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(71) Applicant: **COFERON, INC.** [US/US]; 25 Health Sciences Drive, Mail Box 123, Stony Brook, NY 11790 (US).

(72) Inventors: **ARNOLD, Lee, Daniel**; 3751 East Sterling Avenue, Bloomington, IN 47401 (US). **FOREMAN, Kenneth, W.**; 8 Underhill Avenue, Syosset, NY 11791-5015 (US). **JIN, Meizhong**; 6 Diane Lane, East Northport, NY 11731 (US). **WANNER, Jutta**; 905 Main Street Apt 1-A, Port Jefferson, NY 11777 (US). **WERNER, Douglas, S.**; 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**: C-MYC LIGANDS CAPABLE OF DIMERIZING IN AN AQUEOUS SOLUTION, AND METHODS OF USING SAME

(57) **Abstract**: Described herein are monomers capable of forming a biologically useful multimer when in contact with one, two, three or more other monomers in an aqueous media. In one aspect, such monomers may be capable of binding to another monomer in an aqueous media (e.g. in vivo) to form a multimer (e.g. a dimer). Contemplated monomers may include a ligand moiety, a linker element, and a connector element that joins the ligand moiety and the linker element. In an aqueous media, such contemplated monomers may join together via each linker element and may thus be capable of modulating one or more biomolecules substantially simultaneously, e.g., modulating two or more binding sites on c-Myc.

C-MYC LIGANDS CAPABLE OF DIMERIZING IN AN AQUEOUS SOLUTION, AND METHODS OF USING SAME

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of, and priority to, U.S. provisional application serial numbers 62/103,263, filed January 14, 2015, and 62/159,451, filed May 11, 2015, the contents of each of which is hereby incorporated by reference herein in its entirety.

BACKGROUND

[0002] The basic-helix-loop-helix-leucine-zipper ("bHLH-Zip") transcription factor, c-Myc, is overexpressed in a variety of cancers, including breast cancers, colon cancers, gynecological cancers, and hepatocellular cancers, and is implicated in the carcinogenesis process. Numerous strategies have been explored for inhibiting the action of c-Myc, with the goal of developing a viable treatment for cancer. For example, nucleic acid-based strategies have been employed to interrupt c-Myc transcription or translation, or alternatively to interrupt transcription or translation of downstream c-Myc target genes. However, such strategies have generally been hindered by low efficacy and/or difficulty in delivery of the therapeutic.

[0003] An alternative strategy for targeting c-Myc utilizes traditional small molecule therapeutics to inhibit or disrupt the association of c-Myc with Myc-associated factor X (Max). Max is another member of the bHLH-Zip family of transcription factors and can combine with c-Myc to form a heterodimer that binds to DNA, thereby activating genes that promote both cell proliferation and survival. However, previous attempts to inhibit or disrupt the binding of c-Myc and Max have failed to reach the clinic. Accordingly, there exists a need for viable therapeutics that inhibit c-Myc.

[0004] Current standard drug design and drug therapy approaches typically focus on modulating one protein binding site with limited selectivity and do not address the urgent need to find drugs that are capable of modulating tandem binding sites 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 targeting a single site are generally too small to effectively overcome mutational resistance mechanisms while retaining specificity.

SUMMARY

[0005] Described herein, for example, are monomers capable of forming a biologically useful multimer when in contact with one, two, three or more other monomers in an aqueous media. In one aspect, such monomers may be capable of binding to another monomer in an aqueous media (e.g., *in vivo*) to form a multimer, (e.g., a dimer). Contemplated monomers may include a ligand moiety (e.g., a pharmacophore for the target biomolecule), a linker element, and a connector element that joins the ligand moiety and the linker element. In an aqueous media, such contemplated monomers may join together via each linker element and may thus be capable of modulating one or more biomolecules substantially simultaneously, e.g., modulate two or more binding sites on a protein or on different proteins.

[0006] In one aspect, a first monomer capable of forming a biologically useful multimer capable of modulating c-Myc when in contact with a second monomer in an aqueous media is provided. Such a first monomer may be represented by the formula:

X^1-Y^1-Z^1 (Formula I) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^1 is a first ligand moiety capable of modulating a first binding site on said c-Myc;

Y^1 is absent or is a connector moiety covalently bound to X^1 and Z^1;

Z^1 is a first linker capable of binding to the second monomer; and

the second monomer is represented by the formula:

X^2-Y^2-Z^2 (Formula II) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^2 is a second ligand moiety capable of modulating a second binding site on said c-Myc;

Y^2 is absent or is a connector moiety covalently bound to X^2 and Z^2; and

Z^2 is a second linker capable of binding to the first monomer through Z^1.

[0007] In another aspect, a therapeutic multimer compound formed from the multimerization in an aqueous media of a first monomer and a second monomer is provided. Such a first monomer may be represented by:

X^1-Y^1-Z^1 (Formula I)

and the second monomer represented by

X^2-Y^2-Z^2 (Formula II),

wherein

X^1 is a first ligand moiety capable of modulating a first c-Myc binding site;

Y^1 is absent or is a connector moiety covalently bound to X^1 and Z^1;

Z^1 is a first linker capable of binding to Z^2 to form the multimer;

X^2 is a second ligand moiety capable of modulating a second c-Myc binding site;

Y^2 is absent or is a connector moiety covalently bound to X^2 and Z^2; and

Z^2 is a boronic acid or oxaborale moiety capable of binding with the Z^1 moiety of Formula I to form the multimer; and

pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof.

[0008] In yet another aspect, a first monomer is provided, wherein the first monomer is represented by the formula X^3-Y^3-Z^3 (Formula III) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^3 is a first ligand moiety capable of modulating a c-Myc binding site;

Y^3 is absent or is a connector moiety covalently bound to X^3 and Z^3; and

Z^3 is a linker capable of forming a therapeutic multimer with another monomer or other monomers of Formula III, wherein Z^3 is the same for the first monomer and other monomers of the multimer.

[0009] In still another aspect, a method of treating a disease (e.g., cancer) associated with c-Myc in a patient in need thereof is provided. Such a disclosed method can include administering to said patient a first monomer represented by:

X^1-Y^1-Z^1 (Formula I) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein X^1 is a first ligand moiety capable of modulating a first c-Myc binding site; and administering to said patient a second monomer represented by: X^2-Y^2-Z^2 (Formula II), wherein X^2 is a second ligand moiety capable of modulating a second c-Myc binding site, wherein upon administration, said first monomer and said second monomer forms a multimer *in vivo* that binds to the first and the second c-Myc binding sites.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] 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.

[0011] 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.

[0012] FIG 3. depicts (A) structures of C01 and C02 (10074-G5 analog) and (B) Summary of a library design: Structures of the two parent molecules C01 (left) and C02 (right) and attachment positions; connectors are either alkyl chains or PEG-units; R and R' are linked to the connectors via amide, oxygen, or carbon bonds.

[0013] FIGs. 4A, 4B, and 4C depict structures of representative monomers.

[0014] FIG 5. shows results of combinations of disclosed monomers having synergistic activity in a cell proliferation assay. (5A-C) Dose-response curves for three different combinations, E07+N11 (A), E08+N11 (B), and E10+N11 (C) tested in the cell proliferation screen. In each case the dose-response curve for each individual monomer is plotted. The dose-response curves for the predicted additive response (Bliss) and the combination experimental data are plotted with an increasing concentration of E07, E08 or E10 in the presence of N11 (30 μM). The data is plotted as a mean ± SEM from 3 independent experiments. Statistical significance for a difference between the predicted additive effect (Bliss) and the experimental data for the combinations was calculated using a T-test (*ns*, not significant; * $p< 0.05$, ** $p<0.001$, *** $p<0.0001$; **** $p<0.00001$).

[0015] FIG. 6 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

[0016] Described herein, for example, are monomers capable of forming a biologically useful multimer when in contact with one, two, three or more other monomers in an aqueous media. In one aspect, such monomers may be capable of binding to another monomer in an aqueous media (e.g., *in vivo*) to form a multimer, (e.g., a dimer). Contemplated monomers may include a ligand moiety (e.g., a pharmacophore moiety), a linker element, and a connector

element that joins the ligand moiety and the linker element. In an aqueous media, such contemplated monomers may join together via each linker element and may thus be capable of modulating one or more biomolecules substantially simultaneously, e.g., modulate two or more binding sites on a protein or on different proteins.

[0017] For example, contemplated monomers may be separate or separable in a solid or in an aqueous media under one set of conditions, and when placed in an aqueous media having one or more biomolecules (e.g., under a different set of conditions) can 1) form a multimer with another monomer through the linker on each monomer; and either: 2a) bind to the biomolecule in two or more locations (e.g., protein binding sites) through each ligand moiety of the respective monomer or 2b) bind to two or more biomolecules through each ligand moiety of the respective monomer. In an exemplary embodiment, disclosed monomers may interact with another appropriate monomer (*i.e.*, a monomeric pair) in an aqueous media (e.g., *in vivo*) to form a multimer (e.g., a dimer) that can bind to two separate target biomolecule binding sites (e.g., protein binding sites). In one embodiment, the two separate target binding sites can be proximal binding sites on the same target, for example, a first binding site on c-Myc and a second binding site on c-Myc.

[0018] The ligand moiety of a contemplated monomer, 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 binding site, 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). In some embodiments, the linker element comprises a functional group capable of forming a chemical bond with another linker element. In some embodiments, the linker moiety may also serve as a signaling entity or "reporter," and in some instances the assembly of two or more linkers can produce a fluorescent entity or fluorophore with properties distinct from the individual linker moiety. In another aspect, a plurality of monomers, each comprising a linker element, may react to form a multimer connected by the linker elements. In some embodiments, the multimer may be formed *in vivo*. In some instances, the multimer may have enhanced properties relative to the monomers that form the multimer. For example, in certain embodiments, the multimer may bind to a target with greater affinity than any of the monomers that form the multimer. Also described are methods of making the compositions and methods of administering the compositions.

[0019] In some embodiments, the first ligand moiety and the second ligand moiety may each be capable of binding to a binding site of c-Myc. For example, in some embodiments, X^1,

X^2 , X^3 and X^4 of Formulae I, II, III or IV may each be capable of binding to a binding site of a c-Myc. For instance, in one embodiment, a first ligand moiety may be capable of binding to a first binding pocket on c-Myc and a second ligand moiety may be capable of binding to a second binding pocket c-Myc. In some embodiments, a ligand moiety may bind to Max.

[0020] In some embodiments, a plurality of monomers may assemble to form a multimer. The multimer may be used for a variety of purposes. For example, in some instances, the multimer may be used to perturb a biological system. As described in more detail below, in some embodiments, the multimer may bind to or modulate a target biomolecule, such as a protein (e.g., c-Myc). In certain embodiments, a contemplated multimer may be used as a pharmaceutical. Without wishing to be bound by any theory, it is believed that the contemplated multimers inhibit or disrupt the association of c-Myc with Max. Further, it is believed that inhibiting c-Myc can induce apoptosis in a cancer cell.

[0021] Advantageously, in some embodiments, a multimer may form *in vivo* upon administration of suitable monomers to a subject. Also advantageously, the multimer may be capable of interacting with a relatively large target site as compared to the individual monomers that form the multimer. For example, a target may comprise, in some embodiments, two protein binding sites separated by a distance such that a multimer, but not a monomer, may be capable of binding to both binding sites essentially simultaneously. In some embodiments, contemplated multimers may bind to a target with greater affinity as compared to a monomer binding affinity alone.

[0022] In some embodiments, a contemplated multimer may advantageously exhibit enhanced properties relative to the monomers that form the multimer. As discussed above, a multimer may have improved binding properties as compared to the monomers alone. In some embodiments, a multimer may have improved signaling properties. For example, in some cases, the fluorescent properties of a multimer may be different as compared to a monomer. In some embodiments, the fluorescent brightness of a multimer at a particular wavelength may be significantly different (e.g., greater) than the fluorescent brightness at the same wavelength of the monomers that form the multimer. Advantageously, in some embodiments, a difference in signaling properties between the multimer and the monomers that form the multimer may be used to detect formation of the multimer or map out a second binding site. In some embodiments, detection of the formation of the multimer may be used to screen monomers, as discussed in more detail below. Also as discussed in more detail below, in some embodiments, the multimers may be used for imaging or as diagnostic agents.

[0023] It should be understood that a multimer, as used herein, may be a homomultimer (i.e., a multimer formed from two or more essentially identical monomers) or may be a heteromultimer (i.e., a multimer formed from two or more substantially different monomers). In some embodiments, a contemplated multimer may comprise 2 to about 10 monomers, for example, a multimer may be a dimer, a trimer, a tetramer, or a pentamer.

[0024] In some embodiments, a monomer may comprise a ligand moiety, a linker element, and a connector element that associates the ligand moiety with the linker element. In some embodiments, the linker element of a first monomer may combine with the linker element of a second monomer. In some cases, the linker element may comprise a functional group that can react with a functional group of another linker element to form a bond linking the monomers. In some embodiments, the linker element of a first monomer may be substantially the same as the linker element of a second monomer. In some embodiments, the linker element of a first monomer may be substantially different than the linker element of a second monomer.

[0025] In some cases, the ligand moiety may be a pharmacophore. In some embodiments, the ligand moiety (e.g., a pharmacophore) may bind to a target molecule 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.

[0026] In some embodiments, the IC_{50} of the first monomer against a first target binding site and the IC_{50} of the second monomer against a second target binding site may be greater than the apparent IC_{50} of a combination of the monomers against the first target binding site and the second target binding site. The combination of monomers may be any suitable ratio. For example, the ratio of the first monomer to the second monomer may be between 10:1 to 1:10, in some embodiments between 5:1 and 1:5, and in some embodiments between 2:1 and 1:2. In some cases, the ratio of the first monomer to the second monomer may be essentially 1:1. In some instances, the ratio of the smaller of the IC_{50} of the first monomer and the second monomer to the apparent IC_{50} of the multimer may be at least 3.0. In other instances, the ratio of the smaller IC_{50} of the first monomer or the second monomer to the apparent IC_{50} of the multimer may be at least 10.0. In some embodiments, the ratio of the smaller IC_{50} of the first monomer or the second monomer to the apparent IC_{50} of the multimer may be at least 30.0.

[0027] For example, for disclosed monomers forming a heteromultimer, the apparent IC_{50} resulting from an essentially equimolar combination of monomers against the first target binding site and the second target binding site may be, in some embodiments, at least about 3 to 10 fold lower, at least about 10 to 30 fold lower, at least about 30 fold lower, or at least about 40 to 50 fold lower than the lowest of the IC_{50} of the second monomer against the second target binding site or the IC_{50} of the first monomer against the first target binding site.

[0028] It will be appreciated that for monomers forming homodimers (or homo-oligomeric or homomultimeric, as described below), in aqueous solution, there may be an equilibrium between the monomeric and dimeric (or oligomeric) states with higher concentrations favoring greater extent of oligomer (e.g., dimer) formation. As the binding of monomers to the target binding sites increases their proximity and effectively increases their local concentration on the target, the rate and extent of dimerization (oligomerization) is promoted when geometries are favorable. As a result, the occupancy of the target sites by favorable monomers may be nearly completely in the homodimeric (or oligomeric) state. In this manner the target, for example, may serve as a template for the dimerization (or oligomerization) of the monomers, significantly enhancing the extent and rate of dimerization.

[0029] While the affinity of the multimer for its target biomolecule(s) often cannot be measured directly due to the dynamic reversible equilibrium with its monomers in an aqueous or biological milieu, it may be possible to extract an apparent multimer-target dissociation constant from a series of experimental determinations. Exploring the effects of a matrix of monomer concentrations, monomer ratios, along with changes in concentration(s) in the target biomolecule(s), coupled with determinations of multimer-monomer dissociation constants, and in some cases additional binding competition, kinetic and biophysical methods, one can extract an estimate of the affinity of the multimeric assembly for its target(s). Through such approaches, one can demonstrate that in some embodiments, the affinity of the multimer for the target biomolecule(s) are less than 1 μM, in some embodiments, less than 1 nM, in some embodiments, less than 1 pM, in some embodiments, less than 1 fM, and in some embodiments, less than 1 aM, and in some embodiments, less than 1 zM.

[0030] Affinities of individual heterodimerizing monomers for the target biomolecule can be assessed through the testing of the respective monomers in appropriate assays for the target activity or biology because they do not typically self-associate. In contrast, the testing of homodimerizing monomers may not, in some embodiments, afford an affinity for the monomeric or dimeric state, but rather the observed effect (e.g., IC_{50}) is a result of the

monomer-dimer dynamics and equilibrium, with the apparent binding affinity (or IC_{50}) being, e.g., a weighted measure of the monomer and dimeric inhibitory effects upon the target.

[0031] In some cases, the pH of the aqueous fluid in which the multimer forms may be between pH 1 and 9, in some embodiments, between pH 1 and 3, in some embodiments, between pH 3 and 5, in some embodiments, between pH 5 and 7, and in some embodiments, between pH 7 and 9. In some embodiments, the multimer may be stable in an aqueous solution having a pH between pH 1 and 9, in some embodiments between pH 1 and 3, in some embodiments between pH 3 and 5, in some embodiments between pH 5 and 7, and in some embodiments between pH 7 and 9. In some embodiments, the aqueous solution may have a physiologically acceptable pH.

[0032] In some embodiments, the ligand moiety may be capable of binding to a target and at least partially disrupting a biomolecule-biomolecule interaction (e.g., a protein-protein interaction). In some embodiments, the ligand moiety may be capable of binding to a target and at least partially disrupting a protein subunit-subunit interaction. In some embodiments, the ligand moiety may be capable of at least partially stabilizing a biomolecule-biomolecule interaction. In certain embodiments, the ligand moiety may be capable of at least partially inhibiting a conformational change in a biomolecule target.

[0033] In some instances, the linker element may be capable of generating a signal. For example, in some embodiments, the linker element may be capable of fluorescing. In some cases, the linker element may have greater fluorescence when the monomer to which it is attached is part of a multimer as compared to when the monomer to which it is attached is not part of a multimer. In some embodiments, upon multimer formation, the fluorescent brightness of a linker element may increase by at least 2-fold, in some embodiments, by at least 5-fold, in some embodiments, by at least 10-fold, in some embodiments, by at least 50-fold, in some embodiments, by at least 100-fold, in some embodiments, by at least 1000-fold, and in some embodiments, by at least 10000-fold. In some embodiments, a linker element in a multimer may have a peak fluorescence that is red-shifted relative to the peak fluorescence of the linker element in a monomer. In other embodiments, a linker element may have a peak fluorescence that is blue-shifted relative to the peak fluorescence of a linker element in a monomer.

Monomers

[0034] In certain embodiments, a first monomer may be capable of forming a biologically useful multimer capable of modulating c-Myc when in contact with a second

monomer in an aqueous media. For example, a first monomer may be represented by the formula:

X^1-Y^1-Z^1 (Formula I) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^1 is a first ligand moiety capable of binding to or modulating a first binding site on said c-Myc;

Y^1 is absent or is a connector moiety covalently bound to X^1 and Z^1;

Z^1 is a first linker capable of binding to the second monomer; and

a second monomer may be represented by the formula:

X^2-Y^2-Z^2 (Formula II) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^2 is a second ligand moiety capable of binding to a second binding site on said c-Myc;

Y^2 is absent or is a connector moiety covalently bound to X^2 and Z^2; and

Z^2 is a second linker capable of binding to the first monomer through Z^1.

[0035] For example, when a first and second monomer capable of forming a multimer (e.g., dimer) when in contact in an aqueous solution each has a different linker, e.g., Z^1 and Z^2 are different, the monomers may be referred to as 'hetero' monomers. Conversely, when a first and second monomer capable of forming a multimer (e.g., dimer) when in contact in an aqueous solution each has the same linker, e.g., Z^1 and Z^2 are the same, the monomers may be referred to as 'homo' monomers.

[0036] In one embodiment, X^1 and X^2 are different.

[0037] In another embodiment, a monomer may be represented by the formula:

X^3-Y^3-Z^3 (Formula III) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^3 is a ligand moiety capable of binding to a binding site of c-Myc;

Y^3 is absent or is a connector moiety covalently bound to X^3 and Z^3;

Z^3 is a linker capable of binding to one or more Z^3 moieties from other X^3-Y^3-Z^3 monomers to form a biologically useful multimer.

[0038] In a certain embodiment, a first monomer is capable of forming a biologically useful multimer when in contact with a second monomer in an aqueous media, wherein the first monomer is represented by the formula:

X^1-Y^1-Z^1 (Formula I) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^1 is a first ligand moiety capable of binding to a first binding site of c-Myc;

Y^1 is absent or is a connector moiety covalently bound to X^1 and Z^1;

Z^1 is a first linker capable of binding to the second monomer (e.g., *in vivo*); and the second monomer is represented by the formula:

X^4-Y^4-Z^4 (Formula IV) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^4 is a second ligand moiety capable of binding to a second binding site of c-Myc, wherein the first binding site is e.g., within about 10, 20, 30, 40, 50, 60, 70, 80 or more Å, e.g. within about 50 Å of the second binding site;

Y^4 is absent or is a connector moiety covalently bound to X^4 and Z^4; and

Z^4 is a second linker capable of binding to the first monomer through Z^1.

[0039] In another certain embodiment, a first monomer may be capable of forming a biologically useful multimer when in contact with one, two, three or more monomers . For example, a first and second monomer may be represented by the formula:

X^3-Y^3-Z^3 (Formula III) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^3 is a first ligand moiety capable of binding to and modulating a first binding site of c-Myc;

Y^3 is absent or is a connector moiety covalently bound to X^3 and Z^3;

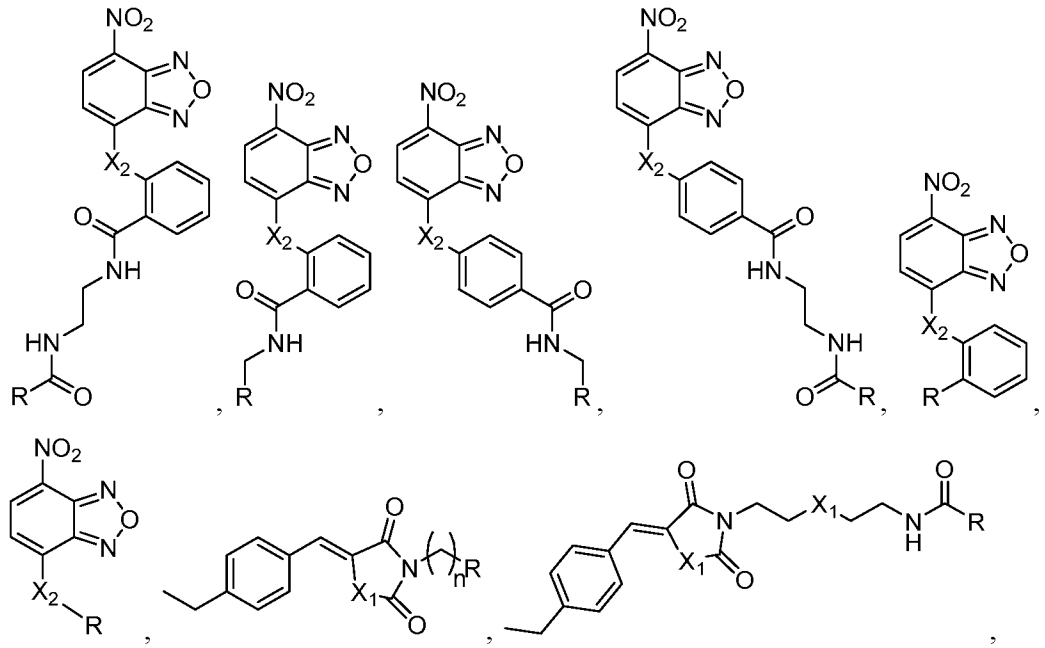
Z^3 is linker capable of forming a therapeutic multimer (e.g., dimer) with another monomer or other monomers of Formula III, wherein Z^3 is the same for the first and second monomer, as noted below. For example, when a first and second monomer capable of forming a multimer (e.g., dimer) when in contact in an aqueous solution and each monomer have the same linker, e.g., Z^3, the monomers may be referred to as 'homo' monomers.

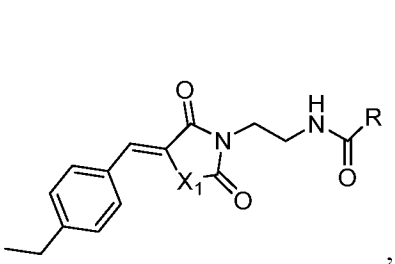
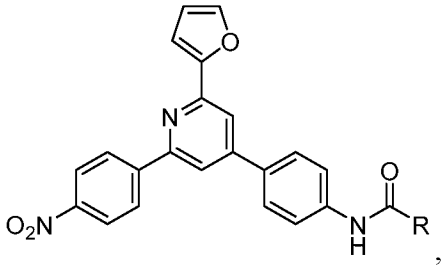
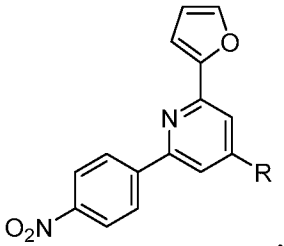
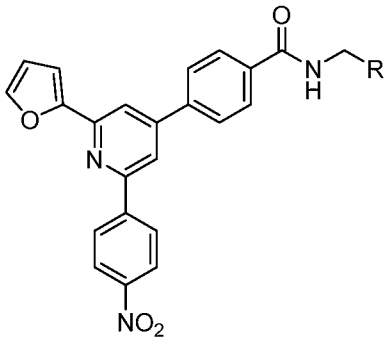
[0040] In certain embodiments, the second binding site may be within 40 Å of the first binding site, or in some embodiments within 30 Å of the first binding site. For example, in some embodiments, the maximum distance between the first ligand moiety (*e.g.*, first binding site) and the second ligand moiety (*e.g.*, second binding site) in the biologically useful

multimer is less than about 25 Å, in some embodiments less than 20 Å, and in some embodiments less than 15 Å.

[0041] In certain embodiments, the connector moiety may have a length of less than about 30 Å. In certain embodiments, the connector moiety may have a length of less than about 25 Å. In certain embodiments, the connector moiety may have a length of less than about 15 Å. In certain other embodiments, the connector moiety may have a length of less than about 10 Å. In still other embodiments, the connector moiety may have a length of less than about 5 Å. In certain embodiments, the connector moiety may have a length of between about 5 Å and about 30 Å.

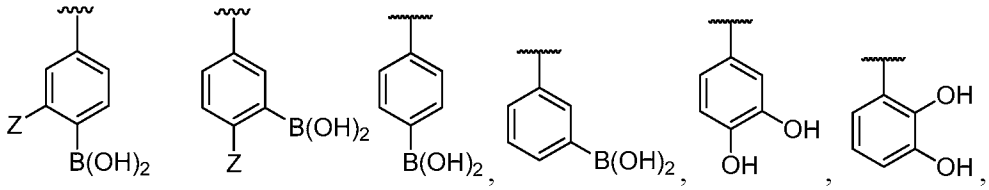
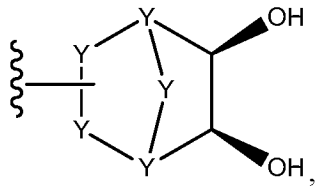
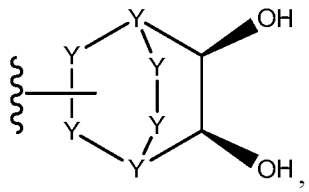
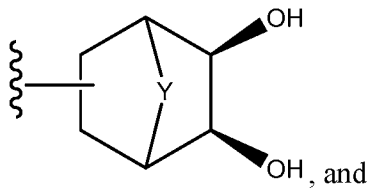
[0042] In some embodiments, a monomer may be selected from the group consisting of:



and pharmaceutically acceptable salts thereof, wherein:

R is selected from the group consisting of:

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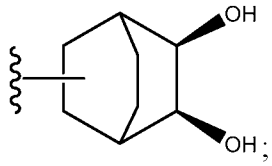


X is independently selected for each occurrence from S, O, NH and N-C_{1-6}alkyl;

Z is selected from the group consisting of H, halo, CF_3, O-C_{1-6}alkyl, hydroxyl, and C_{1-6}alkyl;

Y is NR''', O or CR''$_{1-2}$, wherein R'' is independently selected from the group consisting of H, methyl, O, NH, and N-C_{1-6}alkyl; R''' is independently selected from the group consisting of H, C1-6alkyl, phenyl, optionally substituted with 1-3 halogen, nitrile, C1-3alkyl or haloalkyl; and

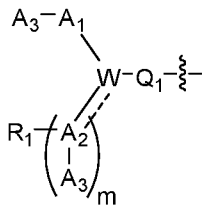
n is 1, 2, or 3.

A) Linkers

[0043] The linker moieties Z^1, Z^2, Z^3 and Z^4 of Formulas I, II, III and IV may, in some embodiments, be the same or different. For example, linker moieties are independently contemplated herein.

[0044] In a certain embodiment, the first monomer is represented by the formula

[0045] X^1-Y^1-Z^1, wherein Z^1 is a first linker that, for example, may form a dimer with a second monomer, e.g., X^2-Y^2-Z^2 or X^4-Y^4-Z^4, wherein, for example, Z^1 may be a diol and Z^2 or Z^4 may independently be a boronic acid or oxaborole moiety. In one embodiment, Z^1 is a first linker selected from the group consisting of



a)

wherein

A_1 is (a) absent; or (b) selected from the group consisting of acyl, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

A_2, independently for each occurrence, is (a) absent; or (b) selected from the group consisting of –N–, acyl, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic, provided that at least one of A_1 and A_2 is present; or

A_1 and A_2, together with the atoms to which they are attached, form a substituted or unsubstituted 4-8 membered cycloalkyl or heterocyclic ring;

A_3 is selected from the group consisting of -NHR', -SH, or -OH;

W is CR' or N;

R' is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or -OH;

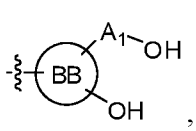
m is 1-6;

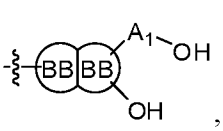
=== represents a single or double bond; and

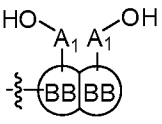
R_1 is (a) absent; or (b) selected from the group consisting of hydrogen, halogen, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or -OH;

Q_1 is (a) absent; or (b) selected from the group consisting of substituted or unsubstituted aliphatic or substituted or unsubstituted heteroaliphatic; or

R_1 and Q_1 together with the atoms to which they are attached form a substituted or unsubstituted 4-8 membered cycloalkyl or heterocyclic ring;

b) 

, 

, or 

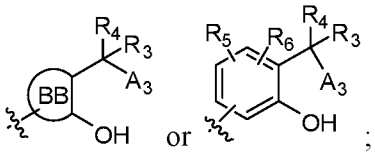
, wherein

BB, independently for each occurrence, is a 4-8 membered cycloalkyl, heterocyclic, phenyl, naphthyl, or heteroaryl moiety, wherein the cycloalkyl, heterocyclic, phenyl, naphthyl, or heteroaryl moiety is optionally substituted with one or more groups represented by R_2, wherein the two substituents comprising -OH have a 1,2 or 1,3 configuration;

each R_2 is independently selected from hydrogen, halogen, oxo, sulfonate, $-NO_2$, -CN, -OH, $-NH_2$, -SH, -COOH, -CONHR', $-CONH-SO_2-R'$, $-SO_2NH-CO-R'$, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, or two R_2 together with the atoms to which they are attached form a fused substituted or unsubstituted 4-6 membered cycloalkyl or heterocyclic bicyclic ring system;

A_1, independently for each occurrence, is (a) absent; or (b) selected from the group consisting of acyl, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

R' is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or -OH;

c)  ;

wherein

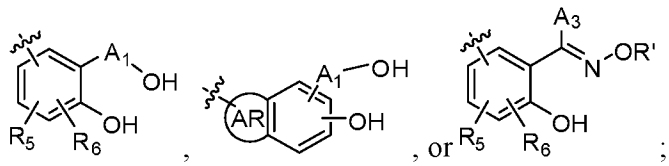
BB is a substituted or unsubstituted 5- or 6-membered cycloalkyl, heterocyclic, phenyl, naphthyl, or heteroaryl moiety;

A_3, independently for each occurrence, is selected from the group consisting of –NHR' or –OH;

R_3 and R_4 are independently selected from the group consisting of H, $C_{1\text{-}4}$alkyl, phenyl, or R_3 and R_4 taken together from a 3-6 membered ring;

R_5 and R_6 are independently selected from the group consisting of H, $C_{1\text{-}4}$alkyl optionally substituted by hydroxyl, amino, halogen, or thio; $C_{1\text{-}4}$alkoxy; halogen; -OH; -CN; -COOH; -CONHR'; or R_5 and R_6 taken together form phenyl or a 4-6 membered heterocycle; and

R' is selected from the group consisting of hydrogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or -OH;

d)  ;

wherein

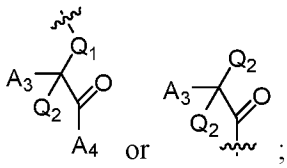
A_1 is (a) absent; or (b) selected from the group consisting of acyl, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

A_3, independently for each occurrence, is selected from the group consisting of –NHR' or –OH;

AR is a fused phenyl or 4-7 membered aromatic or partially aromatic heterocyclic ring, wherein AR is optionally substituted by oxo, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{1-4}alkoxy; -S- C_{1-4}alkyl; halogen; -OH; -CN; -COOH; -CONHR'; wherein the two substituents comprising -OH are ortho to each other;

R_5 and R_6 are independently selected from the group consisting of H, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{1-4}alkoxy; halogen; -OH; -CN; -COOH; CONHR'; and

R' is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or –OH;

e)  ; wherein

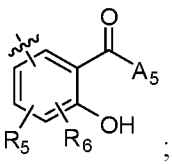
Q_1 is selected from the group consisting of C_{1-4}alkyl, alkylene, or a bond; C_{1-6}cycloalkyl; a 5-6 membered heterocyclic ring; or phenyl;

Q_2, independently for each occurrence, is selected from the group consisting of H, C_{1-4}alkyl, alkylene, or a bond; C_{1-6}cycloalkyl; a 5-6 membered heterocyclic ring; substituted or unsubstituted aliphatic; substituted or unsubstituted heteroaliphatic; substituted or unsubstituted phenyl or naphthyl; or substituted or unsubstituted heteroaryl;

A_3, independently for each occurrence, is selected from the group consisting of $–NH_2$ or -OH;

A_4, independently for each occurrence, is selected from the group consisting of -NH-NH_2; -NHOH, -NH-OR'', or –OH;

R'' is selected from the group consisting of H or C_{1-4}alkyl; and

f)  ; wherein

A_5 is selected from the group consisting of –OH, $-NH_2$, -SH, -NHR''';

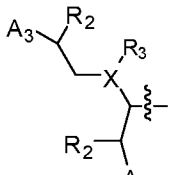
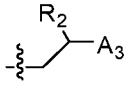
R''' is selected from $-NH_2$; -OH; phenoxy; heteroaryloxy; and C_{1-4}alkoxy;

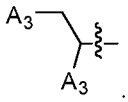
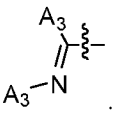
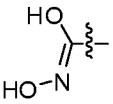
R_5 and R_6 are independently selected from the group consisting of H, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{1-4}alkoxy; halogen; -OH; -CN; -COOH; -CONHR'; or R_5 and R_6 taken together may form a 5-6 membered ring;

R' is selected from the group consisting of hydrogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, -NH_2, -SH, or –OH.

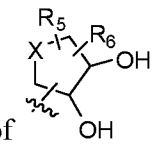
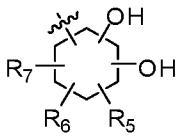
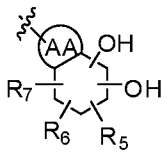
A person of skill in the art appreciates that certain substituents may, in some embodiments, result in compounds that may have some instability and hence would be less preferred.

[0046] In some embodiments, A_1 may be selected from the group consisting of C_1-C_3alkylene optionally substituted with one, two, or three halogens, or –C(O)-.

[0047] In other embodiments, Z^1 may be  , wherein R_2, independently for each occurrence, is selected from H, C_{1-4} alkyl, or two R_1 moieties taken together form a 5- or 6-membered cycloalkyl or heterocyclic ring, wherein R_3 is H, or  .

[0048] In certain embodiments, Z^1 may be  . In some cases, Z^1 may be  . For example, in some instances, Z^1 may be  .

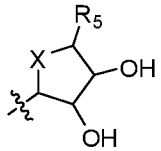
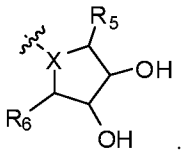
[0049] In some embodiments, Z^1 may be a monosaccharide or a disaccharide.

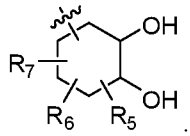
[0050] In some cases, Z^1 may be selected from the group consisting of  ,  , or  ; wherein

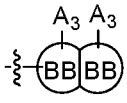
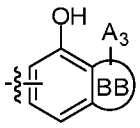
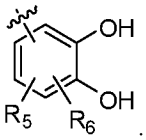
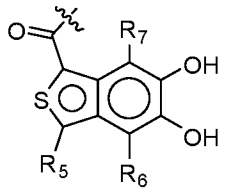
X is selected from O, S, CH, NR', or when X is NR', N may be covalently bonded to Y of Formula I;

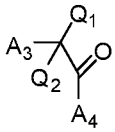
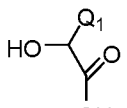
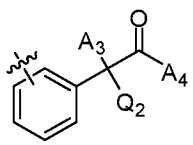
R' is selected from the group consisting of H, C_{1-4}alkyl;

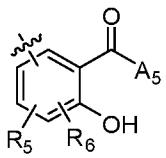
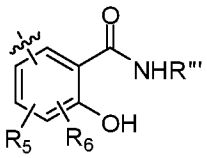
R_5, R_6, and R_7 are independently selected from the group consisting of H, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{1-4}alkoxy; halogen; -OH; -CN; -COOH; -CONHR'; or a mono- or bicyclic heterocyclic optionally substituted with amino, halo, hydroxyl, oxo, or cyano; and

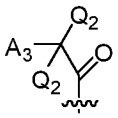
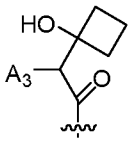
AA is a 5-6 membered heterocyclic ring optionally substituted by C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{1-4}alkoxy; halogen; -OH; -CN; -COOH; -CONHR', or -S- C_{1-4}alkyl. For example, in some embodiments, Z^1 may be  . In some instances, Z^1 may be  . In certain cases, X may be nitrogen.

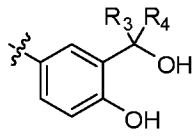
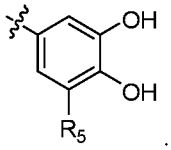
[0051] In some embodiments, Z^1 may be  .

[0052] In other embodiments, Z^1 may be  . For example, in some cases, the Z^1 may be  . In other instances, Z^1 may be  . In some embodiments, Z^1 may be  .

[0053] In some cases, Z^1 may be  . For example, Z^1 may be  . In other embodiments, Z^1 may be  .

[0054] In some cases, Z^1 may be  . In some embodiments, Z^1 may be  .

[0055] In some embodiments, Z^1 may be  . For example, Z^1 may be  .

[0056] In certain embodiments, Z^1 may be  . In other embodiments, Z^1 may be  .

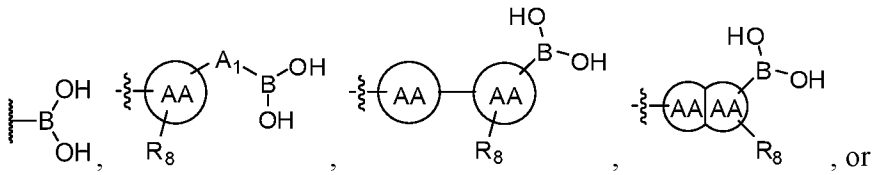
[0057] In some embodiments, the second monomer may be X^2-Y^2-Z^2 (Formula II), wherein Z^2 is a boronic acid or oxaborale moiety, and wherein X^2 is a second ligand capable of binding to a second target biomolecule segment (e.g. a segment of a fusion protein or a binding site of tandem binding sites), and Y^2 is absent or is a connector moiety covalently bound to X^2 and Z^2. In some instances, X^1 and X^2 may be the same. In other instances, X^1 and X^2 may be different.

[0058] In some embodiments, the second monomer may be X^4-Y^4-Z^4 (Formula IV), wherein Z^4 is a boronic acid or oxaborale moiety, and wherein X^4 is a second ligand moiety capable of binding to a protein binding site, wherein the protein binding site is within e.g., about 50 Å of the binding site (e.g., second binding site on same protein as first binding site, or a segment of a fusion protein or a second binding site of tandem binding sites), and Y^4 is absent or is a connector moiety covalently bound to X^4 and Z^4. For example, X^1 may be capable of binding to a first binding site, and X^4 may be capable of binding to a second binding site,

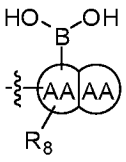
wherein the second binding site is within, e.g., about 50 Å of the first binding site. In some instances, X^1 and X^4 may be the same. In other instances, X^1 and X^4 may be different.

[0059] In some cases, the first target biomolecule and the second target biomolecule may be different. In other embodiments, the first target biomolecule and the second target biomolecule may be the same.

[0060] In some embodiments, the linker of the second monomer, for example, Z^2 or Z^4, may be selected from the group consisting of:



, or



; wherein

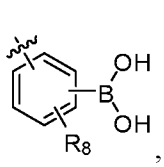
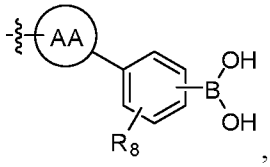
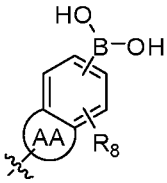
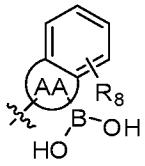
R_8 is selected from the group consisting of H, halogen, oxo, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo or thio; C_{2-4}alkenyl, C_{1-4}alkoxy; -S- C_{1-4}alkyl; -CN; -COOH; or –CONHR';

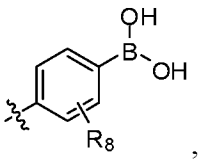
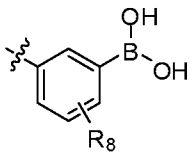
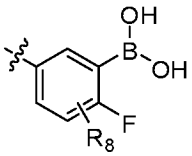
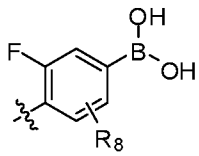
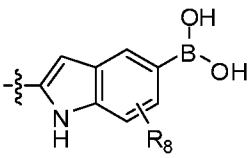
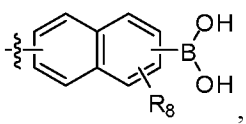
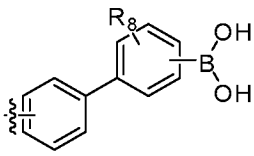
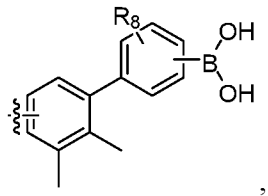
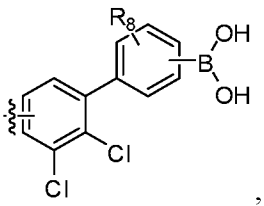
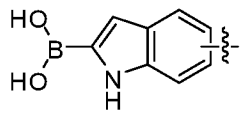
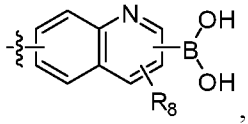
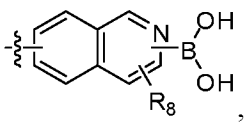
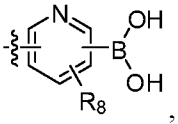
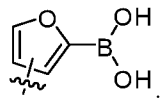
A_1 is (a) absent; or (b) selected from the group consisting of acyl, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

AA, independently for each occurrence, is phenyl, naphthyl, or a 5-7 membered heterocyclic or heteroaryl ring having one, two, or three heteroatoms, wherein AA is optionally substituted by one, two, or three substituents selected from the group consisting of halogen, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halogen, or thio; C_{2-4}alkenyl, C_{1-4}alkoxy; -S-C_{1-4}alkyl; -CN; -COOH; –CONHR'; or two substituents together with the atoms to which they are attached form a fused 4-6 membered cycloalkyl or heterocyclic bicyclic ring system; and R' is H or C_{1-4}alkyl.

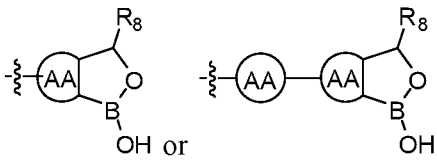
A person of skill in the art appreciates that certain substituents may, in some embodiments, result in compounds that may have some instability and hence would be less preferred.

[0061] In certain embodiments, R_8 and the substituent comprising boronic acid may be ortho to each other, and R_8 may be $–CH_2NH_2$. In some cases, the linker of the second

monomer may be selected from the group consisting of:  ,  ,  ,  .

[0062] In some embodiments, the linker of the second monomer may be selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , and  .

[0063] In some cases, the linker of the second monomer may be selected from the group consisting of:



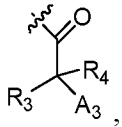
; wherein

R_8 is selected from the group consisting of H, halogen, oxo, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo or thio; C_{2-4}alkenyl, C_{1-4}alkoxy; -S- C_{1-4}alkyl; -CN; -COOH; or –CONHR';

AA, independently for each occurrence, is a 5-7 membered heterocyclic ring having one, two, or three heteroatoms, or phenyl, wherein AA is optionally substituted by one, two, or three substituents selected from the group consisting of halo, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{2-4}alkenyl, C_{1-4}alkoxy; -S- C_{1-4}alkyl; -CN; -COOH; –CONHR'; or two substituents together with the atoms to which they are attached form a fused 4-6 membered cycloalkyl or heterocyclic bicyclic ring system; and

R' is H or C_{1-4}alkyl.

[0064] In another embodiment, a monomer may be represented by the formula: X^3-Y^3-Z^3 (Formula III), wherein Z^3 is independently selected from the group consisting of:

a)  , wherein

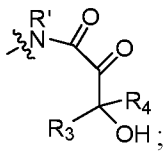
A_3 is –OH, -SH, or -NHR';

R_3 is selected from the group consisting of H, halo, C_{1-4}alkyl, C_{3-6}cycloalkyl, and heterocycle, wherein C_{1-4}alkyl, C_{3-6}cycloalkyl, or heterocycle may be optionally substituted by one, two, or three substituents selected from the group consisting of halo, cyano, amino, or hydroxyl; and

R_4 is selected from the group consisting of H, halo, C_{1-4}alkyl, C_{3-6}cycloalkyl, and heterocycle, wherein C_{1-4}alkyl, C_{3-6}cycloalkyl, or heterocycle may be optionally substituted by one, two, or three substituents selected from the group consisting of halo, cyano, amino, or hydroxyl; or

R_3 and R_4 can be taken together with the atoms to which they are attached to form a substituted or unsubstituted phenyl, substituted or unsubstituted C_{3-6}cycloalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted saturated heterocycle;

R' is H or C_{1-4}alkyl; and

b)  ; wherein

R' is C_{1-4}alkyl optionally substituted with hydroxyl; $-NH_2$; -OH; and C_{1-4}alkoxy;

R_3 is selected from the group consisting of H, halo, C_{1-4}alkyl, C_{3-6}cycloalkyl and heterocycle, wherein C_{1-4}alkyl, C_{3-6}cycloalkyl, or heterocycle may be optionally substituted by one, two, or three substituents selected from the group consisting of halo, cyano, amino, or hydroxyl;

R_4 is selected from the group consisting of H, C_{1-4}alkyl, C_{3-6}cycloalkyl and heterocycle, wherein C_{1-4}alkyl, C_{3-6}cycloalkyl, or heterocycle may be optionally substituted by one, two or three substituents selected from the group consisting of halo, cyano, amino, or hydroxyl; or

R_3 and R_4 can be taken together with the atoms to which they are attached to form a substituted or unsubstituted phenyl, substituted or unsubstituted C_{3-6}cycloalkyl, substituted or unsubstituted heteroaryl or substituted or unsubstituted saturated heterocycle; and

wherein Z^3 is a linker moiety capable of binding to one or more X^3-Y^3-Z^3 monomers to form a biologically useful multimer.

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.

[0065] As discussed above, a monomer may be capable of reacting with one or more other monomers to form a multimer. In some embodiments, a first monomer may react with a second monomer to form a dimer. In other embodiments, a first monomer may react with a second monomer and a third monomer to form a trimer. In still other embodiments, a first monomer may react with a second monomer, a third monomer, and a fourth monomer to form a tetramer. In some embodiments, each of the monomers that form a multimer may be essentially the same. In some embodiments, each of the monomers that form a multimer may be substantially different. In certain embodiments, at least some of the monomers that form a multimer may be essentially the same or may be substantially different.

