Liquid chromatography mass spectrometry

Mm : millimeter

mm : micron

ml : milliliter

Min : minute

mM : milli molar

[00413] Preparative purification of the compounds was performed on Shimadzu preparative HPLC system composed of the following: CBM-20A system controller, LC-8A binary gradient pump, SPD-M20A photodiode array detector, FRC-10A fraction collector, YMC ODS A 500X30mmX10μm preparative column using 0.05% (v/v) Trifluoroacetic acid in HPLC grade water (A) and 0.05% (v/v) Trifluoroacetic acid in HPLC grade acetonitrile (B) at a flow rate of 30.0ml/min and a run time of 40mins. For basic medium purification, the same instrument was utilized with YMC Triart C18, 500X30mmX10μm preparative column using 10mM Ammonium formate and 0.1 %(v/v) liquid ammonia in HPLC grade water (A) and HPLC grade acetonitrile adding 5% (v/v) of mobile phase (A) and 0.1% (v/v) liquid ammonia (B). For both the methods, linear gradient profiles were used depending upon the chromatographic retention and separation of different compounds.

[00414] LCMS data was collected on Shimadzu LCMS system equipped with CBM-20A system controller, LC-20AD binary gradient pump, SPD-M20A photodiode array detector, SIL-20AC autosampler, CTO-20AC column oven, LCMS-2010EV single quadrapole mass spectrometer, YMC ODS A 50X4.6mmX3.0μm column using 0.05% (v/v) Trifluoroacetic acid in HPLC grade water (A) and 0.05% (v/v) Trifluoroacetic acid in HPLC grade acetonitrile (B) at a flow rate of 1.2ml/min and a run time of 5.0mins. The gradient profiles are 20% B to 100% B in 3.0minute, Hold For 0.5min, at 3.51min 20% B Hold till 5.0 min.

[00415] All Shimadzu LCMS-2010EV instruments utilized electrospray ionization in positive (ES+) or negative (ES-) ionization mode. The Shimadzu LCMS-2010EV instruments can also be utilized with Atmospheric pressure chemical ionization in positive (AP+) or negative (AP-) ionization mode.

[00416] HPLC data was collected on Shimadzu HPLC system equipped with LC-2010 CHT module, SPD-M20A photodiode array detector, YMC ODS A 150X4.6mmX5.0μm column using 0.05% (v/v) Trifluoroacetic acid HPLC grade in water (A) and 0.05% (v/v) Trifluoroacetic acid in HPLC grade acetonitrile (B) at a flow rate of 1.4ml/min and a run time of 15.0mins. The gradient profiles are 5% B to 95% B in 8.0min, hold till 9.5minute, 5% at 11.0min, and hold till 15.0mins. For basic medium HPLC, the same instrument was utilized with YMC Triart C18, 150X4.6mmX5.0μm column using 10mM Ammonium formate and 0.1 %(v/v) liquid ammonia in HPLC grade water (A) and HPLC grade acetonitrile adding 5% (v/v) of mobile phase (A) and 0.1% (v/v) liquid ammonia (B) at a flow rate of 1.0ml/min and a run time of 15.0mins. The gradient profile for basic medium method was 15% B to 95% B in 8.0min, hold till 9.5minute, 15% at 13.0min, and hold till 15.0mins.

EXAMPLE 113:

[00417] This example demonstrates binding properties of disclosed compounds.

[00418] ***Differential Scanning Fluorimetry (DSF).*** DSF measurements were performed on 1 μM concentrations of either individual or tandem bromodomain containing proteins in 20 uL volumes of a 50 mM HEPES, 150 mM NCl pH 7.5 buffer containing a 1000-fold dilution of SYPRO Orange dye. Test compounds were added at 0.5, 1 or 2 μM final concentrations and the change in fluorescence was measured on an ABI Fast 7500 real time PCR instrument as the temperature was increased from 4°C to 94°C at a rate of 0.5 °C per minute. The resulting melting curves were analyzed by calculating the first derivative to estimate the melting temperature. The increase in melting temperature caused by a test compound compared to the DMSO treated control sample (Δ Tm) is correlated to the binding affinity with higher affinity compounds resulting in a greater increase in the melting temperature.

DSF Results:

Group A > Group B > Group C in potency:

Temperature Shift (Δ Tm) range	Group	Examples		
		BRD2 tandem	BRD3 tandem	BRD4 tandem
6 – 9 °C	A	BRD-B-13, BRD-B-20, and BRD-B-15	BRD-B-21, BRD-B-22, and BRD-B-04	BRD-B-15, BRD-B-20
3 – 6 °C	B	BRD-B-19, BRD-B-18, BRD-B-17, BRD-B-04, BRD-B-10, BRD-B-22, BRD-B-23, BRD-B-12, BRD-B-21, BRD-B-02, BRD-B-05, and BRD-B-14	BRD-B-08, BRD-B-09, BRD-B-02, BRD-B-16, BRD-B-18, BRD-B-19, BRD-B-15, BRD-B-17, BRD-B-12, BRD-B-05, BRD-B-20, BRD-B-23, BRD-B-13, and BRD-B-14	BRD4: BRD-B-16, BRD-B-13, BRD-B-18, BRD-B-22, BRD-B-17, BRD-B-23, BRD-B-14
0.5 - 3 °C	C	BRD-B-01, BRD-B-03, BRD-B-07, BRD-B-06, BRD-B-11, BRD-B-09, BRD-B-08, and BRD-B-16	BRD-B-01, BRD-B-07, BRD-B-06, BRD-B-10, and BRD-B-11	BRD-B-02, BRD-B-09, BRD-B-11, BRD-B-07, BRD-B-08, BRD-B-06, BRD-B-12, BRD-B-04, BRD-B-05, BRD-B-21, BRD-B-03, BRD-B-10, and BRD-B-19

[00419] ***Surface Plasmon Resonance (SPR) Assay.*** Off rates were determined using surface plasmon resonance measurements on a Bio-Rad ProteOn XPR 36 instrument. N-terminal His6-tagged BRD2 tandem protein was immobilized by capturing on a ProteOn HTG sensor chip and then cross coupled to the surface using standard amine reactive chemistry. Selected bivalent inhibitors were injected on to the chip surface at saturating concentrations for 5 minutes followed by buffer for 20 minutes. The resulting sensorgrams were analyzed using the ProteOn XPR software to determine off-rates. Off rates for selected bivalent inhibitors were >100X slower when binding to the BRD2 tandem protein compared to the monovalent pharmacophores or compared to the bivalents binding to monobromodomain containing protein constructs.

SPR Results:

Example	**kd (1/s)**
BRD-B-02	1.1E-04
BRD-B-03	1.1E-04
BRD-B-14	7.5E-05
BRD-B-15	8.3E-05
BRD-B-02	1.1E-04

EXAMPLE 114:

[00420] This example demonstrates *in vitro* properties of disclosed compounds.

[00421] ***Inhibition of MV4-11 cell proliferation.*** MV4-11 cells (5000 cells in 50 µl volumes) in growth medium containing 10% FBS and 1% Pen/Strep were plated and grown overnight in 96 well plates and treated the next day with 3-fold dilutions of test compounds or with DMSO vehicle. After 72 hours of growth, 30 ul of Cell-Titer Glo reagent (Promega) was added to the wells and the plates incubated for 30 minutes. Luminescence was measured on a Spectramax M5 plate reader and GI_{50} values were calculated for each test compound.

MV4-11 Cell Proliferation Results:

Group A > Group B > Group C in potency:

GI_{50} range	Group	Examples
0.1 nM – 30 nM	A	BRD-B-02, BRD-B-04, BRD-B-05, BRD-B-12, BRD-B-13, BRD-B-14, BRD-B-15, BRD-B-18, BRD-B-19, BRD-B-20, BRD-B-22, BRD-B-23

GI_{50} range	Group	Examples
30 nM – 100 nM	B	BRD-B-03, BRD-B-16, BRD-B-17
100 nM – 30 μM	C	BRD-B-01, BRD-B-06, BRD-B-07, BRD-B-08, BRD-B-09, BRD-B-10, BRD-B-11

[00422] ***Inhibition of Myc expression.*** MV4-11 cells ($5x10^5$ cells in 500 μl volumes in growth medium containing 10% FBS and 1% Pen/Strep were plated and grown overnight in 24 well plates and treated the next day with 10-fold dilutions of test compounds or with DMSO vehicle. After 4 hours of treatment the cells were harvested by centrifugation and the cell pellet was frozen for storage. Cell pellets were re-suspended and RNA was extracted using a (RNeasy Kit Qiagen) following the manufacturer's protocol. Myc mRNA was quantified using the one-step RNA to CT Kit (Life Technologies) and normalized to GAPDH mRNA. The fold change in expression was compared to samples treated with DMSO vehicle and EC_{50} values were determined for each test compound.

Myc Inhibition Results:

Group A > Group B > Group C in potency:

EC_{50} range	Group	Examples
0.1 nM – 30 nM	A	BRD-B-04; BRD-B-14, BRD-B-20
30 nM – 100 nM	B	BRD-B-05, BRD-B-12, BRD-B-16, BRD-B-18, BRD-B-22, BRD-B-23
100 nM – 30 μM	C	BRD-B-02, BRD-B-06, BRD-B-07, BRD-B-08, BRD-B-09, BRD-B-11, BRD-B-13, BRD-B-15, BRD-B-17, BRD-B-19, BRD-B-21, BRD-B-76

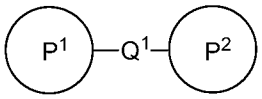
EQUIVALENTS

[00423] While specific embodiments have been discussed, the above specification is illustrative and not restrictive. Many variations will become apparent to those skilled in the art upon review of this specification. The full scope of the embodiments should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

[00424] Unless otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in this specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained.

[00425] What is claimed is:

1. A bivalent compound of the formula:



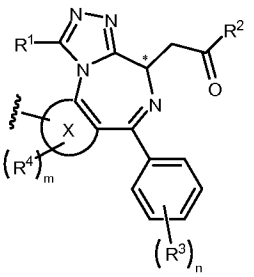
or a pharmaceutically acceptable salt, stereoisomer, metabolite, or hydrate thereof;

wherein:

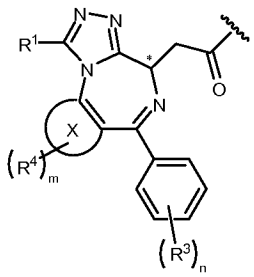
Q^1 is a connecting moiety covalently bound to P^1 and P^2, wherein Q^1 is selected from the group consisting of aliphatic, heteroaliphatic, phenyl, naphthyl, heteroaryl, or a covalently bonded combination thereof;

wherein:

P^1 and P^2 are independently selected from the group consisting of:



I) Formula H and



Formula I

wherein:

X is phenyl, naphthyl, or heteroaryl;

R^1 is C_{1-3}alkyl, C_{1-3}alkoxy or -S- C_{1-3}alkyl;

R^2 is $-NR^{2a}R^{2a'}$ or $-OR^{2b}$; wherein one of R^{2a} or $R^{2a'}$ is hydrogen, and R^{2b} or the other of R^{2a} or $R^{2a'}$ is selected from the group consisting of C_{1-6}alkyl, haloC_{1-6}alkyl, $R^{2c}R^{2c'}N$-C_{2-6}alkyl, carbocyclyl, carbocyclyloC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, wherein any of the carbocyclyl or heterocyclyl groups are optionally substituted by one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, carbonyl, -CO-carbocyclyl, azido, amino, hydroxyl, nitro and cyano, wherein the –CO-carbocyclyl group may be optionally substituted by one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, azido, nitro and cyano; or

two adjacent groups on any of the carbocyclyl or heterocyclyl groups together with the interconnecting atoms form a 5- or 6-membered ring which ring may contain 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; or R^{2a} and $R^{2a'}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered ring which

optionally contains 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; wherein the 4-, 5-, 6 or 7-membered ring is optionally substituted by C_{1-6}alkyl, hydroxyl or amino;

R^{2c} and $R^{2c'}$ are independently hydrogen or C_{1-6}alkyl;

each R^3 is independently selected from the group consisting of hydrogen, hydroxyl, thiol, sulfinyl, amino, halo, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, nitro, cyano, CF_3, -OCF_3, -$COOR^5$, -C_{1-4}alkylamino , phenoxy, benzoxy, and C_{1-4}alkylOH;

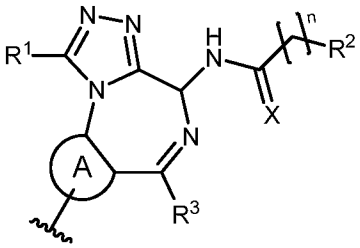
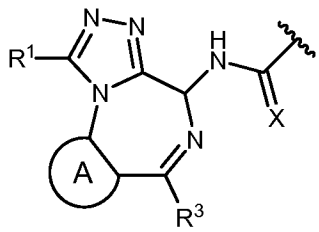
each R^4 is hydroxyl, halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -$COOR^5$; -$OS(O)_2C_{1-4}$alkyl, phenyl, naphthyl, phenyloxy, benzyloxy or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, amino, nitro;

R^5 is C_{1-3}alkyl;

* denotes a chiral center;

m is an integer 1 to 3; and

n is an integer 1 to 5;

II)  Formula F and  Formula G

wherein:

X is O or S;

R^1 is C_{1-6}alkyl, haloC_{1-6}alkyl, -$(CH_2)_nOR^{1a}$, or -$(CH_2)_mNR^{1b}R^{1c}$; wherein R^{1a} is hydrogen, C_{1-6}alkyl or haloC_{1-6}alkyl; R^{1b} and R^{1c}, which may be the same or different, are hydrogen, C_{1-6}alkyl or haloC_{1-6}alkyl; and m and n, which may be the same or different, are 1, 2 or 3;