[0066] In some embodiments, the linker element of a first monomer and the linker element of a second monomer may be substantially different. In other embodiments, a connector element of a first monomer and a connector element of a second monomer may be substantially different. In still other embodiments, the ligand moiety (e.g., a pharmacophore) of a first monomer and the ligand moiety (e.g., a pharmacophore) of the second monomer may be substantially different.

[0067] In some cases, formation of a multimer from a plurality of monomers may be irreversible. In some embodiments, formation of a multimer from a plurality of monomers may be reversible. For example, in some embodiments, the multimer may have an oligomer or dimer dissociation constant between 10 mM and 1 nM, in some embodiments between 1 mM and 100 nM, in some embodiments between 1 mM and 1 μM, and in some embodiments between 500 μM and 1 μM. In certain embodiments, the multimer may have a dissociation

constant of less than 10 mM, in some embodiments less than 1 mM, in some embodiments less than 500 μM, in some embodiments less than 100 μM, in some embodiments less than 50 μM, in some embodiments less than 1 μM, in some embodiments less than 100 nM, and in some embodiments less than 1 nM.

B) Ligands

[0068] The ligand moieties X^1, X^2, X^3 and X^4 of Formulas I, II, III and IV may, in some embodiments, be different. For example, ligand moieties are independently contemplated herein.

[0069] In one embodiment, the ligand moiety 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 c-Myc). 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.

[0070] In one embodiment, monomers that include a pharmacophore may bind to a binding site on c-Myc. In another embodiment, monomers that include a pharmacophore may bind to a binding site on Max. Such monomers may form a multimer, as disclosed herein, that may be capable of binding to a first binding site and a second binding site of c-Myc or a binding site of c-Myc and a binding site of Max. A person skilled in the art may appreciate that additional pharmacophores may be discovered in the future and that the pharmacophores illustrated herein are not intended to limit in any way the claims.

[0071] In some embodiments, a ligand (*e.g.*, a pharmacophore) may have one or more preferred attachment points for connecting the pharmacophore to the linker (e.g., with or without a connector 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 binding

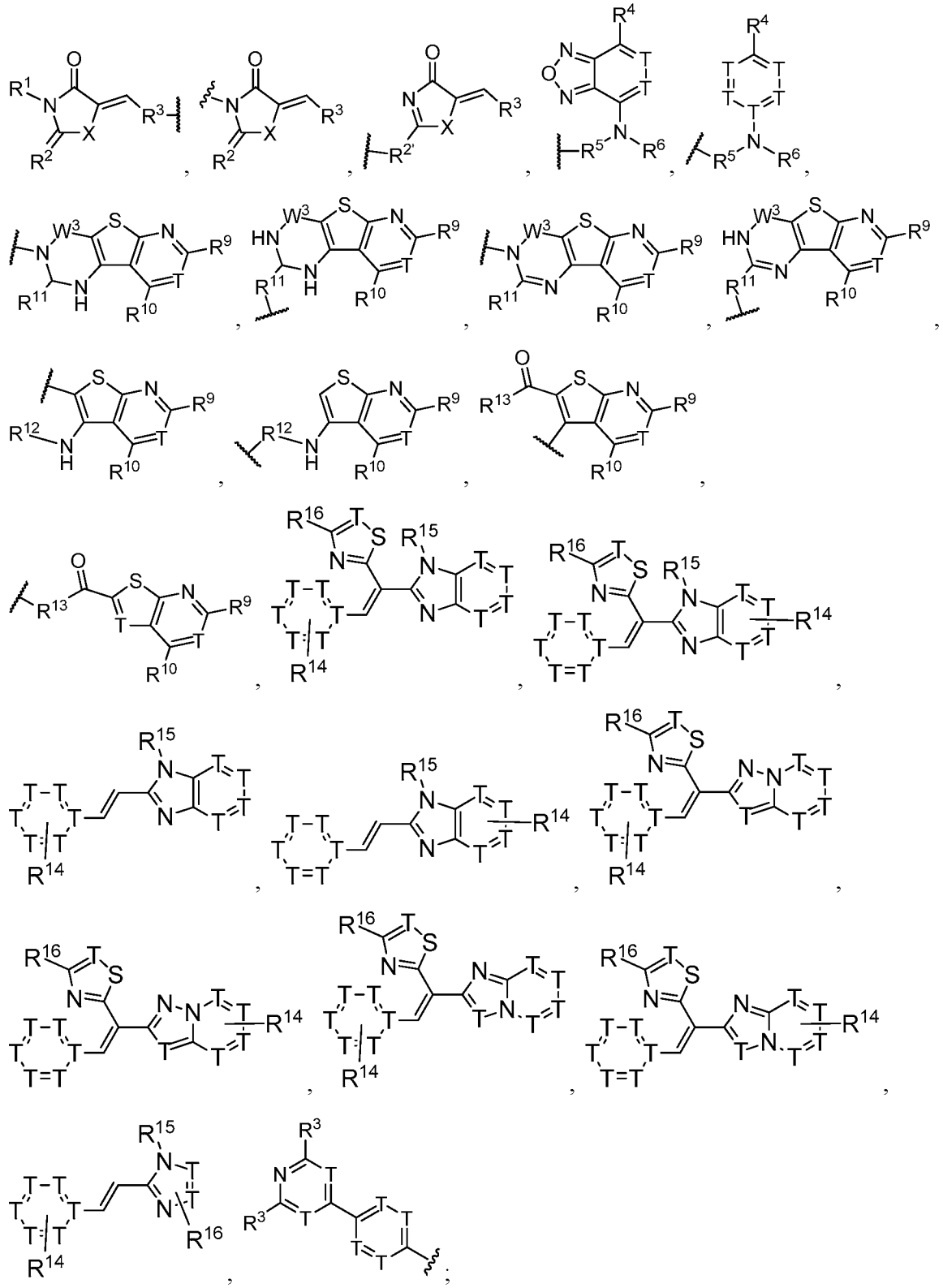
site of a protein (*e.g.*, c-Myc). In one embodiment, preferred attachment points may be identified using X-ray crystallography. The following description of a non-limiting exemplary method illustrates how a preferred attachment point may generically be identified. For example, as shown in FIG. 1, using 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 linkers. It should be apparent to those skilled in the art that overlays of the pharmacophore of interest with other alternate pharmacophores can be used to identify potential attachment points.

[0072] FIG. 2 provides a non-limiting set of pharmacophores (i.e., ligands) showing preferred attachment points (indicated by circled arrows) for connecting the pharmacophore to a linker.

[0073] In one embodiment, X^1 is a first ligand moiety capable of binding to a first binding site of c-Myc. In another embodiment X^2 is a second ligand moiety capable of binding to a second binding site of c-Myc. In still other embodiments, X^1 is a first ligand moiety capable of binding to a first binding site of Max.

[0074] For example, the disclosed ligand moieties, X^1, X^2, X^3 and X^4 of Formulas I, II, III and IV may be or include binding site ligands as described herein. It will be appreciated that the ligands disclosed herein can be attached at any open site to a –Y-Z moiety (e.g., $-Y^1-Z^1$, $-Y^2-Z^2$, $-Y^3-Z^3$, and $-Y^4-Z^4$) as described herein. Such embodiments described below include specific references to each attachment site.

[0075] Exemplary ligand moieties include those represented by the formulae:



wherein:

X is O, S, NR'', or CR''$_2$;

T is independently selected from the group consisting of N and CH;

W^3 is C=O or CH_2;

R^1 is H, alkyl, phenyl, or a 5-10 membered heterocyclyl;

R^2 is O or S;

$R^{2'}$ is NR'', O, S, or a bond;

R^3 is selected from the group consisting of phenyl, diphenyl, naphthyl, 5-10 membered heteroaryl, and cyclohexyl, wherein phenyl, diphenyl, naphthyl, heteroaryl, and cyclohexyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, nitro, cyano, acyl, carboxyl, SO_2R'', $SO_2N(R'')_2$, C(O)-$N(R'')_2$, N(R'')acyl, hydroxy, C_{1-3} alkoxy, C_{1-4}alkyl, C_{1-4}alkenyl, and C_{1-4}alkynyl;

R^4 is nitro N(R'')acyl, $N(R'')_2$, carboxyl, or –C(O)-$N(R'')_2$;

R^5 is selected from the group consisting of phenyl, diphenyl, naphthyl, 5-11 membered heteroaryl, and cyclohexyl, wherein phenyl, diphenyl, naphthyl, heteroaryl, and cyclohexyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, nitro, cyano, acyl, carboxyl, SO_2R'', $SO_2N(R'')_2$, C(O)-$N(R'')_2$, N(R'')acyl, hydroxy, C_{1-3} alkoxy, C_{1-4}alkyl, C_{1-4}alkenyl, and C_{1-4}alkynyl; and

R^6 is H, alkyl, C_{3-10}cycloalkyl, phenyl, 5-10 membered heteroaryl, or 5-10 membered heterocyclyl;

R^9 is selected from the group consisting of H, C_{1-6}alkyl, -CF_3, C_{1-6}alkoxy, -CN, -NO_2, and –COOH;

R^{10} is selected from the group consisting of H, -CN, –COOH, -C_{1-6}alkyl, C_{1-6}cycloalkyl, -O-C_{1-6}alkyl, -OC(O)-C_{1-6}alkyl, -OC(O)-NR'_2, -NR'-C(O)-C_{1-6}alkyl, -NR'-C(O)-O-C_{1-6}alkyl, -NR'-C(O)-NR'_2;

R^{11} is selected from the group consisting of phenyl and heteroaryl, wherein the phenyl and heteroaryl are optionally substituted;

R^{12} is selected from the group consisting of –C(O)-C_{0-6}alkyl-phenyl, –C(O)-C_{0-6}alkyl-heteroaryl, phenyl and heteroaryl, wherein the phenyl and heteroaryl are optionally substituted;

R^{13} is independently selected from the group consisting of –NH-C_{1-6}alkyl-phenyl, –NH-C_{1-6}alkyl-heteroaryl, –N(C_{1-6}alkyl)-C_{1-6}alkyl-phenyl, and piperazine, wherein the alkyl, phenyl, heteroaryl, and piperazine are optionally substituted;

R^{14} is selected from the group consisting of halo, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkoxy, and nitrile;

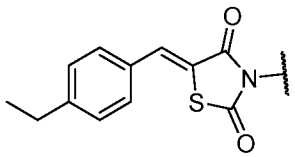
R^{15} and R^{16} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl;

R' is independently selected from the group consisting of H, C_{1-6}alkyl, and phenyl; and

R" is selected from the group consisting of H and C_{1-4}alkyl; or two R" together with the carbon to which they are attached form a C_{3-6}cycloalkyl.

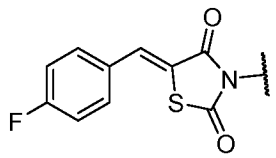
[0076] A person of skill in the art appreciates that certain substituents may, in some embodiments, result in compounds that may have some instability and hence would be less preferred.

[0077] In some embodiments, X^1 may be:

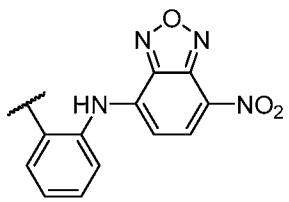


.

[0078] In other embodiments, X^1 may be:



[0079] In certain embodiments, X^2 may be:



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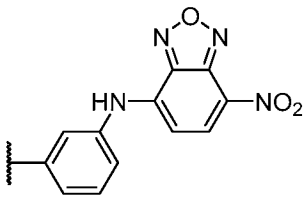
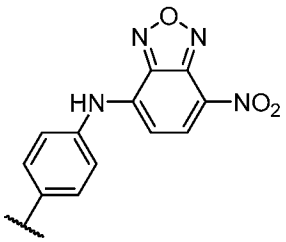
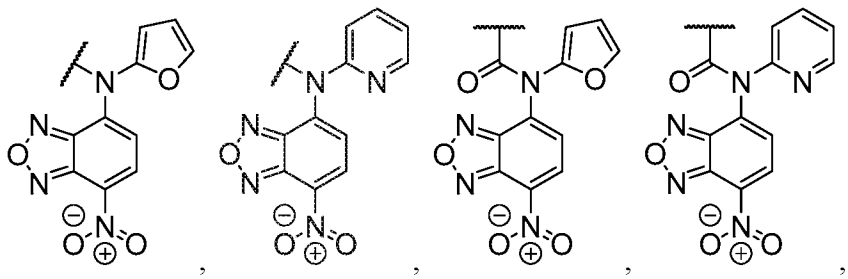
[0080] In other embodiments, X^2 may be:

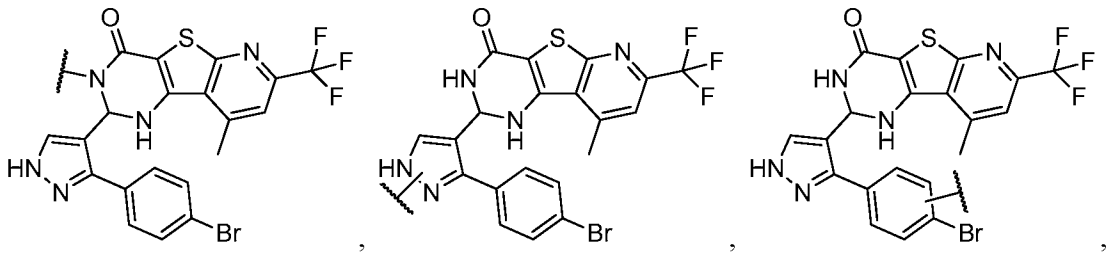


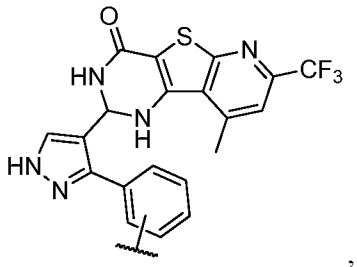
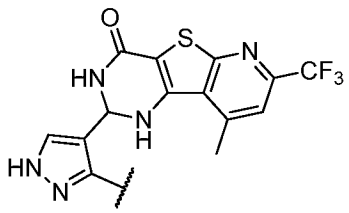
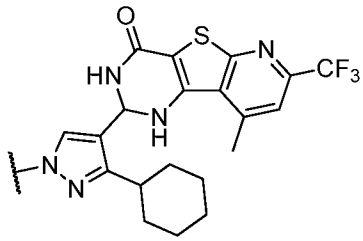
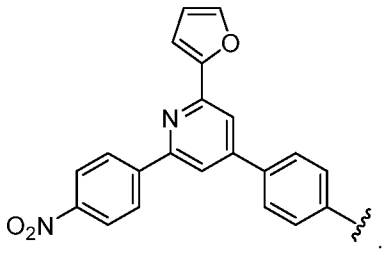
[0081] In some embodiments, X^2 may be:



[0082] In some embodiments, X^1 or X^2 may be selected from the group consisting of:








, and

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C) Connectors

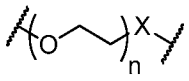
[0083] The connector moieties Y^1, Y^2, Y^3, and Y^4 of Formulas I, II, III and IV may, in some embodiments, be the same or different. For example, connector moieties are independently contemplated herein.

[0084] In some embodiments, a monomer may comprise a connector that joins the ligand moiety with the linker element. In some instances, such connectors do not have significant binding or other affinity to an intended target. However, in certain embodiments, a connector may contribute to the affinity of a ligand moiety to a target.

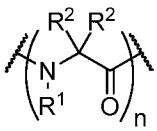
[0085] In some embodiments, a connector element may be used to connect the linker element to the ligand moiety. In some instances, a connector element may be used to adjust spacing between the linker element and the ligand moiety. In some cases, the connector element may be used to adjust the orientation of the linker element and the ligand moiety. In certain embodiments, the spacing and/or orientation the linker element relative to the ligand moiety can affect the binding affinity of the ligand moiety (e.g., a pharmacophore) to a target. In some cases, connectors with restricted degrees of freedom are preferred to reduce the entropic losses incurred upon the binding of a multimer to its target biomolecule. In some embodiments, connectors with restricted degrees of freedom are preferred to promote cellular permeability of the monomer.

[0086] In some embodiments, the connector element may be used for modular assembly of monomers. For example, in some instances, a connector element 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 linker element. In some embodiments, the connector element may comprise a spacer having a first functional group that forms a bond with a ligand moiety and a second functional group that forms a bond with a linker element.

[0087] Contemplated connecters may be any acceptable (e.g., pharmaceutically and/or chemically acceptable) bivalent linker that, for example, does not interfere with multimerization of the disclosed monomers. For instance, such linkers may be substituted or unsubstituted C_1-C_{10} alkylene, substituted or unsubstituted cycloalkylene, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, acyl, sulfone, phosphate, ester, carbamate, or amide. Contemplated connectors 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 C; O; $S(O)_q$, where q is 0, 1, or 2; NH; N-alkyl; or -C(O)- or other pharmaceutically acceptable polymers. For example, contemplated connectors may be a covalent bond or a bivalent C_{1-20} saturated or unsaturated, straight or branched, 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, naphthyl, or a mono or bicyclic heterocycle ring, where R is H or C_{1-6}alkyl. 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. For purposes of counting connector length when a ring is present in the connector group, the ring is counted as three atoms from one end to the other.

[0088] In some embodiments, a connector may have the following structure:

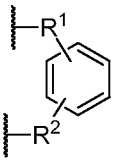
 , where:

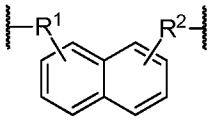
n is 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20;

R^1 and R^2 are, independently for each occurrence, selected from the group consisting of H, C_{1-6}alkyl, C_{1-6}heteroalkyl, phenyl, or heteroaryl, wherein alkyl, heteroalkyl, phenyl, and heteroaryl are optionally substituted with –OH, $-NH_2$, –SH, -COOH, $-C(O)NH_2$, halo, phenyl, and heteroaryl; or

R^1 and R^2, together with the atoms to which they are attached, form a heterocyclic structure optionally substituted with –OH, -NH_2, –SH, -COOH, -$C(O)NH_2$, halo, phenyl, and heteroaryl.

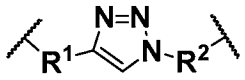
[0089] In some embodiments, a connector may comprise a phenyl, naphthyl, or mono or bicyclic heteroaryl ring, each optionally substituted. For example, a connector may comprise one or more of the following aryl structures:

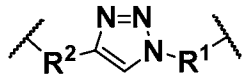


and


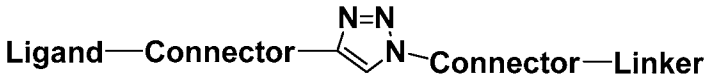
, where R^1 and R^2 are the remainder of the connector. A person of skill in the art would recognize that some substitutions may be chemically less stable and hence less preferred.

[0090] In another embodiment, a connector may comprise a triazole ring having the following structure:

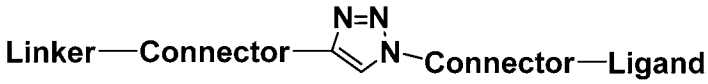


, or


, where R^1 and R^2 are the remainder of the connector. For example, a monomer comprising a triazole-containing connector may have the following general structure:



, or



, with the connectors being the same or different Such triazole-joined compounds may be formed, e.g., as a result of a "click" type reaction (i.e., an azide-alkyne cycloaddition). For example, a first segment of a connector having a terminal alkyne and a second segment of a connector having a terminal azide may be joined by a "click" reaction to form a single connector joined by a triazole, as shown above. In some embodiments, the first connector and the second connector each are less than or equal to 20 atoms in length, or in some embodiments each are less than or equal to 12 atoms in length.

[0091] 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, in some embodiments about 20Å to about 30Å, and in some embodiments about 6Å to about 15Å in length. For purposes of counting connector length when a ring is present in the connector group, the ring is counted as three atoms from one end to the other. In another

embodiment, a connecter moiety may maximally span from about 1Å to about 20Å, in some embodiments about 1Å to about 10Å, in some embodiments about 1Å to about 5Å, and in some embodiments about 5Å to about 15Å in length. For example, a connector moiety may maximally span about 1Å, about 3Å, about 5Å, about 7Å, about 9Å, about 11Å, about 13Å, about 15Å, about 17Å, or about 19Å.

[0092] In some embodiments, a connector may be selected from the group consisting of:

$-NR^{13}-(CH_2-CH_2-O)_s-CH_2-CH_2-NR^{13}-C(O)-$; $-(O-CH_2-CH_2)_t-NR^{13}-C(O)-$; $-O-C_{5-10}$alkyl-$NR^{13}-C(O)-$; -heterocyclyl-C(O)-; $-N(C_{1-3}alkyl)-C_{1-6}alkyl-NH-C(O)-$; $-NH-C_{1-6}alkyl-N(C_{1-3}alkyl)-C(O)-$; $-NR^{13}-C_{6-15}alkyl-NR^{13}-C(O)-$; -heterocyclyl-$C_{0-6}alkyl-NR^{13}-C(O)-$; and $-NR^{13}-C_{0-6}alkyl$-heterocyclyl-C(O)-;

wherein, independently for each occurrence,

R^{13} is selected from the group consisting of H and C_{1-6}alkyl;

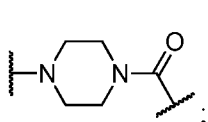
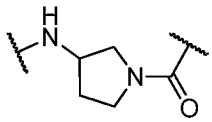
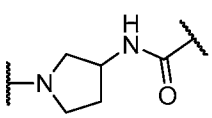
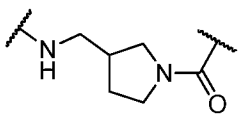
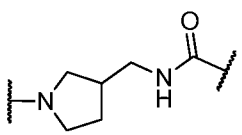
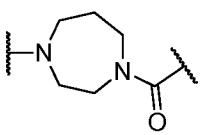
s is an integer from 0-10 (i.e., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10); and

t is an integer from 0-10 (i.e., 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10).

[0093] In certain embodiments, heterocyclyl may be a 5-7 membered heterocyclic ring comprising 1 or 2 nitrogen atoms.

[0094] In certain embodiments, R^{13} may be H. In certain other embodiments, R^{13} may be C_{1-6}alkyl. For example, in some embodiments, R^{13} may be methyl.

[0095] For example, in some embodiments, a connector may be selected from the group consisting of:

$-NH-(CH_2-CH_2-O)_s-$ $CH_2-CH_2-NH-C(O)-$; $-(O-CH_2-CH_2)_t-NH-C(O)-$; $-O-(CH_2)_t-NH-C(O)-$; $-N(CH_3)-(CH_2)_2-NH-C(O)-$; $-NH-(CH_2)_2-N(CH_3)-C(O)$; $-NH-(CH_2)_u-NH-C(O)-$; $-O-CH_2-C(O)-$; $-SO_2-N(R^{13})-$; $-SO_2-N(R^{13})-C(O)-$;  ;  ;  ;  ;  ; and  ; wherein u is an integer from 2-15 (i.e., 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15), and wherein R^{13} is selected from the group consisting of H and C_{1-6}alkyl.

[0096] In certain embodiments, a connector may be selected from the group consisting of:

$-NR^{13}-C_{6-15}alkyl-NR^{13}-C(O)-$; $-NR^{13}-(CH_2-CH_2-O)_s-C_{1-6}alkyl-NR^{13}-C(O)-$; $-(O-CH_2-CH_2)_s-NR^{13}-C(O)-$; $-S-C_{0-6}alkyl-$; $-NR^{13}-C_{3-6}alkyl-$; $-SO_2-NR^{13}-C_{0-6}alkyl-$; $-SO_2-$heterocyclyl-$C_{0-6}alkyl-$; -heterocyclyl-C(O)-; -heterocyclyl-$C_{0-6}alkyl-NR^{13}-C(O)-$; $-NR^{13}-C_{0-6}alkyl-$heterocyclyl-C(O)-; $-O-C_{1-6}alkyl-C(O)-$; $-O-C_{1-15}alkyl-NR^{13}-C(O)-$; $-O-C_{1-15}alkyl-C(O)-NR^{13}-$; and $-O-C_{1-6}alkyl-$, wherein $C_{1-6}alkyl$ is optionally substituted by -OH;

wherein, independently for each occurrence,

R^{13} is selected from the group consisting of H and $C_{1-6}alkyl$; and

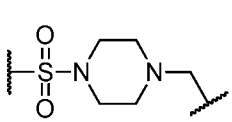
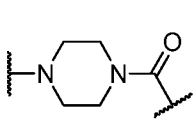
s is an integer from 1-15.

[0097] In certain embodiments, heterocyclyl may be a 5-7 membered heterocyclic ring comprising 1 or 2 nitrogen atoms.

[0098] In certain embodiments, R^{13} may be H. In certain other embodiments, R^{13} may be $C_{1-6}alkyl$. For example, in some embodiments, R^{13} may be methyl.

[0099] In certain embodiments, a connector may be selected from the group consisting of:

$-NH-(CH_2-CH_2-O)_s-$ $CH_2-CH_2-NH-C(O)-$; $-(O-CH_2-CH_2)_s-NH-C(O)-$; -S-; $-S-CH_2-$; $-O-(CH_2)_s-NH-C(O)-$; $-SO_2-NH-$; $-SO_2-NH-CH_2-$; $-N(CH_3)-(CH_2)_2-NH-C(O)-$; $-NH-(CH_2)_2-N(CH_3)-C(O)$; $-NH-(CH_2)_u-NH-C(O)-$; $-O-CH_2-C(O)-$;


;

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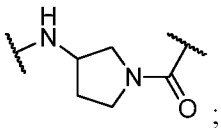
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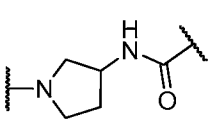
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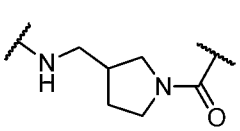
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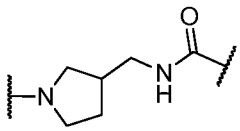
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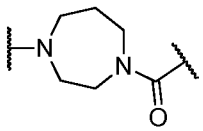
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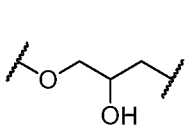

; wherein u is an integer from 6-15.

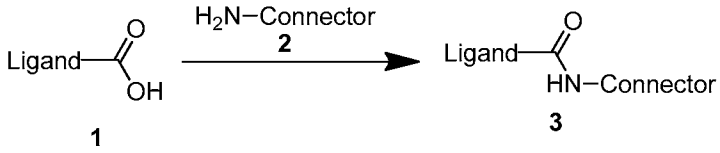
[00100] In some embodiments, a connector may be selected from the group consisting of:

$-NR^{13}-(CH_2-CH_2-O)_s-C_{1-6}alkyl-NR^{13}-C(O)-$; $-(O-CH_2-CH_2)_s-NR^{13}-C(O)-$; $-S-C_{0-6}alkyl-$; $-NR^{13}-C_{0-6}alkyl-$; $-SO_2-NR^{13}-C_{0-6}alkyl-$; $-SO_2-$heterocyclyl-$C_{0-6}alkyl-$; -heterocyclyl-C(O)-; -heterocyclyl-$C_{0-6}alkyl-NR^{13}-C(O)-$; $-NR^{13}-C_{0-6}alkyl-$heterocyclyl-C(O)-; $-O-C_{1-6}alkyl-C(O)-$; -

O-C_{1-15}alkyl-NR^{13}-C(O)-; and -O-C_{1-6}alkyl-, wherein C_{1-6}alkyl is optionally substituted by -OH; wherein, independently for each occurrence, s is an integer from 0-10 and R^{13} is selected from the group consisting of H and C_{1-6}alkyl.

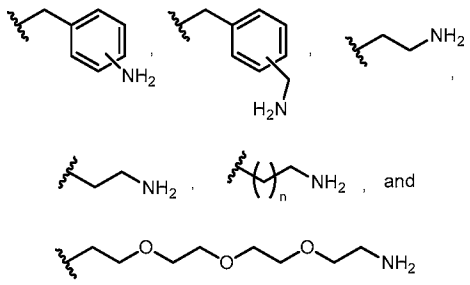
[00101] The synthetic route in Scheme Xa illustrates a general method for preparing ligand-connector derivatives. The method involves attaching the desired substituents to a carboxylic acid of the ligand.

SCHEME Xa



[00102] The desired connector can be installed by reacting the ligand **1** with the appropriate nucleophile **2** to provide **3** (ligand-connector derivative). For example, Scheme Xa provides for a connector Y (e.g. Y^1, Y^2, Y^3 or Y^4). The desired connector attached at the carbonyl substituent can be installed by reacting carboxylic acid **1** with common coupling reagents such as 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and hydroxybenzotriazole (HOBt) and then further reacting the resultant activated ester with the appropriate nucleophile, for example, amine **2**, to provide **3** (ligand-connector derivative).

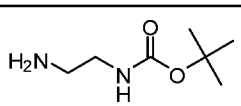
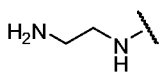
[00103] For example, the connector may be selected from the group consisting of:

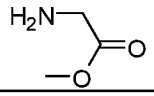
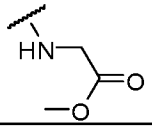
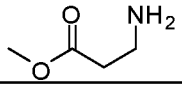
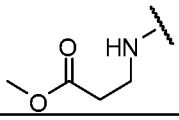
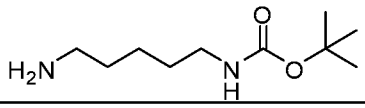
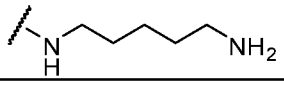
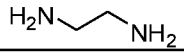
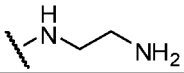
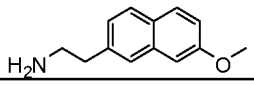
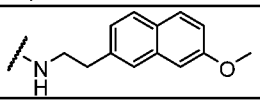
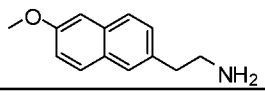
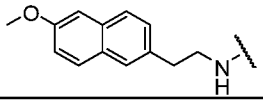
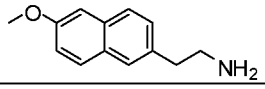
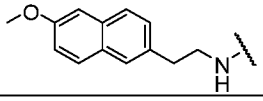
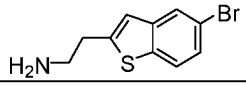
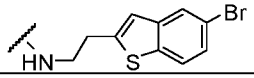
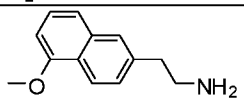
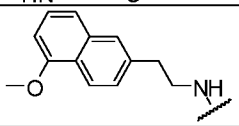
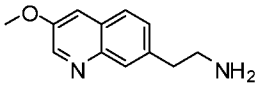
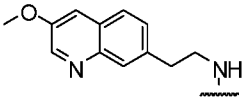
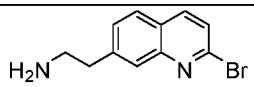
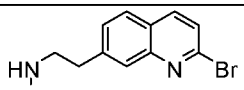
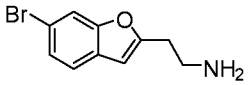
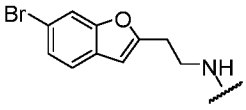
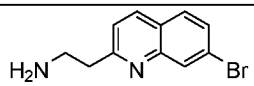
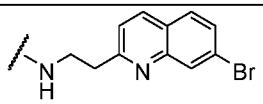
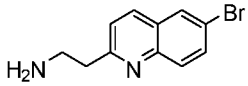
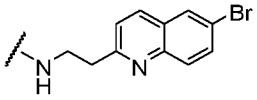


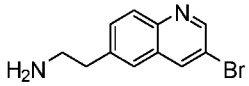
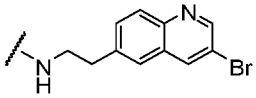
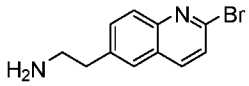
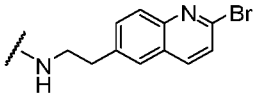
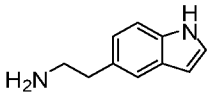
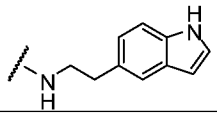
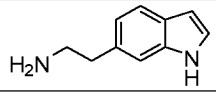
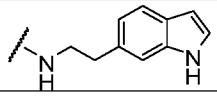
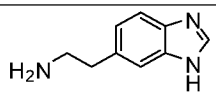
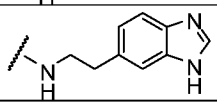
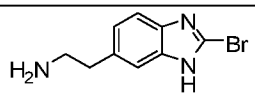
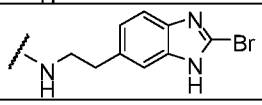
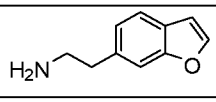
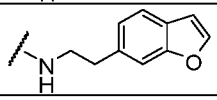
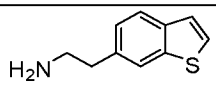
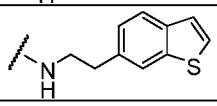
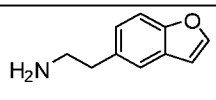
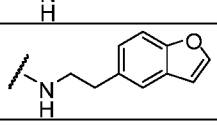
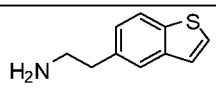
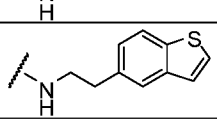
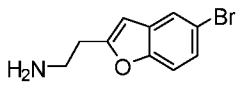
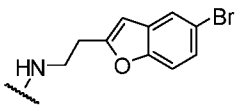
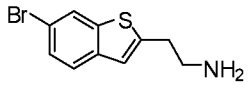
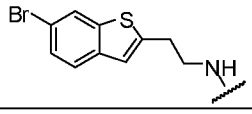
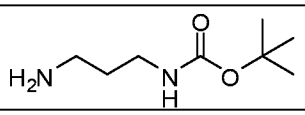
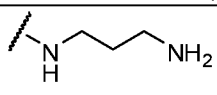
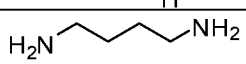
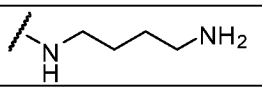
, wherein n is 1, 2, 3, 4 or 5.

[00104] Additional examples for amine **2** and Y can be found in Table A, seen below:

Table A

No.	Amine 2	-NH-R (e.g., -Y)
1		

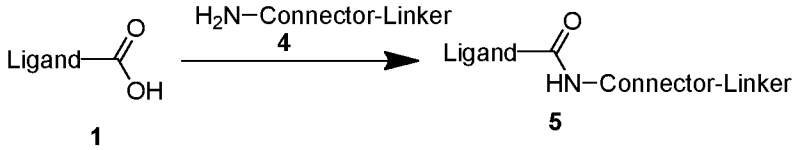
No.	Amine 2	-NH-R (e.g., -Y)
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		

No.	Amine 2	-NH-R (e.g., -Y)
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		

[00105] Any free amino group seen in the connector examples of Table A above may be functionalized further to include additional functional groups.

[00106] In another embodiment, the attachment point on the ligand (e.g., the carboxylic acid of **1** in Scheme Xa) may be further elaborated to incorporate not only the connector moiety but also the linker, as represented by:

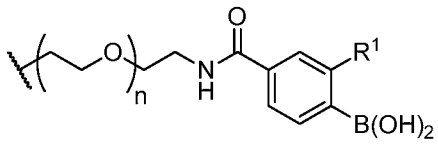
SCHEME Xa'



1 **5**

[00107] The connector-linker moiety (i.e., Y-Z) may be formed from direct attachment of the connector-linker to the ligand (as shown in Scheme Xa'), or the connector-linker moiety may be formed from the further functionalization of any functional group in the connector with the linker (e.g., a boronic acid linker). It should be clear from the linker section described above that a first monomer that has a boronic acid linker may be capable of forming a multimer with a second monomer that has a diol linker.

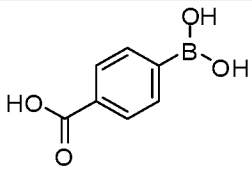
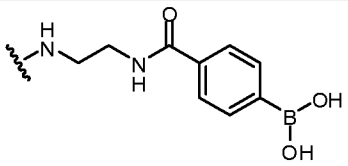
[00108] In one embodiment, the connector-linker moiety may be:

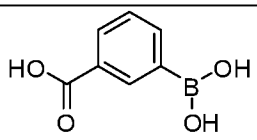
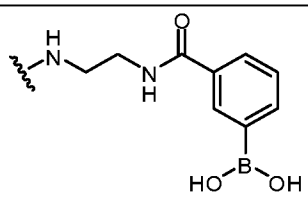
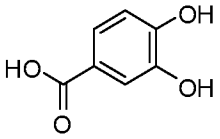
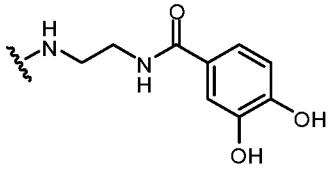
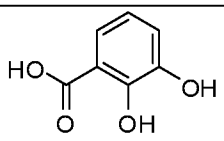
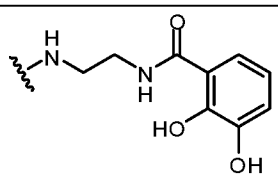
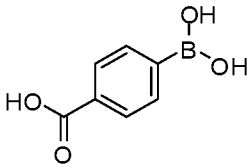
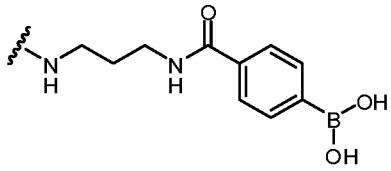
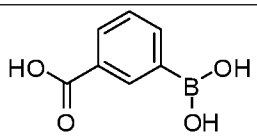
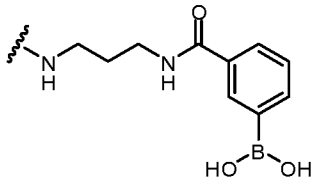
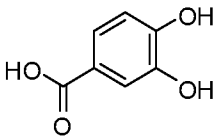
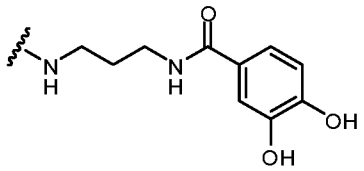
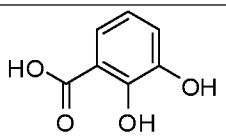
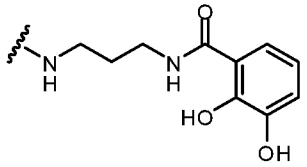
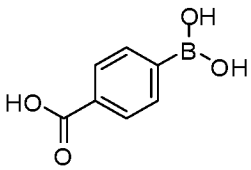
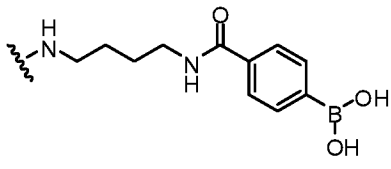


, where R^1 is H or $-C_{1-4}$alkyl.

[00109] The connector-linker (i.e., Y-Z) moiety may be formed from direct attachment of Y-Z to the carbonyl, or the Y-Z moiety may be formed from the further functionalization of any free amino group seen in the –NH-R examples (i.e., Y examples) of Table A above to include the linker moiety (Z). Examples of –NH-R-Z groups (e.g., Y-Z groups) having a boronic acid, diol or silanol linker (Z) can be found in Tables A', A'', and A''', exemplified below. It is clear from the linker section described above that a first monomer that has a boronic acid linker may be capable of forming a multimer with a second monomer that has a diol linker.

Table A'

No.	Reagent	-NH-R-Z (e.g., -Y-Z)
1 (functionalization of No. 1 in Table A)		

2 (functionalization of No. 1 in Table A)		
3 (functionalization of No. 1 in Table A)		
4 (functionalization of No. 1 in Table A)		
5 (functionalization of No. 28 in Table A)		
6 (functionalization of No. 28 in Table A)		
7 (functionalization of No. 28 in Table A)		
8 (functionalization of No. 28 in Table A)		
9 (functionalization of No. 29 in Table A)		

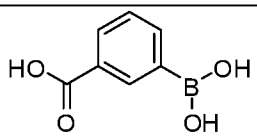
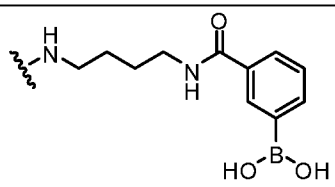
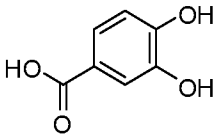
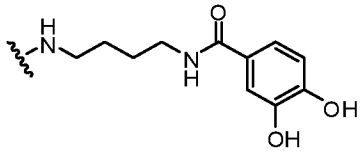
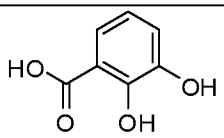
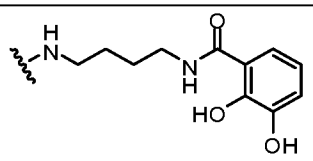
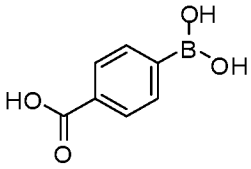
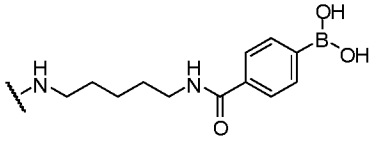
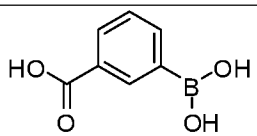
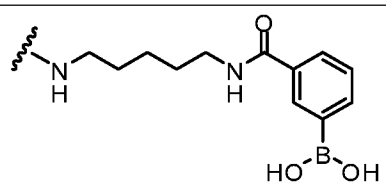
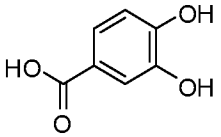
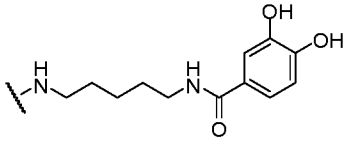
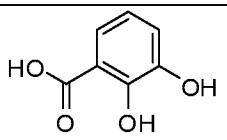
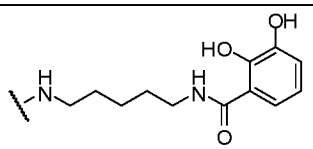
10 (functionalization of No. 29 in Table A)		
11 (functionalization of No. 29 in Table A)		
12 (functionalization of No. 29 in Table A)		
13 (functionalization of No. 4 in Table A)		
14 (functionalization of No. 4 in Table A)		
15 (functionalization of No. 4 in Table A)		
16 (functionalization of No. 4 in Table A)		

Table A''

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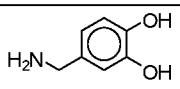
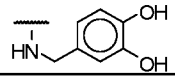
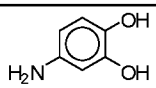
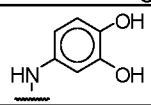
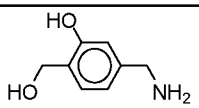
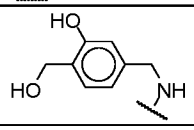
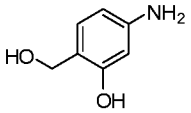
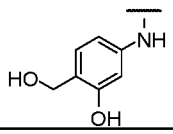
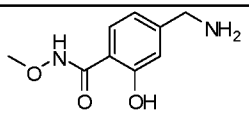
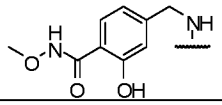
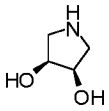
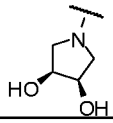
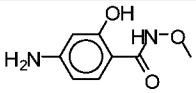
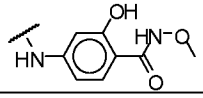
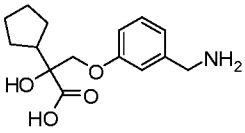
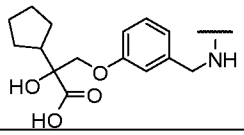
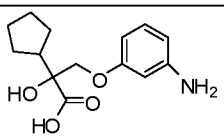
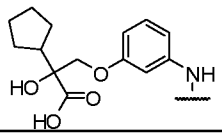
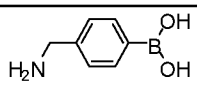
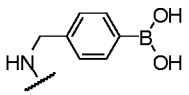
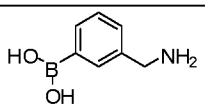
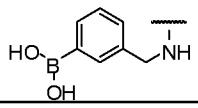
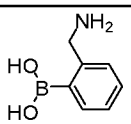
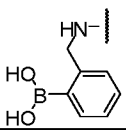
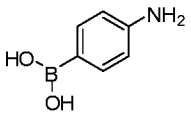
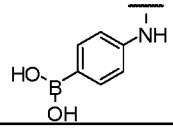
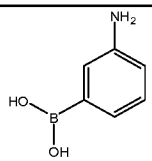
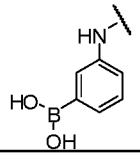
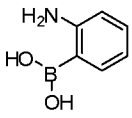
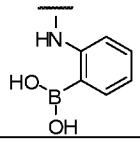
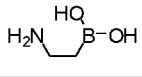
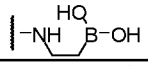
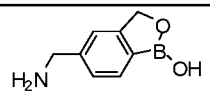
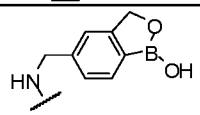
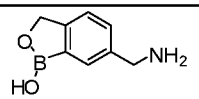
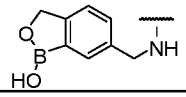
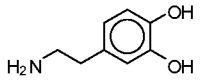
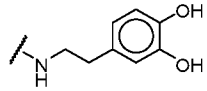
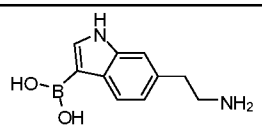
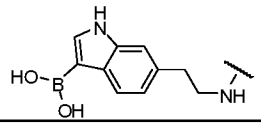
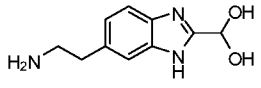
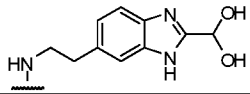
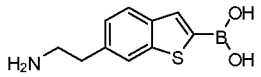
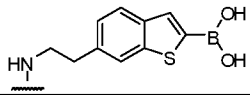
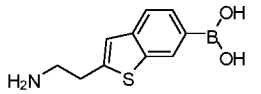
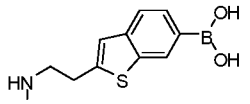
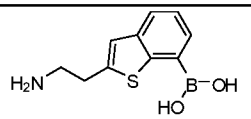
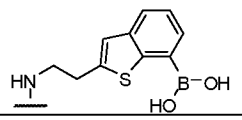
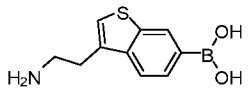
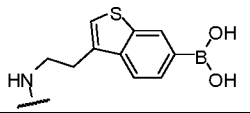
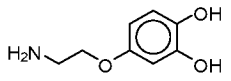
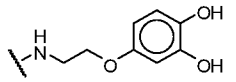
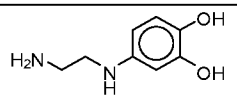
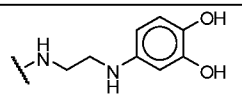
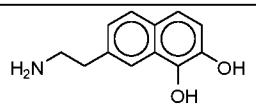
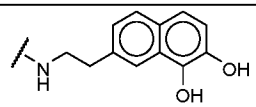
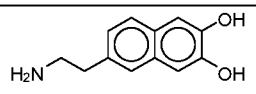
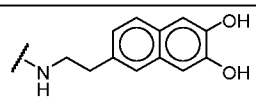
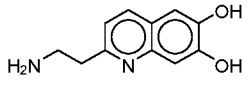
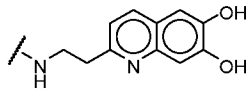
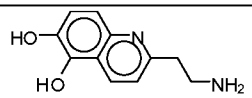
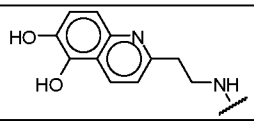
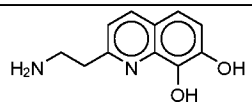
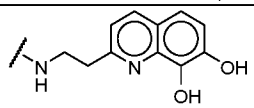
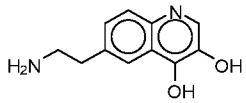
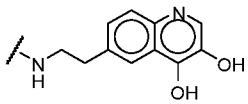
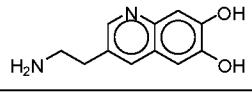
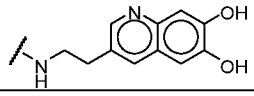
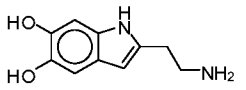
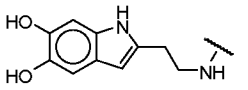
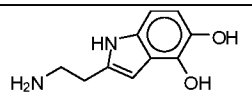
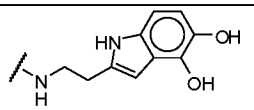
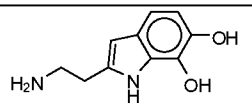
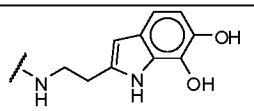
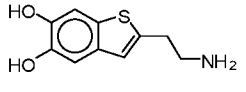
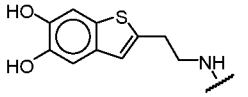
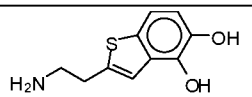
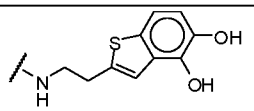
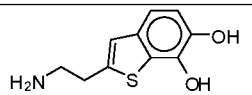
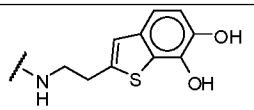
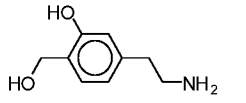
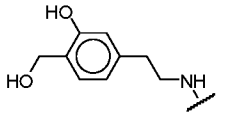
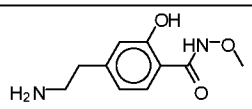
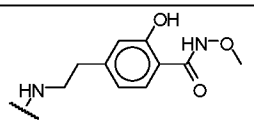
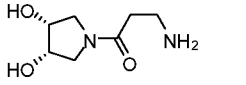
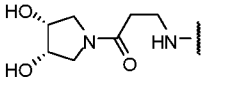
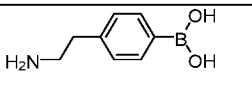
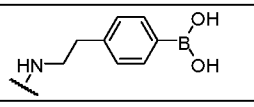
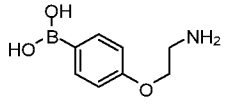
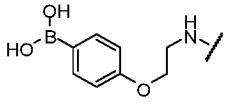
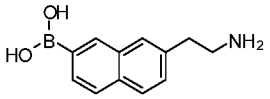
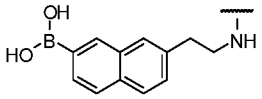
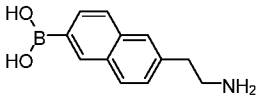
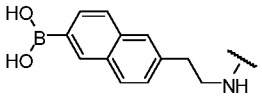
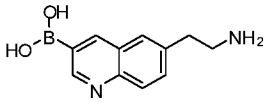
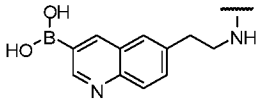
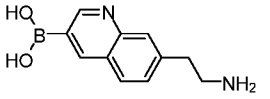
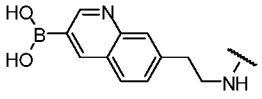
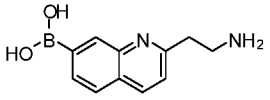
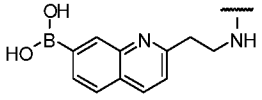
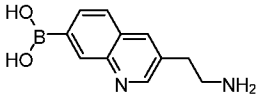
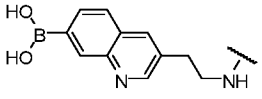
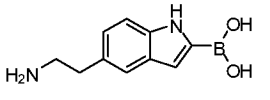
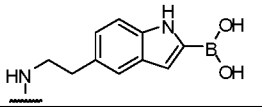
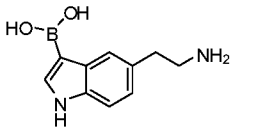
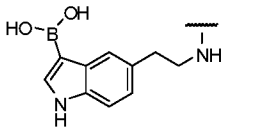
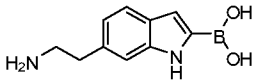
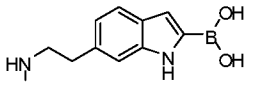
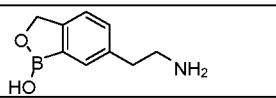
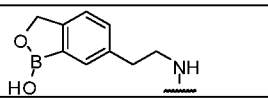
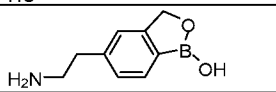
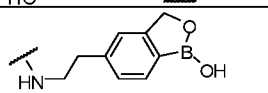
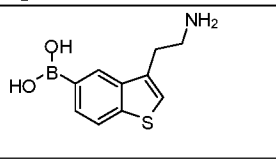
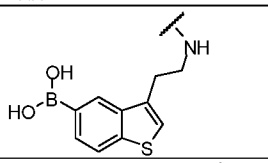
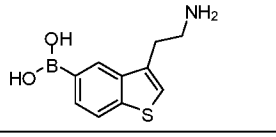
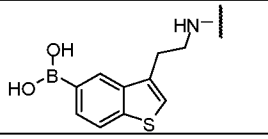
1		
2		
3		