R^2 is R^{2a}, -OR^{2b}, or -$NR^{2c}R^{2d}$; wherein R^{2a} and R^{2b} are carbocyclyl, carbocyclylC_{1-4}alkyl, heterocyclyl or heterocyclylC_{1-4}alkyl, or R^{2a} is carbocyclylethenyl or heterocyclylethenyl, wherein any of the carbocyclyl or heterocyclyl groups defined for R^{2a} or R^{2b} are optionally substituted by one or more groups independently selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, nitro, cyano,

dimethylamino, benzoyl and azido; or two adjacent groups on any of the carbocyclyl or heterocyclyl groups defined for R^{2a} or R^{2b} together with the interconnecting atoms form a 5 or 6-membered ring which ring may contain 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; or

R^{2a} and R^{2b} are C_{1-6}alkyl or haloC_{1-6}alkyl; and R^{2c} and R^{2d}, which may be the same or different, are carbocyclyl, carbocyclylC_{1-4}alkyl, heterocyclyl or heterocyclylC_{1-4}alkyl, wherein any of the carbocyclyl or heterocyclyl groups defined for R^{2c} or R^{2d} are optionally substituted by one or more groups independently selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, nitro, cyano and -CO_2C_{1-4}alkyl; or two adjacent groups on any of the carbocyclyl or heterocyclyl groups defined for R^{2c} and R^{2d} together with the interconnecting atoms form a 5 or 6-membered ring which ring may contain 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; or

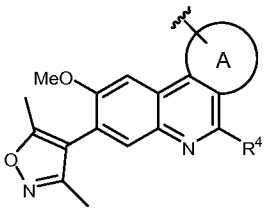
R^{2c} and R^{2d} are independently hydrogen, C_{1-6}alkyl or haloC_{1-6}alkyl;

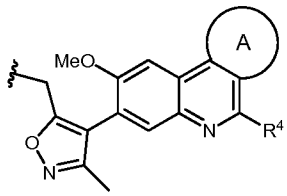
R^3 is C_{1-6}alkyl, phenyl, naphthyl, heteroaryl carbocyclyl or heterocyclyl, optionally substituted independently by one or more substitutents selected from the group consisting of halogen, –SR, -S(O)R', -NHR', -OR', C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, nitro and cyano;

R' is H or C_{1-6}alkyl;

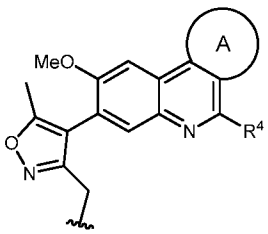
A is a benzene or aromatic heterocyclic ring, each of which is optionally substituted; and

n is 0, 1 or 2;

III) 

Formula A, 

Formula A1, or

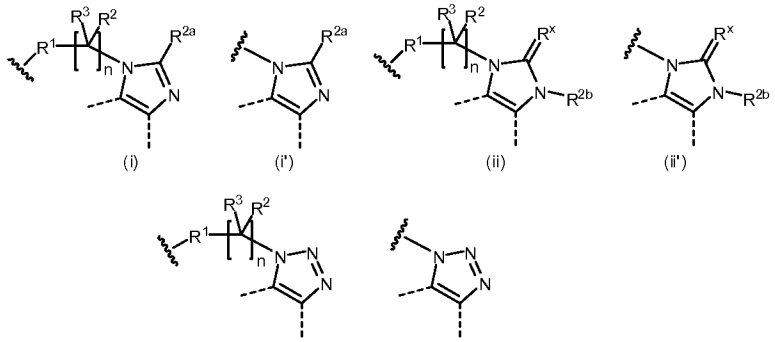


Formula A2,

wherein:

R^4 is hydrogen, cyano or C_{1-6} alkyl;

A is selected from the group consisting of:



;

R^x is O, NR^{2a}, or S;

R^1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, a 5 or 6 membered heterocyclyl, an aromatic group or a heteroaromatic group, wherein the aromatic group or the heteroaromatic group is optionally substituted by one to three groups selected from the group consisting of halogen, hydroxy, cyano, nitro, C_{1-6}alkyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, haloC_{1-4}alkoxy, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy C_{1-4}alkyl, C_{1-4}alkoxycarbonyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfonyloxy, C_{1-4}alkylsulfonyl C_{1-4}alkyl and C_{1-4}alkylsulfonamido;

R^2 is hydrogen or C_{1-6}alkyl;

R^{2a} is selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}haloalkyl, $(CH_2)_m$cyano, $(CH_2)_m$OH, $(CH_2)_mC_{1-6}$alkoxy, $(CH_2)_mC_{1-6}$haloalkoxy, $(CH_2)_mC_{1-6}$haloalkyl, $(CH_2)_mC(O)NR^aR^b$, $(CH_2)_mNR^aR^b$ and $(CH_2)_m$ $C(O)CH_3$, $(CHR^6)_p$phenyl optionally substituted by C_{1-6}alkyl, C_{1-6}alkoxy, cyano, halo C_{1-4}alkoxy, haloC_{1-4}alkyl, $(CHR^6)_p$heteroaromatic, $(CHR^6)_p$heterocyclyl; wherein R^a is H, C_{1-6}alkyl, or heterocyclyl; wherein R^b is H or C_{1-6}alkyl, or

R^a and R^b together with the N to which they are attached form a 5 or 6 membered heterocyclyl;

R^{2b} is H, C_{1-6}alkyl, $(CH_2)_2C_{1-6}$alkoxy, $(CH_2)_2$cyano, $(CH_2)_m$phenyl or $(CH_2)_2$heterocyclyl;

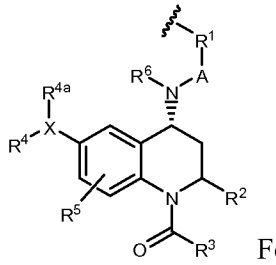
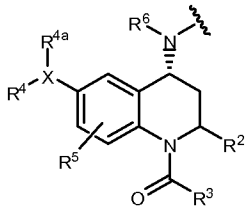
R^3 is hydrogen;

R^6 is hydrogen or C_{1-6}alkyl;

m is 0, 1, 2 or 3;

n is 0, 1 or 2; and

p is 0, 1 or 2;

IV)  Formula B and  Formula C

wherein:

A is a bond, C_{1-4}alkyl or –C(O)-;

X is:

i) a 6 to 10 membered aromatic group, or

ii) a 5 to 10 membered heteroaromatic comprising 1, 2 or 3 heteroatoms selected from the group consisting of O, N and S;

R^1 is:

i) phenyl optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, -SO_2C_{1-6}alkyl and -COR^7,

ii) a 5 to 10 membered heteroaromatic comprising 1, 2 or 3 heteroatoms selected from the group consisting of O, N and S optionally substituted by 1 or 2 substituents independently selected from the group consisting of halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy and -COR^7, or

iii) C_{1-6}alkyl, C_{0-6}alkylcyano, C_{0-6}alkylC_{1-6}alkoxy, C_{0-2}alkyl$C(O)R^7$ or cyclohexyl;

R^2 is C_{1-6}alkyl;

R^3 is C_{1-6}alkyl;

R^4 is:

i) H, halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy, C_{0-6}hydroxyalkyl, -SO_2C_{1-6}alkyl, -$C(O)NR^8R^9$, -$C(O)R^{10}$, -C_{0-6}alkyl-$NR^{11}R^{12}$, or

ii) -O_mC_{1-6}alkyl substituted by a 5 or 6 membered heterocyclyl or heteroaromatic each comprising 1, 2, 3 or 4 heteroatoms independently selected from the group consisting of N, O and S and wherein said hetercyclyl or heteroaromatic is optionally substituted by 1, 2 or 3 groups independently selected from the group consisting of halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl and C_{1-6}alkoxy, wherein m is 0, 1 or 2, wherein when the heterocyclyl or heteroatomic is linked through a heteroatom and m is 1, then

the heteroatom and O are not directly linked if the resultant arrangement would be unstable;

R^{4a} is H, halogen, C_{1-6}alkyl, C_{1-6}haloalkyl, C_{1-6}alkoxy or C_{0-6}hydroxyalkyl;

R^5 is H, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

R^6 is H, C_{1-6}alkyl, C_{0-6}alkylcyano, C_{0-6}alkylC_{1-6}alkoxy or C_{0-2}alkylC(O)R^7;

R^7 is hydroxyl, C_{1-6}alkoxy, -NH_2, -NHC_{1-6}alkyl or $N(C_{1-6}alkyl)_2$;

R^8 and R^9 independently are:

i) H, C_{1-6}alkyl, C_{0-6}alkylphenyl, C_{0-6}alkylheteroaromatic, C_{3-6}cycloalkyl, or

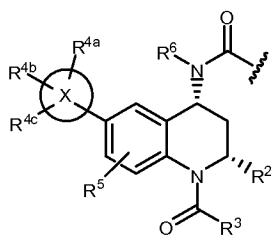
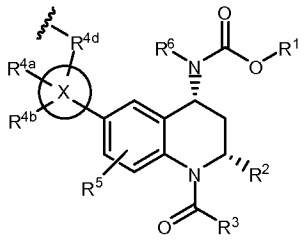
ii) R^8 and R^9 together with the N to which they are attached form a 5 or 6 membered heterocyclyl or heteroaromatic wherein said heterocyclyl or heteroaromatic may comprise 1, 2 or 3 further heteroatoms independently selected from the group consisting of O, N and S;

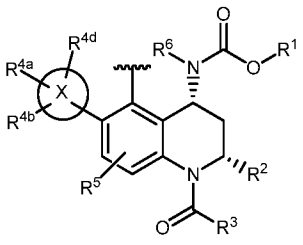
R^{10} is hydroxyl, C_{1-6}alkoxy or a 5 or 6 membered heterocyclyl or heteroaromatic comprising 1, 2, 3 or 4 heteroatoms selected from the group consisting of O, N and S;

$R^{11}$and R^{12} independently are:

i) H, C_{1-6}alkyl; or

ii) R^{11} and R^{12} together with the N to which they are attached form a 5 or 6 membered heterocyclyl or heteroaromatic wherein said heterocyclyl or heteroaromatic may comprise 1, 2 or 3 further heteroatoms independently selected from the group consisting of O, N and S;

V)  Formula D,  Formula E, and



Formula E1

wherein:

R^1 is C_{1-6}alkyl, C_{3-7}cycloalkyl or benzyl;

R^2 is C_{1-4}alkyl;

R^3 is C_{1-4}alkyl;

X is phenyl, naphthyl, or heteroaryl;

R^{4a} is hydrogen, C_{1-4}alkyl or is a group L-Y in which L is a single bond or a C_{1-6}alkylene group and Y is OH, OMe, CO_2H, CO_2C_{1-6}alkyl, CN, or NR^7R^8;

R^7 and R^8 are independently hydrogen, a heterocyclyl ring, C_{1-6}alkyl optionally substituted by hydroxyl, or a heterocyclyl ring; or

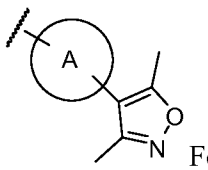
R^7 and R^8 combine together to form a heterocyclyl ring optionally substituted by C_{1-6}alkyl, CO_2C_{1-6}alkyl, NH_2, or oxo;

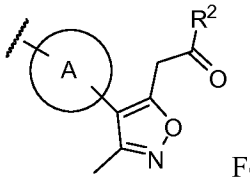
R^{4b} and R^{4c} are independently hydrogen, halogen, C_{1-6}alkyl, or C_{1-6}alkoxy;

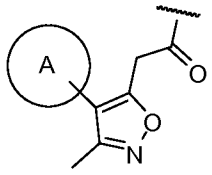
R^{4d} is C_{1-4}alkyl or is a group -L-Y- in which L is a single bond or a C_{1-6}alkylene group and Y is -O-, $-OCH_2-$, $-CO_2-$, $-CO_2C_{1-6}$alkyl-, or $-N(R^7)-$;

R^5 is hydrogen, halogen, C_{1-6}alkyl, or C_{1-6}alkoxy;

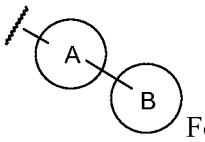
R^6 is hydrogen or C_{1-4}alkyl;

VI) 

Formula J, 

Formula K, 

Formula L,

and 

Formula M

wherein:

A is independently, for each occurrence, a 4-8 membered cycloalkyl, heterocyclic, phenyl, naphthyl, or heteroaryl moiety, each optionally substituted with one, two, three or more R^1 substituents;

R^1 is selected from the group consisting of hydroxy, halogen, oxo, amino, imino, thiol, sulfanylidene, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, -O-C_{1-6}alkyl, –NH-C_{1-6}alkyl, $-CO_2H$, -C(O)C_{1-6}alkyl, –C(O)O-C_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, -C_{1-6}alkylC(O)R^2, -O-C(O)R^2, -NH-C(O)R^2, -O-C_{1-6}alkyl-C(O)R^2, -NHC_{1-6}alkyl-C(O)R^2, acylaminoC_{1-6}alkyl, nitro, cyano, CF_3, $-OCF_3$, $-OS(O)_2C_{1-6}$alkyl, phenyl, naphthyl, phenyloxy, -NH-phenyl, benzyloxy, and phenylmethoxy halogen; wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, amino,