4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		

16		
17		
18		
19		
20		
21		
22		
23		
24		
25		
26		
27		
28		
29		
30		

31		
32		
33		
34		
35		
36		
37		
38		
39		
40		
41		
42		
43		
44		
45		

46		
47		
48		
49		
50		
51		
52		
53		
54		
55		
56		
57		
58		

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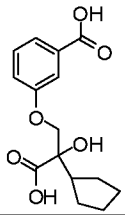
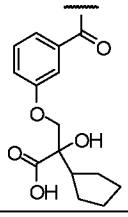
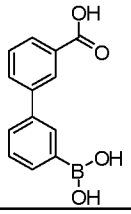
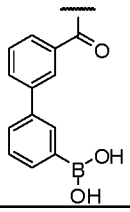
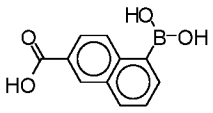
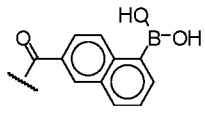
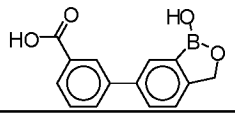
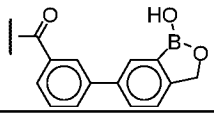
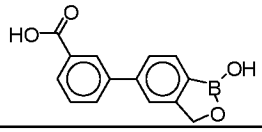
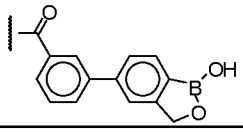
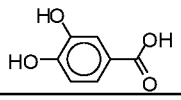
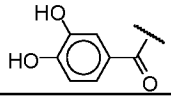
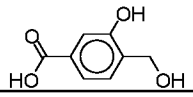
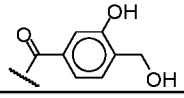
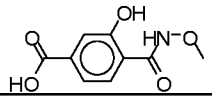
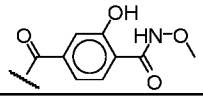
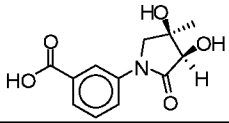
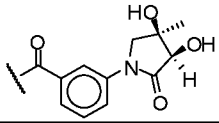
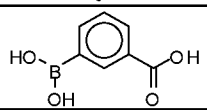
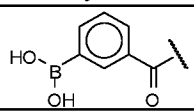
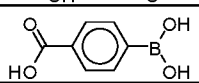
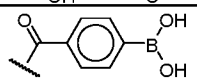
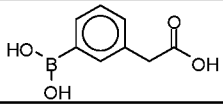
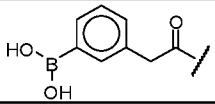
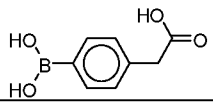
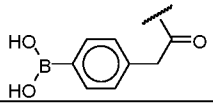
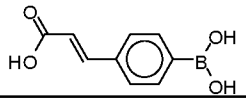
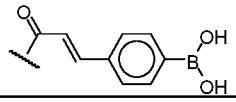
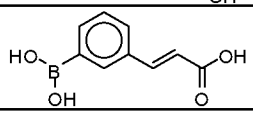
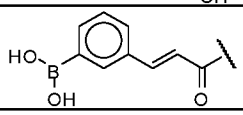
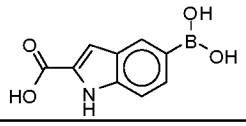
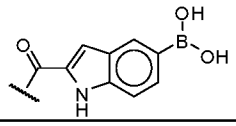
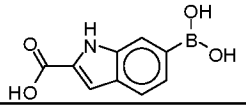
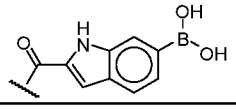
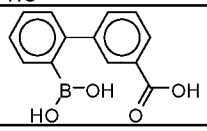
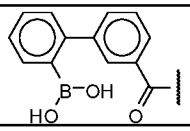
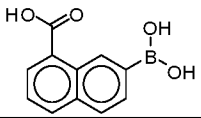
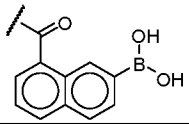
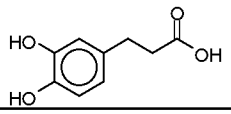
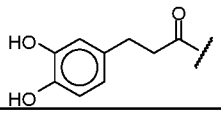
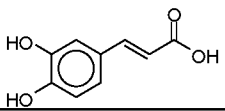
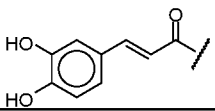
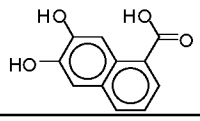
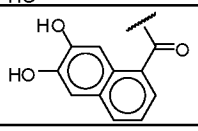
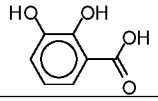
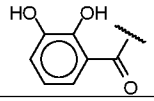
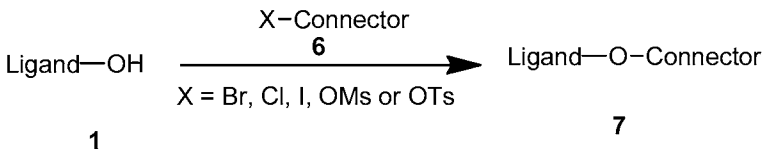
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		

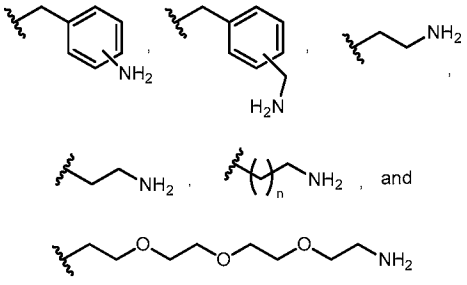
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		

[00110] The synthetic route in Scheme Xb illustrates another general method for preparing ligand-connector derivatives. The method involves attaching the desired substituents for example to an –OH, or NH_2 group (e.g., a phenol group or amine) of the ligand.

SCHEME Xb



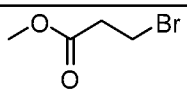
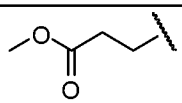
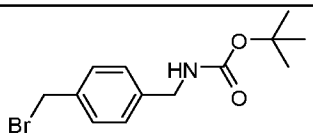
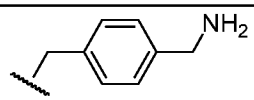
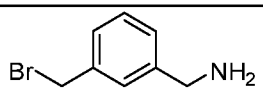
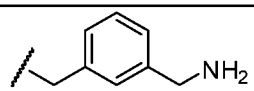
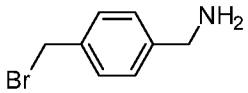
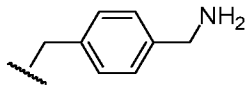
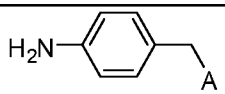
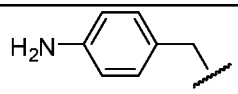
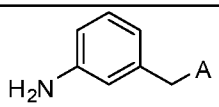
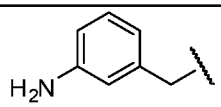
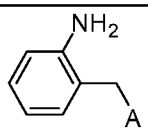
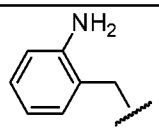
[00111] For example, the connector (Y) may be selected from the group consisting of:

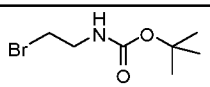
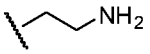
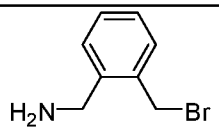
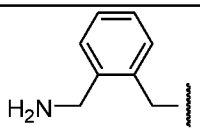
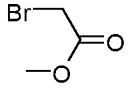
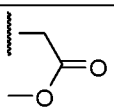
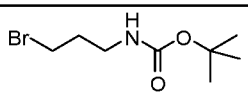
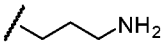
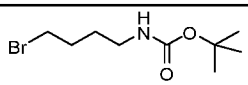
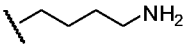
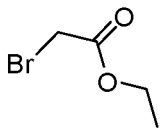
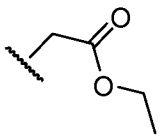


, wherein n is 1, 2, 3, 4 or 5.

[00112] Additional examples for **6** and the connector (Y) can be found in Table B, seen below:

Table B

No.	6	-Y
1		
2		
3		
4		
5	 A=Cl, Br, I, –OMs, or –OTs	
6	 A=Cl, Br, I, –OMs, or –OTs	
7	 A=Cl, Br, I, –OMs, or –	

No.	6	-Y
	OTs	
8		
9		
10		
11		
12		
13		

[00113] Any free amino group seen in the connector examples of Table B above may be functionalized further to include additional functional groups, e.g., a benzoyl group.

[00114] The connector-linker moiety (i.e., Y-Z) may be formed from direct attachment of the connector-linker to the ligand (as shown in Scheme Xb'), or the connector-linker moiety may be formed from the further functionalization of any functional group in the connector with the linker (e.g., a boronic acid linker). Examples of Y-Z groups having a boronic acid linker (Z) can be found in Table B', seen below. It should be clear from the linker section described above that a first monomer that has a boronic acid linker may be capable of forming a multimer with a second monomer that has a diol linker.

SCHEME Xb'

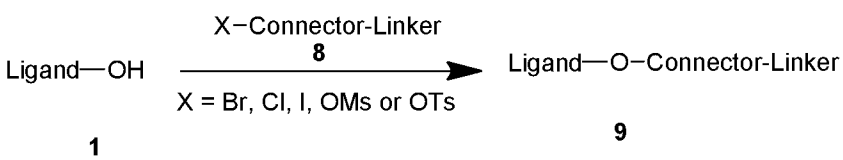
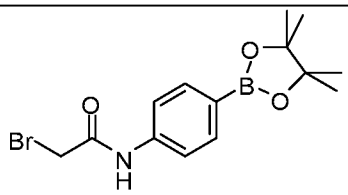
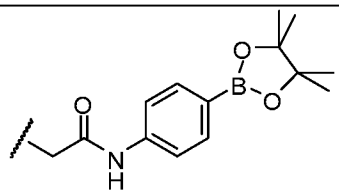
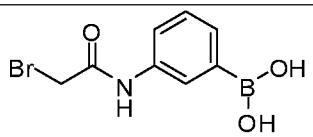
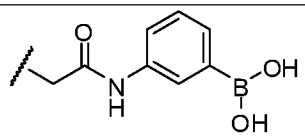
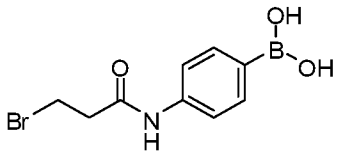
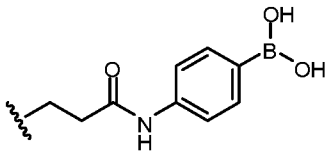
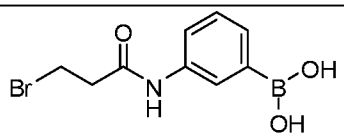
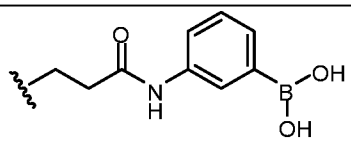
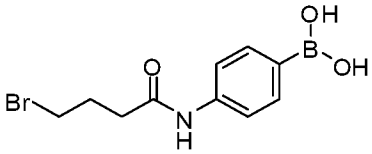
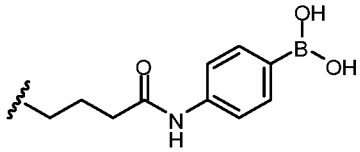
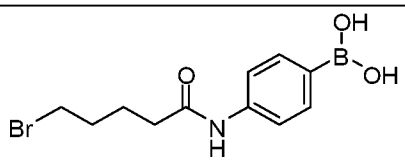
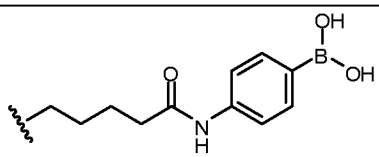
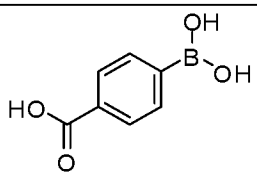
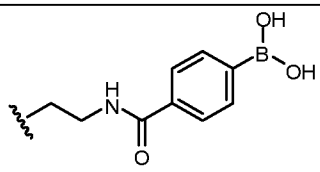
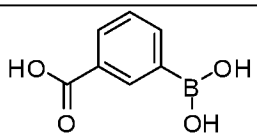
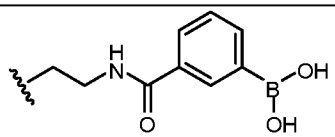
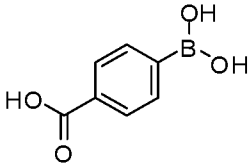
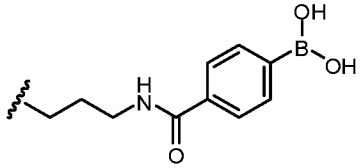
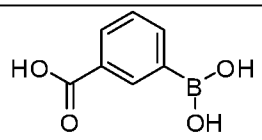
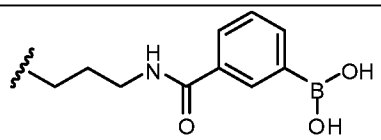
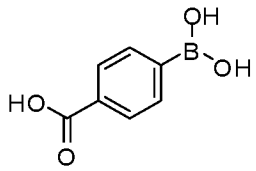
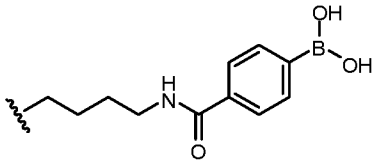
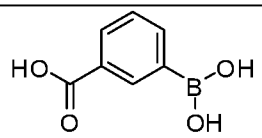
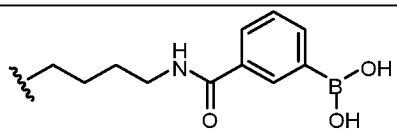


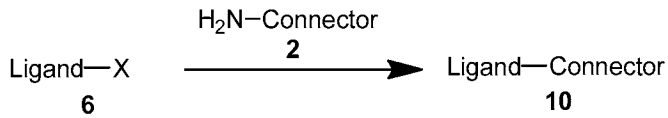
Table B'

No.	Reagent	-Y-Z
1 (direct attachment of Y-Z)		
2 (direct attachment of Y-Z)		
3 (direct attachment of Y-Z)		
4 (direct attachment of Y-Z)		
5 (direct attachment of Y-Z)		
6 (direct attachment of Y-Z)		
7 (functionalization of No. 8 in Table B)		
8 (functionalization of No. 8 in Table B)		
9 (functionalization of No. 11 in Table B)		

10 (functionalization of No. 11 in Table B)		
11 (functionalization of No. 12 in Table B)		
12 (functionalization of No. 12 in Table B)		

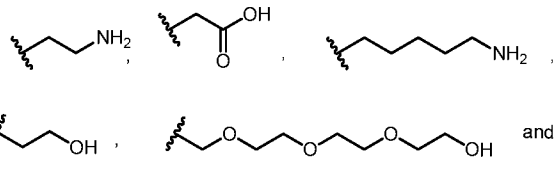
[00115] The synthetic route in Scheme Xc illustrates another general method for preparing ligand-connector derivatives. The method involves attaching the desired substituents to an aryl halide or heteroaryl halide using, e.g., a cross-coupling reaction.

SCHEME Xc



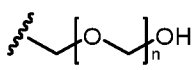
X = Cl, Br, I, -OMs, or -OTs

[00116] For example, the connector (Y) may be selected from the group consisting of:



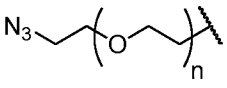
, where n may be 0, 1, 2, 3,4 or 5.

[00117] In some embodiments, the connector may generally be represented for example, by:



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

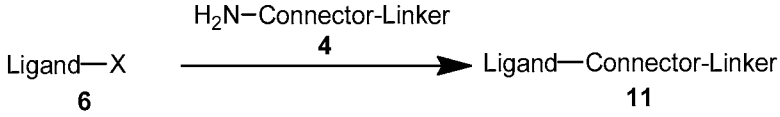
[00118] In one embodiment, the connector may be:



.

[00119] In another embodiment, the ligand may be further elaborated to incorporate not only a connector moiety, but also a linker, as e.g., represented by:

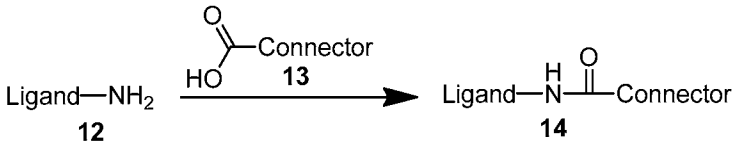
SCHEME Xc'



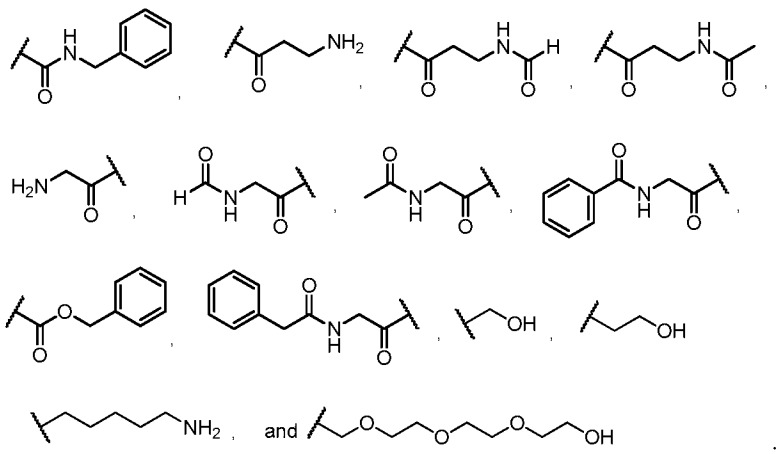
X = Cl, Br, I, -OMs, or -OTs

[00120] The synthetic route in Scheme Xd illustrates a general method for preparing ligand-connector derivatives. The method involves attaching the desired carbonyl substituents to the free amine to form an amide, urea, or carbamate. For example, the carbonyl group can be installed by reacting amine **12** (see Scheme Xd) with carboxylic acid **13** to provide **14** (ligand-connector derivative).

SCHEME Xd



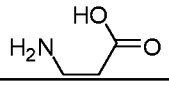
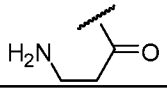
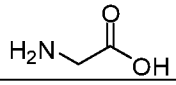
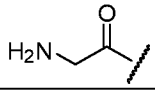
[00121] For example, -C(O)-Connector (i.e., -Y) may be selected from the group consisting of:



[00122] Additional examples for **13** and –C(O)-Connector (i.e., -Y) can be found in Table D, seen below:

Table D

Example No.	13	-C(O)-Connector (i.e., -Y)

1		
2		

Multimers

[00123] In some embodiments, a first monomer and a second monomer may form a dimer in aqueous solution. For example, in some instances, the first monomer may form a biologically useful dimer with a second monomer *in vivo*.

[00124] Without wishing to be bound by any theory, it is believed that molecular self-assembly may be directed through noncovalent interactions, *e.g.*, hydrogen bonding, metal coordination, hydrophobic forces, van der Waals forces, pi-pi interactions, electrostatic, and/or electromagnetic interactions.

[00125] Without wishing to be bound by any theory, pi-pi and pi-cation interactions can be used to drive multimerization. In addition, van der Waals and electromagnetic forces are other interactions that can help to drive multimerization. Alternatively, acid/base pairs and donor-acceptor pairs, *e.g.*, amide and/or sulfonamide pairs, can be employed to help direct self-assembly. In other cases, use of hydrophobic interactions can be used for multimerization targeting a membrane-bound protein. Additionally, metal coordination might be used when the target itself incorporates the metal, but could also be used in other scenarios.

[00126] In one embodiment, a therapeutic multimer compound may be formed from the multimerization in an aqueous media of a first monomer X^1-Y^1-Z^1 with a second monomer X^2-Y^2-Z^2. For example, Z^1 is a first linker capable of binding to the second monomer, wherein Z^2 is a second linker capable of binding to the first monomer through Z^1. In a certain embodiment, Z^2 is a nucleophile moiety capable of binding with the Z^1 moiety of Formula I to form the multimer. In another embodiment, the first monomer forms a biologically useful dimer with a second monomer *in vivo*.

[00127] In another embodiment, a therapeutic multimer compound may be formed from the multimerization in an aqueous media of a first monomer X^1-Y^1-Z^1 with a second monomer X^4-Y^4-Z^4. For example, Z^1 is a first linker capable of binding to the second monomer, wherein Z^4 is a second linker capable of binding to the first monomer through Z^1.

[00128] In certain embodiments, the multimerization may be substantially irreversible in an aqueous media. In some instances, the multimer may be fluorescent.

[00129] It is contemplated herein that while many chemistries are in principle reversible, the extent, probability and rate of the reverse reaction will depend heavily upon a range of conditions including temperature, concentration, solvent, catalysis, and binding to the target biomolecule. The term "irreversible" typically refers to the low probability of the reverse reaction occurring to a significant extent in an aqueous media within the timeframe of associated biological, pharmacologic and metabolic events, *e.g.*, turn-over or degradation of the target biomolecule, signal transduction responses, drug metabolism and clearance, etc. As the affinity of the "irreversible" multimeric assembly for the target biomolecule is at least an order of magnitude higher than that of its monomers, it is likely to persist on the target for a prolonged period and exhibit a very slow off-rate. Additionally, the binding of the "irreversible" multimeric assembly by the target biomolecule may also significantly slow the dissociative reversal of the linker reaction to regenerate monomers. Also, the irreversible extrusion of a small molecule from the multimer linkage, may ensure the linker reaction cannot be revered in an aqueous or biological milieu. Thus, in general the half-life for the "irreversible" multimeric assembly is considered e.g., comparable to, or longer than the half-life for, the associated biological processes, with the potential to provide a relatively long duration of pharmacologic action.

[00130] In some embodiments, X^1 and X^2 may be different. In some embodiments, X^1 and X^4 may be different.

Methods

[00131] In some embodiments, contemplated monomers and multimers may be administered to a patient in need thereof. In some embodiments, a method of administering a pharmaceutically effective amount of a multimeric compound to a patient in need thereof is provided. In some cases, the method comprises administering to the patient thereof an amount of the first monomer and an amount of a second monomer in amounts effective such that the pharmaceutically effective amount of the resulting multimer is formed *in vivo*.

[00132] In some embodiments, a first monomer and a second monomer may be administered substantially sequentially. In other embodiments, the first monomer and the second monomer are administered substantially simultaneously. In some embodiments the monomers may be administered, sequentially or simultaneously, by different routes of

administration or the same route of administration. In still further embodiments, a first monomer and a second monomer may be administered after forming a multimer.

[00133] In some instances, a method of modulating two or more target biomolecule binding sites is provided, e.g., two binding sites of c-Myc. In some embodiments, a first ligand moiety (e.g., bound to a first monomer) may bind to a first binding site of c-Myc and a second ligand moiety (e.g., bound to a second monomer) may bind to a second binding site of c-Myc. In other instances, a method of modulating two or more target biomolecule binding sites is provided, e.g., a binding site of c-Myc and a binding site of Max. In some embodiments, a first ligand moiety (e.g., bound to a first monomer) may bind to a binding site of c-Myc and a second ligand moiety (e.g., bound to a second monomer) may bind to a binding site of Max. In certain embodiments, a multimer comprising the first and second ligand moieties may form prior to binding the first and second binding sites. In other embodiments, a multimer may form after one and/or two of the monomers bind the first and second binding sites.

[00134] In certain embodiments, a multimer contemplated herein may be used to inhibit or facilitate protein subunit-subunit interactions.

[00135] In some embodiments, a multimer contemplated herein may be used to inhibit or facilitate protein-protein interactions. For example, in some cases, a contemplated multimer may be capable of inactivating a signaling pathway (e.g., a c-Myc pathway). Without wishing to be bound by any theory, a multimer 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 multimer does not bind the target protein. In some embodiments monomers may be chosen such that a multimer formed from the monomers binds to at least two regions of a target molecule.

[00136] In one embodiment, a contemplated multimer may be capable of binding to a first protein binding site and a second protein binding site, wherein the second protein binding site is, e.g. between about 5 Å and about 30 Å of the first protein binding site, or in some embodiments within about 40 Å of the first protein binding site.

[00137] In an embodiment, the compounds contemplated herein may be used in a method for treating diseases or conditions for which a c-Myc inhibitor is indicated, for example, a compound may be used for treating cancer. For example, provided herein is a method of treating cancer in a patient in need thereof by administering to the patient a contemplated compound.

[00138] 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 two or more disclosed monomers such that the monomers form a multimer (e.g. dimer) *in-vivo*.

[00139] Also 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 c-Myc inhibitor is indicated. 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.

[00140] 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.

[00141] 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.

[00142] 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.

[00143] 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.

[00144] In another aspect, pharmaceutical compositions comprising monomers, dimers, and/or multimers as disclosed herein formulated together with a pharmaceutically acceptable carrier provided. In particular, the present disclosure provides pharmaceutical compositions comprising monomers, dimers, and/or multimers 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.

[00145] 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.

[00146] 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.

[00147] 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.

[00148] 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.

[00149] 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.

[00150] 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.

[00151] 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.

[00152] 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.

[00153] 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.

[00154] 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.

[00155] 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.

[00156] 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.

[00157] 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

[00158] In another aspect, enteral pharmaceutical formulations including a disclosed pharmaceutical composition comprising monomers, dimers, and/or multimers, 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.

[00159] Advantageously, kits are provided containing one or more compositions each including the same or different monomers. 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.

[00160] 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.

[00161] Also contemplated herein are methods and compositions that include a second active agent, or administering a second active agent.

[00162] 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

[00163] 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.

[00164] 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.

[00165] 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; aryloxy; heteroalkoxy; heteroaryloxy; alkylthio; arylthio; 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.

[00166] 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.

[00167] 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.

[00168] In general, the terms "aryl," "aromatic," "heteroaryl," and "heteroaromatic" 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.

[00169] 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.

[00170] 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.

[00171] 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.

[00172] 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.

[00173] 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_{2-6}alkoxy, respectively. Exemplary alkoxy groups include, but are not limited to methoxy, ethoxy, isopropoxy, etc.

[00174] 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.

[00175] 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.

[00176] 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.

[00177] 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.

[00178] 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.

[00179] 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.

[00180] The term "carbonyl" as used herein refers to the radical -C(O)-.

[00181] The term "carboxylic acid" as used herein refers to a group of formula $-CO_2H$.

[00182] The term "cyano" as used herein refers to the radical -CN.

[00183] The term "cycloalkoxy" as used herein refers to a cycloalkyl group attached to an oxygen (cycloalkyl-O-).

[00184] 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.

[00185] The terms "halo" or "halogen" as used herein refer to F, Cl, Br, or I.

[00186] The term "heterocyclylalkoxy" as used herein refers to a heterocyclyl- alkyl-O- group.

[00187] The term "heterocyclyloxyalkyl" refers to a heterocyclyl-O-alkyl- group.

[00188] The term "heterocyclyloxy" refers to a heterocyclyl-O- group.

[00189] The term "heteroaryloxy" refers to a heteroaryl-O- group.

[00190] The terms "hydroxy" and "hydroxyl" as used herein refers to the radical -OH.

[00191] The term "oxo" as used herein refers to the radical =O.

[00192] 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 linker and a pharmacophore. Contemplated connectors are generally hydrolytically stable.

[00193] "Treating" includes any effect, e.g., lessening, reducing, modulating, or eliminating, that results in the improvement of the condition, disease, disorder and the like.

[00194] "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.

[00195] 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.

[00196] 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.

[00197] "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.

[00198] 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.

[00199] 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.

[00200] 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."

[00201] The term "stereoisomers" when used herein comprises all geometric isomers, enantiomers or diastereomers. Various stereoisomers of these compounds and mixtures thereof are encompassed by this disclosure. 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.

[00202] 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.

[00203] 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.

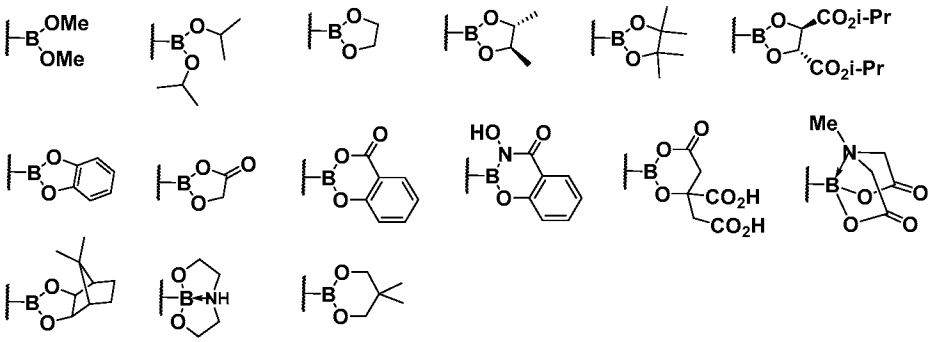
[00204] Also embraced are isotopically labeled compounds which are identical to those recited herein, except that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated 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.

[00205] 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.

[00206] 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.

[00207] Similarly, if a compound contains a boronic acid, a prodrug can be formed by the replacement of the one or both hydrogen atoms of the alcohol groups with a group such as:



[00208] 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})

$_6$)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).

[00209] If a compound incorporates an amine functional group, a prodrug can be formed, for example, by creation of an amide or carbamate, an N-acyloxyalkyl 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

[00210] 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.

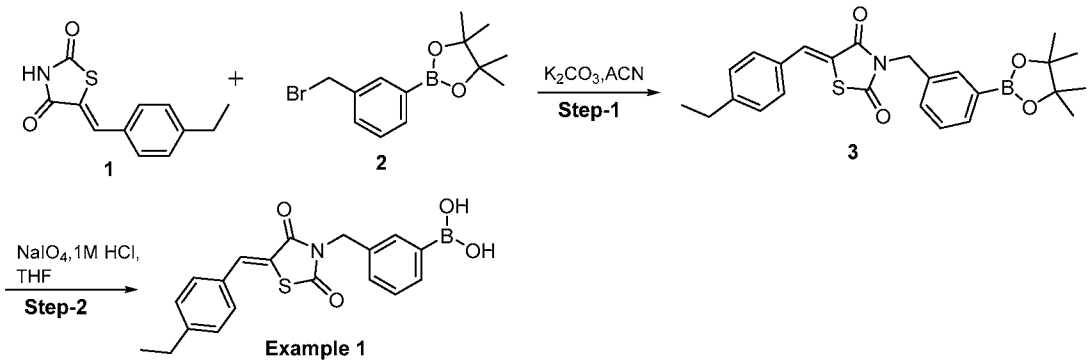
EXAMPLES

[00211] 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. Where a particular stereochemistry is indicated for a compound, one of ordinary skill in the art would recognize that other stereoisomers of the compound may also be formed. In some cases, a starting material or intermediate used in the synthesis of a contemplated compound may have an enantiomeric excess greater than 0, *e.g.*, greater than about 95%, greater than about 98%, greater than about 99%, or essentially 100%. For example, in some cases, a starting material or intermediate may be essentially stereoisomerically pure. However, partial or complete loss of chiral integrity may occur during the synthesis of the contemplated compound thereby reducing or eliminating the enantiomeric excess. For example, where a stereoisomerically pure starting material or intermediate is used in a synthesis of a contemplated compound, partial or complete loss of chiral integrity results in a stereoisomeric mixture. A stereoisomeric mixture may be

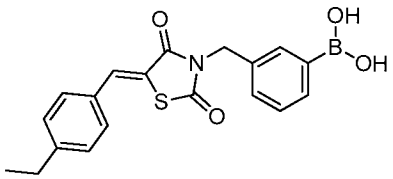
partially or essentially completely resolved by subjecting the stereoisomeric mixture to a chiral purification technique (*e.g.*, chiral HPLC purification).

[00212] Monomers were synthesized according to the procedures described below.

[00213] **Example 1: Synthetic scheme**

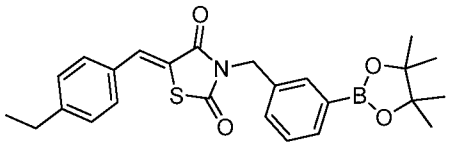


[00214] **(*Z*)-(3-((5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)methyl)phenyl)boronic acid [Example 1]:**



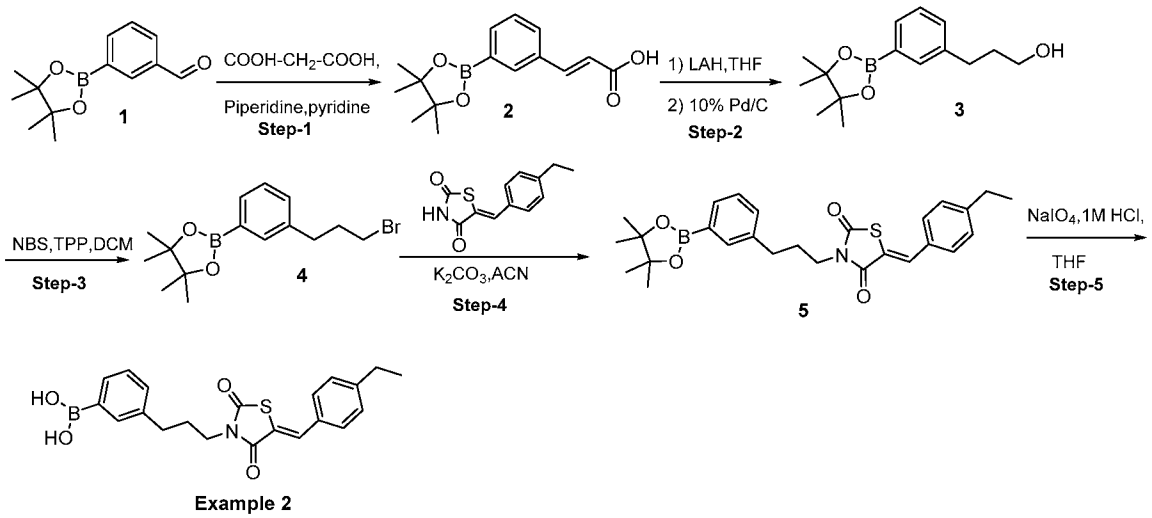
[00215] A solution of (*Z*)-5-(4-ethylbenzylidene)-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)thiazolidine-2,4-dione (200 mg, 0.445 mmol) in THF (5 mL) was charged with sodium periodate (143 mg, 0.668 mmol) and 1M aq HCl (2 mL). The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated to dryness under reduced pressure to obtain a residue which was diluted with water (5 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by column chromatography on silica gel eluting with 5 % methanol in DCM to afford 100 mg, 61% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.09 (bs, 2H), 7.95 (s, 1H), 7.77 – 7.67 (m, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.36 – 7.22 (m, 2H), 4.83 (s, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); MS (ES$^+$): m/z = 368.10 $[M+H]^+$, 369.30 $[M+H]^{++}$; LCMS-t_R = 3.45 min.

(*Z*)-5-(4-Ethylbenzylidene)-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)thiazolidine-2,4-dione (3):

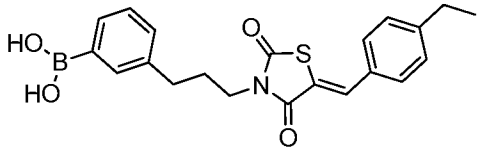


[00216] A solution of (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (150 mg, 0.643 mmol) in ACN (5 mL) was charged with potassium carbonate (346 mg, 2.51 mmol) and 2-(3-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (191 mg, 0.643 mmol). The resulting solution was heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue obtained was diluted with H_2O (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in 200 mg of crude compound as colorless thick oil. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95 (s, 1H), 7.67 – 7.52 (m, 4H), 7.40 – 7.30 (m, 4H), 4.84 (s, 2H), 2.66 (q, J = 7.7 Hz, 2H), 1.29 (s, 12H), 1.21 – 1.16 (m, 3H).

[00217] **Example 2: Synthetic scheme**

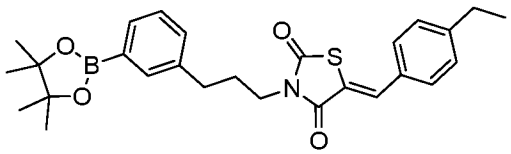


[00218] **(*Z*)-(3-(3-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)propyl)phenyl)boronic acid [Example 2]:**



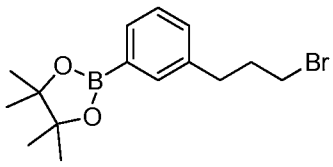
[00219] A solution of (Z)-5-(4-ethylbenzylidene)-3-(3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)thiazolidine-2,4-dione (150 mg, 0.314 mmol) in THF (5 mL) was charged with sodium periodate (100 mg, 0.471 mmol) and 1M aq HCl (2.5 mL). The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was concentrated to dryness under reduced pressure to obtain a residue which was diluted with water (5 mL) and extracted with ethyl acetate (3 X 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to afford 80 mg, 64 % yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.12 (br. s., 2H), 7.90 (s, 1H), 7.63 (s, 1H), 7.59 (d, J = 4.94 Hz, 1H), 7.55 (d, J = 8.53 Hz, 2H), 7.39 (d, J = 8.08 Hz, 2H), 7.28 – 7.18 (m, 2H), 3.69 (t, J = 7.2 Hz, 2H), 2.61 – 2.55 (m, 4H), 1.89 – 1.80 (m, 2H), 1.20 (t, J = 7.6 Hz, 3H); MS (ES$^+$): m/z = 395.20, 396.15 $[M+H]^+$; LCMS-t_R = 3.22 min.

[00220] (*Z*)-5-(4-Ethylbenzylidene)-3-(3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propyl)thiazolidine-2,4-dione (5):



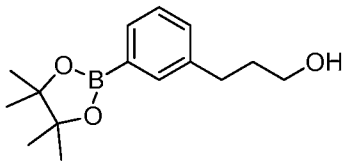
[00221] A solution of (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (143 mg, 0.613 mmol) in ACN (5 mL) was charged with potassium carbonate (338 mg, 2.45 mmol) and 2-(3-(3-bromopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (198 mg, 0.613 mmol). The resulting solution was heated at 80 °C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo.* The residue obtained was diluted with water (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel with 2 % methanol in DCM to give 150 mg, 51% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (s, 1H), 7.58 – 7.44 (m, 4H), 7.43 – 7.24 (m, 4H), 3.68 (t, J = 7.1 Hz, 2H), 2.76 – 2.62 (m, 6H), 1.28 (s, 12H), 1.29 – 1.13 (m, 3H).

[00222] 2-(3-(3-Bromopropyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (4):



[00223] A solution of 3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol (1.0 g, 3.81 mmol) in DCM (15 mL) at 0°C was charged with NBS (0.747 g, 4.19 mmol) and TPP (1.10 g, 4.19 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was partitioned between DCM (50 mL) and water (25 mL) and separated. The aqueous layer was extracted with DCM (3 X 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was dissolved in diethyl ether (100 mL) and stirred at room temperature for 20 min. The solid obtained was collected by filtration and washed with diethyl ether. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2 % methanol in DCM to afford 700 mg, 56% yield of the title compound as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.55 – 7.48 (m, 2H), 7.44 – 7.19 (m, 2H), 3.50 (t, J = 6.6 Hz, 2H), 2.71 (t, J = 7.5 Hz, 2H), 2.08 (q, J = 6.8 Hz, 2H), 1.29 (s, 12H).

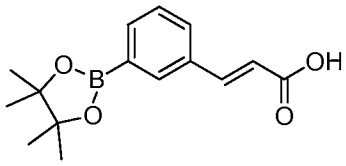
[00224] 3-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-ol (3):



[00225] A solution of LAH (236 mg, 6.22 mmol) in dry THF (15 mL) at 0°C was charged with (*E*)-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acrylic acid (1.10 g, 4.01 mmol). The resulting reaction mixture was refluxed for 4 h. The reaction mixture was cooled to room temperature and quenched with ethyl acetate (10 mL), 10% aq NaOH (2 mL), water (5 mL). The precipitated solid was collected by filtration and the filtrate was concentrated *in vacuo* resulting in 1.0 g of crude compound as yellow oil. The crude compound was dissolved in methanol and charged with 10% Pd/C. The reaction mixture was stirred at room temperature under hydrogen atmosphere (balloon pressure) for 3 h. The reaction mixture was filtered through pad of Celite and the filtrate was concentrated *in vacuo* resulting in 1.0 g of crude compound as yellow oil. The crude compound was used in the next step without

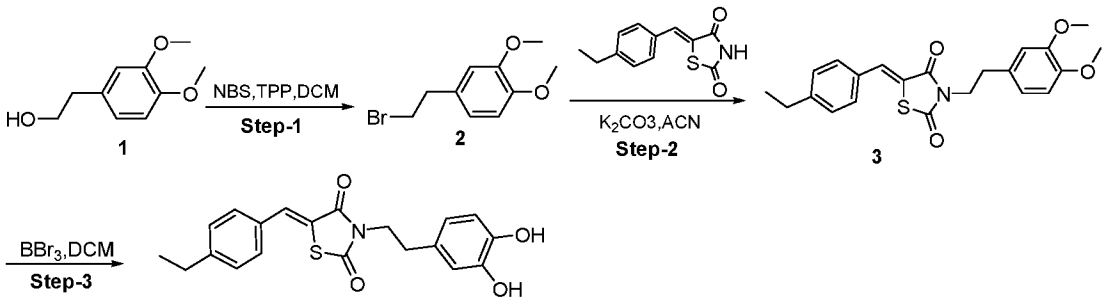
further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.52 – 7.44 (m, 2H), 7.35 – 7.24 (m, 2H), 3.39 (q, J = 6.2 Hz, 2H), 2.58 –2.48 (m, 2H), 1.75 – 1.63 (m, 2H), 1.29 (s, 12H).

[00226] (*E*)-3-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acrylic acid (2):

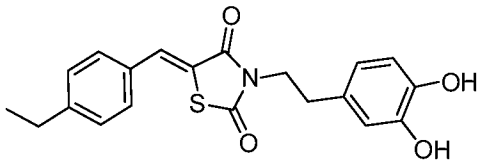


[00227] A solution of malonic acid (941 mg, 9.05 mmol) in pyridine (10 mL) was charged with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (1.20 g, 5.17 mmol) and piperidine (2 mL). The resulting solution was heated at 118°C for 4 h. The reaction mixture was cooled to room temperature and the pH was adjusted to ~2-3 using 1N aq HCl, the solid precipitated was collected by filtration. The residue obtained was purified by crystallization in acetone to afford 1.10 g, 78% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.37 (s, 1H), 7.88 – 7.80 (m, 2H), 7.70 (d, J = 7.3 Hz, 1H), 7.60 (d, J = 16.0 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 6.51 (d, J = 16.0 Hz, 1H), 1.31 (s, 12H).

[00228] Example 3: Synthetic scheme



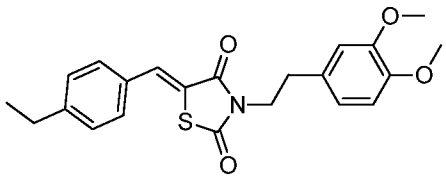
[00229] (*Z*)-3-(3,4-Dihydroxyphenethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione [Example 3]:



[00230] A solution of (*Z*)-3-(3,4-dimethoxyphenethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (150 mg, 0.377 mmol) in DCM (2 mL) was charged

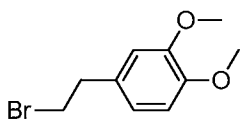
with BBr_3 (472 mg, 1.88 mmol) under nitrogen atmosphere at 0°C. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was quenched using cold water (5 mL) and extracted with diethyl ether (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2% methanol in $CHCl_3$ to afford 55 mg, 39% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.81 (d, J = 1.7 Hz, 1H), 8.70 (d, J = 1.7 Hz, 1H), 7.87 (s, 1H), 7.55 (d, J = 6.8 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 6.65 – 6.54 (m, 2H), 6.40 (dt, J = 8.2, 1.9 Hz, 1H), 3.78 (t, J = 7.4 Hz, 2H), 2.78 –2.60 (m, 4H), 1.19 (t, J = 7.6 Hz, 3H); MS (ES^+): m/z =370.10 $[M + H]^+$; LCMS-t_R = 3.04 min.

[00231] (*Z*)-3-(3,4-Dimethoxyphenethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (3):



[00232] A solution of (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (200 mg, 0.858 mmol) in ACN (5 mL) was charged with potassium carbonate (473 mg, 3.43 mmol) and 4-(2-bromoethyl)-1,2-dimethoxybenzene (231 mg, 0.944 mmol). The resulting solution was heated at 80°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue obtained was diluted with water (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2 % methanol in DCM to afford 150 mg, 44 % yield of the title compound as a white solid. MS (ES^+): m/z =398.10 $[M+H]^+$; LCMS-t_R = 3.54 min.