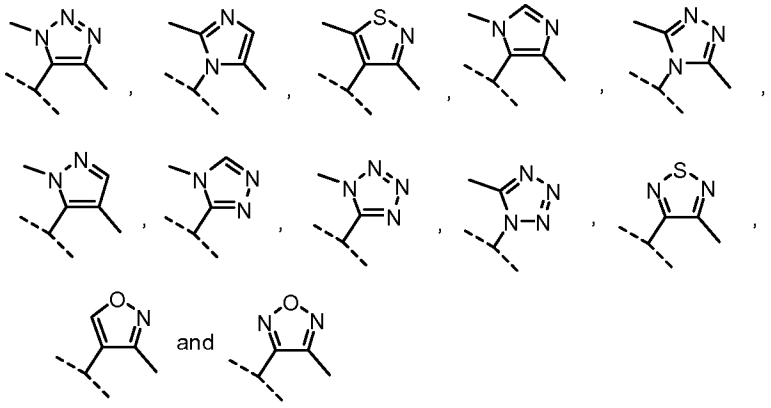
nitro, phenyl and C_{1-6}alkyl; or two R^1 substitutents may be taken together with the atoms to which they are attached to form a fused aliphatic or heterocyclic bicyclic ring system;

R^2 is $-NR^{2a}R^{2a'}$ or $-OR^{2b}$; wherein one of R^{2a} or $R^{2a'}$ is hydrogen, and R^{2b} or the other of R^{2a} or $R^{2a'}$ is selected from the group consisting of C_{1-6}alkyl, haloC_{1-6}alkyl, $R^{2c}R^{2c'}N$-C_{2-6}alkyl, carbocyclyl, carbocyclyloC_{1-4}alkyl, heterocyclyl and heterocyclylC_{1-4}alkyl, wherein any of the carbocyclyl or heterocyclyl groups are optionally substituted by one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, carbonyl, -CO-carbocyclyl, azido, amino, hydroxyl, nitro and cyano, wherein the –CO-carbocyclyl group may be optionally substituted by one or more substituents selected from the group consisting of halogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, azido, nitro and cyano; or

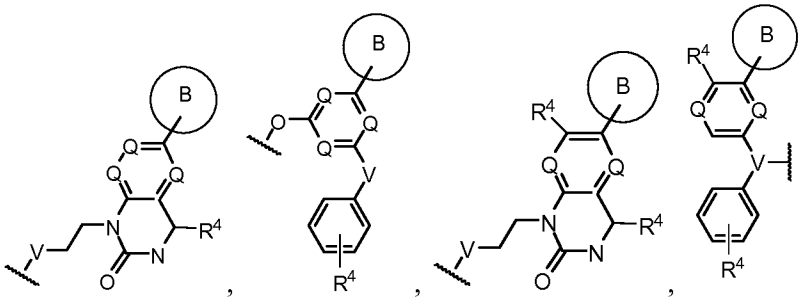
two adjacent groups on any of the carbocyclyl or heterocyclyl groups together with the interconnecting atoms form a 5- or 6-membered ring which ring may contain 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; or R^{2a} and $R^{2a'}$ together with the N atom to which they are attached form a 4-, 5-, 6- or 7-membered ring which optionally contains 1 or 2 heteroatoms independently selected from the group consisting of O, S and N; wherein the 4-, 5-, 6 or 7-membered ring is optionally substituted by C_{1-6}alkyl, hydroxyl or amino;

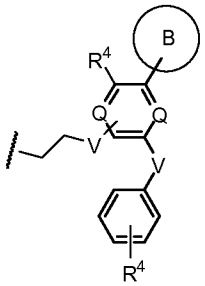
R^{2c} and $R^{2c'}$ are independently hydrogen or C_{1-6}alkyl;

B is selected from the group consisting of:



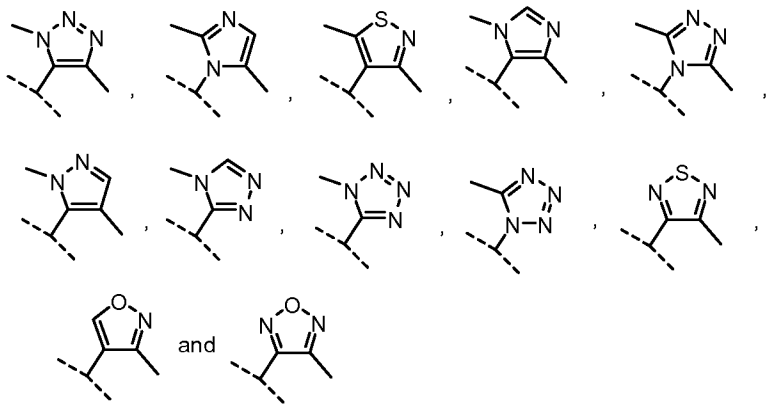
;

VII)  , and



wherein:

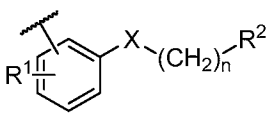
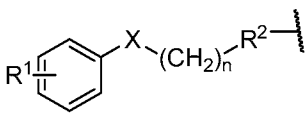
B is selected from the group consisting of:



Q is independently, for each occurrence, N or CH;

V is independently, for each occurrence, O, S, NR^4, or a bond; and

R^4 is independently selected from the group consisting of hydrogen, hydroxyl, halo, amino, thiol, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, -NH-C_{1-6}alkyl, -S-C_{1-6}alkyl, haloC_{1-6}alkoxy, nitro, cyano, $-CF_3$, $-OCF_3$, -C(O)O-C_{1-6}alkyl, -C_{1-4}alkylamino , phenoxy, benzoxy, and C_{1-4}alkylOH;

VIII)  Formula N or  Formula O,

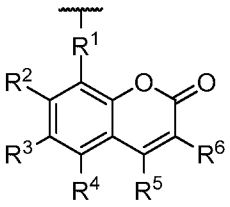
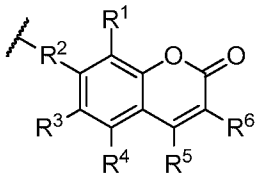
wherein:

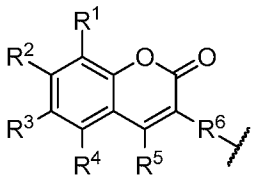
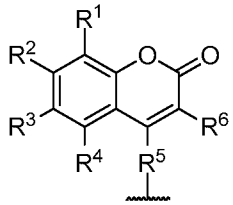
R^1 is selected from the group consisting of hydrogen, lower alkyl, phenyl, naphthyl, aralkyl, heteroalkyl, SO_2, NH_2, NO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, CN, and halogen;

R^2 is selected from the group consisting of hydrogen, lower alkyl, aralkyl, heteroalkyl, phenyl, naphthyl, SO_2, NH_2, NH_3^+, NO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, halogen, carboxy, and alkoxy;

X is selected from the group consisting of lower alkyl, SO_2, NH, NO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, carboxy, and alkoxy; and

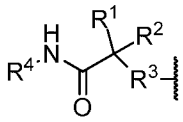
n is an integer from 0 to 10;

IX)  Formula P,  Formula Q,

 Formula R, and  Formula S

wherein:

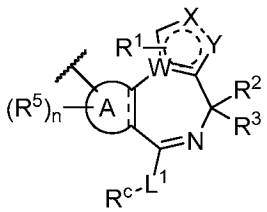
R^1, R^2, R^3, R^4, R^5, and R^6 are independently selected from the group consisting of hydrogen, lower alkyl, phenyl, naphthyl, aralkyl, heteroaryl, SO_2, NH_2, NH_3^+, NO^2, SO^2, CH^3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OCH_2CH_3, $OCH(CH_3)_2$, OCH_2COOH, $OCHCH_3COOH$, OCH_2COCH_3, OCH_2CONH_2, $OCOCH(CH_3)_2$, OCH_2CH_2OH, $OCH_2CH_2CH_3$, $O(CH_2)_3CH_3$, $OCHCH_3COOCH_3$, $OCH_2CON(CH_3)_2$, $NH(CH_2)_3N(CH_3)_2$, $NH(CH_2)_2N(CH_3)_2$, $NH(CH_2)_2OH$, $NH(CH_2)_3CH_3$, $NHCH_3$, SH, halogen, carboxy, and alkoxy;

X)  Formula T,

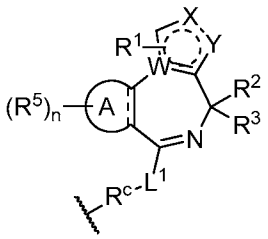
wherein:

R^1, R^2, and R^3 are independently selected from the group consisting of hydrogen, lower alkyl, phenyl, naphthyl, aralkyl, heteroaryl, SO_2, NH_2, NH_3^+, NO_2, SO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, SH, halogen, carboxy, and alkoxy; R^4 is selected from the group

consisting of lower alkyl, phenyl, naphthyl, SO_2, NH, NO_2, CH_3, CH_2CH_3, OCH_3, $OCOCH_3$, CH_2COCH_3, OH, carboxy, and alkoxy;



XI) Formula U and



Formula V,

or a pharmaceutically acceptable salt thereof,

wherein:

X is O or N;

Y is O or N; wherein at least one of X or Y is O;

W is C or N;

R^1 is H, alkyl, alkenyl, alkynyl, aralkyl, phenyl, naphthyl, heteroaryl, halo, CN, OR^A, NR^AR^B, $N(R^A)S(O)_qR^AR^B$, $N(R^A)C(O)R^B$, $N(R^A)C(O)NR^AR^B$, $N(R^A)C(O)OR^A$, $N(R^A)C(S)NR^AR^B$, $S(O)_qR^A$, $C(O)R^A$, $C(O)OR^A$, $OC(O)R^A$, or $C(O)NR^AR^B$;

each R^A is independently alkyl, alkenyl, or alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; phenyl; naphthyl, heteroaryl; heterocyclic; carbocyclic; or hydrogen;

each R^B is independently alkyl, alkenyl, or alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; phenyl; naphthyl; heteroaryl; heterocyclic; carbocyclic; or hydrogen; or

R^A and R^B, together with the atoms to which each is attached, can form a heterocycloalkyl or a heteroaryl; each of which is optionally substituted;

Ring A is cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl;

R^C is alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl, each optionally substituted with 1-5 independently selected R^4, and when L^1 is other than a covalent bond, R^C is additionally selected from H;

R^2 and R^3 are each independently H, halogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, heterocycloalkyl, -OR, -SR, -CN, -N(R')(R''), -C(O)R, -C(S)R, $-CO_2R$, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, $-C(O)CH_2C(O)R$, -C(S)N(R')(R''), -C(S)OR, -S(O)R, $-SO_2R$, $-SO_2N(R')(R'')$, -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R"), $-N(R')SO_2R$, $-N(R')SO_2N(R')(R'')$, -N(R')N(R')(R''), -

N(R')C(=N(R''))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R''))N(R')(R''), -OC(O)R, -OC(O)N(R')(R''), or $-(CH_2)_pR^x$; or

R_2 and R_3 together with the atoms to which each is attached, form an optionally substituted 3-7 membered saturated or unsaturated spiro-fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^x is independently halogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, heterocycloalkyl, -OR, -SR, -CN, -N(R')(R''), -C(O)R, -C(S)R, $-CO_2R$, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, $-C(O)CH_2C(O)R$, -C(S)N(R')(R''), -C(S)OR, -S(O)R, $-SO_2R$, $-SO_2N(R')(R'')$, -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), $-N(R')SO_2R$, $-N(R')SO_2N(R')(R'')$, -N(R')N(R')(R''), -N(R')C(=N(R''))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R''))N(R')(R''), -OC(O)R, -OC(O)N(R')(R'');

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by -NR'-, -N (R')C(O)-, -C(O)N(R')-, $-N(R')SO_2-$, $-SO_2N(R')-$ -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or $-SO_2-$;

each R is independently hydrogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, or heterocycloalkyl;

each R' is independently -R, -C(O)R, -C(S)R, $-CO_2R$, $-C(O)N(R)_2$, $-C(S)N(R)_2$, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, or two R groups on the same nitrogen are taken together with their intervening atoms to form an heteroaryl or heterocycloalkyl group; each R'' is independently -R, -C(O)R, -C(S)R, $-CO_2R$, $-C(O)N(R)_2$, $-C(S)N(R)_2$, -S(O)R, $-SO_2R$, $-SO_2N(R)_2$, or two R groups on the same nitrogen are taken together with their intervening atoms to form an heteroaryl or heterocycloalkyl group; or

R' and R'', together with the atoms to which each is attached, can form cycloalkyl, heterocycloalkyl, phenyl, naphthyl, or heteroaryl; each of which is optionally substituted;

each R^4 is independently alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, or heterocycloalkyl, halogen, -OR, -SR, -N(R')(R''), -CN, $-NO_2$, -C(O)R, -C(S)R, $-CO_2R$, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, $-C(O)CH_2C(O)R$, -C(S)N(R')(R''), -C(S)OR, -S(O)R, $-SO_2R$, $-SO_2N(R')(R'')$, -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), $-N(R')SO_2R$, $-N(R')SO_2N(R')(R'')$, -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R"), -C=NN(R')(R"), -C=NOR, -C(=N(R'))N(R')(R"), -OC(O)R, or -OC(O)N(R')(R'');

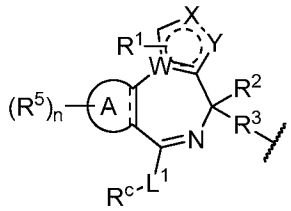
each R^5 is independently -R, halogen, -OR, -SR, -N(R')(R''), -CN, $-NO_2$, -C(O)R, -C(S)R, $-CO_2R$, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, $-C(O)CH_2C(O)R$, -C(S)N(R')(R''), -C(S)OR, -S(O)R, $-SO_2R$, $-SO_2N(R')(R'')$, -N(R')C(O)R, -N(R')C(O)N(R')(R''), -

N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, or -OC(O)N(R')(R'');

n is 0-5;

each q is independently 0, 1, or 2; and

p is 1-6;



XII) Formula W,

wherein:

X is O or N;

Y is O or N; wherein at least one of X or Y is O;

W is C or N;

R^1 is H, alkyl, alkenyl, alkynyl, aralkyl, phenyl, naphthyl, heteroaryl, halo, CN, OR^A, NR^AR^B, $N(R^A)S(O)_qR^AR^B$, $N(R^A)C(O)R^B$, $N(R^A)C(O)NR^AR^B$, $N(R^A)C(O)OR^A$, $N(R^A)C(S)NR^AR^B$, $S(O)_qR^A$, $C(O)R^A$, $C(O)OR^A$, $OC(O)R^A$, or $C(O)NR^AR^B$;

each R^A is independently optionally substituted alkyl, optionally substituted alkenyl or optionally substituted alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; phenyl; naphthyl; heteroaryl; heterocyclic; carbocyclic; or hydrogen;

each R^B is independently alkyl, alkenyl, or alkynyl, each containing 0, 1, 2, or 3 heteroatoms selected from O, S, or N; phenyl; naphthyl; heteroaryl; heterocyclic; carbocyclic; or hydrogen; or

R^A and R^B, together with the atoms to which each is attached, can form a heterocycloalkyl or a heteroaryl; each of which is optionally substituted;

Ring A is cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl;

R^C is alkyl, alkenyl, alkynyl, cycloalkyl, phenyl, naphthyl, heterocycloalkyl, or heteroaryl, each optionally substituted with 1-5 independently selected R^4, and when L^1 is other than a covalent bond, R^C is additionally selected from H;

R^2 is H, halogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, heterocycloalkyl, -OR, -SR, -CN, -N(R')(R''), -C(O)R, -C(S)R, -CO_2R, -

C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R"), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, -OC(O)N(R')(R''), or -$(CH_2)_pR^x$;

R^3 is a bond or optionally substituted alkyl; or

R_2 and R_3 together with the atoms to which each is attached, form an optionally substituted 3-7 membered saturated or unsaturated spiro-fused ring having 0-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R^x is independently halogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, heterocycloalkyl, -OR, -SR, -CN, -N(R')(R''), -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, -OC(O)N(R')(R'');

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by -NR'-, -N (R')C(O)-, -C(O)N(R')-, -N(R')SO_2-, -SO_2N(R')-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, or -SO_2-;

each R is independently hydrogen, alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, or heterocycloalkyl;

each R' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N$(R)_2$, -C(S)N$(R)_2$, -S(O)R, -SO_2R, -SO_2N$(R)_2$, or two R groups on the same nitrogen are taken together with their intervening atoms to form an heteroaryl or heterocycloalkyl group; each R'' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N$(R)_2$, -C(S)N$(R)_2$, -S(O)R, -SO_2R, -SO_2N$(R)_2$, or two R groups on the same nitrogen are taken together with their intervening atoms to form an optionally substituted heteroaryl or heterocycloalkyl group; or

R' and R'', together with the atoms to which each is attached, can form cycloalkyl, heterocycloalkyl, phenyl, naphthyl, or heteroaryl; each of which is optionally substituted;

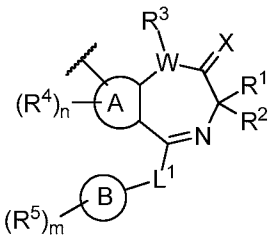
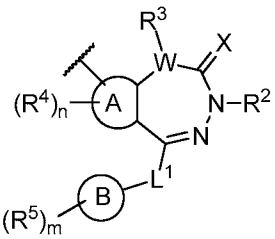
each R^4 is independently alkyl, alkenyl, alkynyl, phenyl, naphthyl, aralkyl, cycloalkyl, heteroaryl, or heterocycloalkyl, halogen, -OR, -SR, -N(R')(R''), -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R"), -C=NN(R')(R"), -C=NOR, -C(=N(R'))N(R')(R"), -OC(O)R, or -OC(O)N(R')(R'');

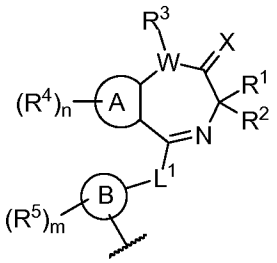
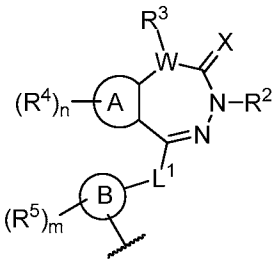
each R^5 is independently -R, halogen, -OR, -SR, -N(R')(R''), -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')(R''), -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')(R''), -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')(R''), -N(R')C(O)R, -N(R')C(O)N(R')(R''), -N(R')C(S)N(R')(R''), -N(R')SO_2R, -N(R')SO_2N(R')(R''), -N(R')N(R')(R''), -N(R')C(=N(R'))N(R')(R''), -C=NN(R')(R''), -C=NOR, -C(=N(R'))N(R')(R''), -OC(O)R, or -OC(O)N(R')(R'');

n is 0-5;

each q is independently 0, 1, or 2; and

p is 1-6;

XIII)  Formula X,  Formula XX,

 Formula Y, and  Formula YY,

wherein:

Ring A is benzo, or a 5-6 membered fused heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is a 3-7 membered saturated or partially unsaturated carbocyclic ring, phenyl, an 8-10 membered bicyclic saturated, partially unsaturated, phenyl or naphthyl ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by –NR'-, -N(R')C(O)-, -C(O)N(R'), -N(R')SO_2-, -SO_2N(R'), -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

R^1 is hydrogen, halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$, or -$(CH_2)_pR^x$;

p is 0-3;

R^x is halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$;

R^2 is hydrogen, halogen, -CN, -SR, or optionally substituted C_{1-6} aliphatic, or:

R^1 and R^2 are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 7-10 membered bicyclic saturated, partially unsaturated, phenyl or naphthyl ring, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R)$_2$, -C(S)N(R)$_2$, -S(O)R, -SO_2R, -SO_2N(R)$_2$, or two R' on the same nitrogen are taken together with their intervening atoms to form an optionally substituted group selected from a 4-7 membered monocyclic saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 7-12 membered bicyclic saturated, partially

unsaturated, or aromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

W is , or ;

R^3 is optionally substituted C_{1-6} aliphatic;

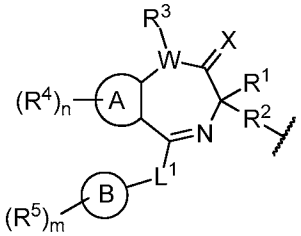
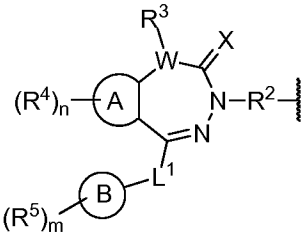
X is oxygen or sulfur, or:

R^3 and X are taken together with their intervening atoms to form an optionally substituted

5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of m and n is independently 0-4, as valency permits; and

each of R^4 and R^5 is independently -R, halogen, -OR, -SR, $-N(R')_2$, -CN, $-NO_2$, -C(O)R, -C(S)R, $-CO_2R$, $-C(O)N(R')_2$, -C(O)SR, -C(O)C(O)R, $-C(O)CH_2C(O)R$, $-C(S)N(R')_2$, -C(S)OR, -S(O)R, $-SO_2R$, $-SO_2N(R')_2$, $-N(R')C(O)R$, $-N(R')C(O)N(R')_2$, $-N(R')C(S)N(R')_2$, $-N(R')SO_2R$, $-N(R')SO_2N(R')_2$, $-N(R')N(R')_2$, $-N(R')C(=N(R'))N(R')_2$, -C=NN(R')$_2$, -C=NOR, $-C(=N(R'))N(R')_2$, -OC(O)R, or $-OC(O)N(R')_2$;

XIV)  Formula Z and  Formula ZZ,

wherein:

Ring A is benzo, or a 5-6 membered fused heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is a 3-7 membered saturated or partially unsaturated carbocyclic ring, phenyl, an 8-10 membered bicyclic saturated, partially unsaturated, phenyl or naphthyl ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by –NR'-, -N(R')C(O)-, -C(O)N(R'), -N(R')SO_2-, -SO_2N(R'), -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

R^1 is hydrogen, halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$, or -$(CH_2)_pR^x$;

p is 0-3;

R^x is halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$;

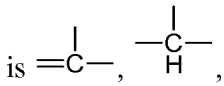
R^2 is a bond or optionally substituted C_{1-6} aliphatic, or:

R^1 and R^2 are taken together with their intervening atoms to form an optionally substituted 3-7 membered saturated or partially unsaturated spiro-fused ring having 0-2 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 7-10 membered bicyclic saturated, partially unsaturated, phenyl, or naphthyl ring, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R)$_2$, -C(S)N(R)$_2$, -S(O)R, -SO_2R, -SO_2N(R)$_2$, or two R' on the same nitrogen are taken together with their intervening atoms to form an optionally substituted group selected from a 4-7 membered monocyclic saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 7-12 membered bicyclic saturated, partially

unsaturated, or aromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

W is ;

R^3 is optionally substituted C_{1-6} aliphatic;

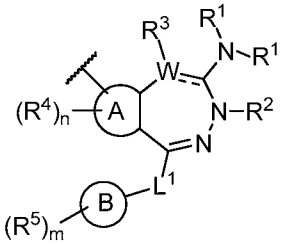
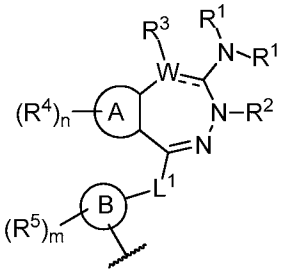
X is oxygen or sulfur, or:

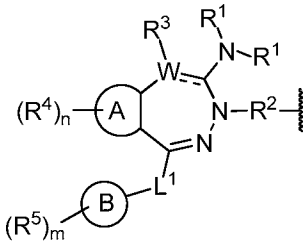
R^3 and X are taken together with their intervening atoms to form an optionally substituted

5-membered heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

each of m and n is independently 0-4, as valency permits; and

each of R^4 and R^5 is independently –R, halogen, -OR, -SR, -N(R')$_2$, -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, or -OC(O)N(R')$_2$;

XV)  Formula XXA,  Formula YYA, and

 Formula ZZA,

wherein:

Ring A is benzo, or a 5-6 membered fused heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, or sulfur;

Ring B is a 3-7 membered saturated or partially unsaturated carbocyclic ring, phenyl, an 8-10 membered bicyclic saturated, partially unsaturated, phenyl, or naphthyl ring, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms

independently selected from nitrogen, oxygen, and sulfur, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a covalent bond or an optionally substituted bivalent C_{1-6} hydrocarbon chain wherein one or two methylene units is optionally replaced by –NR'-, -N(R')C(O)-, -C(O)N(R'), -N(R')SO_2-, -SO_2N(R'), -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO- or -SO_2-;

R^1 is independently hydrogen, halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$, or -$(CH_2)_pR^x$;

p is 0-3;

R^x is halogen, optionally substituted C_{1-6} aliphatic, -OR, -SR, -CN, -N(R')$_2$, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, -OC(O)N(R')$_2$;

R^2 is a bond, hydrogen, or optionally substituted C_{1-6} aliphatic;

each R is independently hydrogen or an optionally substituted group selected from C_{1-6} aliphatic, phenyl, a 3-7 membered saturated or partially unsaturated carbocyclic ring, a 7-10 membered bicyclic saturated, partially unsaturated, phenyl, or naphthyl ring, a 5-6 membered monocyclic heteroaryl ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 4-7 membered saturated or partially unsaturated heterocyclic ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 7-10 membered bicyclic saturated or partially unsaturated heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or an 8-10 membered bicyclic heteroaryl ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

each R' is independently -R, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R)$_2$, -C(S)N(R)$_2$, -S(O)R, -SO_2R, -SO_2N(R)$_2$, or two R' on the same nitrogen are taken together with their

intervening atoms to form an optionally substituted group selected from a 4-7 membered monocyclic saturated or partially unsaturated ring having 1-2 heteroatoms independently selected from nitrogen, oxygen, and sulfur, or a 7-12 membered bicyclic saturated, partially unsaturated, or aromatic fused ring having 1-3 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

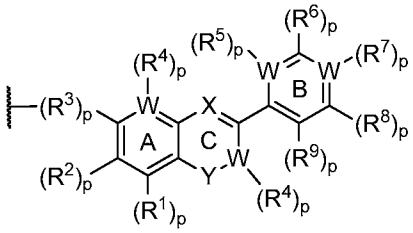
W is C or N;

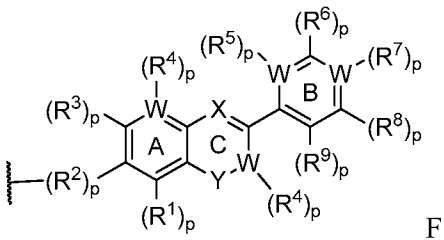
R^3 is optionally substituted C_{1-6} aliphatic;

=== is a single or double bond;