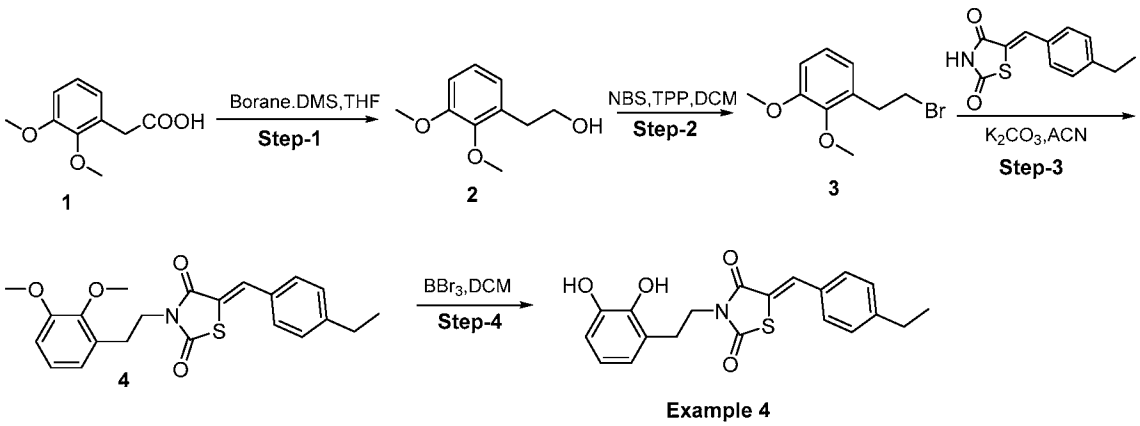
[00233] 4-(2-Bromoethyl)-1,2-dimethoxybenzene (2):



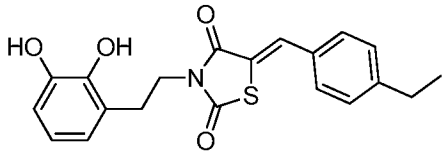
[00234] A solution of 2-(3,4-dimethoxyphenyl)ethanol (1.0 g, 5.49 mmol) in DCM (10 mL) was charged with NBS (1.07 g, 6.04 mmol) and TPP (1.58 g, 6.04 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was partitioned

between DCM (50 mL) and water (25 mL) and separated. The aqueous layer was extracted with DCM (3 X 30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was dissolved in diethyl ether (100 mL) and stirred at room temperature for 20 min. The solid obtained was collected by filtration and washed with diethyl ether. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2% methanol in DCM to afford 700 mg, 52% yield of the title compound as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.86 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 6.74 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.55 (t, J = 7.6 Hz, 2H), 3.11 (t, J = 7.7 Hz, 2H).

[00235] Example 4: Synthetic scheme



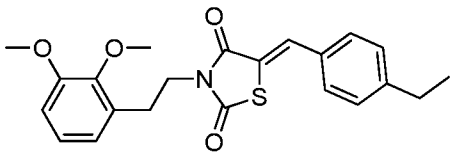
[00236] (*Z*)-3-(2,3-Dihydroxyphenethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione [Example 4]:



[00237] A solution of (*Z*)-3-(2,3-dimethoxyphenethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (150 mg, 0.377 mmol) in DCM (2 mL) was cooled to 0°C and charged with BBr_3 (472 mg, 1.88 mmol) under nitrogen atmosphere. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was quenched using cold water (5 mL) and extracted with diethyl ether (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude

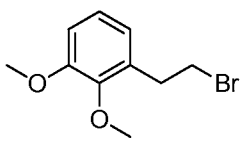
compound which was purified by chromatography on silica gel eluting with 5% methanol in $CHCl_3$ to afford 40 mg, 28% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.23 (bs, 1H), 8.27 (bs, 1H), 7.85 (s, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 6.64 (d, J = 7.6 Hz, 1H), 6.51 (t, J = 7.6 Hz, 1H), 6.45 (d, J = 7.6 Hz, 1H), 3.86 (t, J = 7.1 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); MS (ES$^+$): m/z = 370.05, 372.20 $[M+H]^+$; LCMS-t_R = 3.16 min.

[00238] (*Z*)-3-(2,3-Dimethoxyphenethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (4):



[00239] A solution of (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (200 mg, 0.858 mmol) in ACN (5 mL) was charged with potassium carbonate (473 mg, 3.43 mmol) and 1-(2-bromoethyl)-2,3-dimethoxybenzene (231 mg, 0.944 mmol). The resulting solution was heated at 80°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue obtained was diluted with water (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2 % methanol in $CHCl_3$ to afford 150 mg, 44 % yield of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1H), 7.43 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.97 (t, J = 8.0 Hz, 1H), 6.85 – 6.74 (m, 2H), 3.99 (t, J = 7.5 Hz, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 3.00 (t, J = 7.5 Hz, 2H), 2.70 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.7 Hz, 3H); MS (ES$^+$): m/z = 398.10 $[M+H]^+$; LCMS-t_R = 3.54 min.

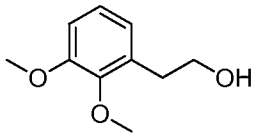
[00240] 1-(2-Bromoethyl)-2,3-dimethoxybenzene (3):



[00241] A solution of 2-(2,3-dimethoxyphenyl)ethanol (900 mg, 4.94 mmol) in DCM (20 mL) was charged with NBS (968 g, 5.43 mmol) and TPP (1.42 g, 5.43 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was partitioned between DCM (50 mL) and water (25 mL) and separated. The aqueous layer was

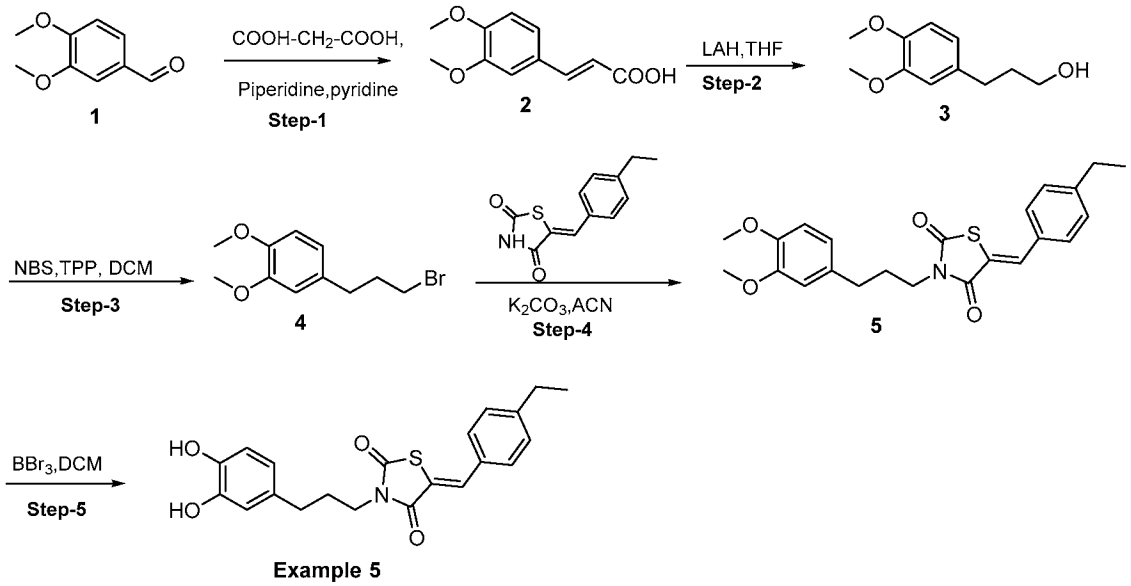
extracted with DCM (3 X 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was dissolved in diethyl ether (30 mL) and stirred at room temperature for 20 min. The solid obtained was collected by filtration and washed with diethyl ether. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 3% methanol in DCM to afford 590 mg, 49% yield of the title compound as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (t, J = 7.9 Hz, 1H), 6.81 (dd, J = 21.3, 7.9 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.57 (t, J = 7.7 Hz, 2H), 3.18 (t, J = 7.8 Hz, 2H).

[00242] 2-(2,3-Dimethoxyphenyl)ethanol (2):

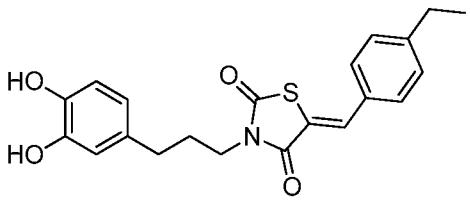


[00243] A solution of 2-(2,3-dimethoxyphenyl)acetic acid (1.0 g, 5.10 mmol) in dry THF (10 mL) was charged with Borane-DMS (0.775 g, 10.20 mmol) at 0°C and the solution was stirred at room temperature for 6 h. The reaction mixture was quenched with 1N aq HCl (25 mL) and extracted with ethyl acetate (3 X 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in 900 mg of the crude compound as light yellow solid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (t, J = 7.9 Hz, 1H), 6.81 (t, J = 8.1 Hz, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.74 (t, J = 6.4 Hz, 2H), 2.91 (t, J = 6.4 Hz, 2H).

[00244] Example 5: Synthetic scheme

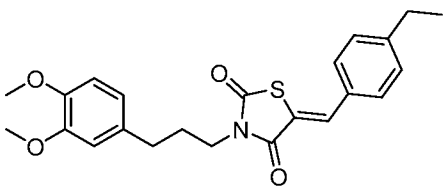


[00245] (*Z*)-3-(3-(3,4-Dihydroxyphenyl)propyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione [Example 5]:



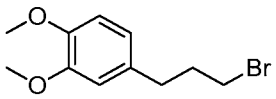
[00246] A solution of (*Z*)-3-(3-(3,4-dimethoxyphenyl)propyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (300 mg, 0.729 mmol) in DCM (3 mL) was cooled to 0°C and charged with BBr_3 (912 mg, 3.65 mmol) under nitrogen atmosphere. The resulting solution was stirred at room temperature for 3 h then quenched using cold water (10 mL) and extracted with diethyl ether (3 X 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 5% methanol in $CHCl_3$ to afford 100 mg, 35% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.16 (bs, 1H), 8.15 (bs, 1H), 7.55 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 6.60 (dd, J = 6.8, 2.0 Hz, 1H), 6.56 – 6.50 (m, 2H), 3.66 (t, J = 7.3 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 2.53 – 2.38 (m, 2H), 1.86 – 1.78 (m, 2H), 1.19 (t, J = 7.6 Hz, 3H); MS (ES^+): m/z = 384.15, 385.10 $[M+H]^+$; LCMS-t_R= 3.27 min.

[00247] (*Z*)-3-(3-(3,4-Dimethoxyphenyl)propyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (5):



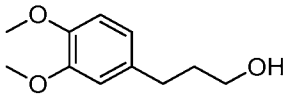
[00248] A solution of (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (200 mg, 0.858 mmol) in ACN (5 mL) was charged with potassium carbonate (473 mg, 3.43 mmol) and 4-(3-bromopropyl)-1,2-dimethoxybenzene (244 mg, 0.944 mmol). The resulting solution was heated at 80°C for 16 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and diluted with water (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2% methanol in $CHCl_3$ to afford 300 mg, 85 % yield of the title compound as a yellow oil. MS (ES+): *m/z* = 412.10 $[M+H]^+$; LCMS-t_R= 4.20 min.

[00249] **4-(3-Bromopropyl)-1,2-dimethoxybenzene(4):**



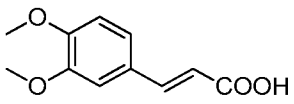
[00250] A solution of 3-(3,4-dimethoxyphenyl)propan-1-ol (2.80 g, 14.28 mmol) in DCM (30 mL) was charged with NBS (2.79 g, 15.71 mmol) and TPP (4.12 g, 15.71 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was partitioned between DCM (50 mL) and water (25 mL) and separated. The aqueous layer was extracted with DCM (3 X 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was dissolved in diethyl ether (50 mL) and stirred at room temperature for 20 min. The solid obtained was collected by filtration and washed with diethyl ether. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 3% methanol in DCM to afford 1.50 g, 40% yield of the title compound as colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.84 – 6.70 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.39 (t, *J* = 6.6 Hz, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.14 (q, *J* = 6.9 Hz, 2H).

[00251] **3-(3,4-Dimethoxyphenyl)propan-1-ol (3):**



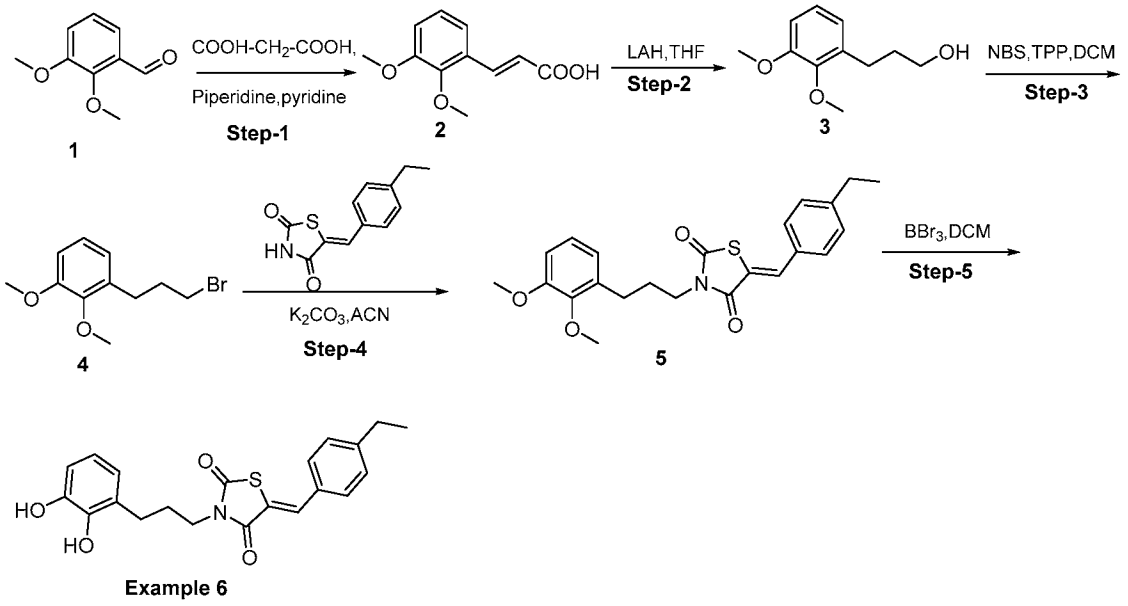
[00252] A solution of LAH (906 mg, 23.84 mmol) in dry THF (40 mL) at 0°C was charged with (*E*)-3-(3,4-dimethoxyphenyl)acrylic acid (3.20 g, 15.38 mmol). The resulting reaction mixture was refluxed for 4 h then cooled to room temperature and quenched with ethyl acetate (20 mL), 10% aq NaOH (5 mL), and water (15 mL). The precipitated solid was collected by filtration and the filtrate was concentrated *in vacuo* resulting in 2.80 g of crude compound as yellow oil. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.96 – 6.70 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.62 (dd, *J* = 8.7, 6.8 Hz, 2H), 2.08 – 1.92 (m, 2H).

[00253] **(*E*)-3-(3,4-Dimethoxyphenyl)acrylic acid (2):**

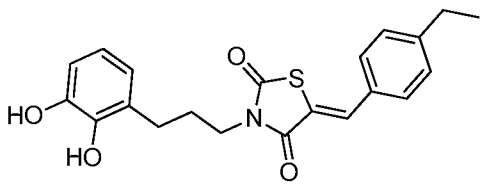


[00254] A solution of malonic acid (3.07 g, 29.51 mmol) in pyridine (15 mL) was charged with 3,4-dimethoxybenzaldehyde (2.80 g, 16.86 mmol) and piperidine (2 mL). The resulting solution was heated at 118°C for 4 h. The reaction mixture was cooled to room temperature and the pH was adjusted to ~2-3 using 1N aq HCl, the precipitated solid was collected by filtration. The residue obtained was purified by crystallization in acetone to afford 3.20 g, 91% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.61 (d, *J* = 15.9 Hz, 1H), 7.23 – 7.12 (m, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 15.8 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H).

[00255] **Example 6: Synthetic scheme**

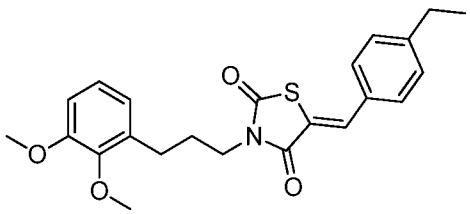


[00256] (*Z*)-3-(3-(2,3-Dihydroxyphenyl)propyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione [Example 6]:



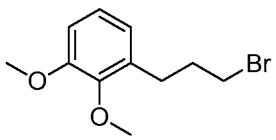
[00257] A solution of (*Z*)-3-(3-(2,3-dimethoxyphenyl)propyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (300 mg, 0.729 mmol) in DCM (3 mL) was charged with BBr_3 (912 mg, 3.65 mmol) under nitrogen atmosphere at 0°C. The resulting solution was stirred at room temperature for 3 h. The reaction mixture was quenched using cold water (10 mL) and extracted with diethyl ether (3 X 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 5% methanol in $CHCl_3$ to afford 100 mg, 35% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.71 (bs, 1H), 8.63 (bs, 1H), 7.88 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 1.6 Hz, 1H), 6.44 (dd, J = 8.4, 2.4 Hz, 1H), 3.64 (t, *J* = 7.4 Hz, 2H), 2.64 (q, J = 15.2, 7.6, 2H), 2.42 (t, *J* = 15.2, 8.0 Hz, 2H), 1.88 – 1.75 (m, 2H), 1.19 (t, *J* = 15.6, 8.0 Hz, 3H); MS (ES$^+$): *m/z* = 384.15, 385.10 $[M+H]^+$; LCMS-t_R= 3.27 min.

[00258] (*Z*)-3-(3-(2,3-Dimethoxyphenyl)propyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (5):



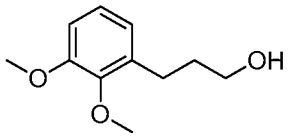
[00259] A solution of (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (200 mg, 0.858 mmol) in ACN (5 mL) was charged with potassium carbonate (473 mg, 3.43 mmol) and 1-(3-bromopropyl)-2,3-dimethoxybenzene (244 mg, 0.944 mmol). The resulting solution was heated at 80°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The residue obtained was diluted with water (5 mL) and extracted with ethyl acetate (3 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2% methanol in $CHCl_3$ to afford 300 mg, 85 % yield of the title compound as a yellow oil. MS (ES^+): m/z = 412.10, 413.15 $[M+H]^+$; LCMS-t_R= 4.20 min.

[00260] 1-(3-Bromopropyl)-2,3-dimethoxybenzene (4):



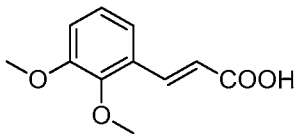
[00261] A solution of 3-(2,3-dimethoxyphenyl)propan-1-ol (2.70 g, 13.77 mmol) in DCM (30 mL) was charged with NBS (2.69 g, 15.15 mmol) and TPP (3.96 g, 15.15 mmol). The resulting reaction mixture was stirred at room temperature for 16 h. The reaction mixture was partitioned between DCM (50 mL) and water (25 mL) and separated. The aqueous layer was extracted with DCM (3 X 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue obtained was dissolved in diethyl ether (50 mL) and stirred at room temperature for 20 min. The solid obtained was collected by filtration and washed with diethyl ether. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 3% methanol in DCM to afford 1.20 g, 34% yield of the title compound as colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.98 (t, J = 7.9 Hz, 1H), 6.83 – 6.75 (m, 2H), 3.86 (s, 3H), 3.85 (s, 3H), 3.41 (t, J = 6.7 Hz, 2H), 2.78 (t, J = 7.4 Hz, 2H), 2.16 (q, J = 7.0 Hz, 2H).

[00262] 3-(2,3-Dimethoxyphenyl)propan-1-ol (3):



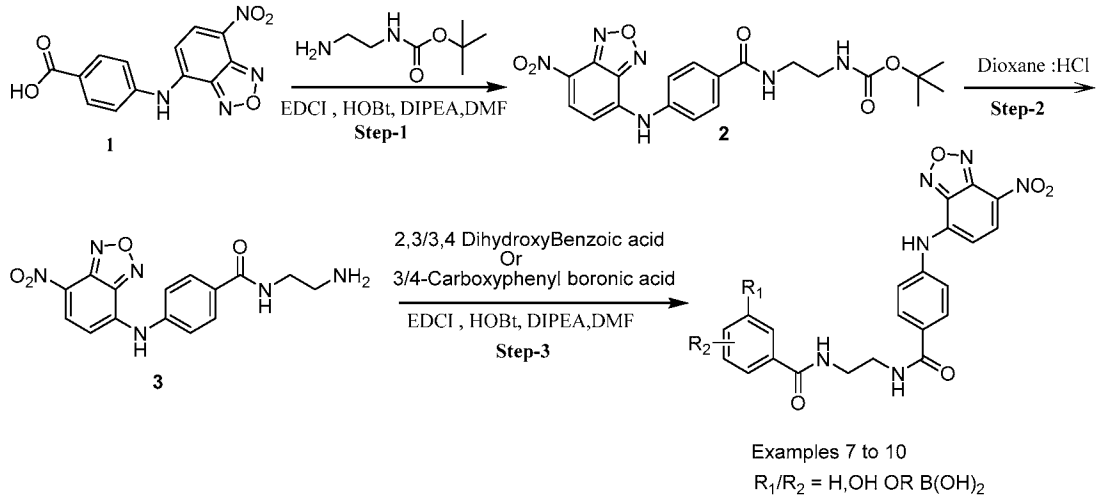
[00263] A solution of LAH (849 mg, 22.35 mmol) in dry THF (40 mL) at 0°C was charged with (*E*)-3-(2,3-dimethoxyphenyl)acrylic acid (3.0 g, 14.42 mmol). The resulting reaction mixture was refluxed for 4 h. The reaction mixture was cooled to room temperature and quenched with ethyl acetate (20 mL), 10% aq NaOH (5 mL), and water (15 mL). The precipitated solid was collected by filtration and the filtrate was concentrated *in vacuo* resulting in 2.70 g of crude compound as yellow oil. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD): δ = 6.96 – 6.70 (m, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.56 (t, *J* = 6.5 Hz, 2H), 2.62 – 2.55 (m, 2H), 2.08 – 1.92 (m, 2H).

[00264] (*E*)-3-(2,3-Dimethoxyphenyl)acrylic acid (2):

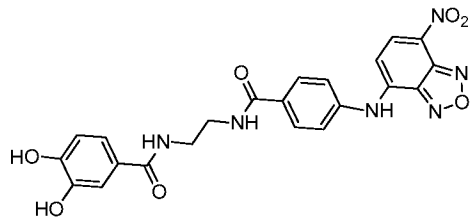


[00265] A solution of malonic acid (3.07 g, 29.51 mmol) in pyridine (15 mL) was charged with 2,3-dimethoxybenzaldehyde (2.80 g, 16.86 mmol) and piperidine (2 mL) and heated at 118°C for 4 h. The reaction mixture was cooled to room temperature and the pH was adjusted to ~2-3 using 1N aq HCl and the precipitate was collected by filtration. The solid obtained was purified by crystallization in acetone to afford 3.0 g, 85% yield of the title compound as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.97 (d, *J* = 16.1 Hz, 1H), 7.23 – 7.08 (m, 3H), 6.49 (d, *J* = 16.2 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H).

[00266] Example 7, 8, 9 and 10: Synthetic scheme

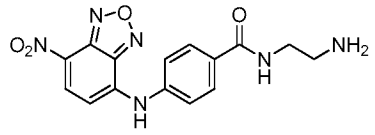


[00267] 3,4-Dihydroxy-*N*-(2-(4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)benzamide [Example 7]:



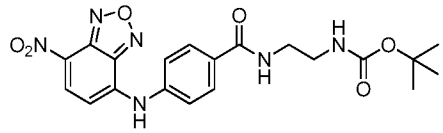
[00268] A solution of 3,4-dihydroxybenzoic acid (75 mg, 0.487 mmol) in DMF (1.5 mL) was charged with EDCI (93 mg, 0.487 mmol), HOBt (66 mg, 0.487 mmol), DIPEA (125 mg, 0.974 mmol) and stirred at room temperature for 10 min. The solution was charged with *N*-(2-aminoethyl)-4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (166 mg, 0.487 mmol) and the resulting solution was stirred at room temperature for 4 h. The reaction mixture was poured in cold water (10 mL), solid precipitated was filtered and dried to obtain crude product which was purified by preparative HPLC to afford 40 mg, 17 % yield of the title compound as a dark red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.81 (s, 1H), 9.42 (s, 1H), 9.14 (s, 1H), 8.92 (t, J = 5.5 Hz, 1H), 8.59 – 8.49 (m, 1H), 8.21 (s, 1H), 7.88 – 7.73 (m, 2H), 7.62 – 7.52 (m, 2H), 7.30 (s, 1H), 7.24 – 7.18 (m, 1H), 6.94 (d, J = 7.0 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 3.41 (d, J = 6.9 Hz, 4H); MS (ES$^+$): m/z = 479.20 [M+H]$^+$; LCMS: t_R = 1.96 min.

[00269] *N*-(2-Aminoethyl)-4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (3):



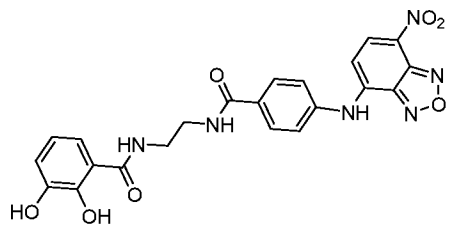
[00270] A solution of *tert*-butyl (4-(2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamate (1.0 g, 2.25 mmol) in 1,4-dioxane (50 mL) was charged with HCl in 1,4-dioxane (4M, 50 mL) and stirred at room temperature for 12 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was triturated with diethyl ether, filtered and dried *in vacuo* resulting in 700 mg (90 % yield) of pure compound as a dark red solid. MS (ES^+): *m/z* = 343.35 $[M+H]^+$; LCMS: t_R = 1.62 min.

[00271] ***tert*-butyl (2-(4-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamate(2):**



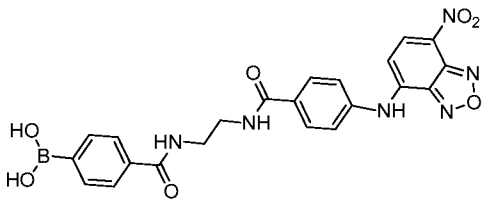
[00272] A solution of 4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzoic acid (1.0 g, 3.33 mmol) in DMF (20 mL) was charged with EDCI (638 mg, 3.33 mmol), HOBt (452 mg, 3.33 mmol), DIPEA (852 mg, 6.66 mmol) and stirred at room temperature for 10 min. The solution was then charged with *tert*-butyl (2-aminoethyl) carbamate (528 mg, 3.33 mmol) and stirred at room temperature for 4 h. The reaction mixture was partitioned between DCM (50 mL) and water (50 mL) and separated. The aqueous layer was extracted with DCM (3 X 25 mL) and the combined organic layers were washed with H_2O (3 X 100 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was crystallized from methanol (100 mL) to afford 1.10 g, 78 % yield of the title compound as an orange solid**.** MS (ES^+): *m/z* = 443.45 $[M+H]^+$; LCMS: t_R = 2.35 min.

[00273] **2,3-Dihydroxy-*N*-(2-(4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)benzamide [Example 8]:**



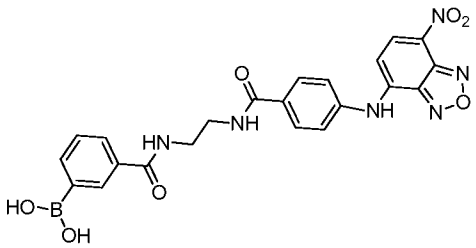
[00274] A solution of 2,3-dihydroxybenzoic acid (75 mg, 0.487 mmol) in DMF (1.5 mL) was charged with EDCI (93 mg, 0.487 mmol), HOBt (66 mg, 0.487 mmol), DIPEA (125 mg, 0.974 mmol) and stirred at room temperature for 10 min. The solution was charged with *N*-(2-aminoethyl)-4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (166 mg, 0.487 mmol) and stirred at room temperature for 4 h. The reaction mixture was poured in cold water (10 mL), solid precipitated was filtered and dried to obtain crude product which was purified by preparative HPLC to afford 55 mg, 24 % yield of the title compound as a dark red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.93 (s, 1H), 8.63 (s, 1H), 8.14 (s, 1H), 8.02 (d, J = 9.8 Hz, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 8.1 Hz, 2H), 6.91 (d, J = 7.7 Hz, 1H), 6.69 (t, J = 7.9 Hz, 1H), 6.07 (s, 1H), 3.50 – 3.41 (m, 4H); MS (ES$^+$): m/z = 479.15 $[M+H]^+$; LCMS: t_R = 2.24 min.

[00275] (4-((2-(4-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamoyl)phenyl)boronic acid [Example 9]:



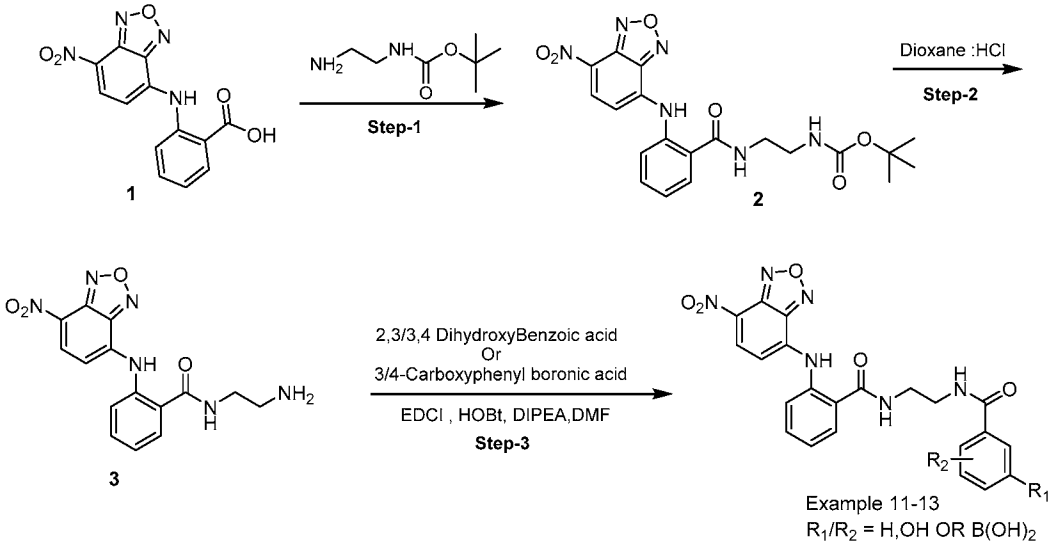
[00276] A solution of 4-carboxy phenyl boronic acid (75 mg, 0.451 mmol) in DMF (1.5 mL) was charged with EDCI (86.6 mg, 0.451 mmol), HOBt (61.3 mg, 0.451 mmol), DIPEA (116.3 mg, 0.902 mmol) and stirred at room temperature for 10 min. The solution was charged with *N*-(2-aminoethyl)-4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (154.3 mg, 0.451 mmol) and stirred at room temperature for 4 h. The reaction mixture was poured in cold water (100 mL) upon which a precipitate formed. The precipitate was filtered and dried to obtain crude product which was purified by preparative HPLC to afford 70 mg, 32 % yield of the title compound as a red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.13 (s, 1H), 8.71 – 8.52 (m, 3H), 8.20 (s, 2H), 8.00 – 7.92 (m, 2H), 7.89 – 7.77 (m, 4H), 7.56 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 1H), 3.49 – 3.36 (m, 4H); MS (ES$^+$): m/z = 491.20, 492.30 $[M+H]^+$; LCMS: t_R = 1.97 min.

[00277] (3-((2-(4-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamoyl)phenyl)boronic acid [Example 10]:

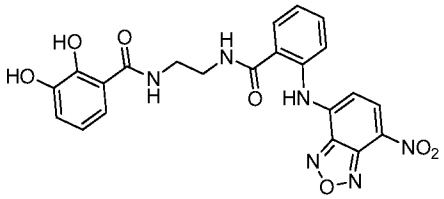


[00278] A solution of 3-carboxy phenyl boronic acid (75 mg, 0.451 mmol) in DMF (1.5 mL) was charged with EDCI (86.6 mg, 0.451 mmol), HOBt (61.3 mg, 0.451 mmol), DIPEA (116.3 mg, 0.902 mmol) and stirred at room temperature for 10 min. The solution was charged with *N*-(2-aminoethyl)-4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (154.3 mg, 0.451 mmol) stirred at room temperature for 4 h. The reaction mixture was poured in cold water (10 mL), solid upon which a precipitate formed. The precipitate was filtered and dried to obtain crude product which was purified by preparative HPLC to afford 50 mg, 23 % yield of the title compound as a red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.08 (s, 1H), 8.67 – 8.47 (m, 3H), 8.24 (s, 1H), 8.15 (s, 2H), 7.97 – 7.79 (m, 4H), 7.52 (d, J = 8.2 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 8.9 Hz, 1H), 3.43 (d, J = 4.6 Hz, 4H); MS (ES$^+$): m/z = 491.25, 492.35 [M+H]$^+$; LCMS: t_R = 2.01 min.

[00279] **Example 11 to 13: Synthetic scheme**

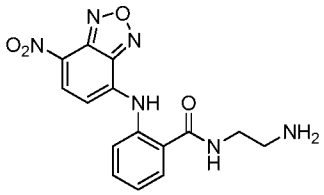


[00280] **2,3-Dihydroxy-*N*-(2-(2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)benzamide [Example 11]:**



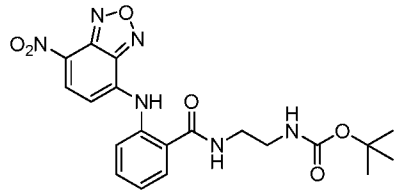
[00281] A solution of 2,3-dihydroxybenzoic acid (75 mg, 0.487 mmol) in DMF (1.5 mL) was charged with EDCI (93 mg, 0.487 mmol), HOBt (66 mg, 0.487 mmol), DIPEA (125 mg, 0.974 mmol) and stirred at room temperature for 10 min. The solution was charged with *N*-(2-aminoethyl)-2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (166 mg, 0.487 mmol) and stirred at room temperature for 4 h. The reaction mixture was poured in cold water (10 mL) upon which a precipitate formed. The precipitate was filtered and dried to obtain crude product which was purified by preparative HPLC to afford 60 mg, 26 % yield of the title compound as a dark red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.69 (s, 1H), 11.74 (s, 1H), 9.04 (s, 1H), 8.96 (s, 1H), 8.85 (d, J = 6.4 Hz, 1H), 8.56 (d, J = 8.8 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.37 (t, J = 7.6 Hz, 1H), 7.15 (d, J = 8.2 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 6.48 (t, J = 7.9 Hz, 1H), 3.48 – 3.39 (m, 4H); MS (ES$^+$): m/z = 479.35 [M+H]$^+$; LCMS: t_R = 2.46 min.

[00282] ***N*-(2-Aminoethyl)-2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (3):**



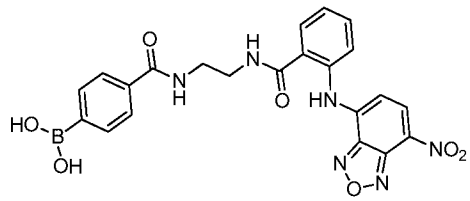
[00283] A solution of *tert*-butyl (2-(2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamate (1.20 g, 2.71 mmol) in 1,4-dioxane (50 mL) was charged with HCl in 1,4-dioxane (4M, 50 mL) and stirred at room temperature for 12 h. The reaction mixture was evaporated under reduced pressure to obtain a solid which was triturated with diethyl ether, filtered, and dried *in vacuo* resulting in a pure compound 800 mg, 86 % yield as a dark red solid. MS (ES$^+$): m/z = 343.45 [M+H] $^+$; LCMS: t_R = 1.78 min.

[00284] ***tert*-Butyl (2-(2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamate (2):**



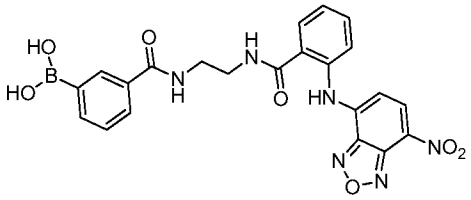
[00285] A solution of 2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzoic acid (1.0 g, 3.33 mmol) in DMF (20 mL) was charged with EDCI (638 mg, 3.33 mmol), HOBt (452 mg, 3.33 mmol), DIPEA (852 mg, 6.66 mmol) and stirred at room temperature for 10 min. The solution was charged with *tert*-butyl (2-aminoethyl) carbamate (528 mg, 3.33 mmol) and stirred at room temperature for 4 h. The reaction mixture was partitioned between DCM (50 mL) and water (50 mL) and separated. The aqueous layer was extracted with DCM (3 X 25 mL) and the combined organic layers were washed with H_2O (3 X 100 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was crystallized from methanol (100 mL) to afford 1.25 mg, 85 % yield of the title compound as an orange solid. MS (ES^+): m/z = 443.45 $[M+H]^+$; LCMS: t_R = 2.30 min.

[00286] (4-((2-(2-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamoyl)phenyl)boronic acid [Example 12]:



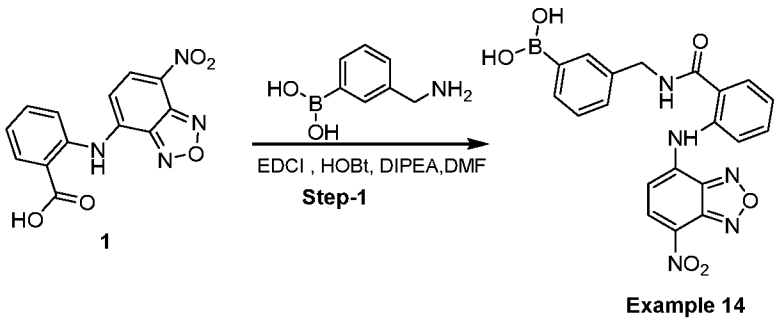
[00287] A solution of 4-carboxy phenyl boronic acid (75 mg, 0.451 mmol) in DMF (1.5 mL) was charged with EDCI (86.6 mg, 0.451 mmol), HOBt (61.3 mg, 0.451 mmol), DIPEA (116.3 mg, 0.902 mmol) and stirred at room temperature for 10 min. The solution was charged with *N*-(2-aminoethyl)-2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (154.3 mg, 0.451 mmol) and stirred at room temperature for 4 h. The reaction mixture was poured in cold water (100 mL) upon which a precipitate formed. The precipitate was filtered and dried to obtain crude product which was purified by preparative HPLC to afford 80 mg, 36 % yield of the title compound as a red solid. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.83 (s, 1H), 8.98 – 8.90 (m, 1H), 8.56 (dd, J = 7.0, 4.4 Hz, 2H), 8.14 (s, 2H), 7.84 (dd, J = 7.8, 1.6 Hz, 1H), 7.80 – 7.70 (m, 5H), 7.68-7.60 (m, 1H), 7.37 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 3.46-3.40 (m, 4H); MS (ES^+): m/z = 491.20, 492.30 $[M+H]^+$; LCMS: t_R = 2.12 min.

[00288] (3-((2-(2-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamoyl)phenyl)boronic acid [Example 13]:



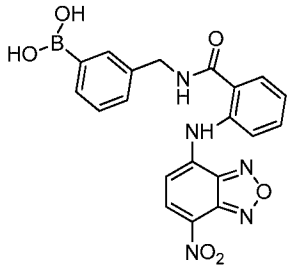
[00289] A solution of 3-carboxy phenyl boronic acid (75 mg, 0.451 mmol) in DMF (1.5 mL) was charged with EDCI (86.6 mg, 0.451 mmol), HOBt (61.3 mg, 0.451 mmol), DIPEA (116.3 mg, 0.902 mmol) and stirred at room temperature for 10 min. The solution was charged with *N*-(2-aminoethyl)-2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (154.3 mg, 0.451 mmol) and stirred at room temperature for 4 h. The reaction mixture was poured in cold water (100 mL) upon which a precipitate formed. The precipitate was filtered and dried to obtain crude product which was purified by preparative HPLC to afford 50 mg, 23 % yield of the title compound as an red solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ = 11.90 (s, 1H), 8.98 (t, J = 6.0 Hz, 1H), 8.68 – 8.50 (m, 2H), 8.22 (s, 1H), 8.20 – 8.14 (m, 2H), 7.94 – 7.82 (m, 2H), 7.82 – 7.74 (m, 2H), 7.70 – 7.60 (m, 1H), 7.40 – 7.30 (m, 1H), 7.30 – 7.24 (m, 1H), 6.88 (d, J = 7.2 Hz, 1H), 3.70 – 3.48 (m, 4H); MS (ES$^+$): m/z = 490.20, 491.20, 492.20 $[M+H]^+$; LCMS: t_R = 2.19 min.

[00290] Example 14: Synthetic scheme



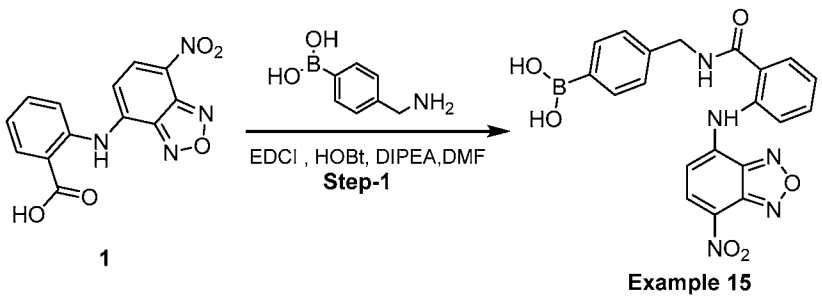
Example 14

[00291] (3-((2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid [Example 14]:



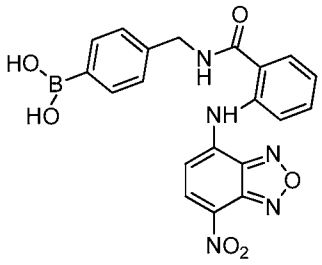
[00292] A solution of 2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (150 mg, 0.499 mmol) in DMF (1.5 mL) was charged with EDCI (143 mg, 0.749 mmol), HOBt (101 mg, 0.749 mmol), DIPEA (193 mg, 1.49 mmol) and stirred at room temperature for 10 min. The solution was charged with (3-(aminomethyl) phenyl) boronic acid (83 mg, 0.549 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 layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 32 mg, 15 % yield of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ = 11.74 (s, 1H), 9.30 (t, J = 6.4 Hz, 1H), 8.52 (d, J = 8.7 Hz, 1H), 7.98 (s, 2H), 7.89 (dd, J = 7.7, 1.6 Hz, 1H), 7.81 – 7.58 (m, 4H), 7.45 – 7.34 (m, 1H), 7.30 – 7.21 (m, 1H), 7.16 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.8 Hz, 1H), 4.43 (d, J = 5.8 Hz, 2H); MS (ES$^+$): m/z = 434.10, 435.15 $[M+H]^+$; LCMS: t_R = 2.76 min.

[00293] **Example 15: Synthetic scheme**



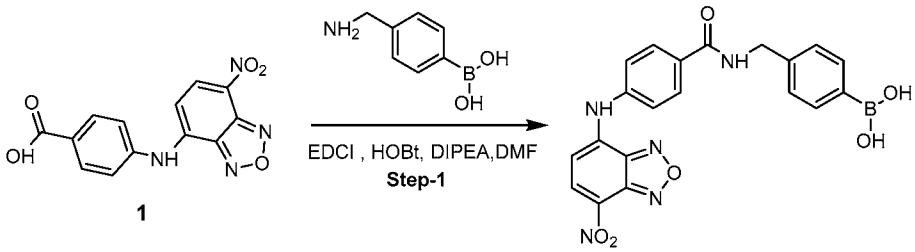
1 Example 15

[00294] **(4-((2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid [Example 15]:**



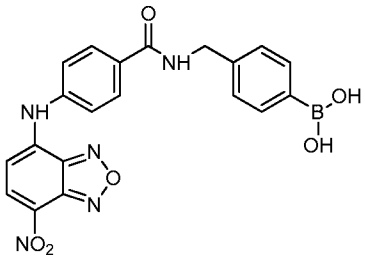
[00295] A solution of 2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (150 mg, 0.499 mmol) in DMF (1.5 mL) was charged with EDCI (143 mg, 0.749 mmol), HOBt (101 mg, 0.749 mmol), DIPEA (193 mg, 1.49 mmol) and stirred at room temperature for 10 min. The solution was charged with (4-(aminomethyl) phenyl) boronic acid (83 mg, 0.549 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 layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 43 mg, 20 % yield of the title compound as an orange solid**.** ^{1}H NMR (400 MHz, DMSO- d_6): δ = 11.72 (s, 1H), 9.31 (t, J = 5.6 Hz, 1H), 8.54 (d, J = 8.7 Hz, 1H), 7.96 (s, 2H), 7.89 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.70 – 7.64 (m, 3H), 7.41 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.6 Hz, 2H), 6.88 (d, J = 8.8 Hz, 1H), 4.44 (d, J = 5.9 Hz, 2H); MS (ES$^+$): m/z = 434.10, 433.10 $[M+H]^+$; LCMS: t_R = 2.80 min.

[00296] **Example 16: Synthetic scheme**



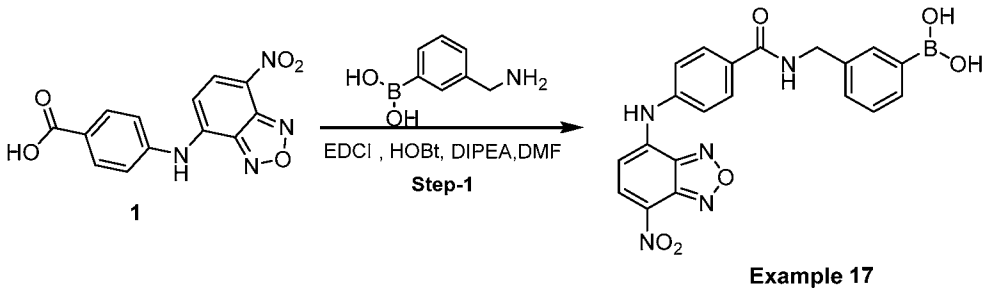
Example 16

[00297] **(3-((4-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid [Example 16]:**

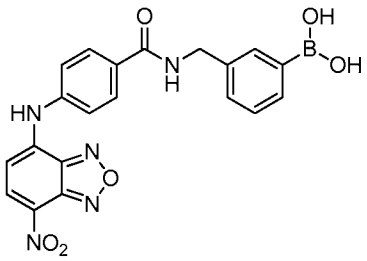


[00298] A solution of 4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (150 mg, 0.499 mmol) in DMF (1.5 mL) was charged with EDCI (143 mg, 0.749 mmol), HOBt (101 mg, 0.749 mmol), DIPEA (193 mg, 1.49 mmol) and stirred at room temperature for 10 min. The solution was charged with (4-(aminomethyl)phenyl)boronic acid (83 mg, 0.549 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 layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 26 mg, 12% yield of the title compound as an orange solid**.** ^{1}H NMR (400 MHz, DMSO- d_6): δ = 11.13 (s, 1H), 9.10 (t, J = 6.0 Hz, 1H), 8.57 (d, J = 8.8 Hz, 1H), 8.07 – 8.00 (m, 3H), 7.75 (d, J = 7.6 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 7.6 Hz, 2H), 6.92 (d, J = 8.4 Hz, 1H), 4.51 (d, J = 6.0 Hz, 2H); MS (ES$^+$): m/z = 434.15, 435.50 $[M+H]^+$; LCMS: t_R = 2.58 min.

[00299] **Example 17: Synthetic scheme**

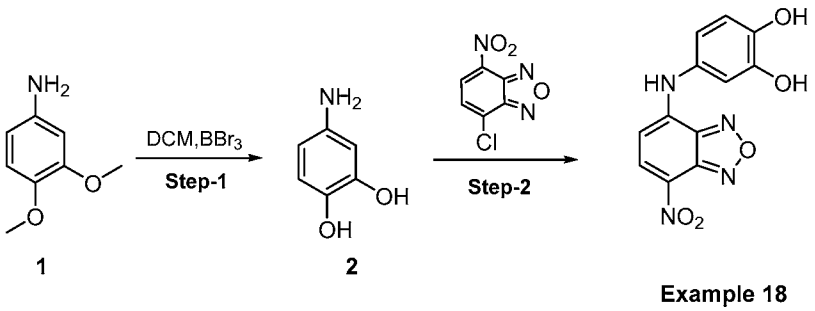


[00300] **(3-((4-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid [Example 17]:**

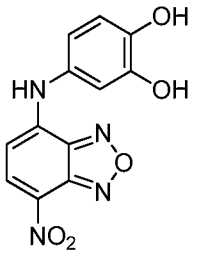


[00301] A solution of 4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (150 mg, 0.499 mmol) in DMF (1.5 mL) was charged with EDCI (143 mg, 0.749 mmol), HOBt (101 mg, 0.749 mmol), DIPEA (193 mg, 1.49 mmol) and stirred at room temperature for 10 min. The solution was charged with (3-(aminomethyl) phenyl)boronic acid (83 mg, 0.549 mmol) and stirred at room temperature for 4 h. The reaction mixture was partitioned between DCM (20 mL) and H_2O (10 mL) and separated. The aqueous layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with H_2O (2 X 20mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 34 mg, 16% yield of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ = 11.13 (s, 1H), 9.09 (t, J = 6.0 Hz, 1H), 8.57 (d, J = 8.8 Hz, 1H), 8.03 – 8.01 (m, 4H), 7.75 (s, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.40 – 7.23 (m, 2H), 6.91 (d, J = 8.8 Hz, 1H), 4.50 (d, J = 5.9 Hz, 2H); MS (ES$^+$): m/z = 433.05, 434.15 $[M+H]^+$; LCMS: t_R = 2.60 min.

[00302] **Example 18: Synthetic scheme**

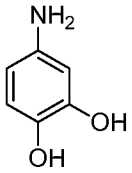


[00303] **4-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzene-1,2-diol [Example 18]:**



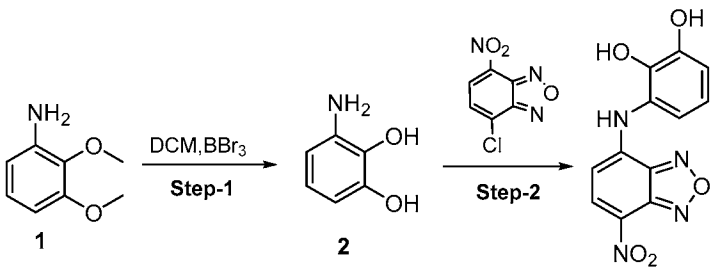
[00304] A solution of 4-aminobenzene-1,2-diol (200 mg, 1.00 mmol) in EtOH (5 mL) was charged with 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole (125 mg, 1.00 mmol) and heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to obtain 28 mg, 10% yield of the title compound as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.23 (s, 1H, formate), 8.04 (d, J = 9.6 Hz, 1H), 6.76 (d, J = 8.1 Hz, 1H), 6.58 (d, J = 2.4 Hz, 1H), 6.45 (dd, J = 8.3, 2.5 Hz, 1H), 6.20 (d, J = 9.7 Hz, 1H); MS (ES$^-$): m/z = 287.15, 288.05 [M-H]$^-$; LCMS: t_R = 2.08 min.

[00305] **4-Aminobenzene-1, 2-diol (2):**



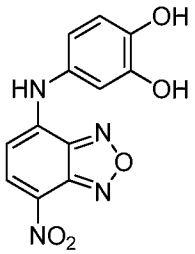
[00306] A solution of 3,4-dimethoxyaniline (500 mg, 3.26 mmol) in DCM (50 mL) at -70°C was charged with BBr_3 (4.0 mL, 16.3 mmol) and stirred at room temperature for 6 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was triturated with diethyl ether, filtered, and dried *in vacuo* resulting in 367 mg, 90% yield of the title compound as an off white solid. MS (ES$^+$): m/z = 126.10 [M+H]$^+$; LCMS: t_R = 0.53 min.

[00307] **Example 19: Synthetic scheme**



Example 19

[00308] 3-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzene-1,2-diol [Example 19]:

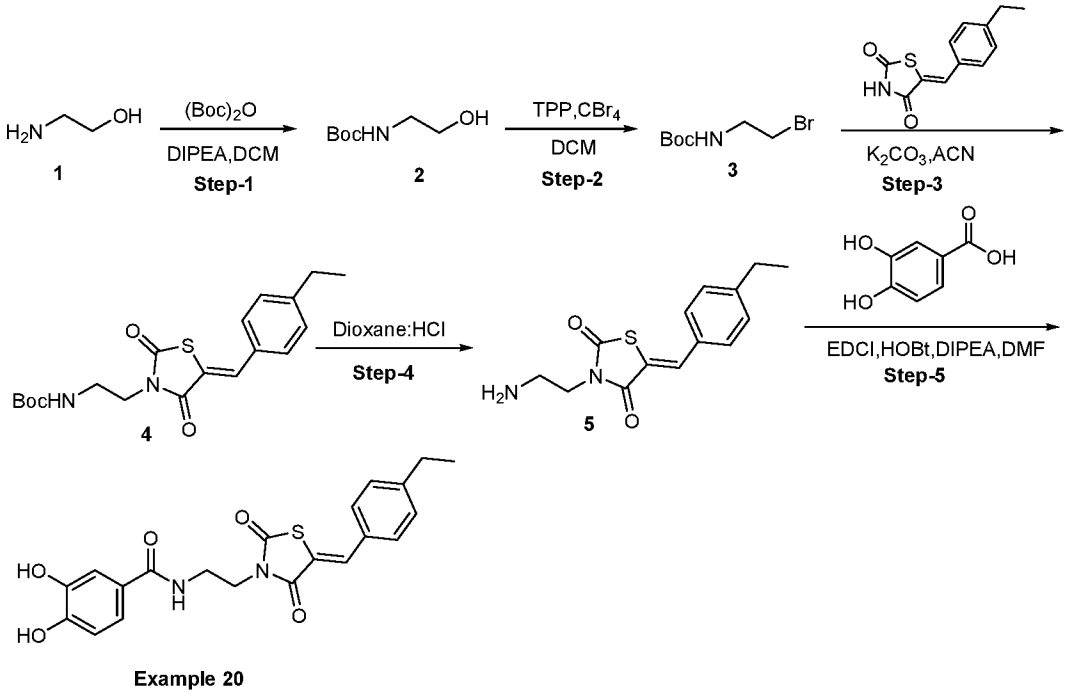


[00309] A solution of 3-aminobenzene-1,2-diol (200 mg, 1.00 mmol) in EtOH (5 mL) was charged with 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole(125 mg, 1.00 mmol) and heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to obtain 24 mg, 3% yield of the title compound as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.29 (d, J = 9.2 Hz, 1H), 8.17 (s, 1H), 6.82 – 6.53 (m, 3H), 5.98 (d, J = 9.2 Hz, 1H). MS (ES^-): m/z =287.10, 288.10 $[M-H]^-$; LCMS: t_R = 2.17 min.

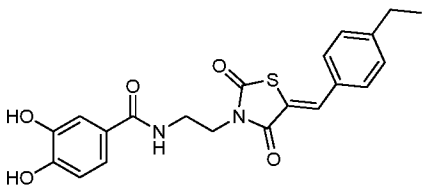
[00310] 3-Aminobenzene-1,2-diol (2):

[00311] A solution of 2,3-dimethoxyaniline (500 mg, 3.26 mmol) in DCM (50 mL) at -70°C was charged with BBr_3 (4.0 mL, 16.3 mmol), and stirred at room temperature for 6 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was triturated with diethyl ether, filtered, and dried *in vacuo* resulting in 387 mg, 95% yield of the title compound as an off white solid**.** MS (ES^+): m/z = 126.00 $[M+H]^+$; LCMS: t_R = 0.60 min.

[00312] Example 20: Synthetic scheme

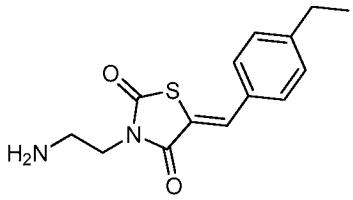


[00313] (*Z*)-*N*-(2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)-3,4-dihydroxybenzamide [Example 20]:



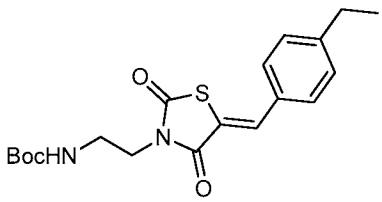
[00314] A solution of 3,4-dihydroxybenzoic acid (56 mg, 0.362 mmol) in DMF (5 mL) was charged with (*Z*)-3-(2-aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (100 mg, 0.362 mmol), EDCI (138 mg, 0.718 mmol), HOBt (97 mg, 0.718 mmol), DIPEA (93 mg, 0.718 mmol). The resulting solution was stirred at room temperature for 12 h and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to afford 30 mg, 20% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.42 (bs, 1H), 9.13 (bs, 1H), 8.30 (t, J = 6.0 Hz, 1H), 7.87 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.18 (d, J = 2.1 Hz, 1H), 7.07 (dd, J = 8.3, 2.1 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 3.79 (dd, J = 6.6, 4.5 Hz, 2H), 3.46 (q, J = 5.9 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); MS (ES$^+$): m/z = 413.15 , 414.15 [M+H]$^+$; LCMS: t_R = 2.56 min.

[00315] (*Z*)-3-(2-Aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (5):



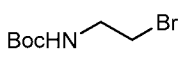
[00316] A solution of (*Z*)-*tert*-butyl (2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamate (410 mg, 1.09 mmol) in THF (5 mL) was charged with HCl in 1,4-dioxane (4M, 10 mL) and stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was triturated with diethyl ether, filtered, and dried *in vacuo* resulting in 300 mg, 98% yield of pure compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.92 (s, 3H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 3.91 (t, *J* = 5.9 Hz, 2H), 3.07 (s, 2H), 2.67 (q, *J* = 7.7 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H).

[00317] **(*Z*)-*tert*-Butyl (2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamate (4):**



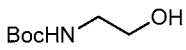
[00318] A solution of (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (500 mg, 2.14 mmol) in ACN (15 mL) was charged with K_2CO_3 (888 mg, 6.44 mmol) and *tert*-butyl (2-bromoethyl)carbamate (480 mg, 2.14 mmol) and heated at 80°C for 16 h. The reaction mixture was partitioned between ethyl acetate (25 mL) and water (10 mL) and separated. The aqueous layer was extracted with ethyl acetate (3 X 25 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 7% ethyl acetate in hexane to obtain 420 mg, 55% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.87 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 6.97 (t, *J* = 6.5 Hz, 1H), 3.69 (t, *J* = 5.4 Hz, 2H), 3.18 (q, *J* = 5.8 Hz, 2H), 2.67 (q, *J* = 7.7 Hz, 2H), 1.33 (s, 9H), 1.20 (t, *J* = 7.6 Hz, 3H).

[00319] ***tert*-Butyl (2-bromoethyl)carbamate (3):**



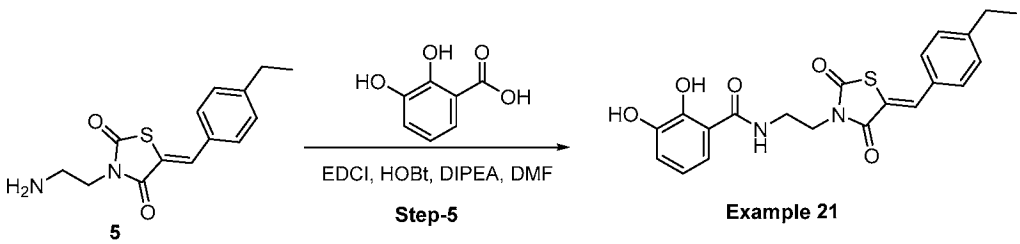
[00320] A solution of *tert*-butyl (2-hydroxyethyl)carbamate (4.0 g, 24.84 mmol) in DCM (50 mL) was charged with TPP (9.76 g, 37.26 mmol) and CBr_4 (12.6 g, 37.26 mmol) at 0°C and stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate (100 mL) and water (50 mL) and separated. The aqueous layer was extracted with ethyl acetate (3 X 100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexane to obtain 2.30 g ,41% yield of the title compound as a colorless oil . ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.93 (s, 1H), 3.49 – 3.42 (m, 4H), 1.46 (s, 9H).

[00321] ***tert*-Butyl (2-hydroxyethyl)carbamate (2):**

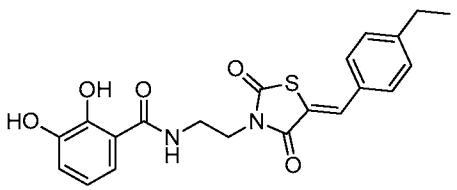


[00322] A solution of 2-aminoethanol (4.9 mL, 81.04 mmol) in DCM (50 mL) was charged with Boc anhydride (22.3 mL, 97.24 mmol) and DIPEA (28.6 mL, 162.1 mmol) and stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* resulting in 15 g of a crude compound as colorless oil. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.91 (s, 1H), 3.71 (t, *J* = 5.0 Hz, 2H), 3.29 (q, *J* = 5.3 Hz, 2H), 1.45 (s, 9H).

[00323] **Example 21: Synthetic scheme**

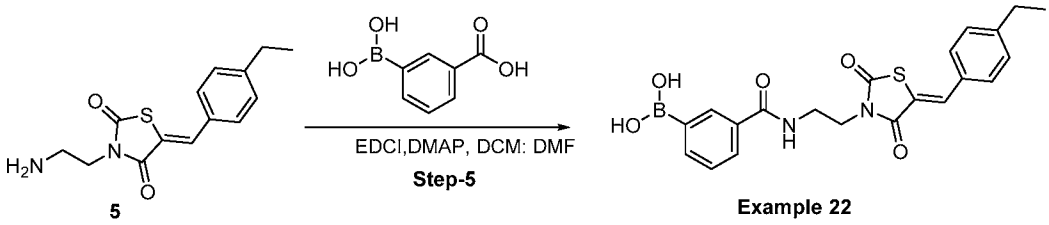


[00324] **(*Z*)-*N*-(2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)-2,3-dihydroxybenzamide [Example 21]:**

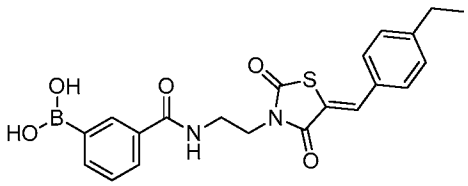


[00325] A solution of 2,3-dihydroxybenzoic acid (56 mg, 0.362 mmol) in DMF (5 mL) was charged with (Z)-3-(2-aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (100 mg, 0.362 mmol), EDCI (138 mg, 0.718 mmol), HOBt (97 mg, 0.718 mmol), DIPEA (93 mg, 0.718 mmol) and stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to afford 45 mg, 30% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ = 12.56 (s, 1H), 9.12 (s, 1H), 8.94 (t, J = 6.2 Hz, 1H), 7.89 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.16 – 7.08 (m, 1H), 6.93 – 6.86 (m, 1H), 6.66 (t, J = 7.9 Hz, 1H), 3.85 (t, J = 5.4 Hz, 2H), 3.54 (q, J = 5.7 Hz, 2H), 2.66 (q, J = 8.7, 7.6 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H); MS (ES$^+$): m/z = 413.10, 414.10 [M+H]$^+$; LCMS: t_R = 2.99 min.

[00326] **Example 22: Synthetic scheme**



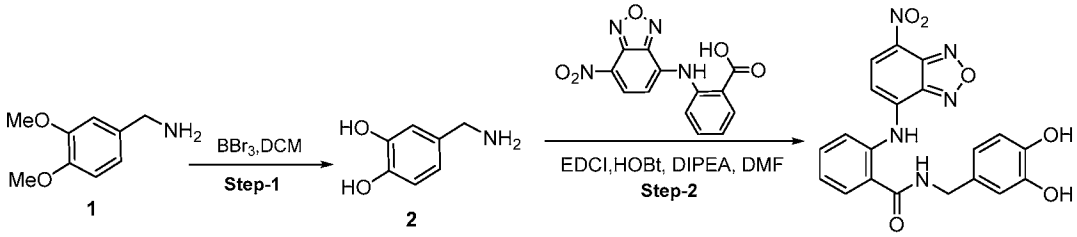
[00327] **(Z)-(3-((2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamoyl)phenyl)boronic acid [Example 22]:**



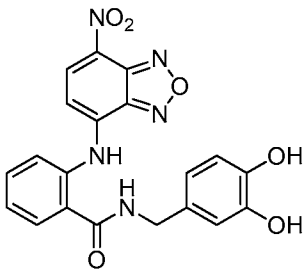
[00328] A solution of 3-boronobenzoic acid (60 mg, 0.362 mmol) and (*Z*)-3-(2-aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (100 mg, 0.362 mmol) in DCM:DMF (5 mL: 1mL) was charged with EDCI (138 mg, 0.718 mmol), DMAP (88 mg, 0.718 mmol) and stirred at room temperature for 12 h. The reaction mixture was partitioned between DCM (10 mL) and water (5 mL) and separated. The aqueous layer was extracted with DCM (3 X 10 mL) and the combined organic layers were washed with aqueous sat. $NaHCO_3$ solution followed by 1N aq HCl, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2% methanol in DCM to afford 45 mg, 30% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.59 (t, J = 6.0 Hz, 1H), 8.17 – 8.13 (m, 3H),

7.93 – 7.85 (m, 2H), 7.74 (dd, J = 7.8, 1.8 Hz, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.41 – 7.37 (m, 3H), 3.84 – 3.82 (m, 2H), 3.52 (m, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H); MS (ES^+): m/z = 425.10, 426.10 $[M+H]^+$; LCMS: t_R = 2.63 min.

[00329] Example 23: Synthetic scheme

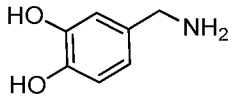


[00330] *N*-(3,4-Dihydroxybenzyl)-2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide [Example 23]:



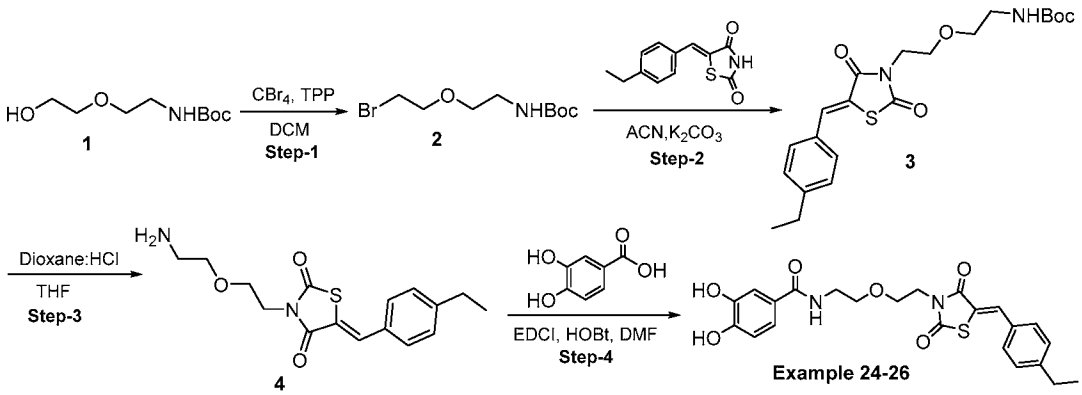
[00331] A solution of 2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (350 mg, 1.16 mmol) in DMF (5 mL) was charged with 4-(aminomethyl)benzene-1,2-diol (324 mg, 2.33 mmol), EDCI (448 mg, 2.33 mmol), HOBt (314 mg, 2.33 mmol), DIPEA (601 mg, 4.66 mmol) and was stirred at room temperature for 12 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 3% methanol in $CHCl_3$ to afford 60 mg, 12% yield of the title compound as an orange solid. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.82 (s, 1H), 9.23 (s, 1H), 8.78 (s, 1H), 8.73 (s, 1H), 8.51 (s, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.72 (s, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 6.91 – 6.82 (m, 1H), 6.67 (d, J = 2.0 Hz, 1H), 6.60 – 6.45 (m, 2H), 4.27 (d, J = 5.9 Hz, 2H); MS (ES^+): m/z = 422.10, 444.10 $[M+Na]^+$;LCMS: t_R = 2.53 min.

[00332] 4-(Aminomethyl)benzene-1,2-diol (2):

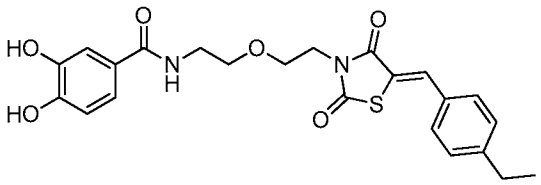


[00333] A solution of (3,4-dimethoxyphenyl)methanamine (200 mg, 1.19 mmol) in DCM (5 mL) at -20°C was charged with BBr_3 (5.90 mL, 5.98 mmol) and stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was triturated with diethyl ether, filtered, and dried *in vacuo* resulting in 400 mg of crude compound as an off white solid. ^{1}H NMR (400 MHz, D_2O): δ = 6.82 -6.62 (m, 3H), 3.81 (s, 2H).

[00334] **Examples 24, 25, and 26: Synthetic scheme**



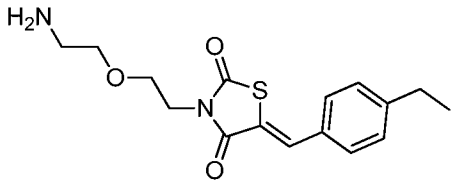
[00335] **(*Z*)-*N*-(2-(2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethoxy)ethyl)-3,4-dihydroxybenzamide [Example 24]:**



[00336] A solution of (*Z*)-3-(2-(2-aminoethoxy)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (200 mg, 0.625 mmol) in DMF (2 mL) was charged with EDCI (180 mg, 0.937 mmol), HOBt (126 mg, 0.937 mmol), DIPEA (161 mg, 1.25 mmol) and stirred at room temperature for 10 min. This solution was charged with 3,4-dihydroxybenzoic acid (96 mg, 0.625 mmol) and stirred at room temperature for 12 h. The reaction mixture was partitioned between DCM (20 mL) and water (10 mL) and separated. The aqueous layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 40 mg, 13 % yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, CD_3OD): δ = 7.78 (s, 1H), 7.47 – 7.25 (m, 5H), 7.19 (dd, *J* = 8.3, 2.2 Hz, 1H), 6.74 (dd, *J* =

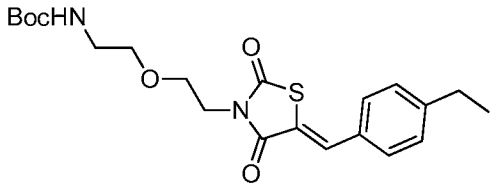
8.2, 1.6 Hz, 1H), 3.96 (t, J = 5.3 Hz, 2H), 3.74 (t, J = 5.3 Hz, 2H), 3.64 (t, J = 5.3 Hz, 2H), 3.49 (t, J = 5.4 Hz, 2H), 3.45 – 3.35 (m, 2H), 2.71 (q, J = 7.6 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H); MS (ES^+): m/z= 457.10, 458.20 $[M+H]^+$; LCMS: t_R = 3.00 min.

[00337] (*Z*)-3-(2-(2-Aminoethoxy)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (4):



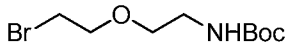
[00338] A solution of (*tert*-butyl (2-(2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethoxy)ethyl)carbamate (400 mg, 0.95 mmol) in dioxane (2 mL) was charged with HCl in 1,4-dioxane (4M, 5 mL) at 0°C and stirred at room temperature for 6 h. The reaction mixture was triturated with diethyl ether (5 mL) and concentrated *in vacuo* resulting in 259 mg of crude compound as a white solid. The crude compound was used in the next step without further purification. MS (ES^+): m/z = 321.10 $[M+H]^+$; LCMS: t_R = 2.40 min.

[00339] (*tert*-Butyl (2-(2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethoxy)ethyl)carbamate (3):



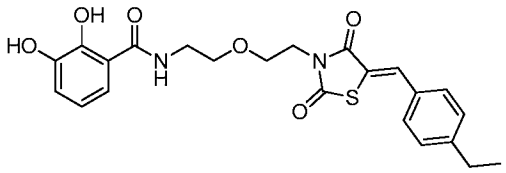
[00340] A solution of *tert*-butyl (2-(2-bromoethoxy)ethyl)carbamate (500 mg, 1.86 mmol) in ACN (4 mL) was charged with K_2CO_3 (771.9 mg, 5.59 mmol) and (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (434.9 mg, 1.86 mmol) and heated at 80°C for 12 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexane to afford 454 mg, 58% yield of the title compound as a light yellow solid. MS (ES^+): m/z = 443.15 $[M+Na]^+$; LCMS: t_R = 3.80 min.

[00341] *tert*-Butyl (2-(2-bromoethoxy)ethyl)carbamate (2):



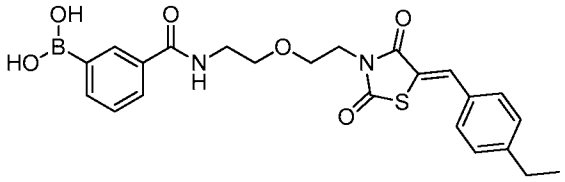
[00342] A solution of *tert*-butyl (2-(2-hydroxyethoxy) ethyl)carbamate (4.0 g, 4.80 mmol) in THF (20 mL) was charged with TPP (5.50 g, 7.60 mmol) and CBr_4 (7.40 g, 7.60 mmol) and stirred at room temperature for 12 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* resulting in a 5.20 g of a crude compound as light yellow oil. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.77 (t, J = 5.9 Hz, 1H), 3.70 (t, J = 5.8 Hz, 2H), 3.57 (t, J = 5.7 Hz, 2H), 3.42 (t, J = 6.1 Hz, 2H), 3.07 (q, J = 6.0 Hz, 2H), 1.37 (s, 9H).

[00343] **(*Z*)-*N*-(2-(2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethoxy)ethyl)-2,3-dihydroxybenzamide [Example 25]:**



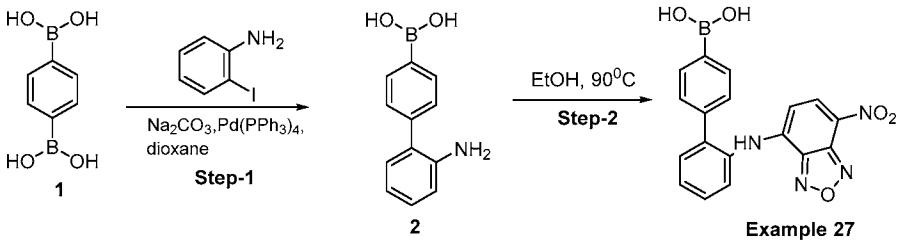
[00344] A solution of (*Z*)-3-(2-(2-aminoethoxy)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (200 mg, 0.625 mmol) in DMF (2 mL) was charged with EDCI (180 mg, 0.937 mmol), HOBt (126 mg, 0.937 mmol), DIPEA (161 mg, 1.25 mmol) and stirred at room temperature for 10 min. The solution was charged with 2,3-dihydroxybenzoic acid (96 mg, 0.625 mmol) and stirred at room temperature for 12 h. The reaction mixture was partitioned between DCM (20 mL) and water (10 mL) and separated. The aqueous layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 30 mg,10% yield of the title compound as a light gray solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.68 (bs, 1H), 9.13 (bs, 1H), 8.75 (t, J = 5.5 Hz, 1H), 7.85 (s, 1H), 7.51 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 7.24 (dd, J = 8.2, 1.5 Hz, 1H), 6.86 (dd, J = 8.0, 1.4 Hz, 1H), 6.60 (t, J = 7.9 Hz, 1H), 3.83 (t, J = 5.6 Hz, 2H), 3.65 (t, J = 5.7 Hz, 2H), 3.57 (t, J = 5.8 Hz, 2H), 3.40 (q, J = 5.7 Hz, 2H), 2.67 (q, J = 7.6 Hz, 2H), 1.20 (t, J = 7.5 Hz, 3H); MS (ES^+): m/z = 457.20, 458.30 $[M+H]^+$; LCMS: t_R = 3.05 min.

[00345] **(*Z*)-(3-((2-(2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethoxy)ethyl)carbamoyl)phenyl)boronic acid [Example 26]:**

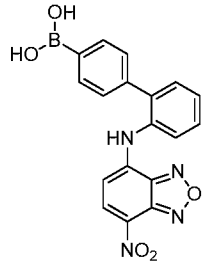


[00346] A solution of (*Z*)-3-(2-(2-aminoethoxy)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (200 mg, 0.625 mmol) in DMF (2 mL) was charged with EDCI (180 mg, 0.937 mmol), HOBt (126 mg, 0.937 mmol), DIPEA (161 mg, 1.25 mmol) and stirred at room temperature for 10 min. The solution was charged with 3-boronobenzoic acid (103 mg, 0.625 mmol) was added and the resulting solution was stirred at room temperature for 12 h. The reaction mixture was partitioned between DCM (20 mL) and water (10 mL) and separated. The aqueous layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 46 mg, 15 % yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.34 (t, *J* = 5.3 Hz, 1H), 8.23 (s, 1H), 8.13 (s, 2H), 7.91 – 7.77 (m, 3H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.43 – 7.30 (m, 3H), 3.84 (t, *J* = 5.6 Hz, 2H), 3.65 (t, *J* = 5.6 Hz, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 3.37 (q, *J* = 5.9 Hz, 2H), 2.67 (q, *J* = 7.7 Hz, 2H), 1.20 (t, *J* = 7.6 Hz, 3H); MS (ES$^+$): *m/z* = 469.15, 470.15 [M +H]$^+$; LCMS: t_R=3.03 min.

[00347] **Example 27: Synthetic scheme**

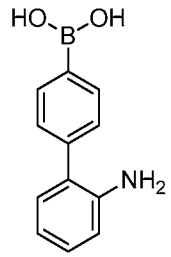


[00348] **(2'-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)-[1,1'-biphenyl]-4-yl)boronic acid [Example 27]:**



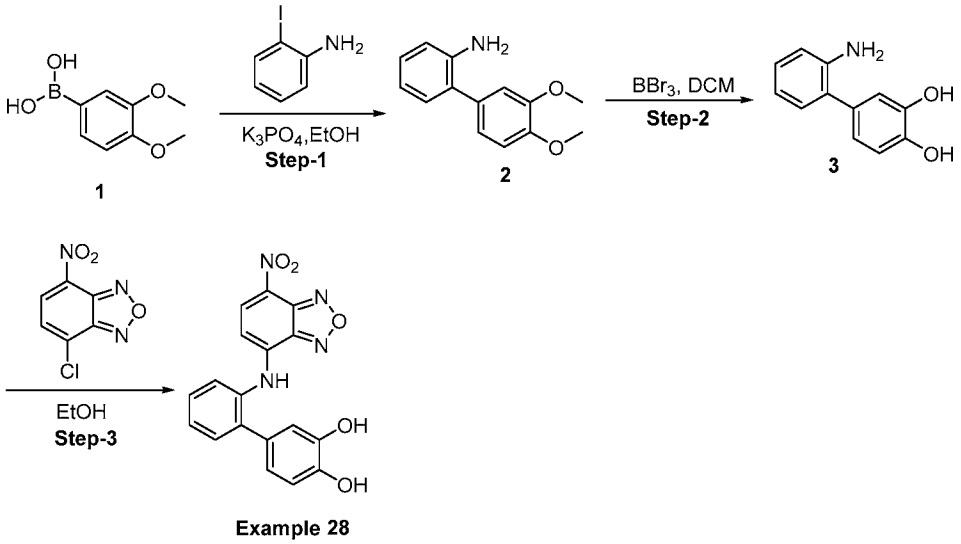
[00349] A solution of (2'-amino-[1,1'-biphenyl]-4-yl)boronic acid (90 mg, 0.422 mmol) in EtOH (2 mL) was charged with (2-aminophenyl)boronic acid (84.3 mg, 0.422 mmol) and heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to obtain 26 mg, 16% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.00 (s, 1H), 8.41 (s, 1H), 8.00 (s, 2H), 7.86 – 7.40 (m, 6H), 7.38 (d, J = 7.7 Hz, 2H), 6.05 (d, J = 8.0 Hz, 1H); MS (ES$^+$): m/z = 374.20 [M-H]$^-$; LCMS: t_R = 2.47 min.

[00350] **(2'-Amino-[1,1'-biphenyl]-4-yl)boronic acid (2):**



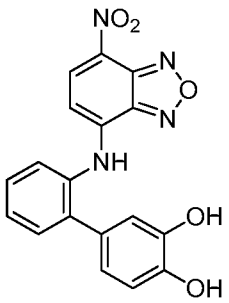
[00351] A solution of 1,4-phenylenediboronic acid (200 mg, 1.20 mmol) in 1,4 dioxane (2mL) in microwave vial under argon atmosphere was charged with 2-iodoaniline (129.0 mg, 0.603 mmol), $Pd(PPh_3)_4$ (14 mg, 0.0120 mmol) and sodium carbonate (381.5 mg, 3.60 mmol) and heated at 100°C for 30 min in microwave. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 50% ethyl acetate in hexane to afford 92 mg, 45 % yield of the title compound as a light yellow solid. MS (ES$^+$): m/z= 214.00, 215.20 [M+H]$^+$; LCMS: t_R = 1.93 min.

[00352] **Example 28: Synthetic scheme**



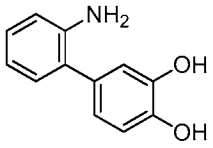
Example 28

[00353] **2'-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)-[1,1'-biphenyl]-3,4-diol [Example 28]:**



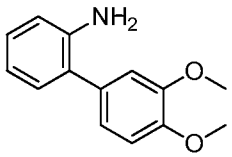
[00354] A solution of 2'-amino-[1,1'-biphenyl]-3,4-diol (101 mg, 0.501 mmol) in EtOH (10 mL) was charged with 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole (100 mg, 0.501 mmol) and heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to obtain 8 mg, 4% yield of the title compound as a dark brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.75 (bs, 2H), 8.17 (s, 1H, formate), 7.82 (d, J = 9.9 Hz, 1H), 7.36 – 7.23 (m, 2H), 7.15 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.8 Hz, 1H), 6.74 (s, 1H), 6.62 (s, 2H), 5.72 (d, J = 9.9 Hz, 1H); MS (ES$^+$): m/z = 365.15 $[M+H]^+$; LCMS: t_R = 2.45 min.

[00355] **2'-Amino-[1,1'-biphenyl]-3,4-diol (3):**



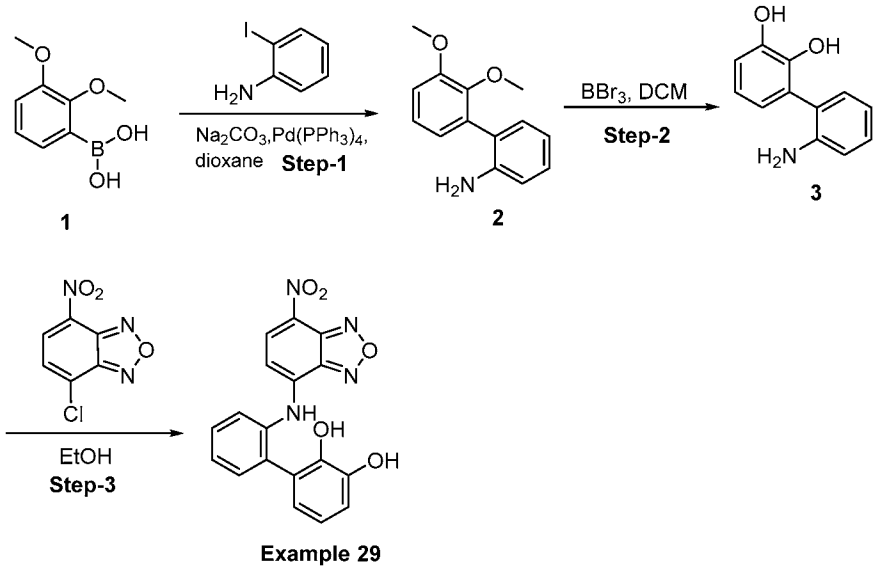
[00356] A solution of 3',4'-dimethoxy-[1,1'-biphenyl]-2-amine (160 mg, 0.698 mmol) in DCM (10 mL) at -30°C was charged with BBr_3 (873 mg, 3.49 mmol) and stirred at room temperature for 16 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was triturated with diethyl ether, filtered and dried *in vacuo* resulting in 114 mg, 81% yield of the title compound as an off white solid**.** The crude compound obtained was used in the next step without further purification.

[00357] **3',4'-Dimethoxy-[1,1'-biphenyl]-2-amine (2):**

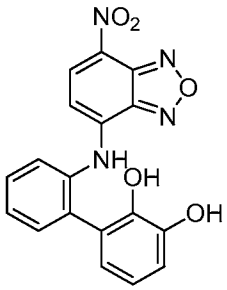


[00358] A solution of (3,4-dimethoxyphenyl)boronic acid (500 mg, 2.75 mmol) in EtOH:H_2O (10 mL:30 mL) was charged with 2-iodoaniline (601 mg, 2.75 mmol), K_3PO_4 (1.75 g, 8.25 mmol) and heated at 80°C for 4h. The reaction mixture was evaporated under reduced pressure and the residue obtained was diluted with water (15 mL) and extracted with DCM (3 X 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2% methanol in DCM to afford 625 mg, 99% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.05 – 6.93 (m, 4H), 6.91 (dd, J = 8.1, 2.0 Hz, 1H), 6.73 (d, J = 7.9Hz, 1H), 6.60 (t, J = 7.4 Hz, 1H), 4.75 (s, 2H), 3.90 (s, 3H), 3.88 (s, 3H).

[00359] **Example 29: Synthetic scheme**

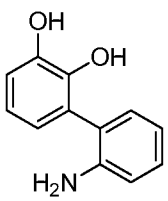


[00360] 2'-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)-[1,1'-biphenyl]-2,3-diol [Example 29]:



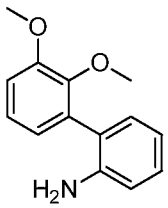
[00361] A solution of 2'-amino-[1,1'-biphenyl]-2,3-diol (50 mg, 1.00 mmol) in EtOH (2 mL) was charged with 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole(50 mg, 1.00 mmol) and heated at 80°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to obtain 35 mg, 38% yield of the title compound as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.21 (bs, 1H), 8.13 (s, 1H), 7.50 – 7.31 (m, 5H), 7.08 (s, 1H), 6.74 – 6.59 (m, 3H), 6.19 (s, 1H); MS (ES$^+$): *m/z* = 365.15 [M+H]$^+$; LCMS: t_R = 2.68 min.

[00362] 2'-Amino-[1,1'-biphenyl]-2,3-diol (3):



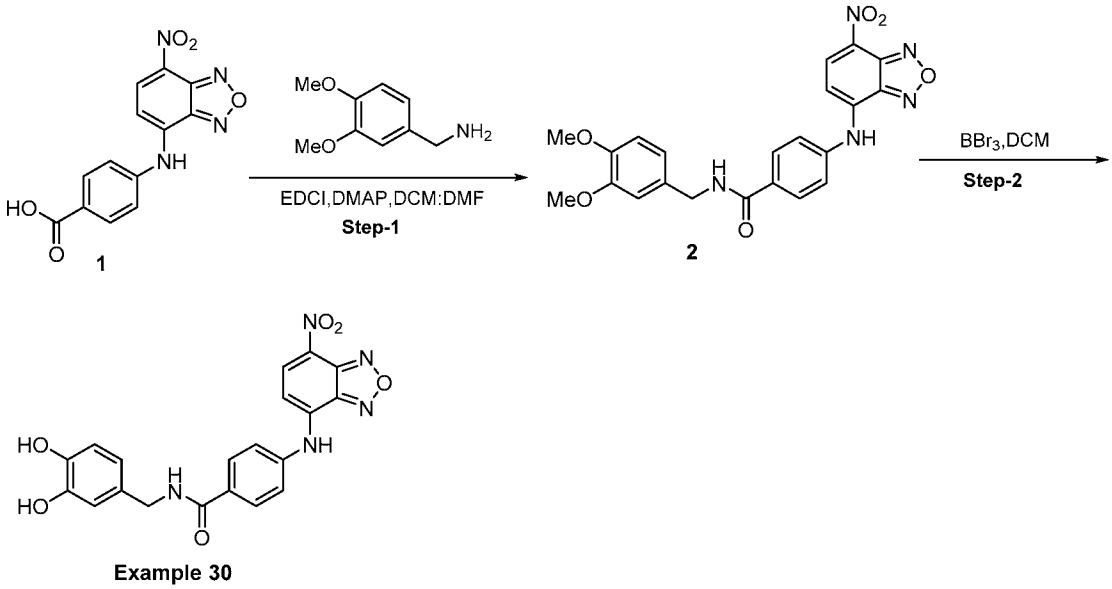
[00363] A solution of 2',3'-dimethoxy-[1,1'-biphenyl]-2-amine (90 mg, 0.393 mmol) in DCM (5 mL) at -30°C was charged with BBr_3 (491 mg, 1.965 mmol) and stirred at room temperature for 16 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was triturated with diethyl ether, filtered and dried *in vacuo* resulting in 50 mg, 64% yield of the title compound as an off white solid**.** The crude compound obtained was used in the next step without further purification.

[00364] **2',3'-Dimethoxy-[1,1'-biphenyl]-2-amine (2):**

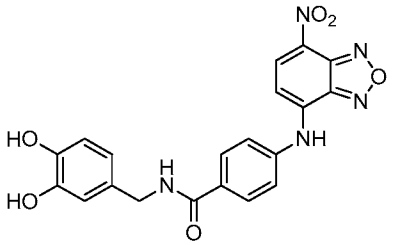


[00365] A solution of (2,3-dimethoxyphenyl)boronic acid (200 mg, 1.09 mmol) in EtOH:H_2O (2 mL: 1mL) under argon atmosphere was charged with 2-iodoaniline (241 mg, 1.09 mmol), $Pd(PPh_3)_4$ (63 mg, 0.054 mmol) and sodium carbonate (349 mg, 3.29 mmol) and heated at 80°C for 2 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 5% ethyl acetate in hexane to afford 164 mg, 65% yield of the title compound as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.18 – 7.05 (m, 3H), 6.92 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.77 – 6.69 (m, 2H), 6.65 – 6.58 (m, 1H), 4.50 (s, 2H), 3.83 (s, 3H), 3.33 (s, 3H).

[00366] **Example 30: Synthetic scheme**

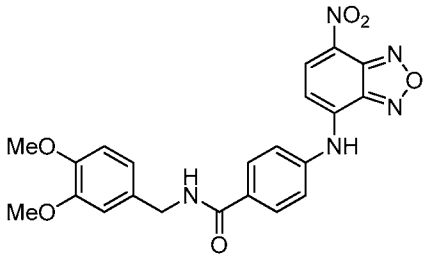


[00367] ***N*-(3,4-Dihydroxybenzyl)-4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide [Example 30]:**



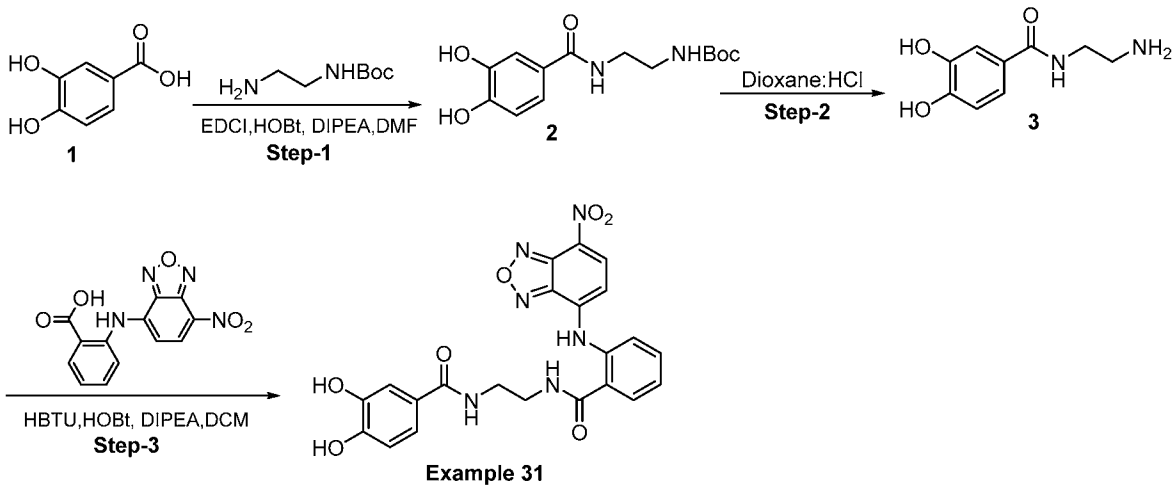
[00368] A solution of *N*-(3,4-dimethoxybenzyl)-4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide (50 mg, 0.11 mmol) in DCM (5 mL) at -30°C was charged with BBr_3 (137 mg, 0.55 mmol) and stirred at room temperature for 16 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was purified by preparative HPLC to afford 40 mg, 87% yield the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.78 (t, J = 6.0 Hz, 1H), 8.24 (s, 2H), 7.90 – 7.77 (m, 3H), 6.97 (d, J = 8.1 Hz, 2H), 6.76 – 6.56 (m, 3H), 5.73 (d, J = 10.0 Hz, 1H), 4.31 (d, J = 5.9 Hz, 2H); MS (ES^+): m/z = 422.10 $[M+H]^+$; LCMS: t_R = 2.13 min.

[00369] ***N*-(3,4-Dimethoxybenzyl)-4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide (2):**

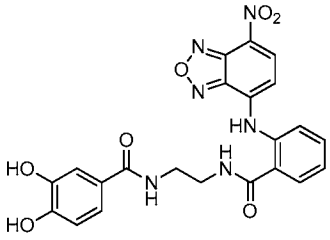


[00370] A solution of 4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (400 mg, 1.33 mmol) in DCM:DMF (10 mL:5 mL)mixture was charged with (3,4-dimethoxyphenyl)methanamine (267 mg, 1.59 mmol), EDCI (384 mg, 1.99 mmol) and DMAP (325 mg, 2.66 mmol). The reaction mixture was partitioned between ethyl acetate (50 mL) and water (25 mL) and separated. The aqueous layer was extracted with ethyl acetate (3 X 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2% methanol in DCM to afford 229 mg, 38% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.89 (t, J = 6.1 Hz, 1H), 8.13 (d, J = 6.2 Hz, 1H), 7.98 (d, J = 9.7 Hz, 1H), 7.91 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 11.1 Hz, 2H), 6.90 – 6.72 (m, 3H), 6.65 – 6.60 (m, 1H), 3.90 (s, 2H), 3.88 (s, 3H), 3.75 (s, 3H).

[00371] **Example 31: Synthetic scheme**

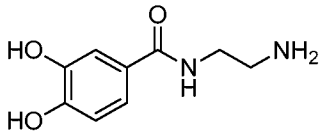


[00372] **3,4-Dihydroxy-*N*-(2-(2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)benzamide [Example 31]:**



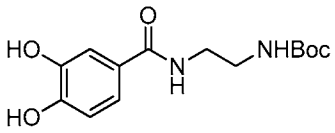
[00373] A solution of 2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (100 mg, 0.333 mmol) in DCM:DMF (5 mL/2 mL) mixture was charged with EDCI (253 mg, 0.666 mmol), HOBt (112mg, 0.834 mmol), DIPEA (129 mg, 1.00 mmol) and stirred at room temperature for 10 min. The solution was charged with *N*-(2-aminoethyl)-3,4-dihydroxybenzamide (85 mg, 0.366 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 layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 30 mg, 19% yield of the title compound as an orange solid**.** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.0 (bs, 1H), 9.37 (bs, 1H), 9.03 (s, 1H), 8.19 (t, J = 5.2 Hz, 1H), 8.13 (s, 1H, formate), 7.91 (d, J = 7.6 Hz, 1H), 7.60 – 7.47 (m, 2H), 7.30 – 7.26 (m, 1H), 7.23 (d, J = 1.6 Hz, 1H), 7.10 (dd, J = 8.3, 2.2 Hz, 2H), 6.67 (d, J = 8.3 Hz, 1H), 3.38-3.30 (m, 4H); MS (ES^+): m/z = 479.25, 480.25 $[M+H]^+$; LCMS: t_R = 2.07 min.