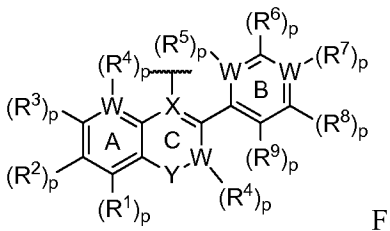
each of m and n is independently 0-4, as valency permits; and

each of R^4 and R^5 is independently –R, halogen, -OR, -SR, -N(R')$_2$, -CN, -NO_2, -C(O)R, -C(S)R, -CO_2R, -C(O)N(R')$_2$, -C(O)SR, -C(O)C(O)R, -C(O)CH_2C(O)R, -C(S)N(R')$_2$, -C(S)OR, -S(O)R, -SO_2R, -SO_2N(R')$_2$, -N(R')C(O)R, -N(R')C(O)N(R')$_2$, -N(R')C(S)N(R')$_2$, -N(R')SO_2R, -N(R')SO_2N(R')$_2$, -N(R')N(R')$_2$, -N(R')C(=N(R'))N(R')$_2$, -C=NN(R')$_2$, -C=NOR, -C(=N(R'))N(R')$_2$, -OC(O)R, or -OC(O)N(R')$_2$;

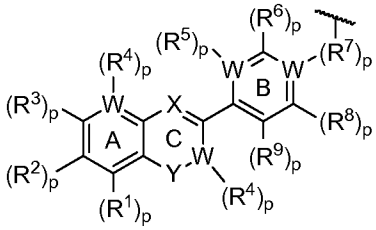
XVI)  Formula AA,



Formula AA1,



Formula AA2,



Formula AA3,

wherein:

X is selected from N and CH;

Y is CO;

R^1 and R^3 are each independently selected from alkoxy and hydrogen;

R^2 is selected from alkoxy, alkyl, and hydrogen;

R^6 and R^8 are each independently selected from alkyl, alkoxy, chloride, and hydrogen;

R^5 and R^9 are each hydrogen;

R^7 is selected from amino, hydroxyl, alkoxy, and alkyl substituted with a heterocyclyl;

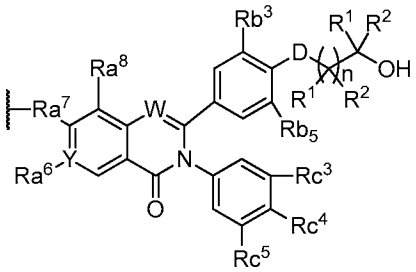
R^{10} is hydrogen; or

two adjacent substituents selected from R^6, R^7, and R^8 are connected to form a heterocyclyl;

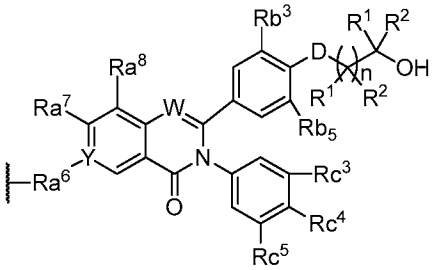
each W is independently selected from C and N, wherein if W is N, then p is 0 or 1, and if W is C, then p is 1;

for W-$(R^{10})_p$, W is N and p is 1; and

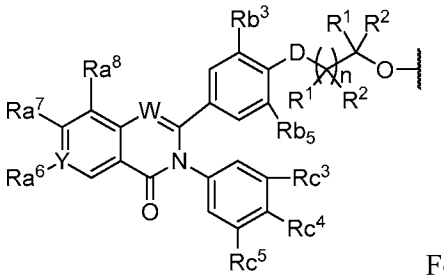
for W-$(R^4)_p$, W is C, p is 1 and R^4 is H, or W is N and p is 0;



XVII) Formula BB,



Formula CC, or



Formula DD,

wherein:

Y and W are each independently selected from carbon and nitrogen;

Ra^6 is selected from fluoride, hydrogen, C_1-C_3 alkoxy, cyclopropyloxy, SO_2R_3, SOR_3, and SR_3, wherein if Y is nitrogen then Ra^6 is absent;

Ra^7 is selected from hydrogen, fluoride, SO_2R_3, SOR_3, and SR_3;

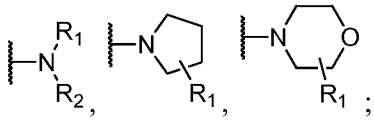
Ra^8 is selected from hydrogen, C_1-C_3 alkoxy, cyclopropyloxy, chloride, and bromide;

n is selected from 1, 2, or 3;

D is selected from O, NH, NR_1, S, or C;

Rb^3 and Rb^5 are independently selected from hydrogen and C_1-C_3 alkyl;

R_C^3 and R_C^5 are independently selected from hydrogen, C_1-C_3 alkyl, and cyclopropyl;

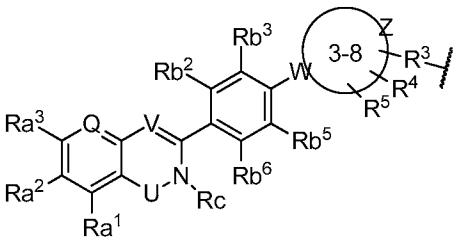
R_C^4 is selected from F, Cl, Br, I, CF_3, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, $NHC(O)R^4$, $NHSO_2R^4$, $C(O)OR^4$, and ;

R^1, R'^1, R^2 and R'^2 are independently selected from hydrogen, fluoride, C_1-C_3 alkyl, and cyclopropyl, wherein R^1 and R^2 and/or R'^1 and R'^2 may be connected to form a 3-6 membered ring;

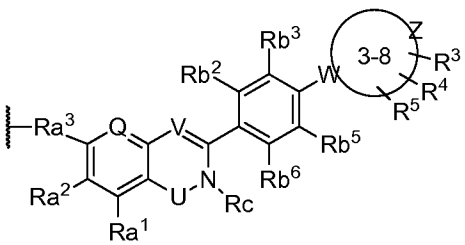
R^3 is selected from C_1-C_3 alkyl and cyclopropyl; and

R^4 is selected from hydrogen, C_1-C_4 alkyl, C_3-C_5 cycloalkyl, phenyl, and naphthyl,

provided that if Ra^7 or Ra^6 is fluoride, then R_C^4 is not bromide;



XVIII) Formula DD or



Formula EE,

wherein:

Q and V are independently selected from CH and nitrogen;

U is selected from C=O, C=S, SO_2, S=O, SR^1, CR^1R^2, CR^1OR^2, CR^1SR^2;

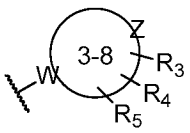
R^1 and R^2 are independently selected from hydrogen and C_1-C_6 alkyl;

Rc is selected from hydrogen, C_1-C_6 alkyl, and C_3-C_6 cycloalkyl;

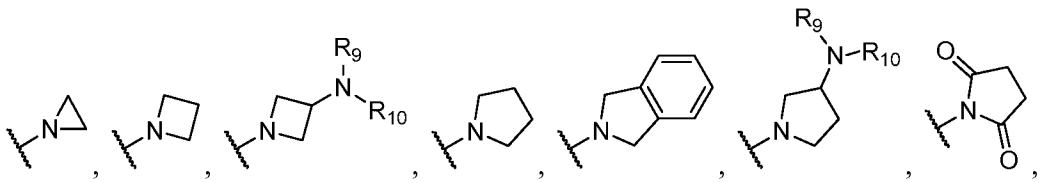
Ra^1, Ra^2, and Ra^3 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 alkoxy, halogen, amino, amide, hydroxyl, heterocycle, and C_3-C_6 cycloalkyl, wherein Ra^1 and Ra^2 and/or Ra^2 and Ra^3 may be connected to form a cycloalkyl or a heterocycle;

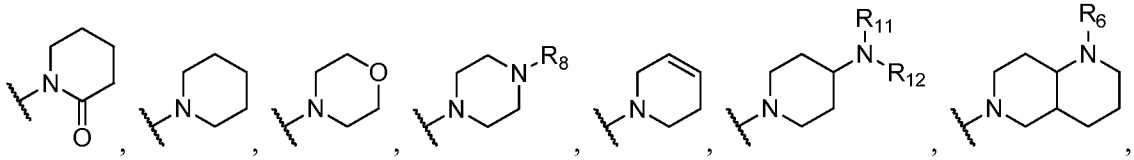
Rb^2 and Rb^6 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_3-C_6 cycloalkyl, hydroxyl, and amino;

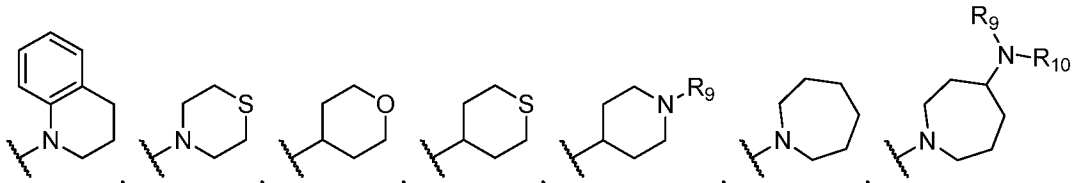
Rb^3 and Rb^5 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, hydroxyl, and amino, wherein Rb^2 and Rb^3 and/or Rb^5 and Rb^6 may be connected to form a cycloalkyl or a heterocycle;

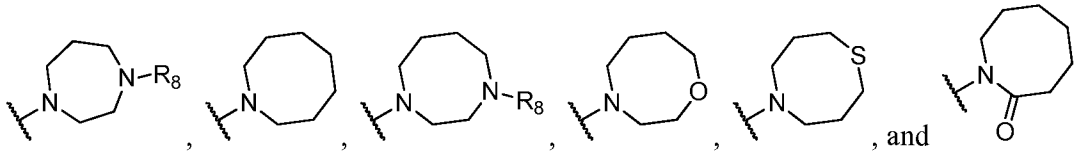


represents a 3-8 membered ring system wherein: W is selected from carbon and nitrogen; Z is selected from CR^6R^7, NR^8, oxygen, sulfur, -S(O)-, and -SO_2-; said ring system being optionally fused to another ring selected from cycloalkyl, heterocycle, and phenyl, and wherein said ring system is optionally selected from rings having the structures:









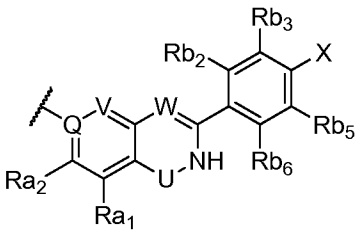
, and ;

R^3, R^4, and R^5 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, phenyl, naphthyl, phenoxy, hydroxy1, amino, amide, oxo, -CN, and sulfonamide;

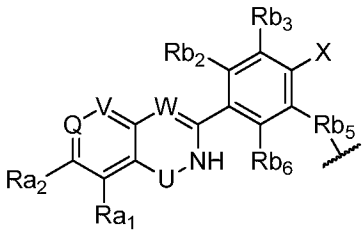
R^6 and R^7 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, naphthyl, halogen, hydroxyl, -CN, amino, and amido; and

R^8 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, acyl, and C_3-C_6 cycloalkyl; and

R^9, R^{10}, R^{11}, and R^{12} are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkenyl, C_1-C_6 alkynyl, C_3-C_6 cycloalkyl, phenyl, naphthyl, heterocycle, hydroxyl, sulfonyl, and acyl;



XIX) Formula FF and



Formula GG,

wherein:

Q is selected from N and CRa^3;

V is selected from N and CRa^4;

W is selected from N and CH;

U is selected from C=O, C=S, SO_2, S=O, and SR^1;

X is selected from OH, SH, NH_2, S(O)H, $S(O)_2H$, $S(O)_2NH_2$, $S(O)NH_2$, NHAc, and $NHSO_2Me$;

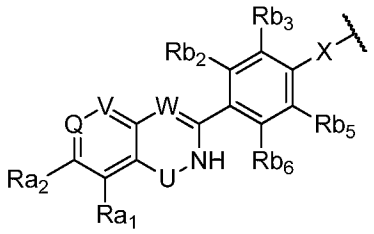
Ra^1, Ra^3, and Ra^3 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, and halogen;

Ra^2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, amino, amide, and halogen;

Rb^2 and Rb^6 are independently selected from hydrogen, methyl and fluorine;

Rb^3 and Rb^5 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy; and

Rb^2 and Rb^3 and/or Rb^5 and Rb^6 may be connected to form a cycloalkyl or a heterocycle, provided that at least one of Ra^1, Ra^2, Ra^3, and Ra^4 is not hydrogen;



XX) Formula HH,

wherein:

Q is selected from N and CRa^3;

V is selected from N and CRa^4;

W is selected from N and CH;

U is selected from C=O, C=S, SO_2, S=O, and SR^1;

X is selected from OH, SH, NH_2, S(O)H, $S(O)_2H$, $S(O)_2NH_2$, $S(O)NH_2$, NHAc, and $NHSO_2Me$;

Ra^1, Ra^3, and Ra^3 are independently selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, and halogen;

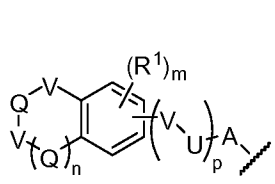
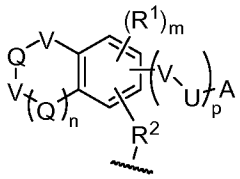
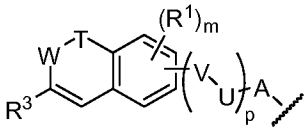
Ra^2 is selected from hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, amino, amide, and halogen;

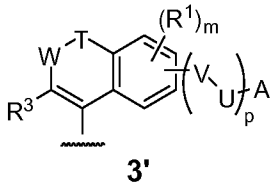
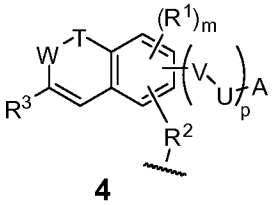
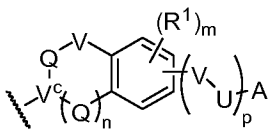
Rb^2 and Rb^6 are independently selected from hydrogen, methyl and fluorine;