[00374] ***N*-(2-Aminoethyl)-3,4-dihydroxybenzamide (3):**



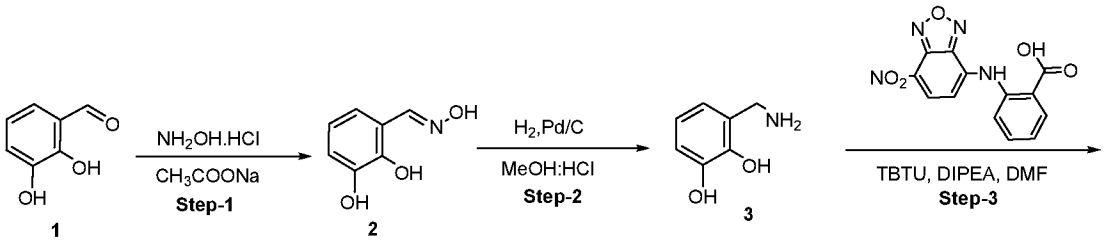
[00375] A solution of *tert*-butyl (2-(3,4-dihydroxybenzamido)ethyl)carbamate (200 mg, 0.670 mmol) in 1-4 dioxane (5 mL) was charged with HCl in 1,4-dioxane (4M, 5 mL) and stirred at room temperature for 12 h. The reaction mixture was evaporated under reduced pressure to obtain a residue which was triturated with diethyl ether, filtered, and dried *in vacuo* resulting in a pure compound 140 mg, 88 % yield as a dark red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.34 – 7.22 (m, 2H), 6.78 (d, J = 8.2 Hz, 1H), 3.46 – 3.40 (m, 2H), 2.95 – 2.90 (m, 2H).

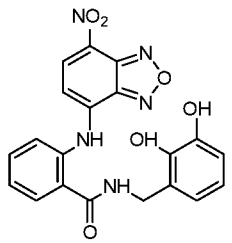
[00376] ***tert*-Butyl (2-(3,4-dihydroxybenzamido)ethyl)carbamate (2):**



[00377] A solution of 3,4-dihydroxybenzoic acid (400 mg, 2.59 mmol) in DCM:DMF (10 mL:2.5 mL) mixture was charged with EDCI (994 mg, 5.18 mmol), HOBt (701 mg, 5.18 mmol), DIPEA (1.32 mL, 7.77 mmol) and stirred at room temperature for 10 min. The solution was charged with *tert*-butyl (2-aminoethyl)carbamate (415 mg, 2.59 mmol) and stirred at room temperature for 16 h. The reaction mixture was partitioned between DCM (50 mL) and water (20 mL) and separated. The aqueous layer was extracted with DCM (2 X 50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 200 mg, 26% yield of the title compound as an orange solid**.** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.10 (t, J = 5.8 Hz, 1H), 7.27 (d, J = 2.2 Hz, 1H), 7.15 (dd, J = 8.3, 2.2 Hz, 1H), 6.90 – 6.85 (m, 1H), 6.74 (d, J = 8.2 Hz, 1H), 3.25 – 3.18 (m, 2H), 3.18 – 3.10 (m, 2H), 1.37 (s, 9H).

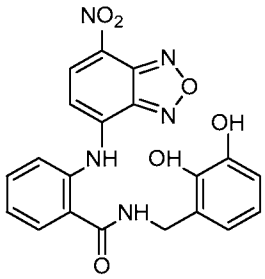
[00378] **Example 32: Synthetic scheme**





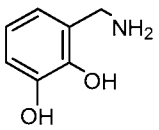
Example 32

[00379] ***N*-(2,3-Dihydroxybenzyl)-2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide [Example 32]:**



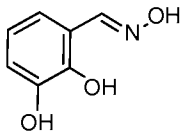
[00380] A solution of 2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (200 mg, 0.666 mmol) in DMF (2 mL) was charged with TBTU (230 mg, 0.730 mmol), DIPEA (0.35 mL, 2.00 mmol) and stirred at room temperature for 10 min. This solution was charged with 3-(aminomethyl)benzene-1,2-diol (120 mg, 0.666 mmol) and stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (10 mL) and separated. The aqueous layer was extracted with ethyl acetate (2 X 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 100 mg, 39% yield of the title compound as a red solid**.** ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.64 (s, 1H), 9.15 – 9.10 (m, 2H), 8.52 (s, 1H), 8.48 – 8.40 (bs, 1H), 7.88 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 8.9 Hz, 2H), 7.42 – 7.38 (m, 1H), 6.78 – 6.74 (m, 1H), 6.60 (d, J = 7.7 Hz, 1H), 6.49 (d, J = 8.1 Hz, 1H), 6.40 (t, J = 7.7 Hz, 1H), 4.36 (d, J = 5.8 Hz, 2H); MS (ES$^+$): m/z = 422.20 [M+H]$^+$; LCMS: t_R = 2.44 min

[00381] **3-(Aminomethyl)benzene-1,2-diol (3):**



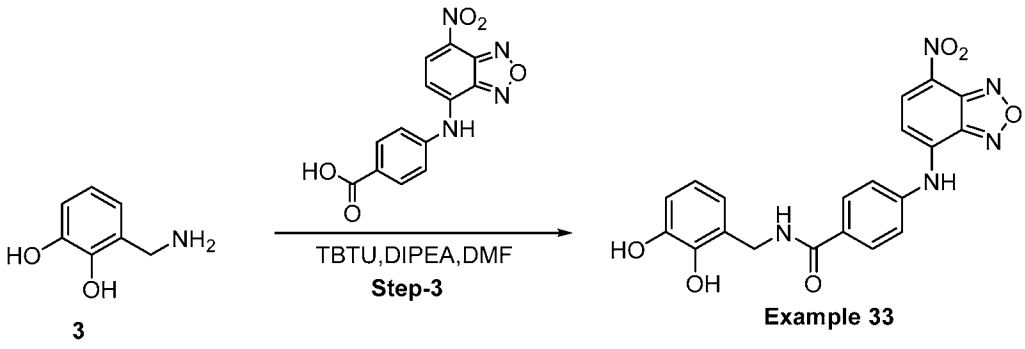
[00382] A solution of (*E*)-2,3-dihydroxybenzaldehyde oxime (1.0 g, 6.53 mmol) in EtOH (10 mL) at 0°C was charged with 10% Pd/C (100 mg) and methanolic HCl (20 mL) and stirred at room temperature under hydrogen gas at atmospheric pressure for 4 h. The reaction mixture was filtered through a pad of celite and washed with ethanol. The filtrate was concentrated *in vacuo* resulting in 500 mg of HCl salt of the crude compound as an off white solid**.** The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.85 – 6.80 (m, 2H), 6.65 (t, J = 7.7 Hz, 1H), 3.91 (q, J = 5.8 Hz, 2H).

[00383] **(*E*)-2,3-Dihydroxybenzaldehyde oxime (2):**



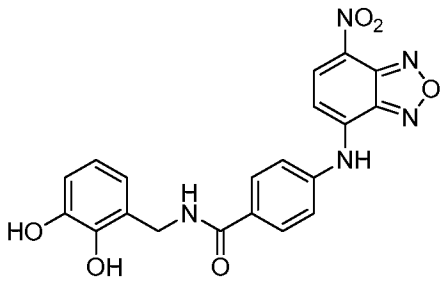
[00384] A solution of hydroxylamine hydrochloride (1.0 g, 14.40 mmol) and sodium acetate (2.0 g, 24.40 mmol) in water (10 mL) was charged with 2,3-dihydroxybenzaldehyde (1.0 g, 7.24 mmol). Ethanol (10 mL) was added to the reaction mixture and sonicated at 60°C to get clear solution. The solution was poured into ice cold water (50 mL) upon which a precipitate formed. The precipitate was collected by filtration and dried *in vacuo* resulting in 1.0 g of the crude compound as a white solid**.** The crude compound was used in the next step without further purification.

[00385] **Example 33: Synthetic scheme**



3 **Example 33**

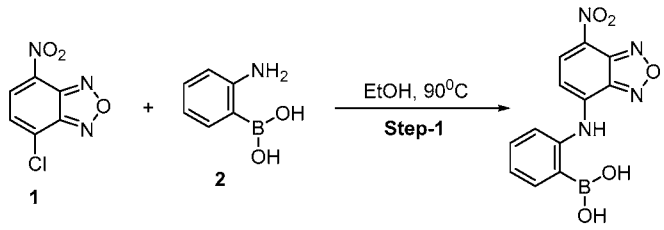
[00386] ***N*-(2,3-Dihydroxybenzyl)-4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide [Example 33]:**



[00387] A solution of 4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (200 mg, 0.666 mmol) in DMF (2 mL) was charged with TBTU (230 mg, 0.730 mmol), DIPEA (0.35 mL, 0.666 mmol) and stirred at room temperature for 10 min. This solution was charged with 3-(aminomethyl)benzene-1,2-diol (120 mg, 0.666 mmol) and stirred at room temperature for 2 h. The reaction mixture was partitioned between ethyl acetate (20 mL) and water (10 mL)

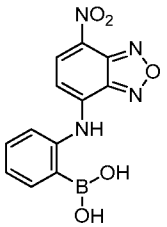
and separated. The aqueous layer was extracted with ethyl acetate (2 X 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 100 mg, 39% yield of the title compound as a red solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.09 – 8.96 (m, 2H), 8.84 (bs, 1H), 8.29 (d, J = 9.2 Hz, 1H), 8.13 (bs, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.37 (d, J = 8.1 Hz, 2H), 6.72 – 6.55 (m, 3H), 6.50 (d, J = 9.2 Hz, 1H), 4.42 (d, J = 5.8 Hz, 2H); MS (ES$^+$): m/z = 422.20 [M+H]$^+$; LCMS: t_R = 2.41 min.

[00388] Example 34: Synthetic scheme



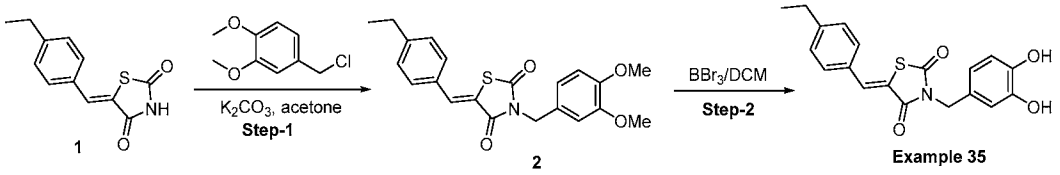
Example 34

[00389] (2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)phenyl)boronic acid [Example 34]:

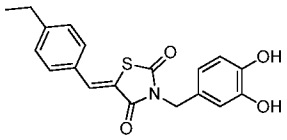


[00390] A solution of 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole (200 mg, 1.00 mmol) in EtOH (5 mL) was charged with (2-aminophenyl)boronic acid (151 mg, 1.10 mmol) and heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to give 20 mg, 6% yield of the title compound as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.02 (s, 1H), 8.59 (bs, 2H), 8.55 (d, J = 9.2 Hz, 1H), 7.84 (d, J = 7.4 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.34 – 7.28 (m, 1H), 6.75 (d, J = 8.8 Hz, 1H); MS (ES$^+$): m/z = 299.15 [M-H]$^-$; LCMS: t_R = 2.52 min.

[00391] Example 35: Synthetic scheme

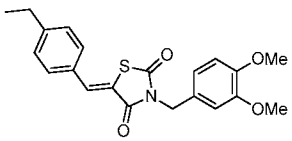


[00392] (*Z*)-3-(3,4-Dihydroxybenzyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione [Example 35]:



[00393] A solution of (*Z*)-3-(3,4-Dimethoxybenzyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione(450 mg , 1.17 mmol) in DCM (10 mL) was charged with BBr_3 (883 mg, 3.52 mmol) at 0°C and the solution was stirred at room temperature for 2 h. The reaction mixture was quenched with ice cold water (5 mL) and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 20% ethyl acetate in hexanes to give 160 mg, 38% yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.99 (bs, 1H), 8.91 (bs, 1H), 7.93 (s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.39 (d, J = 7.8 Hz, 2H), 6.75 – 6.64 (m, 2H), 6.59 (dd, J = 8.0, 2.1 Hz, 1H), 4.64 (s, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.5 Hz, 3H); MS (ES$^+$): m/z = 356.5 $[M+H]^+$; LCMS: t_R = 2.99 min.

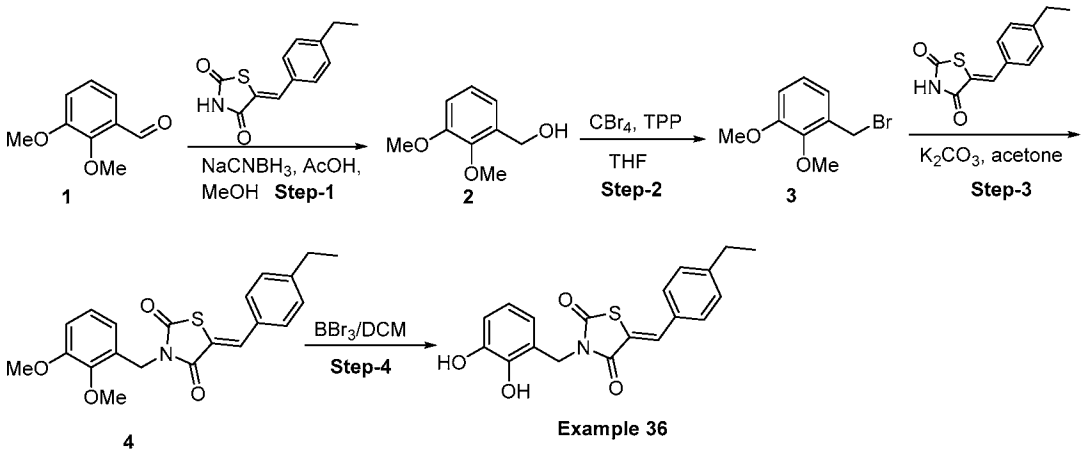
[00394] (*Z*)-3-(3,4-Dimethoxybenzyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (2):



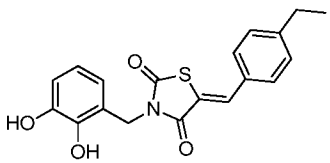
[00395] A solution of 4-(chloromethyl)-1,2-dimethoxybenzene (1.0 g, 5.37 mmol) in acetone (10 mL) were charged with K_2CO_3 (2.23 g, 16.13 mmol) and (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (1.50 g, 6.43 mmol) and refluxed for 48 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 15% ethyl acetate in hexane to give 450 mg, 22% yield of the title compound as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.94 (s, 1H), 7.54 (t, J = 11.3 Hz, 2H),

7.39 (d, J = 7.8 Hz, 2H), 6.96 – 6.87 (m, 2H), 6.82 (d, J = 8.2 Hz, 1H), 4.76 (s, 2H), 3.72 (s, 3H), 3.70 (s, 3H), 2.69 – 2.61 (m, 2H), 1.19 (t, J = 7.6 Hz, 3H).

[00396] Example 36: Synthetic scheme

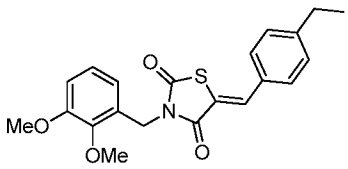


[00397] (*Z*)-3-(2,3-Dihydroxybenzyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione [Example 36]:



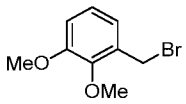
[00398] A solution of (*Z*)-3-(2,3-Dimethoxybenzyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (120 mg, 0.313 mmol) in DCM (10 mL) was charged with BBr_3 (1M in DCM, 235 mg, 0.939 mmol) at 0°C and The resulting reaction mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with ice cold water (5 mL) and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexane to give 60 mg, 54% yield of the title compound as off white solid. ^{1}H NMR (400 MHz, , DMSO-d_6): δ = 9.41 (s, 1H), 8.63 (s, 1H), 7.93 (s, 1H), 7.58 – 7.56 (d, J = 8.0 Hz, 2H), 7.41-7.39 (d, J = 8.0 Hz, 2H), 6.70 (dd, J = 7.9, 1.6 Hz, 1H), 6.57 (t, J = 7.8 Hz, 1H), 6.37 (dd, J = 7.7, 1.5 Hz, 1H), 4.78 (s, 2H), 2.67 (q, J = 7.6 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); MS (ES^+): m/z = 356.10 $[M+H]^+$; LCMS: t_R = 3.12 min.

[00399] (*Z*)-3-(2,3-Dimethoxybenzyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (4):



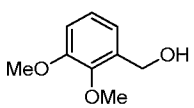
[00400] A solution of 1-(bromomethyl)-2,3-dimethoxybenzene (110 mg , 0.476 mmol) in acetone (10 mL) was charged with K_2CO_3 (197 mg, 1.42 mmol) and (*Z*)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (133 mg, 0.571 mmol) and refluxed for 48 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexane to give 120 mg, 66% yield of the title compound as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.95 (s,1H), 7.57 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.07 – 6.96 (m, 2H), 6.65 – 6.60 (m, 1H), 4.84 (s, 2H), 3.78 (s,3H), 3.76 (s, 3H) , 2.66 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H).

[00401] **1-(Bromomethyl)-2,3-dimethoxybenzene (3):**



[00402] A solution of 2,3-dimethoxyphenyl)methanol (80 mg, 0.476 mmol) in THF (5 mL) was charged with TPP (200 mg, 0.761 mmol) and CBr_4 (253 mg, 0.761 mmol) and stirred at room temperature for 16 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* resulting in a crude compound 120 mg as a light yellow solid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.04 (s, 1H), 7.10 – 6.95 (m, 2H), 4.63 (s, 2H), 3.82 (s, 3H), 3.80 (s, 3H)..

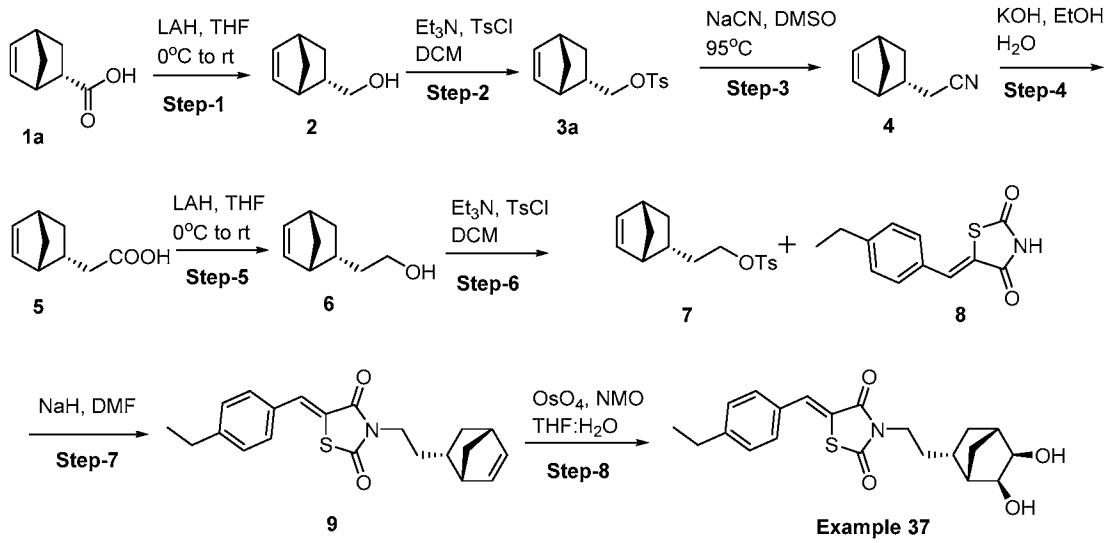
[00403] **<u>(2,3-Dimethoxyphenyl)methanol (2):</u>**



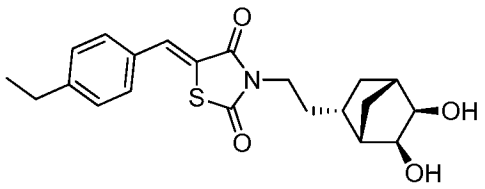
[00404] A solution of 2,3-dimethoxybenzaldehyde (100 mg, 0.602 mmol) in methanol (5 mL) was charged with (Z)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (140 mg, 0.602 mmol) and acetic acid (0.2 mL) and stirred at room temperature for 2 h. This solution was charged with sodium cyanoborohydride (114 mg, 1.81 mmol) and stirred at room temperature for 16 h. The solvent was removed under reduced pressure and the residue obtained was partitioned between water (10 mL) and ethyl acetate and separated. The aqueous was extracted with ethyl

acetate (3 X 15 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 10% ethyl acetate in hexane to give 80 mg, 79% yield of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.04 – 6.95 (m, 3H), 4.99 (t, J = 5.6 Hz, 1H), 4.50 (d, J = 5.6 Hz, 2H), 3.78 (s, 3H), 3.70 (s, 3H).

[00405] Synthetic scheme: Example 37



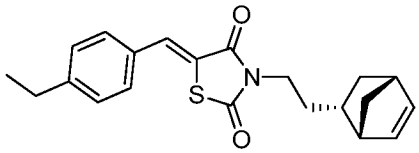
[00406] (*Z*)-3-(2-((1*S*,2*S*,4S,5*R*,6*S*)- 5,6-Dihydroxybicyclo[2.2.1]heptane-2-yl)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione [Example 37]:



[00407] A solution of (*Z*)-3-(2-((1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-yl)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (130 mg, 0.368 mmol) in THF:H_2O (2:0.5 mL) was charged with NMO (47 mg, 0.405 mmol) and OsO_4 (14 mg, 0.055 mmol). The resulting solution was stirred at room temperature for 16 h and was concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to give 55 mg, 38% yield of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (s, 1H), 7.52 – 7.59 (m, 2H), 7.39 (d, J = 7.9 Hz, 2H), 4.56 (bs, 2H), 3.79 (d, J = 6.0 Hz, 1H), 3.62 (t, J = 7.1 Hz, 2H), 3.40 – 3.46 (m, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.93 (dd, J = 18.9, 3.4 Hz, 2H), 1.54 – 1.76 (m,

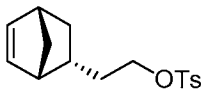
4H), 1.20 (t, J = 7.6 Hz, 3H), 0.97 – 1.05 (m, 1H), 0.46 – 0.56 (m, 1H); MS (ES^+): m/z = 405.20 [M + H_2O]; LCMS: t_R = 3.17 min.

[00408] (*Z*)-3-(2-((1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-yl)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (9):



[00409] A solution of (*Z*)-5-(4-methylbenzylidene)thiazolidine-2,4-dione (380 mg, 1.63 mmol) in DMF (20 mL) was charged with sodium hydride (61 mg, 2.57 mmol) at 0°C. The reaction mixture was stirred at 0°C for 15 min, followed by addition of 2-((1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-yl)ethyl 4-methylbenzenesulfonate (375 mg, 1.63 mmol). The resulting solution was stirred at room temperature for 14 h. The reaction mixture was diluted with water (10 mL) and extracted with DCM (3 X 20 mL). The combined organic layer was washed with water (30 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2-4% ethyl acetate in hexane to afford 130 mg, 28% yield of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (s, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.39 (d, J = 7.9 Hz, 2H), 6.05 – 6.20 (m, 1H), 5.94 (dd, J = 5.9, 2.8 Hz, 1H), 3.63 (t, J = 7.3 Hz, 2H), 2.62 – 2.84 (m, 4H), 1.79 – 1.91 (m, 2H), 1.30 – 1.52 (m, 3H), 1.08- 1.22 (m, 5H).

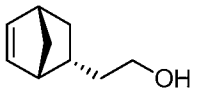
[00410] 2-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)ethyl 4-methylbenzenesulfonate (7):



[00411] A solution of 2-((1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-yl)ethanol (500 mg, 3.62 mmol) in DCM (10 mL) was charged with triethylamine (424 mg, 4.20 mmol) and tosyl chloride (2.06 g, 10.86 mmol) at 0 °C. The reaction mixture was cooled to room temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was purified by column chromatography on silica gel eluting with 2-4% ethyl acetate in hexane to afford 700 mg, 66% yield of the title compound as colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.74 – 7.82 (m, 2H), 7.49 (d, J = 7.9 Hz, 2H), 6.10 (dd, J =

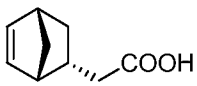
5.9, 3.0 Hz, 1H), 5.84 (dd, J = 5.9, 2.8 Hz, 1H), 3.91 – 4.06 (m, 2H), 2.70 (d, J = 3.5 Hz, 1H), 2.62 (s, 1H), 2.45 (s, 3H), 1.97-2.01 (m, 1H), 1.66 – 1.77 (m, 1H), 1.10 – 1.42 (m, 5H).

[00412] 2-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)ethanol (6):



[00413] A solution of LAH (271 mg, 7.1 mmol) in THF (10 mL) was charged with 2-((1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-yl)acetic acid (700 mg, 4.6 mmol) at 0°C and stirred at room temperature for 2 h. The reaction mixture was quenched with 1N aq NaOH and ethyl acetate at 0°C. The reaction mixture was filtered through pad of celite and the filtrate was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with water (30 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 500 mg of crude compound as colorless liquid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.12 (dd, J = 5.8, 3.0 Hz, 1H), 5.92 (dd, J = 5.8, 2.8 Hz, 1H), 4.30 (t, J = 5.2 Hz, 1H), 3.32 – 3.41 (m, 2H), 2.69 – 2.71 (m, 2H), 1.94 – 2.11 (m, 1H), 1.72 – 1.87 (m, 1H), 1.02 – 1.38 (m, 5H).

[00414] 2-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)acetic acid (5):

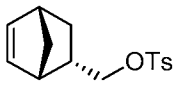


[00415] A solution of 2-((1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-yl)acetonitrile (700 mg, 5.26 mmol) in EtOH: H_2O (3:3 mL) was charged with KOH (884 mg, 15.8 mmol) at room temperature. The resulting reaction mixture was refluxed at 95 °C for 16 h. The solvent was removed *in vacuo* and the residue obtained was acidified with 1N HCl to pH ~2-3 and extracted with DCM (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 700 mg of crude compound as colorless liquid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.94 (s, 1H), 6.17 (dd, J = 5.8, 3.0 Hz, 1H), 5.93 (dd, J = 5.8, 2.9 Hz, 1H), 2.71 – 2.81 (m, 2H), 2.28 – 2.48 (m, 2H), 2.02 (dd, J = 15.4, 7.5 Hz, 1H), 1.70 – 1.95 (m, 2H), 1.16 – 1.38 (m, 2H).

[00416] 2-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)acetonitrile (4):

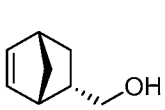
[00417] A solution of (1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-ylmethyl 4-methylbenzenesulfonate (1.5 g, 5.38 mmol) in DMSO (10 mL) was charged with sodium cyanide (527 mg, 10.79 mmol) at room temperature. The resulting reaction mixture was refluxed at 95 °C for 16 h. The reaction mixture was cooled to room temperature and quenched with water, extracted with ethyl acetate (3 X 50mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 700 mg of crude compound as light yellow liquid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.24 (dt, *J* = 4.6, 2.2 Hz, 1H), 5.97 (dd, *J* = 5.8, 2.9 Hz, 1H), 2.76 – 2.87 (m, 2H), 2.29 – 2.42 (m, 2H), 2.09 – 2.26 (m, 2H), 1.86 – 1.92 (m, 1H), 1.22 – 1.43 (m, 2H).

[00418] **(1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-ylmethyl 4-methylbenzenesulfonate (3a):**



[00419] A solution of (1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-ylmethanol (760 mg, 6.12 mmol) in DCM (7 mL) was charged with triethylamine (0.98 mL, 7.11 mmol) and tosyl chloride (4.65 g, 24.5 mmol) at 0°C and stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 10-20% ethyl acetate in hexane to afford 1.5 g, 88% yield of the title compound as colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.78 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 7.9 Hz, 2H), 6.10 (dd, *J* = 5.8, 3.0 Hz, 1H), 5.59 (dd, *J* = 5.8, 2.9 Hz, 1H), 3.74 (dd, *J* = 9.6, 6.5 Hz, 1H), 3.49 (t, *J* = 9.6 Hz, 1H), 2.76 (d, *J* = 13.2 Hz, 2H), 2.31 (s, 3H), 2.28 –2.10 (m, 2H), 1.74 (ddd, *J* = 12.4, 9.3, 3.8 Hz, 1H), 1.26 – 1.34 (m, 1H), 1.20 (d, *J* = 8.2 Hz, 1H).

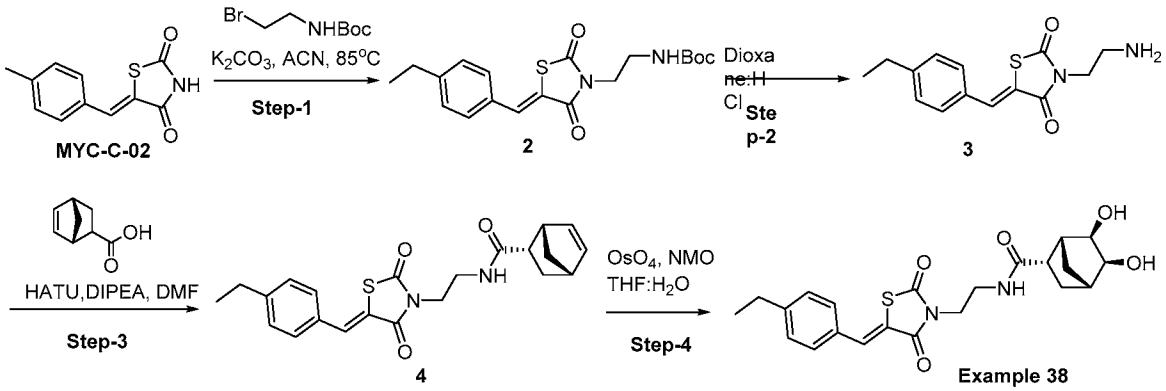
[00420] **(1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-ylmethanol (2):**



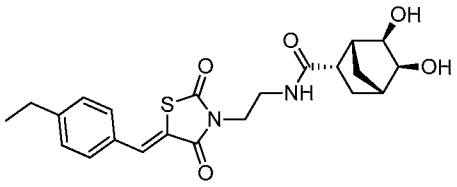
[00421] A solution of LAH (533 mg, 14.3 mmol) in THF (10 mL) was charged with (1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-carboxylic acid (1.25 g, 9.05 mmol) at 0 °C and stirred at room temperature for 2 h. The reaction mixture was quenched at 0 °C with 1N aq NaOH and ethyl acetate. The reaction mixture was filtered through pad of celite and the filtrate was

extracted with ethyl acetate (3 X 50 mL). The combined organic layers were washed with water (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 760 mg of crude compound as colorless liquid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.10 (dd, *J* = 5.5, 2.9 Hz, 1H), 5.92 (dd, *J* = 6.0, 2.9 Hz, 1H), 4.36 (t, *J* = 5.3 Hz, 1H), 3.11 (dt, *J* = 11.1, 5.8 Hz, 1H), 2.93 (td, *J* = 9.7, 5.3 Hz, 1H), 2.84 (s, 2H), 2.73 (d, *J* = 5.3 Hz, 1H), 2.16 (tt, *J* = 9.1, 4.4 Hz, 1H), 1.71 (ddd, *J* = 12.5, 9.1, 3.8 Hz, 1H), 1.16 – 1.38 (m, 2H).

[00422] Synthetic scheme: Example 38:



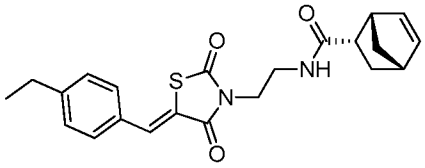
[00423] (1*R*,2*R*,4*S*,5*S*,6*R*)-*N*-(2-((*Z*)-5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxamide [Example 38]:



[00424] A solution of (1*R*,2*R*,4*S*)-*N*-(2-((*Z*)-5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide (230 mg, 0.580 mmol) in THF:H_2O (4:1 mL) was charged with NMO (74 mg, 0.632 mmol) and OsO_4 (22 mg, 0.086 mmol). The resulting solution was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to afford 100 mg, 40% yield of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.97 (t, *J* = 6.1Hz, 1H), 7.89 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 3.57 – 3.79 (m, 3H), 3.38 – 3.43 (m, 2H), 3.20 (dq, *J* = 12.5, 5.9 Hz, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.34 – 2.53 (m, 1H), 2.15 (d, *J* = 4.2 Hz, 1H), 1.93 (d, *J* = 4.7 Hz, 1H), 1.71 (d, *J* = 9.8 Hz,

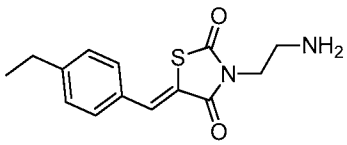
1H), 1.28 – 1.50 (m, 5H), 1.20 (t, J = 7.6 Hz, 1H), 1.07 (d, J = 9.8 Hz, 1H); MS (ES^+): m/z = 431.20 $[M+H]^+$, 453.20 $[M+Na]^+$; LCMS: t_R = 2.43 min.

[00425] (1*R*,2*R*,4*S*)-*N*-(2-((*Z*)-5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide (4):



[00426] A solution of (*Z*)-3-(2-aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (260 mg, 0.942 mmol) in DMF (4 mL) was charged with (1*R*,2*R*,4*S*)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (129 mg, 0.942 mmol) , HATU (536 mg, 1.41 mmol) and DIPEA (364 mg, 2.82mmol). The reaction mixture was stirred at room temperature for 2 h then diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were washed with water (50mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2-4% methanol in DCM to afford 250 mg, 67% yield of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.89 (s, 1H), 7.78 (t, J = 6.1 Hz, 1H), 7.56 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 7.9 Hz, 2H), 6.04 (dd, J = 5.6, 3.0 Hz, 1H), 5.80 (dd, J = 5.6, 2.8 Hz, 1H), 3.67 (t, J = 5.6 Hz, 2H), 3.18 – 3.38 (m, 2H), 3.03 (d, J = 4.3 Hz, 1H), 2.60 – 2.80 (m, 4H), 1.70 (ddd, J = 11.5, 9.3, 3.8 Hz, 1H), 1.15 – 1.29 (m, 6H); MS (ES^+): m/z = 397.05, 398.10 $[M+H]^+$; LCMS: t_R = 3.53 min.

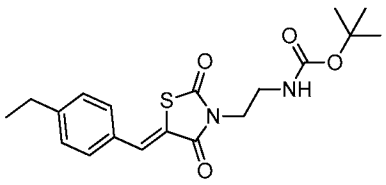
[00427] (*Z*)-3-(2-Aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (3):



[00428] A solution of (*Z*)-*tert*-butyl(2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamate (330 mg, 0.876 mmol) in dioxane (3 mL) was charged with HCl in 1,4-dioxane (4M, 5 mL) at 0°C and stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was washed with hexane and ether and dried to afford 260 mg, 95% yield of title compound as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 (s, 2H), 7.91 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 8.1 Hz,

2H), 3.91 (t, J = 6.0 Hz, 2H), 3.07 (d, J = 6.3 Hz, 2H), 2.67 (q, J = 7.7 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); MS (ES^+): m/z = 277.10, 278.09, 279.20 $[M+H]^+$; LCMS: t_R = 1.28 min.

[00429] (*Z*)-*tert*-Butyl(2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamate (2):

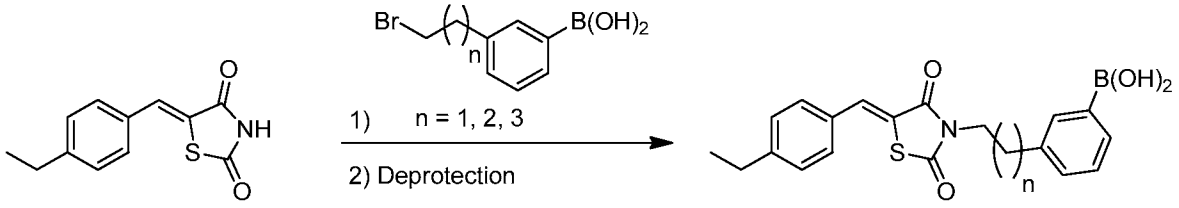


[00430] A solution of (*Z*)-5-(4-methylbenzylidene)thiazolidine-2,4-dione (650 mg, 2.78 mmol) in acetonitrile (10 mL) was charged with *tert*-butyl (2-bromoethyl)carbamate (624 mg, 2.78 mmol) and potassium carbonate (1.15 g, 8.36 mmol) and refluxed at 85°C for 16 h. The reaction mixture was concentrated *in vacuo* and the residue obtained was diluted with water (20 mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 10-30% ethyl acetate in hexane to give 330 mg, 31% yield of the title compound as off white solid. ^1H NMR (400 MHz, DMSO-d_6): δ = 7.87 (s, 1H), 7.54 (t, J = 9.3 Hz, 2H), 7.40 (d, J = 7.7 Hz, 2H), 6.98 (t, J = 6.2 Hz, 1H), 3.69 (t, J = 5.3 Hz, 2H), 3.18 (q, J = 5.8 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.33 (s, 9H), 1.20 (t, J = 7.6 Hz, 3H); MS (ES^+): m/z = 277.14, 278.15 $[M\text{-Boc}]^+$; LCMS: t_R = 2.03 min.

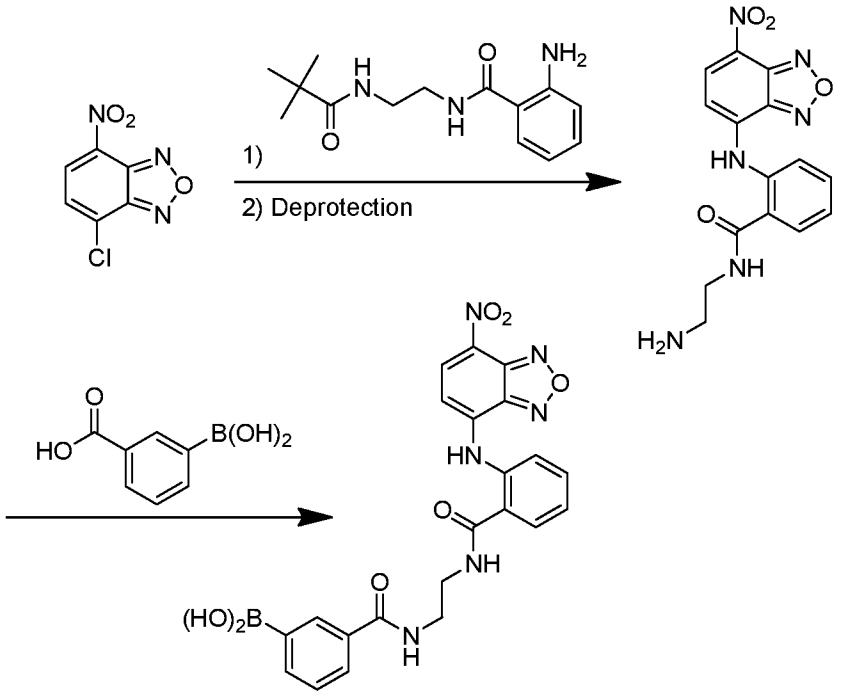
EXAMPLE 39

[00431] Monomers are synthesized according to the procedures described below. Reagents are either purchased commercially or prepared according to previously described methods.

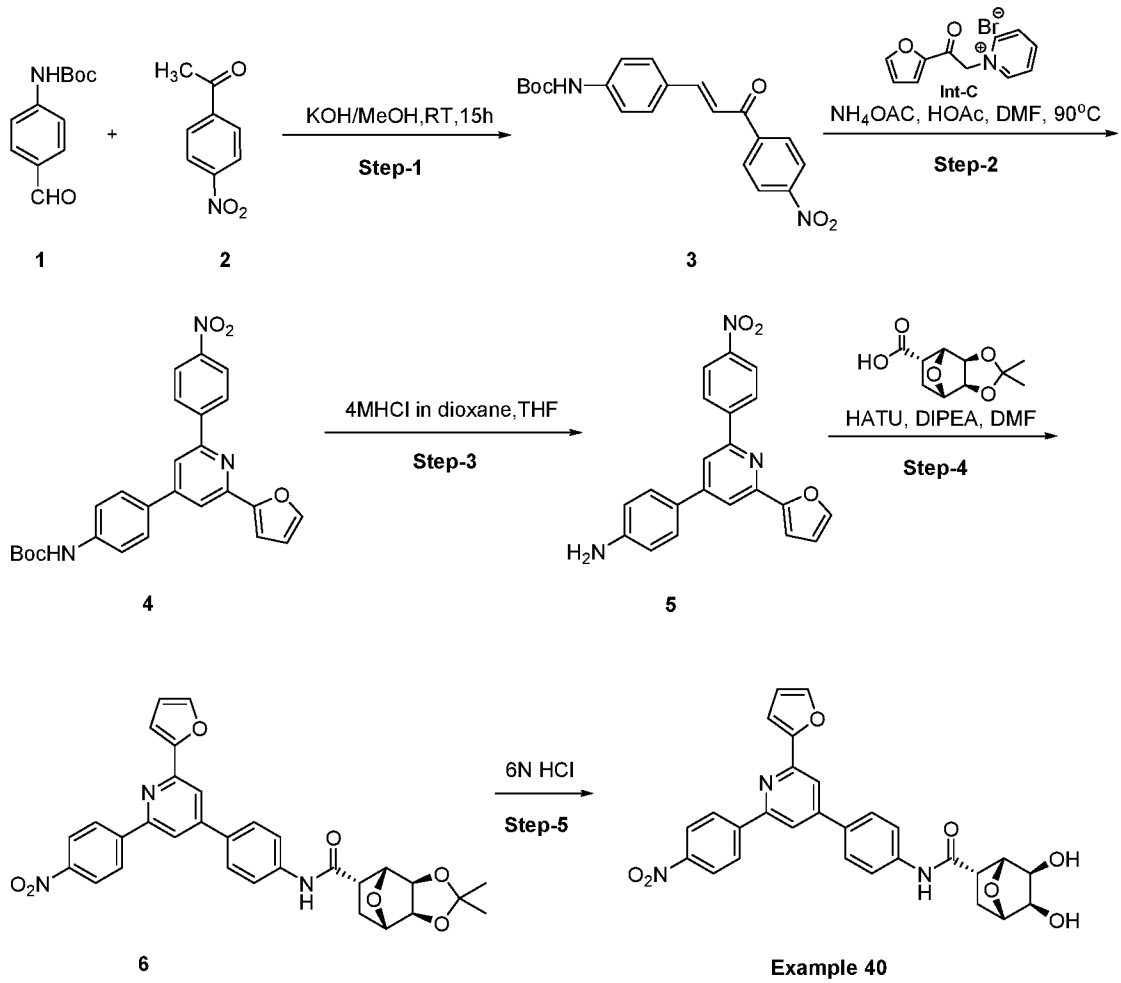
Scheme 1.



Scheme 2.

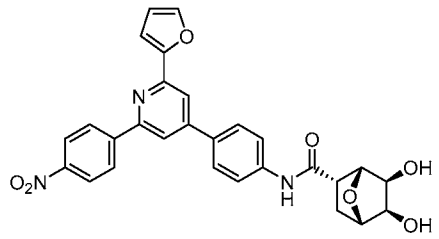


Example 40: Synthetic Scheme



1 2 3 4 5 6 Example 40

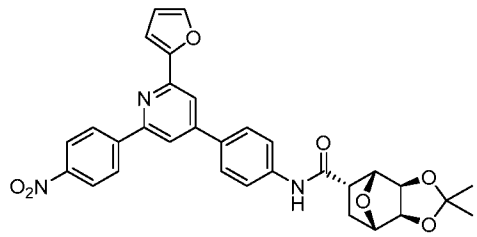
(1*R*,2*S*,4*S*,5*R*,6*S*)-*N*-(4-(2-(Furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)phenyl)-5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide [Example 40]:



[00432] A solution of (3a*R*,4*R*,5*S*,7*S*,7a*S*)-*N*-(4-(2-(furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)phenyl)-2,2-dimethylhexahydro-4,7-epoxybenzo[*d*][1,3]dioxole-5-carboxamide (200 mg, 0.36 mmol) in THF (5 mL) was charged with 6N aq HCl (10 mL) was stirred at room temperature for 15 h. The reaction mixture was concentrated *in vacuo* and the residue was stripped with toluene resulting in the crude compound which was purified by preparative HPLC to afford 40 mg (21% yield) of **title compound** as light yellow solid. ^{1}H NMR (400 MHz,

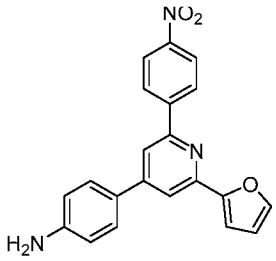
DMSO-d_6) δ = 10.34 (s, 1 H), 8.59 (d, J = 8.31 Hz, 2 H), 8.38 (d, J = 8.80 Hz, 2 H), 8.31 (s, 1 H), 8.02 - 8.08 (m, 3 H), 7.94 (s, 1 H), 7.81 (d, J = 8.31 Hz, 2 H), 7.39 (d, J = 3.42 Hz, 1 H), 6.74 (d, J = 1.47 Hz, 1 H), 4.80 (d, J = 6.36 Hz, 1 H), 4.69 (d, J = 5.87 Hz, 1 H), 4.41 (d, J = 5.87 Hz, 1 H), 4.23 (d, J = 5.38 Hz, 1 H), 3.84 (t, J = 6.11 Hz, 1 H), 3.73 (t, J = 6.11 Hz, 1 H), 2.98 (td, J = 5.50, 10.52 Hz, 1 H), 1.69 - 1.84 (m, 2 H), ^{1}H NMR (400 MHz, D_2O exchange) δ = 8.57 (d, J = 9.29 Hz, 2 H), 8.37 (d, J = 8.80 Hz, 2 H), 8.28 (s, 1 H), 7.98 - 8.06 (m, 3 H), 7.91 (s, 1 H), 7.80 (d, J = 8.31 Hz, 2 H), 7.37 (d, J = 2.93 Hz, 1 H), 6.71 - 6.75 (m, 1 H), 4.41 (d, J = 5.38 Hz, 1 H), 4.22 (d, J = 4.89 Hz, 1 H), 3.83 (d, J = 6.36 Hz, 1 H), 3.72 (d, J = 5.87 Hz, 1 H), 2.98 (td, J = 5.38, 10.76 Hz, 1 H), 1.69 - 1.83 (m, 2 H); MS (ES+): m/z = 514.13 $[M+H]^+$; LCMS: t_R = 3.16 min.

(3a*R*,4*R*,5*S*,7*S*,7a*S*)-*N*-(4-(2-(Furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)phenyl)-2,2-dimethylhexahydro-4,7-epoxybenzo[*d*][1,3]dioxole-5-carboxamide:



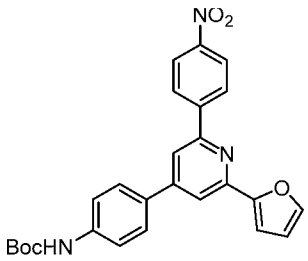
A solution of (3a*R*,4*R*,5*S*,7*S*,7a*S*)-2,2-dimethylhexahydro-4,7-epoxybenzo[*d*][1,3]dioxole-5-carboxylic acid (90 mg, 0.42 mmol) in DMF (5 mL) was charged with HATU (239 mg, 0.63 mmol), DIPEA (0.22 mL, 1.26 mmol) and stirred at room temperature for 10 min. To the resulting solution was added 4-(2-(furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)aniline (150 mg, 0.42 mmol) and stirred at room temperature for 14 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (3 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in the crude compound which was purified by column chromatography on silica gel eluting with 0-50% ethyl acetate in *n*-hexane followed by preparative HPLC purification to afford 20 mg (9% yield) of **title compound** as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.36 (s, 1 H), 8.58 (d, J = 8.80 Hz, 2 H), 8.38 (d, J = 8.80 Hz, 2 H), 8.31 (s, 1 H), 8.01 - 8.09 (m, 3 H), 7.93 (s, 1 H), 7.80 (d, J = 8.31 Hz, 1 H), 7.77 - 7.85 (m, 1 H), 7.38 (d, J = 2.93 Hz, 1 H), 6.74 (dd, J = 1.71, 3.18 Hz, 1 H), 4.57 (d, J = 5.38 Hz, 1 H), 4.40 (d, J = 5.38 Hz, 1 H), 4.26 - 4.35 (m, 2 H), 3.04 (td, J = 5.38, 10.76 Hz, 1 H), 1.70 - 1.86 (m, 2 H), 1.33 (s, 3 H), 1.18 (s, 3 H); MS (ES+): m/z = 554.18 $[M + H]^+$; LCMS: t_R = 3.66 min.

4-(2-(Furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)aniline:



[00433] A solution of tert-butyl (4-(2-(furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)phenyl)carbamate (450 mg, 0.98 mmol) in THF (5 mL) at 0 °C was charged with HCl in 1,4-dioxane (4M, 5 mL) and stirred at room temperature for 14 h. The reaction mixture was concentrated *in vacuo* resulting in the crude compound which was stirred in ethyl acetate (10 mL), filtered and dried to afford 300 mg (85% yield) of as brown solid. ^{1}H NMR (400 MHz, CD_3OD) δ = 8.36 - 8.46 (m, 4 H), 8.22 (d, *J* = 7.34 Hz, 2 H), 8.14 (d, *J* = 7.83 Hz, 2 H), 7.83 (s, 1 H), 7.60 (d, *J* = 7.83 Hz, 2 H), 7.51 (br. s, 1 H), 6.74 (br. s, 1 H); MS (ES+): *m/z* = 358.04 [M + H]$^+$; LCMS: t_R = 3.57 min.