Rb^3 and Rb^5 are independently selected from hydrogen, halogen, C_1-C_6 alkyl, C_3-C_6 cycloalkyl, and C_1-C_6 alkoxy; and

Rb^2 and Rb^3 and/or Rb^5 and Rb^6 may be connected to form a cycloalkyl or a heterocycle,

provided that at least one of Ra^1, Ra^2, Ra^3, and Ra^4 is not hydrogen;

XXI)  1 ,  2 ,  3 ,

 3' ,  4 and  5 ,

wherein:

V is independently selected, for each occurrence, from the group consisting of NH, S, N(C_{1-6}alkyl), O, or CR^4R^4;

Q is independently selected, for each occurrence, from the group consisting of C(O), C(S), C(N), SO_2, or CR^4R^4;

U is independently selected from the group consisting of a bond, C(O), C(S), C(N), SO_2, or CR^4R^4

W and T are independently selected from the group consisting of NH, N(C_{1-6}alkyl), O, or Q;

V^C is selected from the group consisting of N, SH or CR^4;

A is selected from the group consisting of aliphatic, cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl or bicyclic moiety, wherein the cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl, or bicyclic moiety is optionally substituted with one, two, three, four or more groups represented by R^4;

R^1 is independently selected, for each occurrence, from the group consisting of hydroxyl, halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -C(O)OC_{1-6}alkyl, -OS(O)$_2C_{1-4}$alkyl, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^2 is selected from the group consisting of -O-, amino, C_{1-6}alkyl, -O-C_{1-6}alkyl-, hydroxylC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, -C(O)-, -C(O)O-, -C(O)NC_{1-6}alkyl-, -OS(O)$_2C_{1-4}$alkyl-, -OS(O)$_2$-, -S-C_{1-6}alkyl-, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^3 is selected from the group consisting of hydrogen or C_{1-6}alkyl;

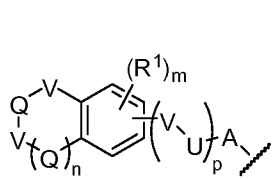
R^4 is independently selected, for each occurrence, from the group consisting of hydrogen, hydroxyl, oxo, imino, amino, halo, C_{1-6}alkyl, cycloalkyl, phenyl, naphthyl, heterocyclyl, -O-C_{1-6}alkyl, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)C_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -C(O)OC_{1-6}alkyl, -C(O)NHC_{1-6}alkyl, -C(O)NH_2 or -OS(O)$_2C_{1-4}$alkyl;

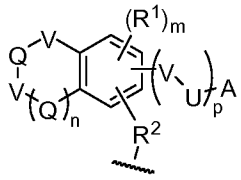
m is selected from the group consisting of 0, 1, 2, or 3;

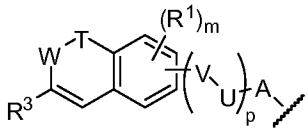
n is selected from the group consisting of 0, 1, or 2; and

p is selected from the group consisting of 0 or 1;

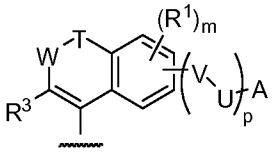
XXII)

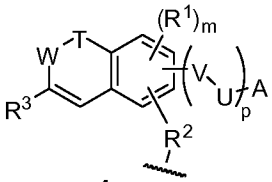

1

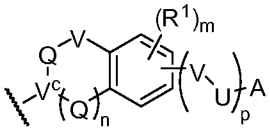

2


3

,


3'


4


5

, and ;

wherein:

V is independently selected, for each occurrence, from the group consisting of NH, S, N(C_{1-6}alkyl), O, or CR^4R^4;

Q is independently selected, for each occurrence, from the group consisting of C(O), C(S), C(N), SO_2, or CR^4R^4;

U is independently selected from the group consisting of a bond, C(O), C(S), C(N), SO_2, or CR^4R^4

W and T are independently selected from the group consisting of NH, N(C_{1-6}alkyl), O, or Q;

V^C is selected from the group consisting of N, SH or CR^4;

A is selected from the group consisting of aliphatic, cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl or bicyclic moiety, wherein the cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl, or bicyclic moiety is optionally substituted with one, two, three, four or more groups represented by R^4;

R^1 is independently selected, for each occurrence, from the group consisting of hydroxyl, halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -C(O)OC_{1-6}alkyl, -OS(O)$_2C_{1-4}$alkyl, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^2 is selected from the group consisting of -O-, amino, C_{1-6}alkyl, -O-C_{1-6}alkyl-, hydroxylC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, -C(O)-, -C(O)O-, -C(O)NC_{1-6}alkyl-, -OS(O)$_2C_{1-4}$alkyl-, -OS(O)$_2$-, -S-C_{1-6}alkyl-, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

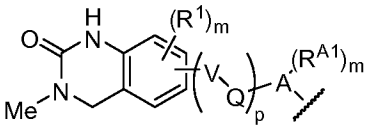
R^3 is selected from the group consisting of hydrogen or C_{1-6}alkyl;

R^4 is independently selected, for each occurrence, from the group consisting of hydrogen, hydroxyl, oxo, imino, amino, halo, C_{1-6}alkyl, cycloalkyl, phenyl, naphthyl, heterocyclyl, -O-C_{1-6}alkyl, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)C_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -C(O)OC_{1-6}alkyl, -C(O)NHC_{1-6}alkyl, -C(O)NH_2 or -OS(O)$_2C_{1-4}$alkyl;

m is selected from the group consisting of 0, 1, 2, or 3;

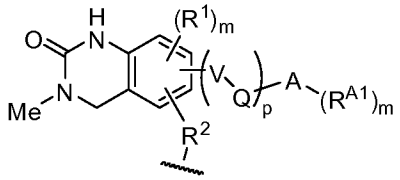
n is selected from the group consisting of 0, 1, or 2; and

p is selected from the group consisting of 0 or 1;



1b

XXIII) and



2b

;

wherein:

V is selected from the group consisting of a NH, S, N(C_{1-6}alkyl), O, or CR^4R^4;

Q is selected from the group consisting of a bond, C(O), C(S), C(N), SO_2, or CR^4R^4;

A is a ring selected from the group consisting of: phenyl, a 5-6 membered cycloalkyl, a 5-6 membered heteroaryl having 1, 2 or 3 heteroatoms each selected from S, N or O, and a 4-7 membered heterocycle having 1, 2 or 3 heteroatoms each selected from N or O;

R^{A1} is R^1; or two R^{A1} substituents may be taken together with the atoms to which they are attached to form phenyl, a 5-6 membered heteroaryl having 1, 2 or 3 heteroatoms each selected from S, N or O, and a 4-7 membered heterocycle having 1, 2 or 3 heteroatoms each selected from N or O;

R^1 is independently selected, for each occurrence, from the group consisting of hydroxyl, halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -C(O)OC_{1-6}alkyl, -OS(O)$_2C_{1-4}$alkyl, -S(C_{1-4}alkyl)C(O)R', phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-}

$_{6}$alkyl, phenyl, and napththyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^2 is selected from the group consisting of -O-, amino, C_{1-6}alkyl, -O-C_{1-6}alkyl-, hydroxylC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, -C(O)-, -C(O)O-, -C(O)NC_{1-6}alkyl-, -OS(O)$_2C_{1-4}$alkyl-, -OS(O)$_2$--S(C_{1-4}alkyl)C(O)R''-, -S-C_{1-6}alkyl-, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^3 is selected from the group consisting of hydrogen or C_{1-6}alkyl;

R^4 is independently selected, for each occurrence, from the group consisting of hydrogen, hydroxyl, oxo, imino, amino, halo, C_{1-6}alkyl, cycloalkyl, phenyl, naphthyl, heterocyclyl, -O-C_{1-6}alkyl, -NH-C_{1-6}alkyl, -N(C_{1-6}alkyl)C_{1-6}alkyl, nitro, cyano, CF_3, -OCF_3, -C(O)OC_{1-6}alkyl, -C(O)NHC_{1-6}alkyl, -C(O)NH_2 or -OS(O)$_2C_{1-4}$alkyl;

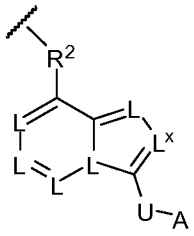
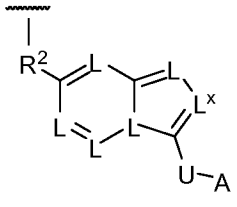
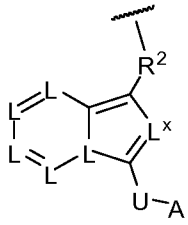
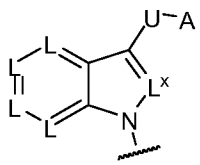
R' is independently selected, for each occurrence, from the group consisting of hydroxyl, amino, thio, phenyl, naphthyl, or C_{1-6}alkyl, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

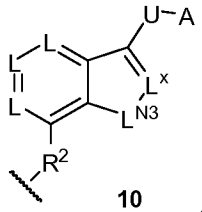
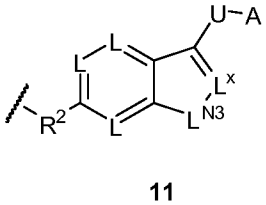
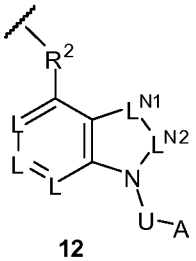
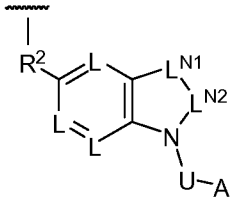
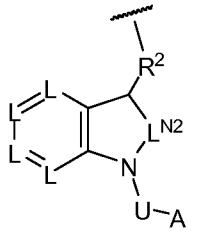
R'' is independently selected, for each occurrence, from the group consisting of –O-, amino, thio, phenyl, naphthyl, or C_{1-6}alkyl, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

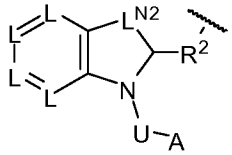
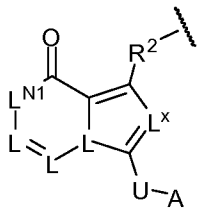
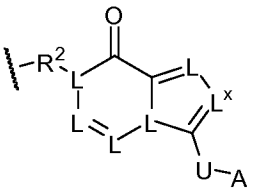
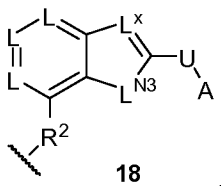
m is independently selected, for each occurrence, from the group consisting of 0, 1, 2, or 3;

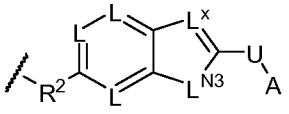
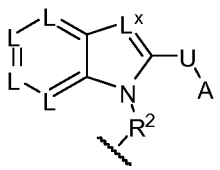
n is selected from the group consisting of 0, 1, or 2; and

p is selected from the group consisting of 0 or 1; and

XXIV)  **6** ,  **7** ,  **8** ,  **9** ,

 **10** ,  **11** ,  **12** ,  **13** ,  **14** ,

 **15** ,  **16** ,  **17** ,  **18** ,

 **19** , and  **20** ;

wherein:

L and L^X are independently selected, for each occurrence, from the group consisting of N, CH, and CR^1;

L^{N1} and L^{N2} are independently selected from the group consisting of CH_2, CHR^1, CR^1R^1, NH, and $N(C_{1\text{-}6}alkyl)$; wherein $C_{1\text{-}6}$alkyl is optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1\text{-}6}$alkyl, amino, or nitro;

L^{N3} is selected from the group consisting of O, S, NH, and $N(C_{1\text{-}6}alkyl)$; wherein $C_{1\text{-}6}$alkyl is optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, $C_{1\text{-}6}$alkyl, amino, or nitro;

U is independently selected from the group consisting of a bond, C(O), C(S), C(N), SO_2, or CR^4R^4;

A is selected from the group consisting of aliphatic, cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl, or bicyclic moiety, wherein the cycloalkyl, heterocyclic, phenyl, naphthyl, heteroaryl, or bicyclic moiety is optionally substituted with one, two, three, four or more groups represented by R^4;

R^1 is independently selected, for each occurrence, from the group consisting of hydroxyl, halo, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, C_{1-6}alkoxy, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}$alkyl, $-OS(O)_2C_{1-4}$alkyl, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

R^2 is selected from the group consisting of -O-, amino, C_{1-6}alkyl, $-O-C_{1-6}$alkyl-, hydroxylC_{1-6}alkyl, aminoC_{1-6}alkyl, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, acylaminoC_{1-6}alkyl, -C(O)-, -C(O)O-, $-C(O)NC_{1-6}$alkyl-, $-OS(O)_2C_{1-4}$alkyl-, $-OS(O)_2$-, $-S-C_{1-6}$alkyl-, phenyl, naphthyl, phenyloxy, benzyloxy, or phenylmethoxy, wherein C_{1-6}alkyl, phenyl, and naphthyl are optionally substituted by one two or three substituents selected from the group consisting of hydroxyl, halogen, oxo, C_{1-6}alkyl, amino, or nitro;

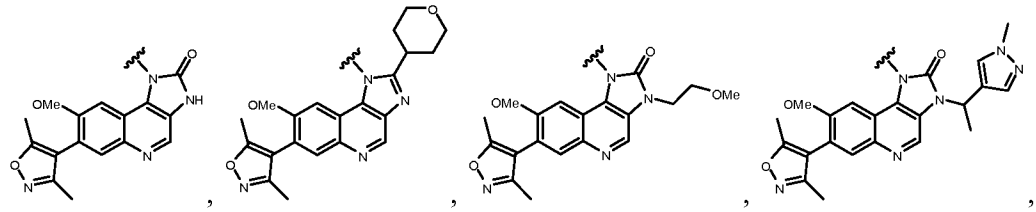
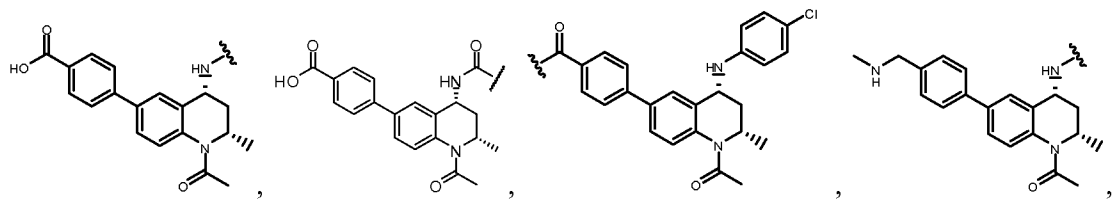
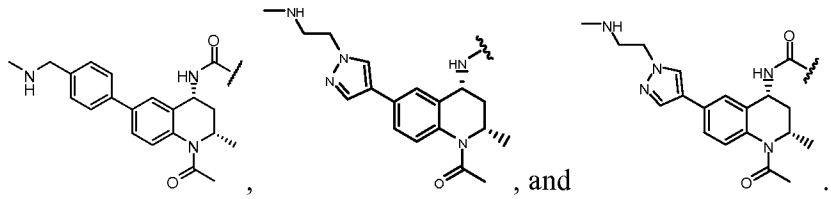
R^3 is selected from the group consisting of hydrogen or C_{1-6}alkyl; and

R^4 is independently selected, for each occurrence, from the group consisting of hydrogen, hydroxyl, oxo, imino, amino, halo, C_{1-6}alkyl, cycloalkyl, phenyl, naphthyl, heterocyclyl, $-O-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl, $-N(C_{1-6}$alkyl$)C_{1-6}$alkyl, nitro, cyano, CF_3, $-OCF_3$, $-C(O)OC_{1-6}$alkyl, $-C(O)NHC_{1-6}$alkyl, $-C(O)NH_2$ or $-OS(O)_2C_{1-4}$alkyl.

2. The bivalent compound of claim 1, wherein P^1 and P^2 are the same.

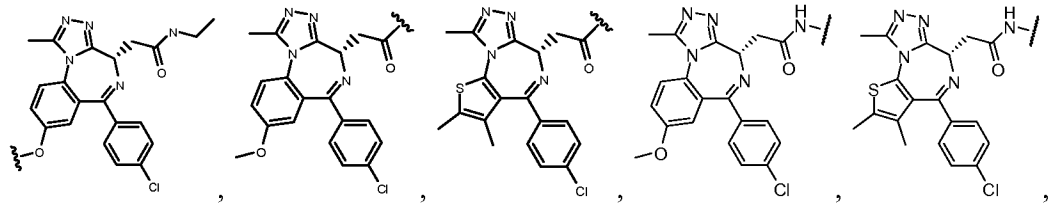
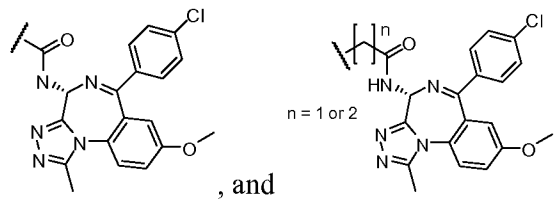
3. The bivalent compound of claim 1, wherein P^1 and P^2 are different.

4. The bivalent compound of any one of claims 1-3, wherein P^1 and P^2 are each independently selected from the group consisting of:

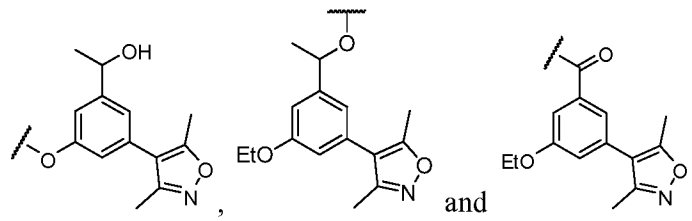
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5. The bivalent compound of any one of claims 1-3, wherein P^1 and P^2 are each independently selected from the group consisting of:

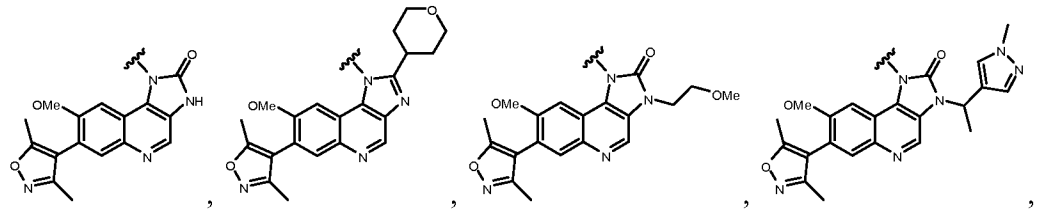
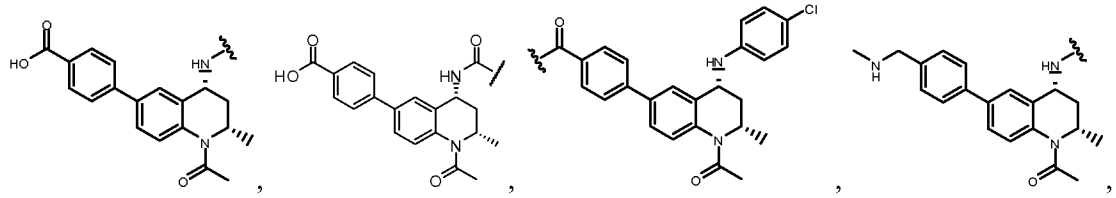
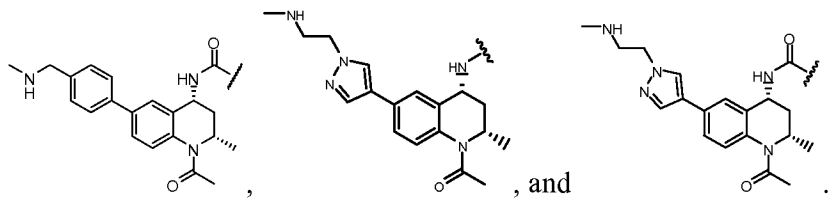
, and .

6. The bivalent compound of any one of claims 1-3, wherein P^1 and P^2 are each independently selected from the group consisting of:

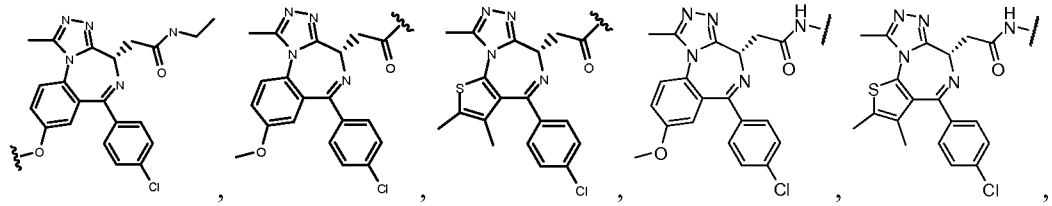
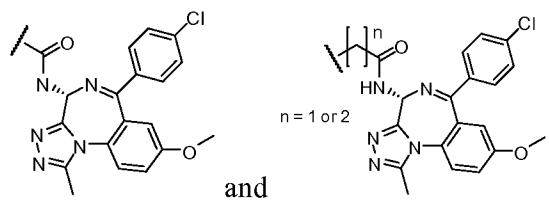


, and .

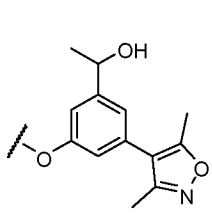
7. The bivalent compound of any one of claims 1-3, wherein P^1 and P^2 are each independently selected from the group consisting of:

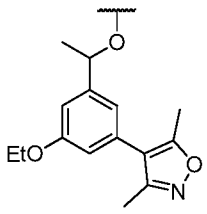



, and .

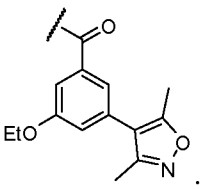
8. The bivalent compound of any one of claims 1-3, wherein P^1 and P^2 are each independently selected from the group consisting of:



and .

9. The bivalent compound of any one of claims 1-3, wherein P^1 and P^2 are each independently selected from the group consisting of:



, 

, and 

.

10. The bivalent compound of any one of claims 1-9, wherein the first bromodomain and the second bromodomain are each independently associated with a protein selected from the group consisting of BRD2, BRD3, BRD4 and BRD-t.

11. The bivalent compound of claim 10, wherein the protein is a fusion gene product selected from BRD4-NUT or BRD3-NUT.

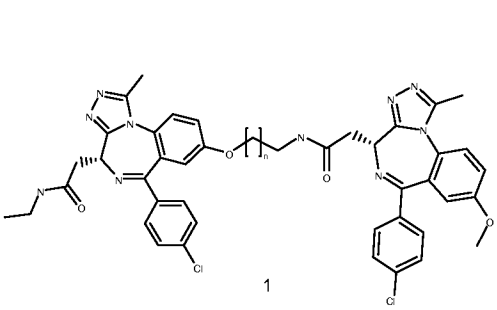
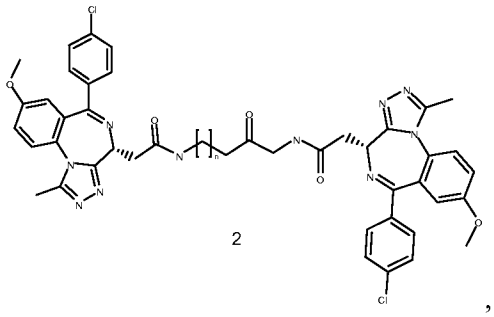
12. The bivalent compound of any one of claims 1-11, wherein the second bromodomain is within 50Å of the first bromodomain.

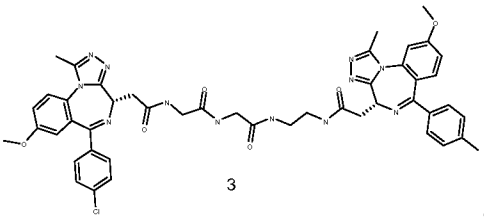
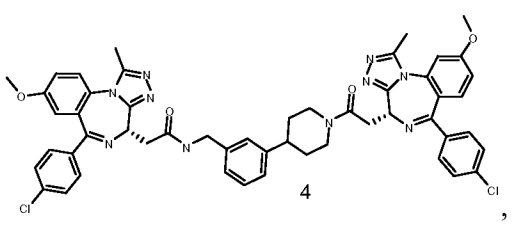
13. A method of treating a disease associated with a protein having tandem bromodomains in a patient in need thereof comprising:

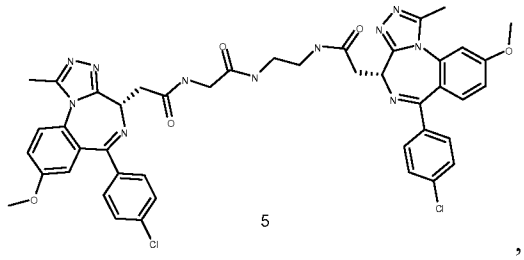
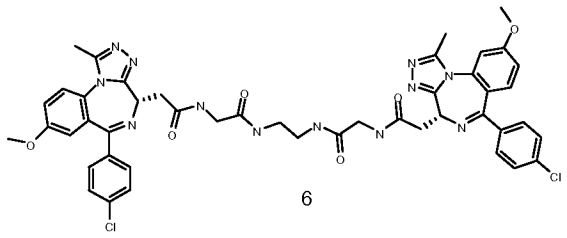
administering to the patient the bivalent compound of any one of claims 1-12.

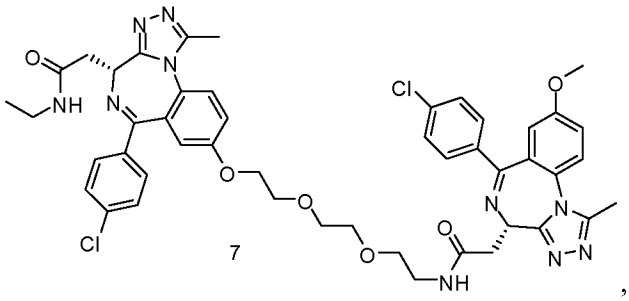
14. The method of claim 13, wherein the disease is acute myeloid leukemia or midline carcinoma.