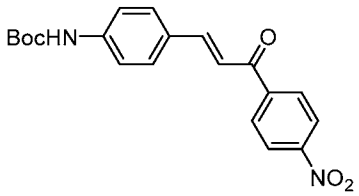
***tert*-Butyl (4-(2-(furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)phenyl)carbamate:**



[00434] A solution of tert-butyl (*E*)-(4-(3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate (650 mg, 1.76 mmol) and 1-(2-(furan-2-yl)-2-oxoethyl)pyridin-1-ium bromide (994 mg, 3.71 mmol) in DMF (25 mL) was charged with acetic acid (14 mL) and ammonium acetate (2.04 g, 26.4 mmol) sequentially and heated to 90 °C for 8 h. The reaction mixture was diluted with H_2O (30 mL), the solid precipitated was filtered and dried resulting in the crude compound which was purified by column chromatography on silica gel eluting with 0-10% ethyl acetate in *n*-hexane to afford (500 mg, 62% yield) of as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.62 (s, 1 H), 8.58 (d, *J* = 8.80 Hz, 2 H), 8.38 (d, *J* = 8.80 Hz, 2 H), 8.28 (s, 1 H), 8.03 (s, 1 H), 7.91 - 8.00 (m, 3 H), 7.66 (d, *J* = 8.31 Hz, 2 H), 7.37 (d, *J* = 2.93

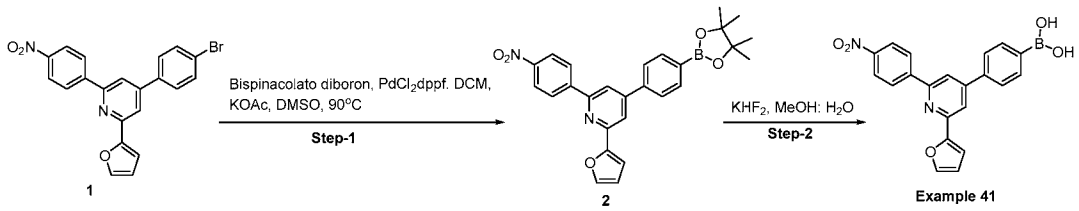
Hz, 1 H), 6.73 (dd, J = 1.71, 3.18 Hz, 1 H), 1.51 (s, 9 H); MS (ES+): m/z = 457.80 $[M + H]^+$; LCMS: t_R = 4.15 min.

***tert*-Butyl (*E*)-(4-(3-(4-nitrophenyl)-3-oxoprop-1-en-1-yl)phenyl)carbamate (3):**

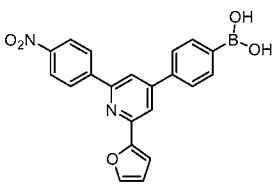


[00435] A solution of tert-butyl (4-formylphenyl)carbamate (1.2 g, 5.42 mmol) in methanol (30 mL) was charged with 1-(4-nitrophenyl)ethan-1-one (1.3 g, 8.14 mmol), 15% solution of potassium hydroxide (45 mg, 8.14 mmol) in H_2O (0.3 mL) and stirred at room temperature for 16 h. The reaction mixture was quenched with H_2O (15 mL), the solid precipitated was filtered and dried resulting in the crude compound which was purified by column chromatography on silica gel eluting with 0-8% ethyl acetate in *n*-hexane to afford 980 mg (49% yield) of the title compound **3** as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.68 (s, 1 H), 8.31 - 8.41 (m, 4 H), 7.74 - 7.86 (m, 4 H), 7.56 (d, J = 7.83 Hz, 2 H), 1.49 (s, 9 H); MS (ES+): m/z = 369.09 $[M + H]^+$; LCMS: t_R = 3.50 min.

Example 41: Synthetic scheme



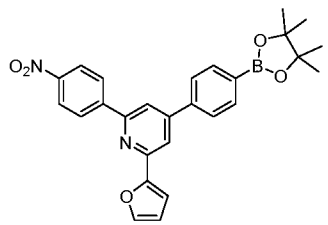
(4-(2-(Furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)phenyl)boronic acid [Example 41]:



[00436] A solution of 2-(furan-2-yl)-6-(4-nitrophenyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine **1** (95 mg, 0.20 mmol) in methanol: H_2O (2.5: 2.5 mL) was charged with potassium bifluoride (79 mg, 1.01 mmol) and stirred at room temperature for 30 min. The reaction mixture was concentrated *in vacuo* and washed with hot acetone (2 X 5 mL).

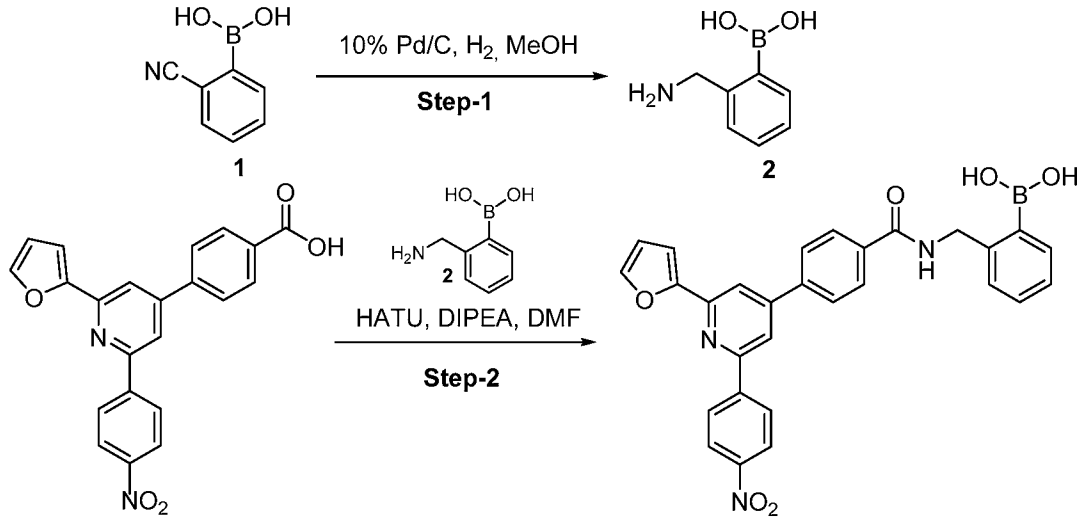
The acetone layer was concentrated *in vacuo* resulting in the crude compound which was purified by preparative HPLC to afford 25 mg (32% yield) of the title compound as a light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.60 (d, J = 8.31 Hz, 2 H), 8.38 (d, J = 8.31 Hz, 2 H), 8.35 (s, 1 H), 8.21 (br. s, 2 H), 8.10 (s, 1 H), 7.93 - 8.03 (m, 5 H), 7.40 - 7.43 (m, 1 H), 6.73 - 6.76 (m, 1 H), ^{1}H NMR (400 MHz, D_2O exchange) δ 8.52 (d, J = 7.83 Hz, 2 H), 8.36 (d, J = 7.83 Hz, 2 H), 8.25 (br. s, 1 H), 8.04 (s, 1 H), 7.84 - 7.98 (m, 5 H), 7.36 - 7.40 (m, 1 H), 6.68 - 6.73 (m, 1 H); MS (ES+): m/z = 387.05 $[M+H]^+$; LCMS: t_R = 3.37 min.

2-(Furan-2-yl)-6-(4-nitrophenyl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pyridine (1):

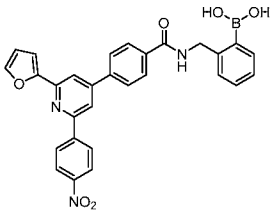


[00437] A solution of 4-(4-bromophenyl)-2-(furan-2-yl)-6-(4-nitrophenyl)pyridine (100 mg, 0.23 mmol) in DMSO (2.5 mL) was charged with potassium acetate (56 mg, 0.57 mmol), bispinacolato diboron (180 mg, 0.71 mmol) and purged with argon at room temperature for 15 min. To the resulting solution was added [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II) DCM adduct (8.6 mg, 0.01 mmol) and purged with argon for 10 min and further heated to 90 °C for 6 h. The reaction mixture was filtered through a pad of Celite and the filtrate was diluted with H_2O (10 mL) and extracted with ethyl acetate (3 X 10 mL) and separated. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to afford 95 mg of the title compound as dark brown semisolid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.56 - 8.62 (m, 2 H), 8.36 - 8.43 (m, 3 H), 8.34 (s, 1 H), 8.02 - 8.11 (m, 3 H), 7.86 (d, J = 8.31 Hz, 2 H), 7.40 (d, J = 3.42 Hz, 1 H), 6.74 (dd, J = 1.47, 3.42 Hz, 1 H), 1.33 (s, 12 H); MS (ES^+): m/z = 469.35 $[M+H]^+$; LCMS: t_R = 4.34 min.

Example 42: Synthetic Scheme:



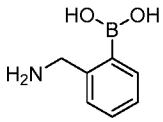
(2-((4-(2-(Furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)benzamido)methyl)phenyl)boronic acid [Example 42]:



[00438] A solution of 4-(2-(furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)benzoic acid (150 mg, 0.38 mmol) in DMF (3 mL) was charged with (2-(aminomethyl)phenyl)boronic acid (59 mg, 0.38 mmol), HATU (221 mg, 0.58 mmol) and DIPEA (0.09 mL, 0.58 mmol) and stirred at room temperature for 1 h. The reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in the crude compound which was purified by preparative HPLC to afford 40mg (20% yield) of the title compound as light yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.29 (br. s, 1 H), 8.60 (d, J = 8.31 Hz, 2 H), 8.44 (s, 2 H), 8.39 (d, J = 7.83 Hz, 3 H), 8.06 - 8.20 (m, 5 H), 7.95 (s, 1 H), 7.53 (d, J = 6.85 Hz, 1 H), 7.42 (br. s, 1 H), 7.35 (d, J = 2.93 Hz, 2 H), 7.22 (d, J = 3.42 Hz, 1 H), 6.73 - 6.77 (m, 1 H), 4.63 (d, J = 5.38 Hz, 2 H)

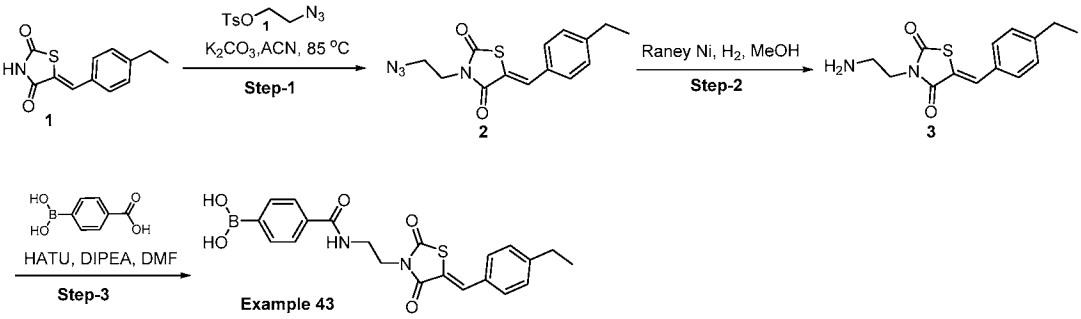
^{1}H NMR (400 MHz, D_2O exchange) δ = 8.54 (d, J = 9.29 Hz, 2 H), 8.37 (d, J = 8.80 Hz, 2 H), 8.29 (s, 1 H), 8.02 - 8.13 (m, 5 H), 7.89 (s, 1 H), 7.52 (d, J = 7.34 Hz, 1 H), 7.39 (d, J = 3.42 Hz, 1 H), 7.32 - 7.36 (m, 2 H), 7.19 - 7.26 (m, 1 H), 6.72 (dd, J = 1.96, 3.42 Hz, 1 H), 4.60 (s, 2 H); MS (ES+): m/z = 520.15 $[M + H]^+$; LCMS: t_R = 3.42 min.

(2-(Aminomethyl)phenyl)boronic acid (2):

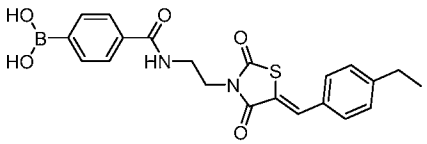


[00439] A solution of (2-cyanophenyl)boronic acid (200 mg, 1.36 mmol) in methanol (5 mL) was charged with 10% Pd/C (40 mg, 50% moisture) at room temperature under argon atmosphere. The resulting solution was stirred under hydrogen atmosphere at room temperature for 14 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* resulting in the crude compound which was purified by trituration in diethyl ether (10 mL) and dried to afford 128 mg (62% yield) of the title compound **3** as off white solid. MS (ES+): m/z = 151.85 $[M + H]^+$; LCMS: t_R = 0.60 min.

Example 43: Synthetic Scheme:



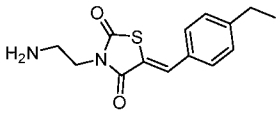
(*Z*)-(4-((2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamoyl)phenyl) boronic acid [Example 43]:



[00440] A solution of (*Z*)-3-(2-aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (108 mg, 0.39 mmol) in DMF (2.5 mL) was charged with 4-boronobenzoic acid (65 mg, 0.39 mmol), HATU (223 mg, 0.58 mmol), DIPEA (0.19 mL, 1.17 mmol) and stirred at room temperature for 5 h. The reaction mixture was diluted with H_2O (10 mL) and extracted with DCM (3 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered

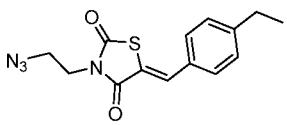
and concentrated *in vacuo* resulting in the crude compound which was purified by preparative HPLC to afford 15 mg (9% yield) of the title compound as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.63 (t, J = 6.11 Hz, 1 H), 8.19 (s, 2 H), 7.86 - 7.90 (m, 1 H), 7.82 (d, J = 8.31 Hz, 2 H), 7.68 (d, J = 8.31 Hz, 2 H), 7.55 (d, J = 7.83 Hz, 2 H), 7.39 (d, J = 8.31 Hz, 2 H), 3.83 (t, J = 5.38 Hz, 2 H), 3.49 - 3.56 (m, 2 H), 2.66 (q, J = 7.34 Hz, 2 H), 1.19 (t, J = 7.58 Hz, 3 H); MS (ES+): m/z = 424.85 $[M + H]^+$; LCMS: t_R = 3.03 min.

(*Z*)-3-(2-Aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (3):



[00441] A solution of (*Z*)-3-(2-azidoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (400 mg, 1.32 mmol) in ethyl acetate (50 mL) was charged with Raney nickel (80 mg, 20% by wt) under argon atmosphere at room temperature. The resulting solution was stirred under hydrogen atmosphere at room temperature for 14 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to afford 255 mg (70% yield) of the title compound **3** as brown oil. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.94 (br. s, 2 H), 7.92 (s, 1 H), 7.57 (d, J = 8.31 Hz, 2 H), 7.41 (d, J = 7.83 Hz, 2 H), 3.91 (t, J = 5.62 Hz, 2 H), 3.05 - 3.10 (m, 2 H), 2.67 (q, J = 7.83 Hz, 2 H), 1.20 (t, J = 7.58 Hz, 3 H); MS (ES+): m/z = 276.95 $[M+H]^+$; LCMS: t_R = 2.18 min.

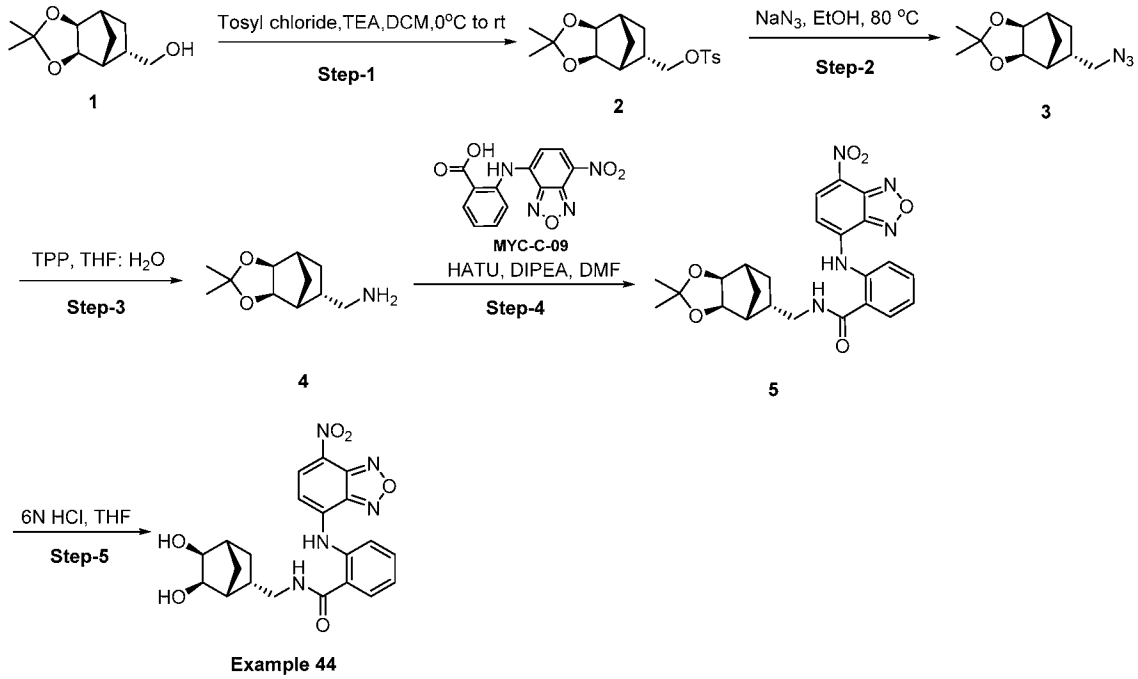
(*Z*)-3-(2-Azidoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (2):



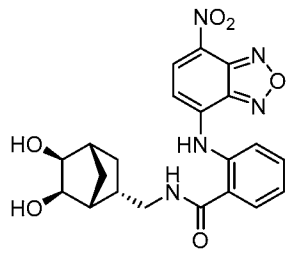
[00442] A solution of (*Z*)-5-(4-methylbenzylidene)thiazolidine-2,4-dione (500 mg, 2.14 mmol) in acetonitrile (10 mL) was charged with 2-azidoethyl 4-methylbenzenesulfonate (621 mg, 2.57 mmol), potassium carbonate (888 mg, 6.43 mmol) and heated to 85 °C for 14 h. The reaction mixture was concentrated *in vacuo*, diluted with H_2O (10 mL) and extracted with DCM (3 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered

and concentrated *in vacuo* resulting in the crude compound which was purified by column chromatography on silica gel eluting with 10-30% ethyl acetate in *n*-hexane to afford 421 mg (65% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.94 (s, 1 H), 7.56 (d, J = 7.83 Hz, 2 H), 7.40 (d, J = 7.83 Hz, 2 H), 3.86 (t, J = 5.62 Hz, 2 H), 3.56 - 3.65 (m, 2 H), 2.63 - 2.72 (m, 2 H), 1.20 (t, J = 7.58 Hz, 3 H); MS (ES+): m/z = 302.75 [M + H]$^+$; LCMS: t_R = 3.68 min.

Example 44: Synthetic Scheme:



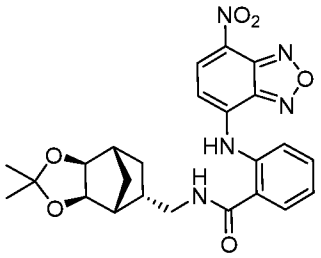
***N*-(((1*R*,2*S*,4*R*,5*S*,6*R*)-5,6-Dihydroxybicyclo[2.2.1]heptan-2-yl)methyl)-2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide [Example 44]:**



[00443] A solution of *N*-(((3a*R*,4*R*,5*S*,7*R*,7a*S*)-2,2-dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxol-5-yl)methyl)-2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide (150 mg, 0.31 mmol) in THF (5 mL) was charged with 6N aq HCl (5 mL)

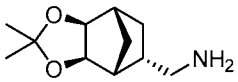
and stirred at room temperature for 16 h. The reaction mixture was triturated with diethyl ether (10 mL) and concentrated *in vacuo* resulting in the crude compound which was purified by preparative HPLC to afford 40 mg (29% yield) of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.74 (s, 1 H), 8.76 (br. s, 1 H), 8.56 (d, J = 8.80 Hz, 1 H), 7.81 (d, J = 7.34 Hz, 1 H), 7.74 (d, J = 7.83 Hz, 1 H), 7.65 (t, J = 7.83 Hz, 1 H), 7.39 (t, J = 7.34 Hz, 1 H), 6.90 (d, J = 8.80 Hz, 1 H), 4.61 (br. s, 1 H), 4.38 (br. s, 1 H), 3.83 (d, J = 5.38 Hz, 1 H), 3.45 (d, J = 5.87 Hz, 1 H), 3.10 - 3.20 (m, 2 H), 1.86 - 2.04 (m, 3 H), 1.67 (d, J = 9.29 Hz, 1 H), 1.58 (dt, J = 4.89, 11.98 Hz, 1 H), 0.95 (d, J = 9.78 Hz, 1 H), 0.51 - 0.61 (m, 1 H); MS (ES+): m/z = 439.43 $[M + H]^+$; LCMS: t_R = 2.59 min.

***N*-(((3a*R*,4*R*,5*S*,7*R*,7a*S*)-2,2-Dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxol-5-yl)methyl)-2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamide:**



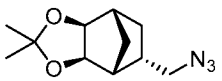
[00444] A solution of 2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzoic acid (304 mg, 1.01 mmol) in DMF (3 mL) was charged with HATU (1.15 g, 3.04 mmol), DIPEA (0.6 mL, 3.04 mmol) and stirred at room temperature for 10 min. To the resulting solution was added ((3a*R*,4*R*,5*S*,7*R*,7a*S*)-2,2-dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxol-5-yl)methanamine (200 mg, 1.01 mmol) and stirred at room temperature for 2 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (3 X 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in the crude compound which was purified by preparative HPLC to afford 198 mg (41% yield) of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.58 (s, 1 H), 8.74 (br. s, 1 H), 8.54 (d, J = 7.34 Hz, 1 H), 7.78 (d, J = 6.85 Hz, 1 H), 7.60 - 7.73 (m, 2 H), 7.42 (br. s, 1 H), 6.76 (d, J = 7.83 Hz, 1 H), 4.22 (d, J = 4.89 Hz, 1 H), 3.91 (d, J = 4.89 Hz, 1 H), 3.13 (br. s, 2 H), 1.98 - 2.05 (m, 3 H), 1.61 - 1.64 (m, 1 H), 1.48 (d, J = 9.78 Hz, 1 H), 1.24 (s, 3 H), 1.11 (s, 3 H), 0.93 (d, J = 9.29 Hz, 1 H), 0.47 (d, J = 14.67 Hz, 1 H); MS (ES+): m/z = 502.15 $[M + Na]^+$; LCMS: t_R = 3.25 min.

((3a*R*,4*R*,5*S*,7*R*,7a*S*)-2,2-Dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxol-5-yl)methanamine (4):



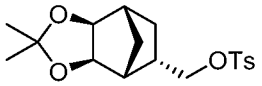
[00445] A solution of (3a*R*,4*R*,5*S*,7*R*,7a*S*)-5-(azidomethyl)-2,2-dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxole **3** (410 mg, 1.83 mmol) in THF: H_2O (3:7 mL) was charged with triphenyl phosphine (1.64 g, 6.28 mmol) and stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* resulting in the crude compound which was purified by column chromatography on neutral alumina eluting with 4-10% methanol in DCM to afford 250 mg (69% yield) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 4.28 (d, *J* = 5.38 Hz, 1 H), 3.97 (d, *J* = 5.38 Hz, 1 H), 2.46 - 2.53 (m, 2 H), 2.26 (br. s, 1 H), 2.14 (d, *J* = 4.89 Hz, 1 H), 1.80 - 1.91 (m, 2 H), 1.62 - 1.76 (m, 3 H), 1.38 (s, 3 H), 1.27 (s, 3 H), 1.08 (d, *J* = 9.78 Hz, 1 H), 0.47 - 0.56 (m, 1 H).

(3a*R*,4*R*,5*S*,7*R*,7a*S*)-5-(Azidomethyl)-2,2-dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxole (3):



[00446] A solution of ((3a*R*,4*R*,5*S*,7*R*,7a*S*)-2,2-dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxol-5-yl)methyl 4-methylbenzenesulfonate (700 mg, 1.98 mmol) in ethanol (20 mL) was charged with sodium azide (387 mg, 5.96 mmol) and heated to 90 °C for 24 h. The reaction mixture was cooled to room temperature and concentrated *in vacuo*, dissolved in DCM and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to afford 421 mg of the title compound as a colorless oil. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 4.24 (d, *J* = 4.89 Hz, 1 H), 3.98 (d, *J* = 4.89 Hz, 1 H), 3.13 - 3.31 (m, 2 H), 2.05 - 2.41 (m, 3 H), 1.71 - 1.89 (m, 2 H), 1.39 - 1.50 (m, 3 H), 1.25 - 1.32 (m, 3 H), 1.15 (d, *J* = 10.27 Hz, 1 H), 0.51 - 0.63 (m, 1 H).

((3a*R*,4*R*,5*S*,7*R*,7a*S*)-2,2-Dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxol-5-yl)methyl 4-methylbenzenesulfonate (2):



[00447] A solution of ((3a*R*,4*R*,5*S*,7*R*,7a*S*)-2,2-dimethylhexahydro-4,7-methanobenzo[*d*][1,3]dioxol-5-yl)methanol (500 mg, 2.52 mmol) in DCM (10 mL) at 0 °C was charged with triethyl amine (1 mL, 7.57 mmol), tosyl chloride (571 mg, 3.00 mmol) and stirred at room temperature for 14 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with DCM (3 X 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in the crude compound which was purified by column chromatography on silica gel eluting with 5-15% ethyl acetate in *n*-hexane to afford 711 mg (80% yield) of the title compound **2** as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.80 (d, *J* = 8.31 Hz, 2 H), 7.49 (d, *J* = 7.83 Hz, 2 H), 3.80 - 4.04 (m, 4 H), 2.42 (s, 3 H), 2.03 - 2.16 (m, 3 H), 1.51 - 1.64 (m, 2 H), 1.28 (s, 3 H), 1.13 (s, 3 H), 1.02 (d, *J* = 9.78 Hz, 1 H), 0.42 - 0.52 (m, 1 H).

EXAMPLE 45: Compound Library with two distinct ligands which bind Myc transcription factor

[00448] A library of monomers was synthesized by appending catechol/alkyl diol and boronic acid linkers via appropriate connectors to C01 and C02 ligands that bind Myc (Figure 3A). Monomers bearing boronic acid linkers are designated as "E" (electrophilic) monomers and those bearing catechol or alkyl diol linkers as "N" (nucleophilic) monomers. This library allowed for the efficient identification of "E+N" pairs which most synergistically inhibit Myc. These dimers have maximal spanning distances between their ligands of approximately 7-25Å and feature linker regioisomers for each particular spanning distance. Representative library members were prepared as follows are shown in Figure 4.

[00449] **General procedures**. Preparative purification of the compounds were 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 500 X 30 mm X10 µm 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 30.0 mL/min and a run time of 40mins. For basic medium purification, the same instrument was utilized with YMC triart C18, 500X30 mm X 10 µm preparative column using 10 mM ammonium formate and 0.1 % (v/v) ammonia in HPLC grade water (A) and HPLC grade acetonitrile adding 5% (v/v) of mobile phase (A) and 0.1% (v/v) ammonia (B). For both the methods, linear gradient profiles were used depending upon the chromatographic retention and separation of different compounds.

[00450] 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 50 X 4.6 mm X 3.0 µm 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 1.2 mL/min and a run time of 5.0 min. The gradient profiles are 20% B to 100% B in 3.0minute, Hold For 0.5 min, at 3.51 min 20% B, Hold until 5.0 min.

[00451] HPLC Max plot 210-400 nm.

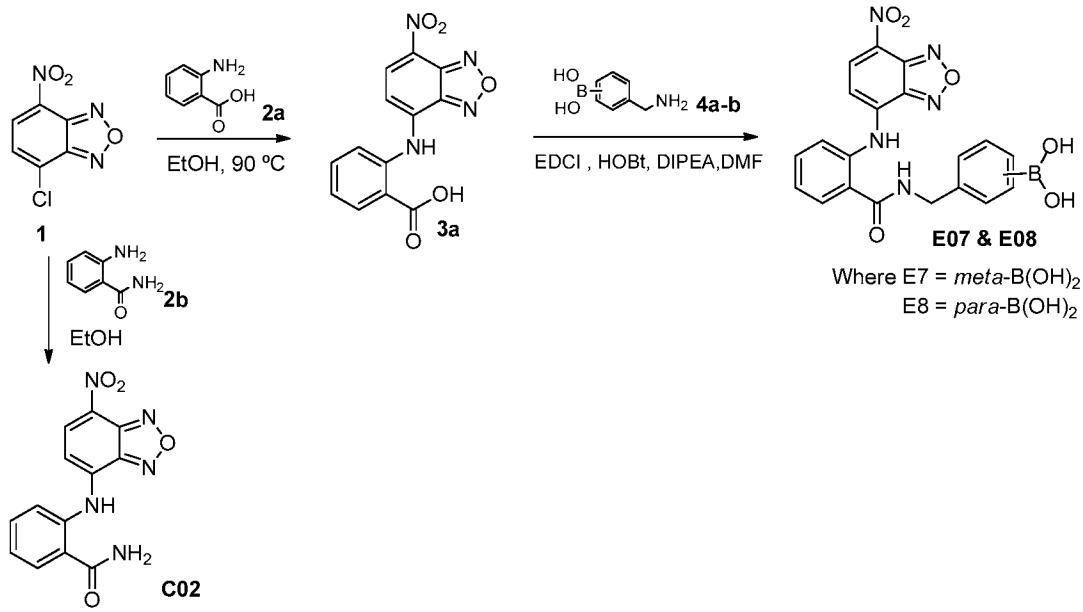
[00452] All Shimadzu LCMS-2010EV instruments utilized electrospray ionization in positive (ES+) or negative (ES-) ionization mode. The Shimadzu LCMS-2010EV instruments can also be utilized with atmospheric pressure chemical ionization in positive (AP+) or negative (AP-) ionization mode.

[00453] LCMS data for all final compounds were collected on a Waters LCMS system equipped with a Waters Acquity UPLC Sample manager FTN, Waters Acquity UPLC quaternary solvent manager, Waters Acquity UPLC PDA detector and a Waters single quadrapole SQ Detector 2 with ZSpray, ACE Excel 2 SuperC18 100 X 2.1 mm X 2.0µM column using 0.01% (v/v) formic acid in LCMS grade water (A) and 0.01% (v/v) formic acid in LCMS grade acetonitrile (B) at a flow rate of 0.800 mL/min and a run time of 3 min. Gradient profile (polar_3min_1500): 5% B to 90% B in 1.50 min, hold for 0.5 min, at 2.00 min to 2.20 min 90% B to 5% B, Hold until 3 min. Gradient profile (non_polar_3min_1500): 15% B to 99% B in 1.60 min, hold for 0.6 min, at 2.00 min to 2.80 min 99% B to 15% B, Hold until 3 min.

[00454] Waters instrument utilized electrospray ionization in positive (ES+) or negative (ES-) ionization mode

[00455] Nuclear Magnetic Resonance (NMR) spectra were recorded on a Varian spectrometer at 400 MHz for proton (^{1}H NMR) and 100 MHz for carbon (^{13}C NMR); chemical shifts are reported in ppm (δ) relative to residual protons in dueterated solvent peaks.

[00456] **Scheme 1: Synthetic scheme for E07, E08 and C02**



[00457] **(3-((2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid (E07):** A solution of 2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (**3a**) (150 mg, 0.499 mmol) in DMF (1.5 mL) was charged with EDCI (143 mg, 0.749 mmol), HOBt (101 mg, 0.749 mmol), DIPEA (193 mg, 1.49 mmol) and stirred at room temperature for 10 min. The solution was charged with (3-(aminomethyl) phenyl) boronic acid (**4a**) (83 mg, 0.549 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 layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 32 mg, 15 % yield of the title compound as an orange solid**.** ^{1}H NMR (400 MHz, DMSO-d6): δ = 11.74 (s, 1H), 9.30 (br. s., 1H), 8.52 (d, *J* = 8.8 Hz, 1H), 7.98 (s, 2H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.73 – 7.80 (m, 1H), 7.60 – 7.71 (m, 3H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.13 – 7.19 (m, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.43 (d, *J* = 5.7 Hz, 2H); MS (ES$^-$): *m/z* = 431.33, 432.36, 433.36 [M-H]$^-$; LCMS: t_R = 1.89 min (polar_3min_1500).

[00458] **(4-((2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid (E08):** A solution of 2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (**3a**) (150 mg, 0.499 mmol) in DMF (1.5 mL) was charged with EDCI (143 mg, 0.749 mmol), HOBt (101 mg, 0.749 mmol), DIPEA (193 mg, 1.49 mmol) and stirred at room temperature for 10 min. The solution was charged with (4-(aminomethyl) phenyl) boronic acid (**4b**) (83 mg, 0.549 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 layer was extracted with DCM (2 X 10 mL) and the combined organic layers were washed with water (2 X 20 mL) and dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC purification to afford 43 mg, 20 % yield of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.71 (s, 1H), 9.29 (t, J = 5.5 Hz, 1H), 8.54 (d, J = 8.4 Hz, 1H), 7.93 (s, 2H), 7.87 – 7.91 (m, 1H), 7.76 (d, J = 7.9 Hz, 1H), 7.63 – 7.70 (m, 3H), 7.41 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.9 Hz, 2H), 6.89 (d, J = 8.4 Hz, 1H), 4.44 (d, J = 5.7 Hz, 2H); MS (ES^-): m/z = 431.34, 432.33, 433.37 $[M-H]^-$; LCMS: t_R = 1.88 min (polar_3min_1500).

[00459] **4-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzoic acid (3a):** A solution of 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole (**1**) (8.0 g, 40.08 mmol) in EtOH (200 mL) was charged with 2-aminobenzoic acid (**2a**) (6.05 mg, 44.09 mmol) and heated at 90°C for 16 h. The reaction mixture was cooled to room temperature upon which a precipitate formed. The precipitate was collected by filtration, washed with diethyl ether followed by pentane and dried *in vacuo* resulting in 4.26 g, 35% yield of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.99 (s, 1H), 11.15 (s, 1H), 8.58 (dd, J = 8.7, 2.0 Hz, 1H), 8.04 (dd, J = 8.6, 2.1 Hz, 1H), 7.80 - 7.68 (m, 2H), 7.40 (d, J = 7.2Hz, 1H), 7.00 (dd, J = 8.8, 2.0 Hz, 1H). MS (ES^+): m/z =299.20 $[M-H]^+$; LCMS: t_R = 0.47 min.

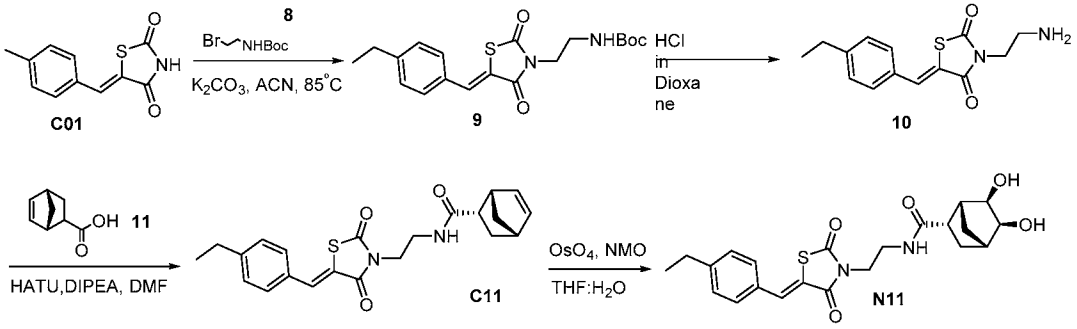
[00460] **2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide (C02):**

[00461] A solution of 4-chloro-7-nitrobenzo[c][1,2,5]oxadiazole (**1**) (250 mg, 1.25 mmol) in EtOH (15 mL) was charged with 2-aminobenzamide (**2b**) (188 mg, 1.38 mmol) and heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and the precipitate was collected by filtration and washed with diethyl ether followed by pentane and dried *in vacuo* to give 180 mg, 48% yield of the title compound as an orange solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.13 (s, 1H), 8.59 (d, J = 8.7 Hz, 1H), 8.33 (s, 1H), 7.92 – 7.76 (m,

3H), 7.66 (td, J = 6.8, 1.2 Hz, 1H), 7.35 (td, J = 7.2, 1.1 Hz, 1H), 7.04 (d, J = 8.8 Hz, 1H); MS (ES^+): m/z =300.00 $[M+H]^+$, 322.00 $[M+Na]^+$; LCMS: t_R = 0.48 min.

[00462]

[00463] Scheme 3: Synthetic scheme for N11



[00464] (1*R*,2*R*,4*S*,5*S*,6*R*)-*N*-(2-((*Z*)-5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxamide (N11): A solution of (1*R*,2*R*,4*S*)-*N*-(2-((*Z*)-5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide (**C11**) (230 mg, 0.580 mmol) in THF:H_2O (4:1 mL) was charged with NMO (74 mg, 0.632 mmol) and OsO_4 (22 mg, 0.086 mmol) and stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to afford 100 mg, 40% yield of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.97 (t, J = 6.0 Hz, 1H), 7.89 (s, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H), 4.54 (br. s., 1H), 4.43 (d, J = 4.4 Hz, 1H), 3.62 – 3.79 (m, 2H), 3.60 (br. s., 1H), 3.38 – 3.48 (m, 2H), 3.19 (dd, J = 12.8, 6.2 Hz, 1H), 2.67 (q, J = 7.5 Hz, 2H), 2.36 – 2.43 (m, 1H), 2.15 (d, J = 3.1 Hz, 1H), 1.93 (d, J = 4.0 Hz, 1H), 1.71 (d, J = 9.3 Hz, 1H), 1.43 (td, J = 12.0, 5.1 Hz, 1H), 1.29 – 1.37 (m, 1H), 1.20 (t, J = 7.5 Hz, 3H), 1.06 (d, J = 9.3 Hz, 1H); MS (ES^-): m/z = 429.38 $[M-H]^-$, 475.38 $[M+HCOOH]^+$; LCMS: t_R = 1.98 min (polar_3min_1500).

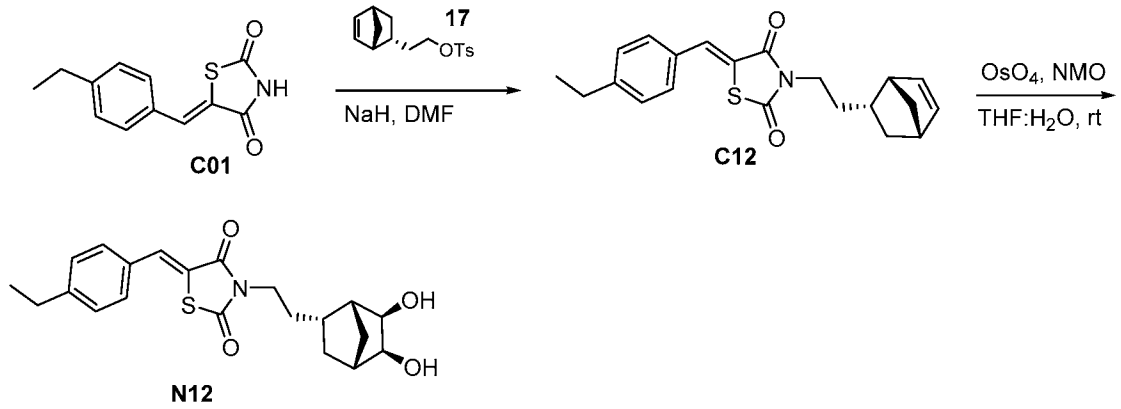
[00465] (1*R*,2*R*,4*S*)-*N*-(2-((*Z*)-5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)bicyclo[2.2.1]hept-5-ene-2-carboxamide (C11): A solution of (*Z*)-3-(2-aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (**10**) (260 mg, 0.942 mmol) in DMF (4 mL) was charged with (1*R*,2*R*,4*S*)-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**11**) (129 mg, 0.942 mmol)(Ref: *Science of Synthesis*, vol 6, pg 321-335, **2004**), HATU (536 mg, 1.41 mmol) and DIPEA (364 mg, 2.82mmol) and stirred at room temperature for 2 h. The reaction was diluted with water (10 mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic layers

were washed with water (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2-4% methanol in DCM to give 250 mg, 67% yield of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.89 (s, 1H), 7.78 (t, J = 6.1 Hz, 1H), 7.56 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.1 Hz, 2H), 6.04 (dd, J = 5.6, 2.9 Hz, 1H), 5.80 (dd, J = 5.4, 2.7 Hz, 1H), 3.67 (t, J = 5.4 Hz, 2H), 3.19 – 3.29 (m, 2H), 3.04 (br. s., 1H), 2.78 (br. s., 1H), 2.63 – 2.72 (m, 3H), 1.65 – 1.76 (m, 1H), 1.14 – 1.27 (m, 6H); MS (ES$^+$): *m/z* = 397.42, 398.43 $[M+H]^+$; LCMS: t_R = 2.31 min (polar_3min_1500).

[00466] (*Z*)-3-(2-Aminoethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (10): A solution of (*Z*)-*tert*-butyl(2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamate (**9**) (330 mg, 0.876 mmol) in dioxane (3 mL) was cooled to 0°C and charged with 4M HCl in dioxane (5 mL) then stirred at room temperature for 3 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was washed with hexanes and ether and dried *in vacuo* to give 260 mg, 95% yield of title compound as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.07 (s, 2H), 7.91 (s, 1H), 7.57 (d, J = 7.9 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 3.91 (t, J = 6.0 Hz, 2H), 3.07 (d, J = 6.3 Hz, 2H), 2.67 (q, J = 7.7 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H); MS (ES$^+$): *m/z* = 277.10, 278.09, 279.20 $[M+H]^+$; LCMS: t_R = 1.28 min.

[00467] (*Z*)-*tert*-Butyl(2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamate (9): A solution of (*Z*)-5-(4-methylbenzylidene)thiazolidine-2,4-dione (**C01**) (650 mg, 2.78 mmol) in acetonitrile (10 mL) was charged with *tert*-butyl (2-bromoethyl)carbamate (**8**) (624 mg, 2.78 mmol) and potassium carbonate (1.15 g, 8.36 mmol) and refluxed at 85 °C for 16 h. The reaction mixture was concentrated *in vacuo* and the residue obtained was diluted with water (20 mL) and extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 10-30% ethyl acetate in hexanes to give 330 mg, 31% yield of the title compound as off white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.87 (s, 1H), 7.54 (t, J = 9.3 Hz, 2H), 7.40 (d, J = 7.7 Hz, 2H), 6.98 (t, J = 6.2 Hz, 1H), 3.69 (t, J = 5.3 Hz, 2H), 3.18 (q, J = 5.8 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.33 (s, 9H), 1.20 (t, J = 7.6 Hz, 3H); MS (ES$^+$): *m/z* = 277.14, 278.15 [M-Boc]$^+$; LCMS: t_R = 2.03 min.

Scheme 2: Synthetic scheme for N12

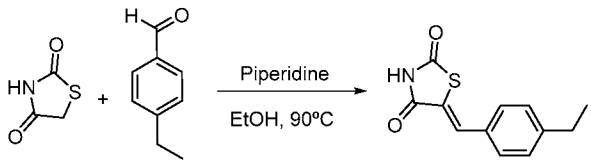


[00468] (*Z*)-3-(2-((1*S*,2*S*,4S,5*R*,6*S*)-5,6-Dihydroxybicyclo[2.2.1]heptane-2-yl)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (N12): A solution of (*Z*)-3-(2-((1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-yl)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (**C12**) (130 mg, 0.368 mmol) in THF:H_2O (2:0.5 mL) was charged with NMO (47 mg, 0.405 mmol) and OsO_4 (14 mg, 0.055 mmol) and stirred at room temperature for 16 h. The reaction was concentrated *in vacuo* resulting in a crude compound which was purified by preparative HPLC to give 55 mg, 38% yield of the title compound as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.90 (s, 1H), 7.55 (d, J = 7.9 Hz, 2H), 7.39 (d, J= 8.4 Hz, 2H), 4.55 (br. s., 2H), 3.79 (d, J = 5.6 Hz, 1H), 3.62 (t, J= 7.0 Hz, 2H), 3.43 (d, J = 5.6 Hz, 1H), 2.66 (q, J = 7.6 Hz, 2H), 1.88 – 1.99 (m, 2H), 1.64 – 1.75 (m, 3H), 1.59 (dd, J = 13.3, 6.7 Hz, 1H), 1.44 – 1.53 (m, 1H), 1.20 (t, J = 7.4 Hz, 3H), 1.00 (d, J = 9.8 Hz, 1H), 0.49 (d, J = 8.8 Hz, 1H); MS (ES$^+$): m/z = 388.43 $[M+H]^+$, 405.46 $[M+H_2O]$; LCMS: t_R = 2.29 min (polar_3min_1500).

[00469] (*Z*)-3-(2-((1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-yl)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (C12): A solution of (*Z*)-5-(4-methylbenzylidene)thiazolidine-2,4-dione (**C01**) (380 mg, 1.63 mmol) in DMF (20 mL) was cooled to 0°C and charged with sodium hydride (61 mg, 2.57 mmol). The reaction mixture was stirred at 0°C for 15 min, followed by the addition of 2-((1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-yl)ethyl 4-methylbenzenesulfonate (**17**) (375 mg, 1.63 mmol) then stirred at room temperature for 14 h. The reaction mixture was diluted with water (10 mL) and extracted with DCM (3 X 20 mL). The combined organic layer was washed with water (30 mL) and dried over

anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2-4% ethyl acetate in hexanes to give 130 mg, 28% yield of the title compound as white solid. 1H NMR (400 MHz, DMSO-d_6): δ = 7.90 (s, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 6.15 (dd, J = 5.6, 2.9 Hz, 1H), 5.89 – 6.00 (m, 1H), 3.63 (t, J = 7.3 Hz, 2H), 2.81 (br. s., 1H), 2.74 (br. s., 1H), 2.66 (q, J = 7.8 Hz, 2H), 1.92 – 2.02 (m, 1H), 1.80 – 1.90 (m, 1H), 1.40 (dq, J = 13.9, 7.2 Hz, 1H), 1.27 – 1.34 (m, 2H), 1.19 (t, J = 7.5 Hz, 3H), 0.46 (d, J = 10.8 Hz, 1H); MS (ES^+): *m/z* = no ionization observed; LCMS: t_R = 2.83 min (nonpolar_3min_1500).

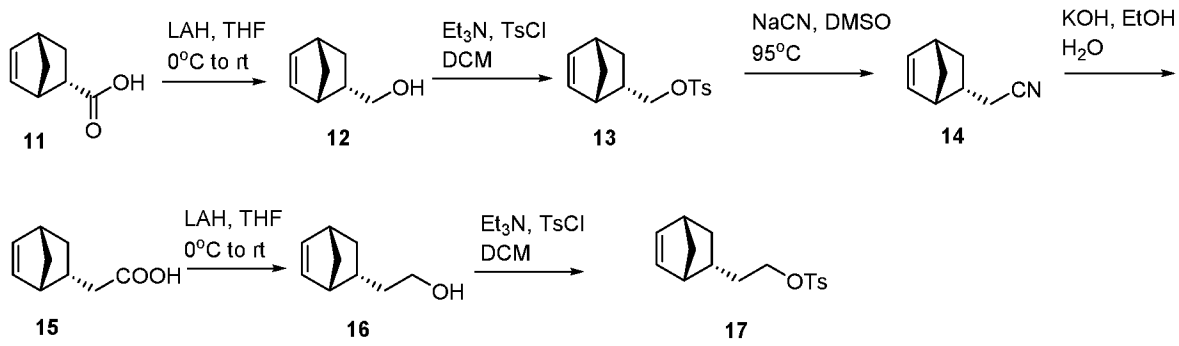
[00470] Scheme 4: Synthetic scheme for compound C01



[00471]

[00472] (Z)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione (C01): A solution of thiazolidine-2,4-dione (**5**) (6.0 g , 51.15 mmol) in ethanol (120 mL) was charged with piperidine (2.18 g, 25.57 mmol) and 4-ethylbenzaldehyde (**6**) (8.24 g, 61.38 mmol) and the solution was heated at 90°C for 16 h. The reaction mixture was cooled to room temperature and evaporated *in vacuo*. The crude product was partitioned between ethyl acetate (100 mL) and water (50 mL) and separated. The aqueous layer was extracted with ethyl acetate (3 x 100 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 10% ethyl acetate in *n*-hexane to obtain 10 g, 84 % yield of the title compound as an off white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.58 (s, 1H, NH), 7.76 (s, 1H, Olefin), 7.52 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 2.65 (q, J = 7.4 Hz, 2H), 1.19 (t, J = 7.4 Hz, 3H). MS (ES+): *m/z* = 232.15 $[M-H]^-$; LCMS: t_R = 2.88 min.