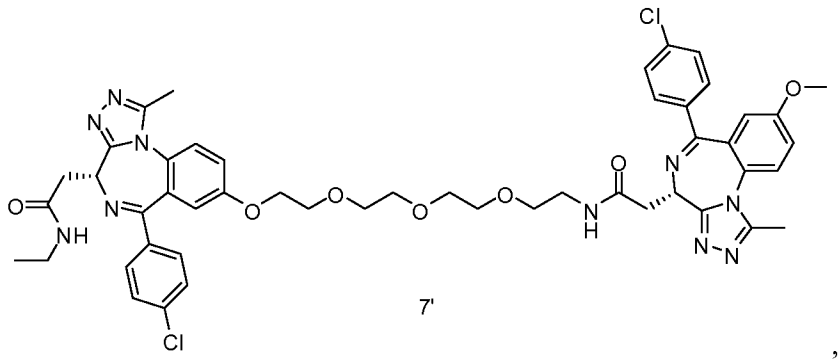
15. A bivalent compound selected from the group consisting of:

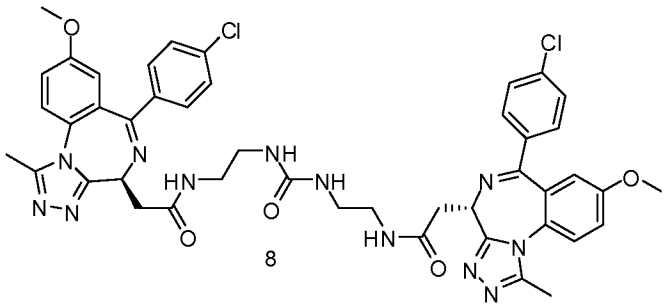

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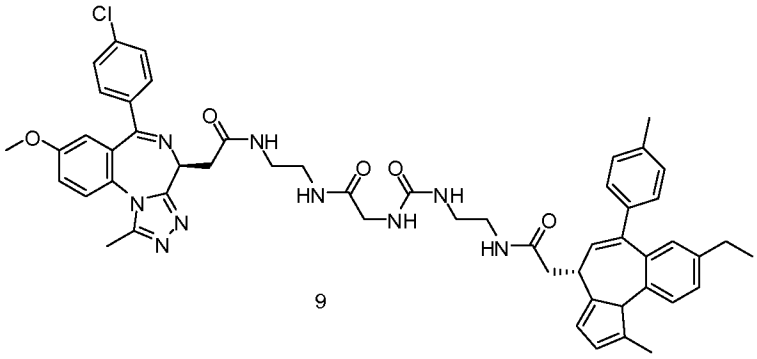

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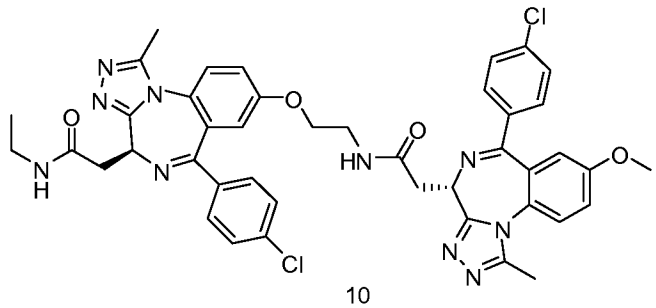
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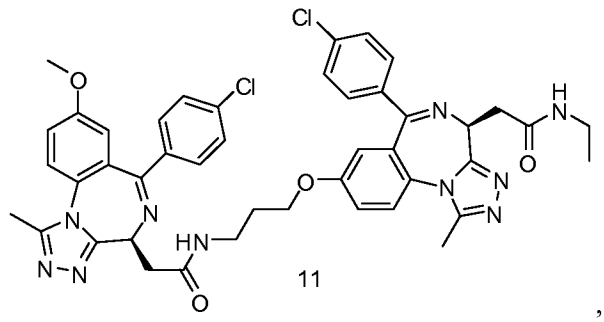
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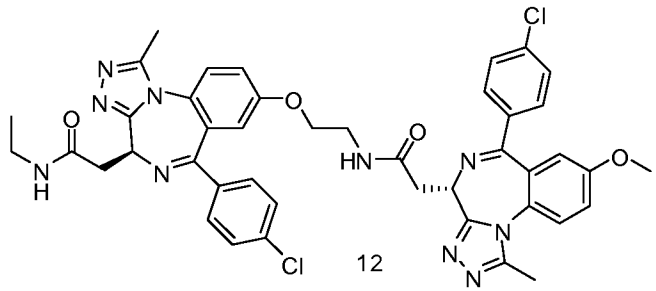
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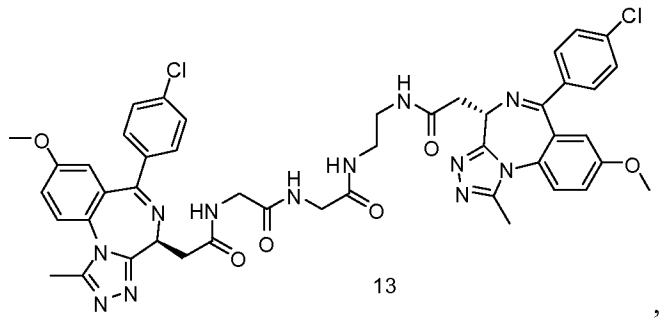
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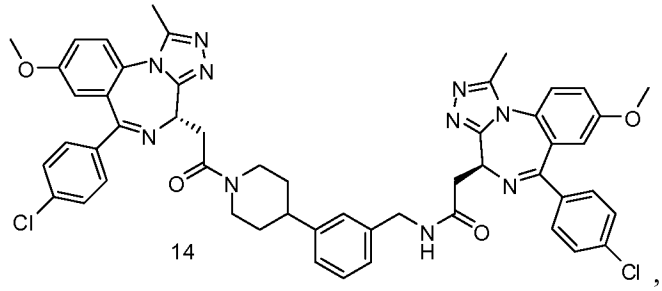
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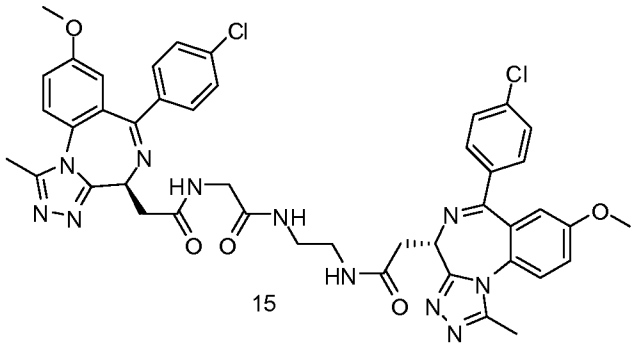
9  10 ,

10  11 ,

11  12 ,

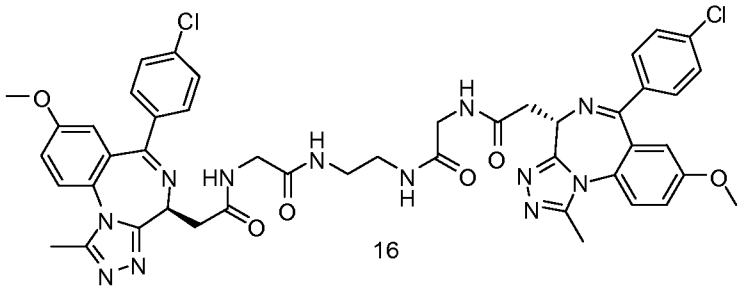
12  13 ,

13  14 ,



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14 ,



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15 ,

16 and pharmaceutically acceptable salts thereof, wherein n is 0, 1, 2, 3, 4 or 5.

FIGURES

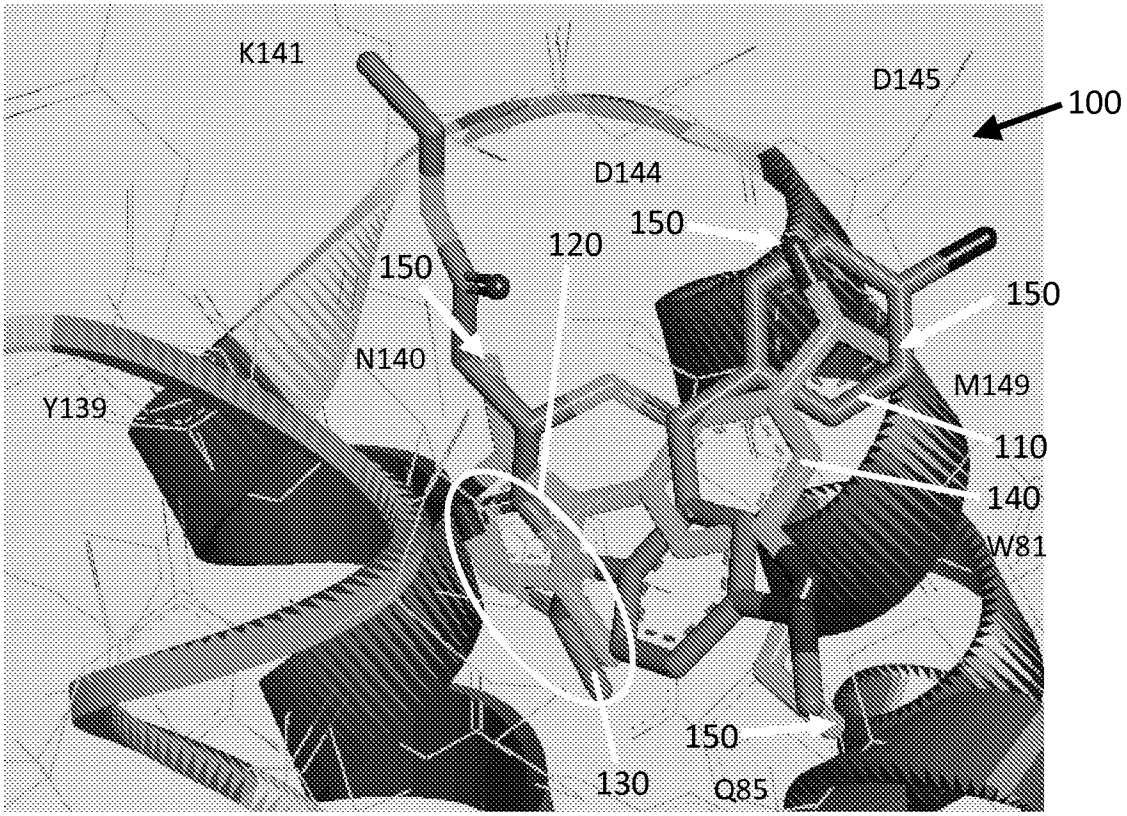


FIG. 1

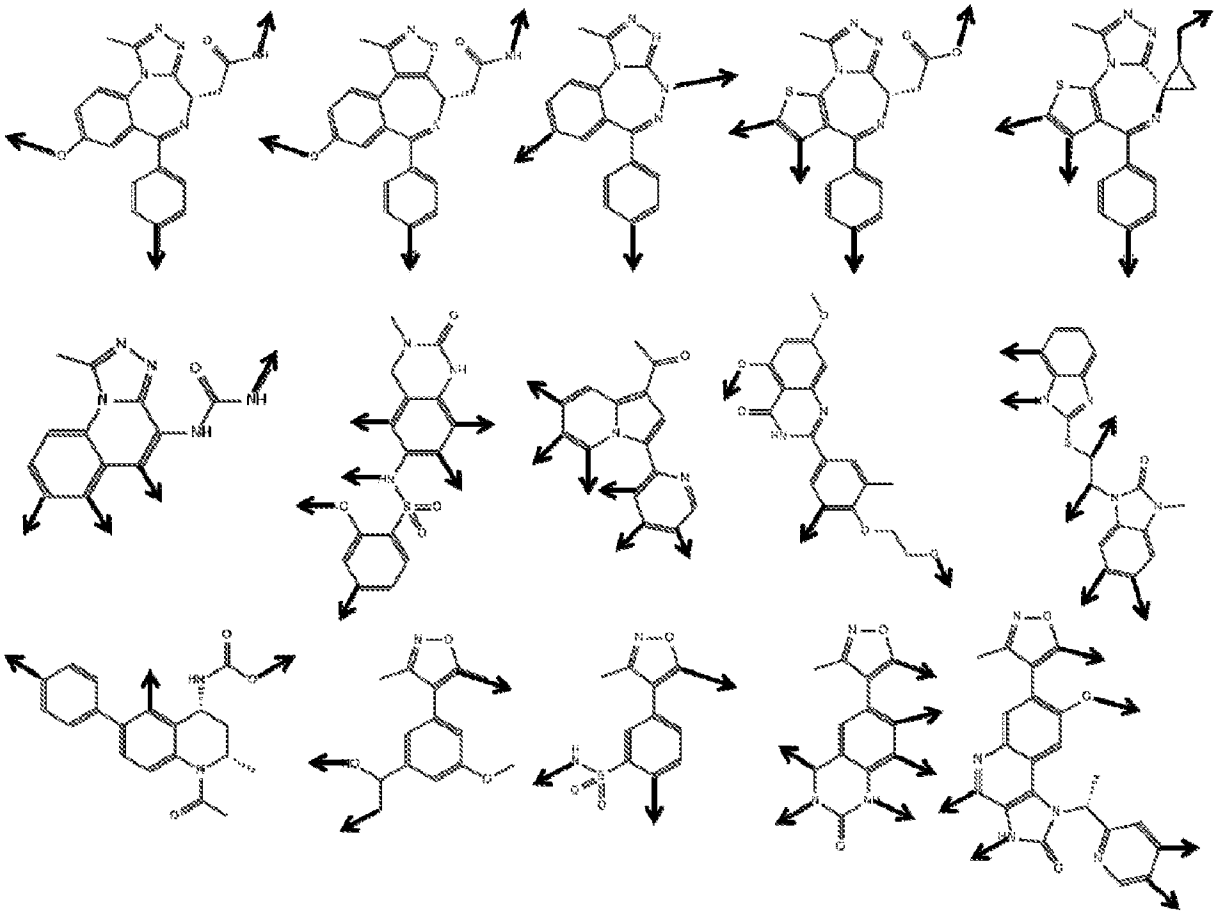


FIG. 2