[00473] Scheme 5: Synthetic scheme for intermediate 17



[00474] **2-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)ethyl 4-methylbenzenesulfonate (17):** A solution of 2-((1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-yl)ethanol (**16**) (500 mg, 3.62 mmol) in DCM (10 mL) was cooled to 0 °C then charged with triethylamine (424 mg, 4.20 mmol) and tosyl chloride (2.06 g, 10.86 mmol). The reaction mixture was warmed to room temperature and stirred for 16 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 2-4% ethyl acetate in hexane to give 700 mg, 66% yield of the title compound as colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.74 – 7.82 (m, 2H), 7.49 (d, J = 7.9 Hz, 2H), 6.10 (dd, J = 5.9, 3.0 Hz, 1H), 5.84 (dd, J = 5.9, 2.8 Hz, 1H), 3.91 – 4.06 (m, 2H), 2.70 (d, J = 3.5 Hz, 1H), 2.62 (s, 1H), 2.45 (s, 3H), 1.97-2.01 (m, 1H), 1.66 – 1.77 (m, 1H), 1.10 – 1.42 (m, 5H).

[00475] **2-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)ethanol (16):** A solution of lithium aluminum hydride (LAH) (271 mg, 7.1 mmol) in THF (10 mL) was cooled 0 °C and charged with 2-((1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-yl)acetic acid (**15**) (700 mg, 4.6 mmol) then stirred at room temperature for 2 h. The reaction mixture was quenched with 1N aq NaOH and ethyl acetate at 0 °C and filtered through pad of celite. The filtrate was extracted with ethyl acetate (3 X 20 mL) and the combined organic layers were washed with water (30 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 500 mg of crude compound as colorless liquid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.12 (dd, J = 5.8, 3.0 Hz, 1H), 5.92 (dd, J = 5.8, 2.8 Hz, 1H), 4.30 (t, J = 5.2 Hz, 1H), 3.32 – 3.41 (m, 2H), 2.69 – 2.71 (m, 2H), 1.94 – 2.11 (m, 1H), 1.72 – 1.87 (m, 1H), 1.02 – 1.38 (m, 5H).

[00476] **2-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)acetic acid (15):** A solution of 2-((1*R*,2*R*,4*R*)-bicyclo[2.2.1]hept-5-en-2-yl)acetonitrile (**14**) (700 mg, 5.26 mmol) in EtOH:H_2O (1:1) (6 mL) at room temperature was charged with KOH (884 mg, 15.8 mmol) and refluxed at

95°C for 16 h. The solvent was removed *in vacuo* and the residue obtained was acidified with 1N HCl to pH ~2-3 and extracted with DCM (3 X 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 700 mg of crude compound as colorless liquid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.94 (s, 1H), 6.17 (dd, *J* = 5.8, 3.0 Hz, 1H), 5.93 (dd, *J* = 5.8, 2.9 Hz, 1H), 2.71 – 2.81 (m, 2H), 2.28 – 2.48 (m, 2H), 2.02 (dd, *J* = 15.4, 7.5 Hz, 1H), 1.70 – 1.95 (m, 2H), 1.16 – 1.38 (m, 2H).

[00477] 2-((1*R*,2*R*,4*R*)-Bicyclo[2.2.1]hept-5-en-2-yl)acetonitrile (14): A solution of (1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-ylmethyl 4-methylbenzenesulfonate (**13**) (1.5 g, 5.38 mmol) in DMSO (10 mL) at room temperature was charged with sodium cyanide (527 mg, 10.79 mmol) and refluxed at 95 °C for 16 h. The reaction mixture was cooled to room temperature and quenched with water, extracted with ethyl acetate (3 X 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 700 mg of crude compound as light yellow liquid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.24 (dt, *J* = 4.6, 2.2 Hz, 1H), 5.97 (dd, *J* = 5.8, 2.9 Hz, 1H), 2.76 – 2.87 (m, 2H), 2.29 – 2.42 (m, 2H), 2.09 – 2.26 (m, 2H), 1.86 – 1.92 (m, 1H), 1.22 – 1.43 (m, 2H).

[00478] (1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-ylmethyl 4-methylbenzenesulfonate (13): A solution of (1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-ylmethanol (**12**) (760 mg, 6.12 mmol) in DCM (7 mL) was cooled to 0 °C and charged with triethylamine (0.98 mL, 7.11 mmol) and tosyl chloride (4.65 g, 24.5 mmol) then stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* resulting in a crude compound which was purified by chromatography on silica gel eluting with 10-20% ethyl acetate in hexanes to afford 1.5 g, 88% yield of the title compound as colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.78 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 7.9 Hz, 2H), 6.10 (dd, *J* = 5.8, 3.0 Hz, 1H), 5.59 (dd, *J* = 5.8, 2.9 Hz, 1H), 3.74 (dd, *J* = 9.6, 6.5 Hz, 1H), 3.49 (t, *J* = 9.6 Hz, 1H), 2.76 (d, *J* = 13.2 Hz, 2H), 2.31 (s, 3H), 2.28 –2.10 (m, 2H), 1.74 (ddd, *J* = 12.4, 9.3, 3.8 Hz, 1H), 1.26 – 1.34 (m, 1H), 1.20 (d, *J* = 8.2 Hz, 1H).

[00479] (1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-ylmethanol (12): A solution of LAH (533 mg, 14.3 mmol) in THF (10 mL) was cooled to 0°C and charged with (1*S*,2*S*,4*S*)-bicyclo[2.2.1]hept-5-en-2-carboxylic acid (**11**) (1.25 g, 9.05 mmol). The reaction was stirred at room temperature for 2 h then cooled to 0 °C and quenched with 1N aq NaOH and ethyl

acetate. The reaction mixture was filtered through pad of celite and the filtrate was extracted with ethyl acetate (3 X 50 mL). The combined organic layers were washed with water (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* resulting in 760 mg of crude compound as colorless liquid. The crude compound was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.10 (dd, J = 5.5, 2.9 Hz, 1H), 5.92 (dd, J = 6.0, 2.9 Hz, 1H), 4.36 (t, J = 5.3 Hz, 1H), 3.11 (dt, J = 11.1, 5.8 Hz, 1H), 2.93 (td, J = 9.7, 5.3 Hz, 1H), 2.84 (s, 2H), 2.73 (d, J = 5.3 Hz, 1H), 2.16 (tt, J = 9.1, 4.4 Hz, 1H), 1.71 (ddd, J = 12.5, 9.1, 3.8 Hz, 1H), 1.16 – 1.38 (m, 2H).

EXAMPLE 46: Identification of working pairs designed to target Myc with synergistic anti-proliferative activity

[00480] Pairwise combinations of monomers from the library were screened in a cell proliferation assay. Increasing concentrations of each compound were dosed in a 8x6 matrix format and their effects on cell proliferation monitored to identify combinations that showed a synergistic inhibition of cell proliferation.

Cell Culture

[00481] K562 (Human chronic myelogenous leukemia), Daudi (Human B-lymphoblastoid) and MV4-11 (Human myeloid leukemia) cells were purchased from American Type Culture Collection (Manassas, VA). The K562 and MV4-11 were cultured in Iscove's Modified Dulbecco's Media plus 1% L-Glutamine. The Daudi cells were cultured in RPMI 1640 Media plus 1% L-Glutamine. Cell lines were maintained in suspension in media supplemented with 10% fetal bovine serum at 37°C and 5% CO_2.

Cell proliferation and Synergy analysis

[00482] Growth and proliferation was determined by use of Cell Titer 96 Aqueous One Solution (Promega, Madison, WI). All suspension lines were plated at 10,000 cells per well in growth media in a clear 96 well plate. The following day compounds were diluted into media and then added to the cells. DMSO was used as the control treatment. After 3 days of growth reagent was added, incubated for 4 hours at 37°C, and absorbance at 490 nm was read. A control plate of compound diluted in media at the same concentrations was treated in a similar way and these values subtracted from the cell plate data to control for any compound interference in the assay. Data was normalized to the DMSO control and plotted as a fraction of

proliferation in relation to the DMSO treated cells. Synergy was determined using the Bliss model of independence (Bliss 1939).

[00483] Representative graphs showing dose dependent inhibition of proliferation with 3 different combinations, two that displayed significant synergy (E07+N11 and E08+N11) and one that did not (E10+N11), are shown in Figure 5A-C. There was no activity of the individual compounds E07, E08, E10, or N11 in the proliferation assay at concentrations up to 30 μM. However, the activity of E07 (Figure 5A) or E08 (Figure 5B), but not E10 (Figure 5C) was dramatically improved in the presence of 30 μM N11. The IC_{50} values of inhibition of proliferation for E07 or E08 in the presence of N11 were 2.3 μM and 1.7 μM respectively, in comparison to an IC_{50} >30 μM for each individual monomer. In addition, the activity of the E07+N11 and E08+N11 was significantly greater than the predicted additive effect (Bliss line), indicating synergy between these compounds. Similar results were obtained with N12, a close analog of N11, in combination with E07.

EXAMPLE 47: Dimers selectively inhibit Myc: Max interaction in cell- free assay

[00484] To confirm that the working pairs directly bound to Myc and inhibited interaction with its heterodimerization partner Max, an ELISA was developed using purified Myc and Max protein that measured Myc:Max binding.

Cell-free Myc:Max ELISA

[00485] High binding 96-well plates were coated with GST-conjugated full-length Max protein (Sino Biologicals) at 1ng/μL in 100μl of PBS overnight at 4°C. The plate was washed 4x 200 μl/well with PBS and blocked in 200 μl/well of 5% nonfat dry milk in PBS for 2 hours at room temperature. Full length Myc protein (Origene) was diluted to 1 ng/μL in Buffer A (50 mM Tris-HCl, pH 7.4, 0.1 mM EDTA, 150 mM NaCl, 0.002% NP-40). Compounds were serially diluted in 100% DMSO and then sequentially diluted 1:100 into the Myc solution before incubation for one hour at room temperature. For internal consistency, final DMSO concentrations were kept at 2%. The blocked plate was washed 4x 200μl/well with Buffer A, before addition of 100 μl of the Myc compound mixture. Plates were incubated for four hours at RT, and washed 4x 200 μl Buffer A/well. Anti-Myc antibody (Cell Signaling) was diluted 1:1000 in 5% nonfat dry milk in Buffer A. 100 μL/well diluted primary antibody was added to each well and incubated for one hour at room temperature. Plates were washed 4x 200 μl/well Buffer A. HRP-conjugated goat anti-rabbit antibody (GE Healthcare) was diluted 1:5000 in 5%

nonfat dry milk in Buffer A. 100 µL/well diluted secondary antibody was added to each well and incubated for thirty minutes at room temperature. The plates were washed 4x 200 µL/well Buffer A. 50 µL/well of FEMTO chemiluminescent reagent (Thermo Scientific) was added, and luminescence was immediately read on a Victor X5 plate reader (PerkinElmer) with a 0.1 sec integration time. IC_{50}s were generated through non-linear fitting of data with prism (GraphPad).

[00486] The parent ligand molecules, C01 and C02, were initially tested and observed little inhibition of either the monomers (IC_{50} >30 µM) or the combination (IC_{50} 23 µM) on the Myc:Max interaction (Table 1).

Table 1.

Parent ligand inhibition of cell-free MYC-MAX heterodimer formation*.	
C01	>30
C02	>30
Combination†	23 ± 8.8

*Average IC_{50} values (Cnnd inhibition of cell-free MYC-MAX heterodimer formationphPad).in Experimental Procedures. †Combination is an equimolar titration of C01 and C02.

[00487] The individual monomers E07 and N12 showed little inhibition of the Myc:Max interaction (IC_{50} 24 µM and >30 µM respectively Table 2). In contrast, the combination of E07+N12, dosed in a 1:1 ratio, inhibited Myc binding to Max in a dose dependent fashion (IC_{50} =3.3 µM) (Figure 4A and Table 2), an 8 fold enhancement over the most active individual monomer. We observe similar effects for the combinations E08+N12, E07+N11 and E08+N11, although the E08 based pairs are slightly less active (Table 2).

Table 2.

Inhibition of cell-free Myc-Max heterodimer formation*.	
E07	24 ± 7.4
E08	>30

N11	>30
N12	>30
C11	>30
C12	>30
E07+N11	5.0 ± 0.89
E07+N12	3.3 ± 1.8
E08+N11	12 ± 3.7
E08+N12	16 ± 6.1
E07+C11	15 ± 7.5
E08+C11	>30
E07+C12	>30
E08+C12	>30

*Average IC_{50} values (μM) with standard deviation from the Myc-Max ELISA, as described in Experimental Procedures. IC_{50}s of E, N, and C monomers alone are listed first, followed by IC_{50}s from equimolar titrations of combinations of monomers. The IC_{50} values refer to the concentration of each monomer in the combination (1:1 ratio). C11 and C12 are non-dimerizable control compounds corresponding to N11 and N12, respectively.

[00488] The key premise of the platform library is the ability of two distinct small molecules to dimerize, thus generating a large molecule inhibitor. In order to demonstrate that dimerization was in fact critical for the inhibitory effect of the working pair dimer versus Myc an analog of N12 was synthesized that was similar in every aspect except it lacks the diol group required for reaction with its boronic acid counterpart (C12, Figure 4). The combination of C12 with E07 failed to show any activity in the Myc:Max ELISA over the activity of E07 alone suggesting that the ability of E07+N12 to dimerize was driving the significantly improved inhibitory effect. Limited effects were observed with the additional control combinations E08+C12, E07+C11, and E08+C11 (Table 2). These experiments also provide evidence that increased total inhibitor concentration of the combinations does not drive the enhanced inhibition, as the total concentration of the control combination is identical to that of the working pair/dimer.

EQUIVALENTS

[00489] 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.

[00490] 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.

What is claimed is:

1. A first monomer capable of forming a biologically useful multimer when in contact with a second monomer in an aqueous media, the multimer capable of modulating c-Myc, wherein the first monomer is represented by the formula:

X^1-Y^1-Z^1 (Formula I) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^1 is a first ligand moiety capable of modulating a first binding site on said c-Myc;

Y^1 is a connector moiety covalently bound to X^1 and Z^1;

Z^1 is a first linker capable of binding to the second monomer; and

the second monomer is represented by the formula:

X^2-Y^2-Z^2 (Formula II) and pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof, wherein

X^2 is a second ligand moiety capable of modulating a second binding site on said c-Myc;

Y^2 is absent or is a connector moiety covalently bound to X^2 and Z^2; and

Z^2 is a second linker capable of binding to the first monomer through Z^1.

2. The first monomer of claim 1, wherein X^1 and X^2 are different.

3. The first monomer of any one of claims 1-2, wherein Y^1 and Y^2 are the same.

4. The first monomer of any one of claims 1-2, wherein Y^1 and Y^2 are different.

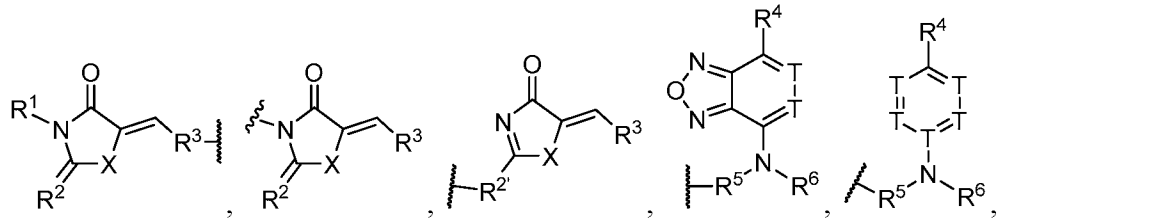
5. The first monomer of any one of claims 1-4, wherein Z^1 and Z^2 are the same.

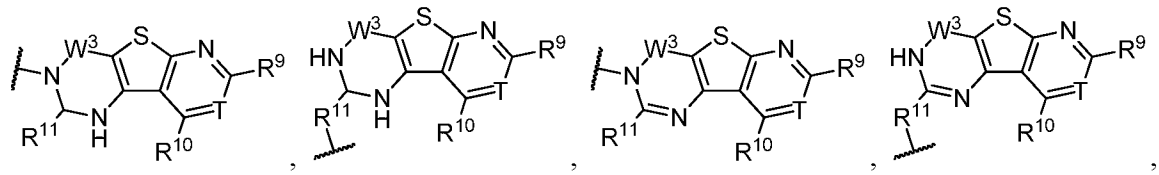
6. The first monomer of any one of claims 1-4, wherein Z^1 and Z^2 are different.

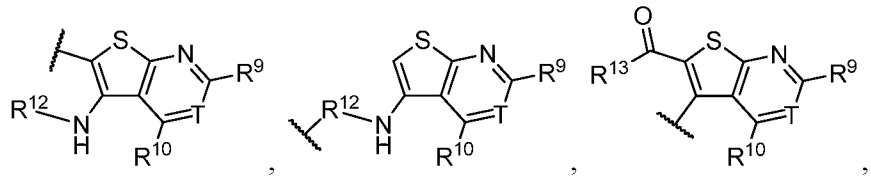
7. The first monomer of any one of claims 1-6, wherein the aqueous media has a physiologically acceptable pH.

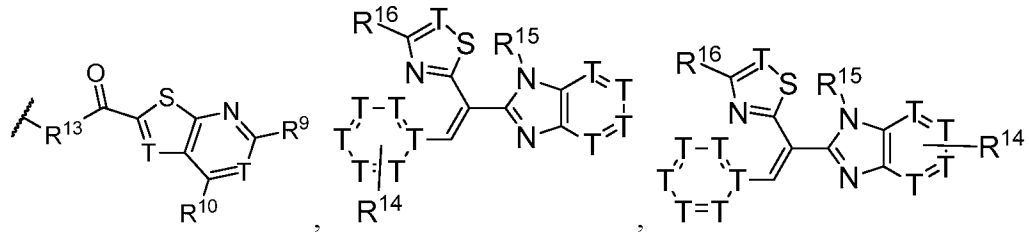
8. The first monomer of any one of claims 1-7, wherein the first monomer forms a biologically useful dimer with a second monomer *in vivo*.

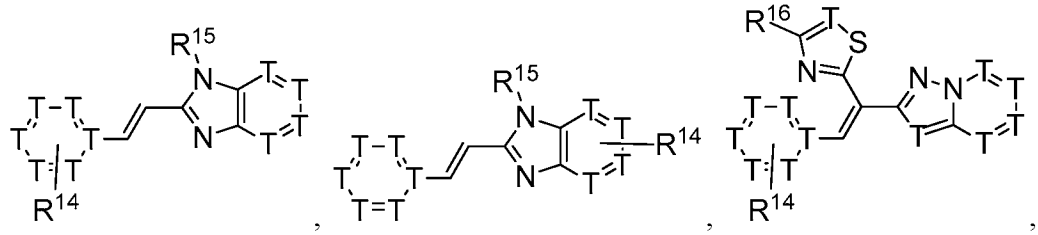
9. The first monomer of any one of claims 1-8, wherein X^1 and X^2 are independently selected from the group consisting of:

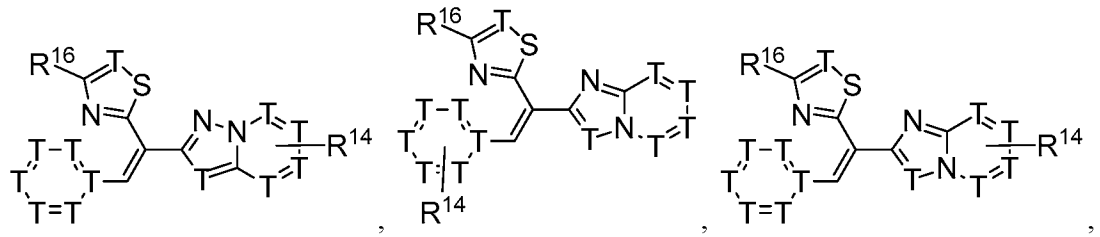
3 

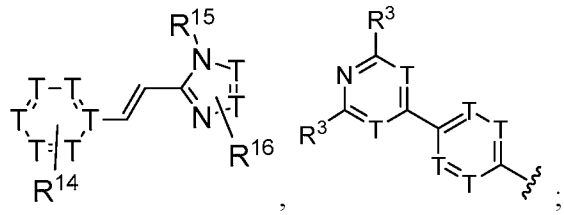
4 

5 

6 

7 

8 

9  ;

10 wherein:

X is O, S, NR'', or CR''$_2$;

T is independently selected from the group consisting of N and CH;

W^3 is C=O or CH_2;

R^1 is H, alkyl, phenyl, or a 5-10 membered heterocyclyl;

R^2 is O or S;

$R^{2'}$ is NR'', O, S, or a bond;

R^3 is selected from the group consisting of phenyl, diphenyl, naphthyl, 5-10 membered heteroaryl, and cyclohexyl, wherein phenyl, diphenyl, naphthyl, heteroaryl, and cyclohexyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, nitro, cyano, acyl, carboxyl, SO_2R'', $SO_2N(R'')_2$, C(O)-$N(R'')_2$, N(R'')acyl, hydroxy, C_{1-3} alkoxy, C_{1-4}alkyl, C_{1-4}alkenyl, and C_{1-4}alkynyl;

R^4 is nitro N(R'')acyl, $N(R'')_2$, carboxyl, or –C(O)-$N(R'')_2$;

R^5 is selected from the group consisting of phenyl, diphenyl, naphthyl, 5-11 membered heteroaryl, and cyclohexyl, wherein phenyl, diphenyl, naphthyl, heteroaryl, and cyclohexyl are optionally substituted with one, two, or three substituents selected from the group consisting of halo, nitro, cyano, acyl, carboxyl, SO_2R'', $SO_2N(R'')_2$, C(O)-$N(R'')_2$, N(R'')acyl, hydroxy, C_{1-3} alkoxy, C_{1-4}alkyl, C_{1-4}alkenyl, and C_{1-4}alkynyl; and

R^6 is H, alkyl, C_{3-10}cycloalkyl, phenyl, 5-10 membered heteroaryl, or 5-10 membered heterocyclyl;

R^9 is selected from the group consisting of H, C_{1-6}alkyl, -CF_3, C_{1-6}alkoxy, -CN, -NO_2, and –COOH;

R^{10} is selected from the group consisting of H, -CN, –COOH, -C_{1-6}alkyl, C_{1-6}cycloalkyl, -O-C_{1-6}alkyl, -OC(O)-C_{1-6}alkyl, -OC(O)-NR'_2, -NR'-C(O)-C_{1-6}alkyl, -NR'-C(O)-O-C_{1-6}alkyl, -NR'-C(O)-NR'_2;

R^{11} is selected from the group consisting of phenyl and heteroaryl, wherein the phenyl and heteroaryl are optionally substituted;

R^{12} is selected from the group consisting of –C(O)-C_{0-6}alkyl-phenyl, –C(O)-C_{0-6}alkyl-heteroaryl, phenyl and heteroaryl, wherein the phenyl and heteroaryl are optionally substituted;

R^{13} is independently selected from the group consisting of –NH-C_{1-6}alkyl-phenyl, –NH-C_{1-6}alkyl-heteroaryl, –N(C_{1-6}alkyl)-C_{1-6}alkyl-phenyl, and piperazine, wherein the alkyl, phenyl, heteroaryl, and piperazine are optionally substituted;

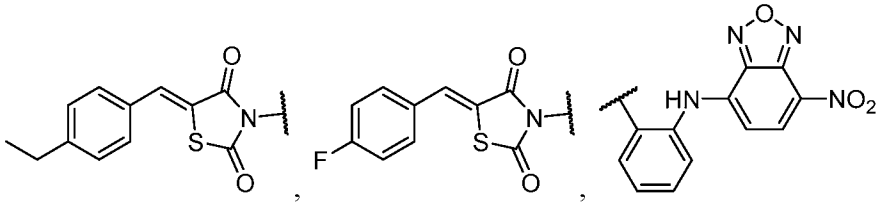
R^{14} is selected from the group consisting of halo, optionally substituted C_{1-6}alkyl, optionally substituted C_{1-6}alkoxy, and nitrile;

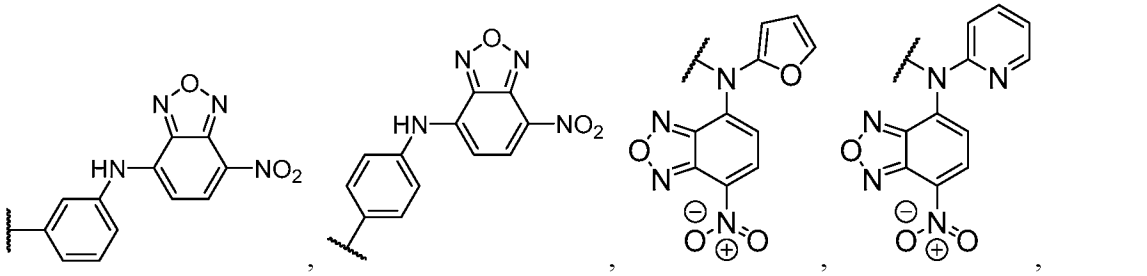
R^{15} and R^{16} are independently selected from the group consisting of H and optionally substituted C_{1-6}alkyl;

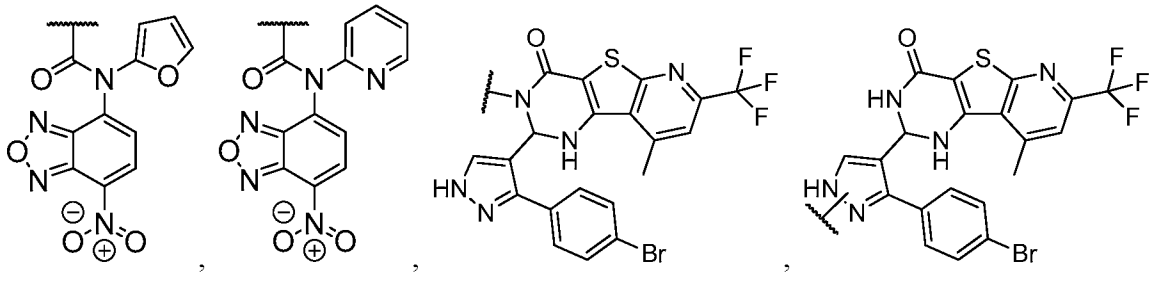
R' is independently selected from the group consisting of H, C_{1-6}alkyl, and phenyl; and

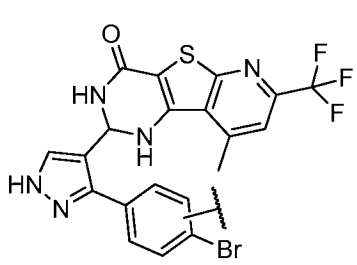
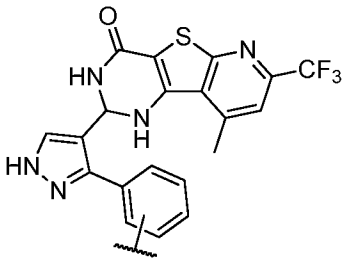
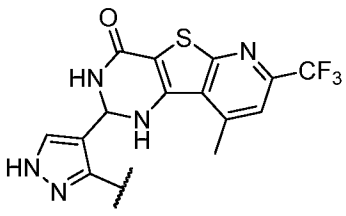
R" is selected from the group consisting of H and C_{1-4}alkyl; or two R" together with the carbon to which they are attached form a C_{3-6}cycloalkyl.

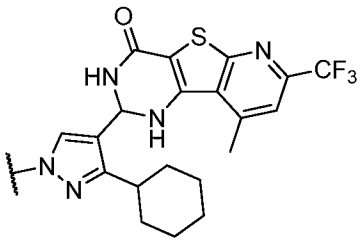
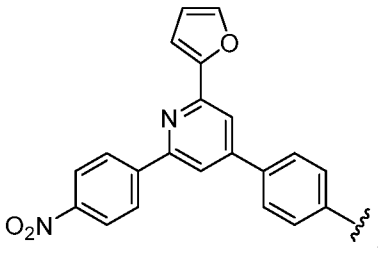
10. The first monomer of any one of claims 1-9, wherein X^1 is selected from the group consisting of:





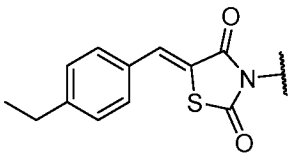
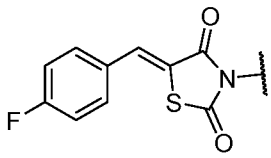
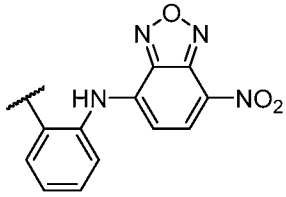


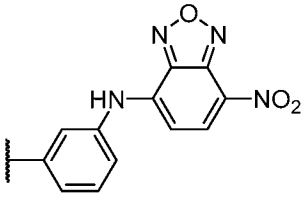
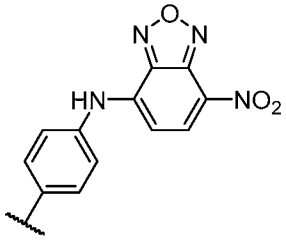
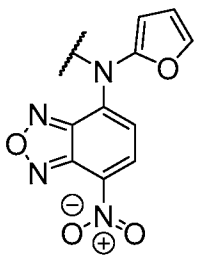
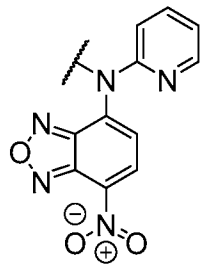
6  ,  ,  ,

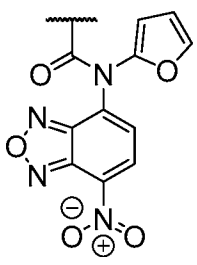
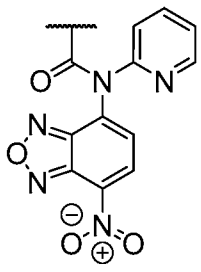
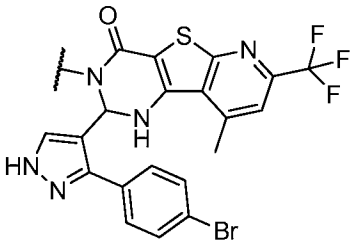
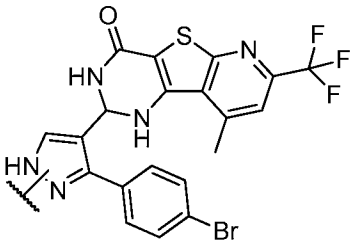
7  , and  .

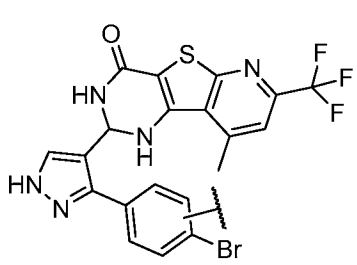
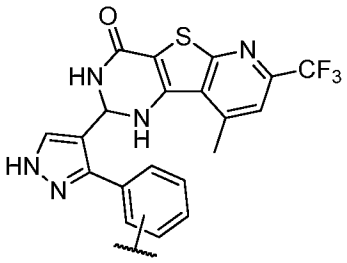
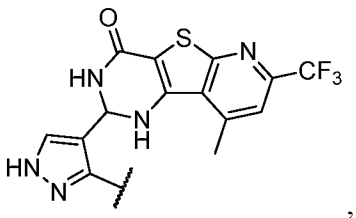
1 11. The first monomer of any one of claims 1-10, wherein X^2 is selected from the group

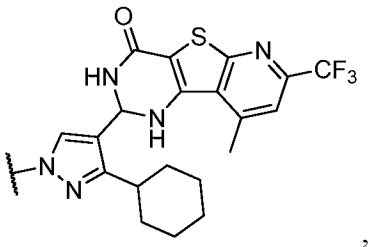
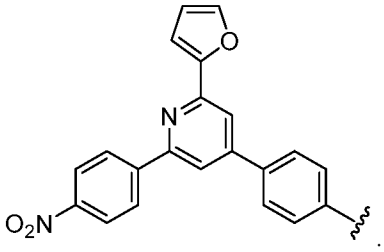
2 consisting of:

3  ,  ,  ,

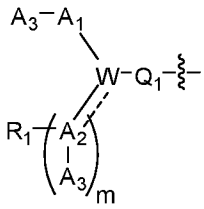
4  ,  ,  ,  ,

5  ,  ,  ,  .

6  ,  ,  ,

7  , and  .

1 12. The first monomer of any one of claims 1-11, wherein Z^1 or Z^2 is selected from the
2 group consisting of:

3 a) 

4 wherein

5 A_1 is (a) absent; or (b) selected from the group consisting of acyl, substituted or
6 unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

7 A_2, independently for each occurrence, is (a) absent; or (b) selected from the
8 group consisting of –N–, acyl, substituted or unsubstituted aliphatic, or substituted or
9 unsubstituted heteroaliphatic, provided that at least one of A_1 and A_2 is present; or

10 A_1 and A_2, together with the atoms to which they are attached, form a
11 substituted or unsubstituted 4-8 membered cycloalkyl or heterocyclic ring;

12 A_3 is selected from the group consisting of -NHR', -SH, or -OH;

13 W is CR' or N;

14 R' is selected from the group consisting of hydrogen, halogen, substituted or
15 unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or

unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or -OH;

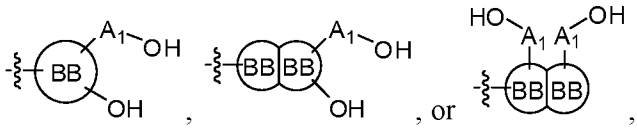
m is 1-6;

=== represents a single or double bond; and

R_1 is (a) absent; or (b) selected from the group consisting of hydrogen, halogen, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or -OH;

Q_1 is (a) absent; or (b) selected from the group consisting of substituted or unsubstituted aliphatic or substituted or unsubstituted heteroaliphatic; or

R_1 and Q_1 together with the atoms to which they are attached form a substituted or unsubstituted 4-8 membered cycloalkyl or heterocyclic ring;

b) 

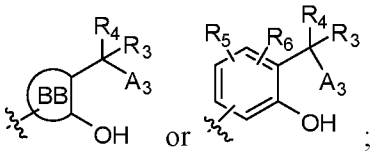
, wherein

BB, independently for each occurrence, is a 4-8 membered cycloalkyl, bicycloalkyl with or without bridge head containing C, O, NH, NR, heterocyclic, phenyl, naphthyl, or heteroaryl moiety, wherein the cycloalkyl, heterocyclic, phenyl, naphthyl, or heteroaryl moiety is optionally substituted with one or more groups represented by R_2, wherein the two substituents comprising -OH have a 1,2 or 1,3 configuration;

each R_2 is independently selected from hydrogen, halogen, oxo, sulfonate, $-NO_2$, -CN, -OH, $-NH_2$, -SH, -COOH, -CONHR', $-CONH-SO_2-R'$, $-SO_2NH-CO-R'$, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, or two R_2 together with the atoms to which they are attached form a fused substituted or unsubstituted 4-6 membered cycloalkyl or heterocyclic bicyclic ring system;

A_1, independently for each occurrence, is (a) absent; or (b) selected from the group consisting of acyl, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

R' is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or -OH;

c)  ;

wherein

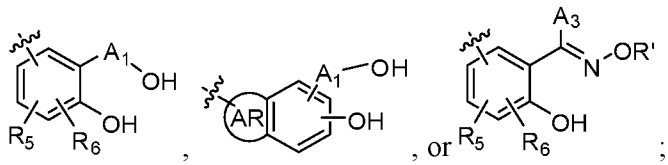
BB is a substituted or unsubstituted 5- or 6-membered cycloalkyl, heterocyclic, phenyl or naphthyl, or heteroaryl moiety;

A_3, independently for each occurrence, is selected from the group consisting of –NHR' or –OH;

R_3 and R_4 are independently selected from the group consisting of H, OH, C_{1-4}alkyl, phenyl, or R_3 and R_4 taken together from a 3-6 membered ring;

R_5 and R_6 are independently selected from the group consisting of H, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halogen, or thio; C_{1-4}alkoxy; halogen; -OH; -CN; -COOH; -CONHR'; or R_5 and R_6 taken together form phenyl or a 4-6 membered heterocycle; and

R' is selected from the group consisting of hydrogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or -OH;

d)  ;

wherein

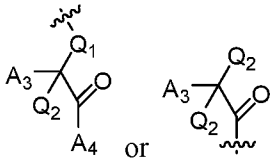
A_1 is (a) absent; or (b) selected from the group consisting of acyl, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

A_3, independently for each occurrence, is selected from the group consisting of –NHR' or –OH;

AR is a fused phenyl or 4-7 membered aromatic or partially aromatic heterocyclic ring, wherein AR is optionally substituted by oxo, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{1-4}alkoxy; -S- C_{1-4}alkyl; halogen; -OH; -CN; -COOH; -CONHR'; wherein the two substituents comprising -OH are ortho to each other;

R_5 and R_6 are independently selected from the group consisting of H, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{1-4}alkoxy; halogen; -OH; -CN; -COOH; CONHR'; and

R' is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, $-NH_2$, $-NO_2$, -SH, or –OH;

e)  or ; wherein

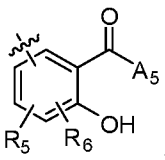
Q_1 is selected from the group consisting of C_{1-4}alkyl, alkylene, or a bond; C_{1-6}cycloalkyl; a 5-6 membered heterocyclic ring; or phenyl;

Q_2, independently for each occurrence, is selected from the group consisting of H, C_{1-4}alkyl, alkylene, or a bond; C_{1-6}cycloalkyl; a 5-6 membered heterocyclic ring; substituted or unsubstituted aliphatic; substituted or unsubstituted heteroaliphatic; substituted or unsubstituted phenyl or naphthyl; or substituted or unsubstituted heteroaryl;

A_3, independently for each occurrence, is selected from the group consisting of –NH_2 or -OH;

A_4, independently for each occurrence, is selected from the group consisting of -NH-NH_2; -NHOH, -NH-OR'', or –OH;

R'' is selected from the group consisting of H or C_{1-4}alkyl; and

f)  ; wherein

A_5 is selected from the group consisting of –OH, -NH_2, -SH, -NHR’’’;

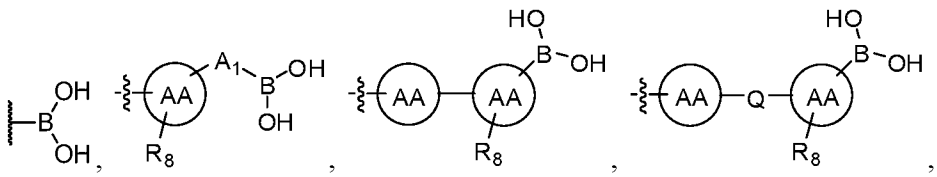
R’’’ is selected from -NH_2; -OH; phenoxy; and C_{1-4}alkoxy;

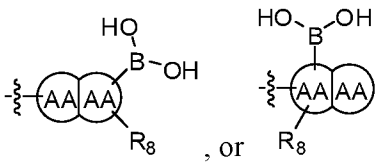
R_5 and R_6 are independently selected from the group consisting of H, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo, or thio; C_{1-4}alkoxy; halogen; -OH; -CN; -COOH; -CONHR’; or R_5 and R_6 taken together may form a 5-6 membered ring;

R’ is selected from the group consisting of hydrogen, substituted or unsubstituted aliphatic, substituted or unsubstituted heteroaliphatic, substituted or unsubstituted phenyl or naphthyl, substituted or unsubstituted heteroaryl, -NH_2, -SH, or –OH; and

the second monomer has a boronic acid or oxaborole moiety capable of binding with the Z_1 moiety of Formula I to form the multimer.

13. The first monomer of claim 12, wherein Z^1 or Z^2 is selected from the group consisting of:



 ; wherein

R_8 is selected from the group consisting of H, halogen, oxo, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halo or thio; C_{2-4}alkenyl, C_{1-4}alkoxy; -S- C_{1-4}alkyl; -CN; -COOH; or –CONHR’;

A_1 is (a) absent; or (b) selected from the group consisting of acyl, substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

Q is selected from the group consisting of substituted or unsubstituted aliphatic, or substituted or unsubstituted heteroaliphatic;

AA, independently for each occurrence, is phenyl, naphthyl, 3-7 membered cycloalkyl, or a 5-7 membered heterocyclic or heteroaryl ring having one, two, or three heteroatoms, wherein AA is optionally substituted by one, two, or three substituents selected from the group consisting of halogen, C_{1-4}alkyl optionally substituted by hydroxyl, amino, halogen, or thio; C_{2-4}alkenyl, C_{1-4}alkoxy; -S- C_{1-4}alkyl; -CN; -COOH; –CONHR'; or two substituents together with the atoms to which they are attached form a fused 4-6 membered cycloalkyl or heterocyclic bicyclic ring system; and

R' is H or C_{1-4}alkyl.

14. The first monomer of any one of claims 1-13, wherein Y^1 is selected from the group consisting of:

C_{1-20}alkylene, wherein one, two, or three or four methylene units of the hydrocarbon chain are optionally and independently replaced by cyclopropylene, -NR^{1Y}-, -$N(R^{1Y})C(O)$-, -$C(O)N(R^{1Y})$-, -$N(R^{1Y})SO_2$-, -$SO_2N(R^{1Y})$-, -O-, -C(O)-, -OC(O)-, -C(O)O-, -S-, -SO-, -SO_2-, -C(=S)-, -$C(=NR^{1Y})$-, phenyl, naphthyl, or a mono or bicyclic heterocycle ring; -NR^{1Y}-C_{1-15}alkyl-NR^{1Y}-C(O)-; -NR^{1Y}-$(CH_2$-CH_2-$O)_s$-C_{1-6}alkyl-NR^{1Y}-C(O)-; -$(O$-CH_2-$CH_2)_s$-NR^{1Y}-C(O)-; -S-C_{0-6}alkyl-; -NR^{1Y}-C_{1-6}alkyl-; -$N(C_{1-3}$alkyl)-C_{1-6}alkyl-NH-C(O)-; -NH-C_{1-6}alkyl-$N(C_{1-3}$alkyl)-C(O)-; -SO_2-NR^{1Y}-C_{0-6}alkyl-; -SO_2-heterocyclyl-C_{0-6}alkyl-; -heterocyclyl-C(O)-; -heterocyclyl-C_{0-6}alkyl-NR^{1Y}-C(O)-; -NR^{1Y}-C_{0-6}alkylene-heterocyclene-C(O)-; -O-C_{1-6}alkylene-C(O)-; -O-C_{1-15}alkylene-NR^{1Y}-C(O)-; -O-C_{1-15}alkylene-C(O)-NR^{1Y}-; and -O-C_{1-6}alkylene-, wherein C_{1-6}alkylene is optionally substituted by -OH;

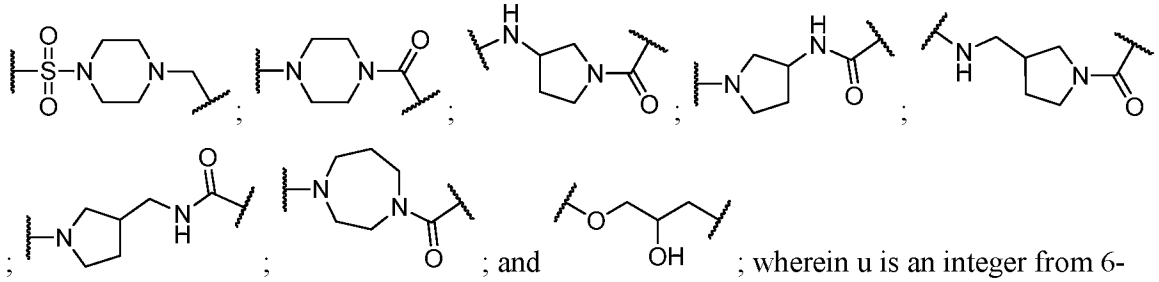
wherein, independently for each occurrence,

R^{1Y} is selected from the group consisting of H and C_{1-6}alkyl; and

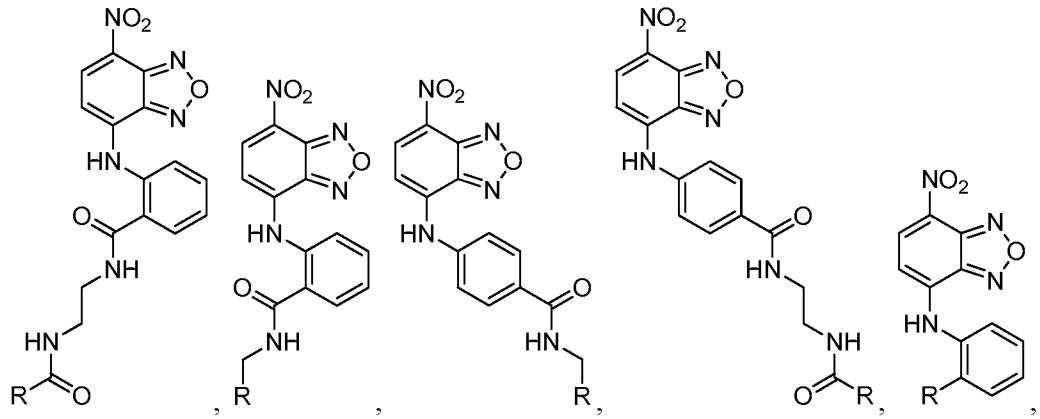
s is an integer from 1-15.

15. The first monomer of claim 14, wherein Y^1 is selected from the group consisting of:

-NH-$(CH_2$-CH_2-$O)_s$- CH_2-CH_2-NH-C(O)-; -$(O$-CH_2-$CH_2)_s$-NH-C(O)-; -S-; -S-CH_2-; -O-$(CH_2)_s$-NH-C(O)-; -SO_2-NH-; -SO_2-NH-CH_2-; -$N(CH_3)$-$(CH_2)_2$-NH-C(O)-; -NH-$(CH_2)_2$-$N(CH_3)$-C(O); -NH-$(CH_2)_u$-NH-C(O)-; -O-CH_2-C(O)-;


;
;
;
;
;
;
; and
; wherein u is an integer from 6-15.

16. A first monomer selected from the group consisting of: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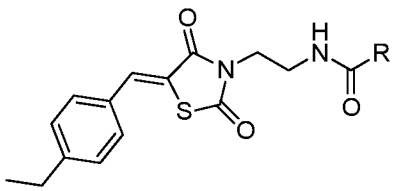
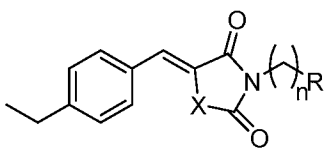
, , 
, 
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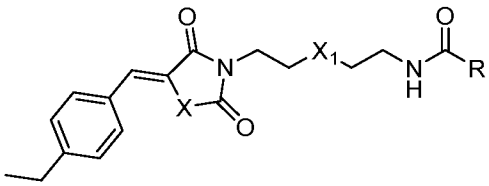
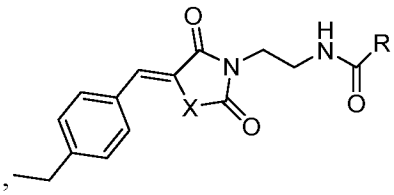

, 
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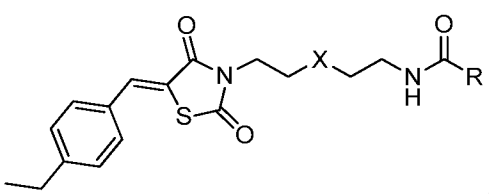
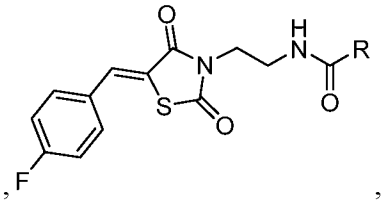
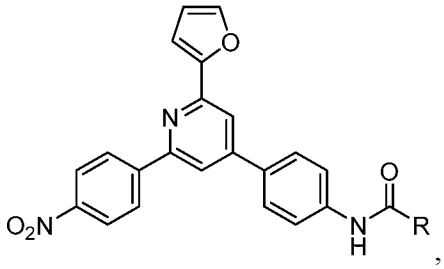
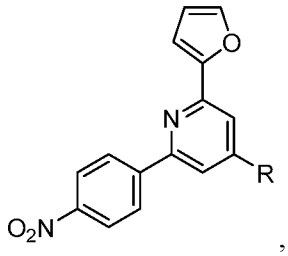
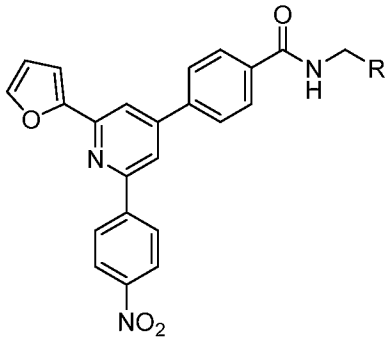
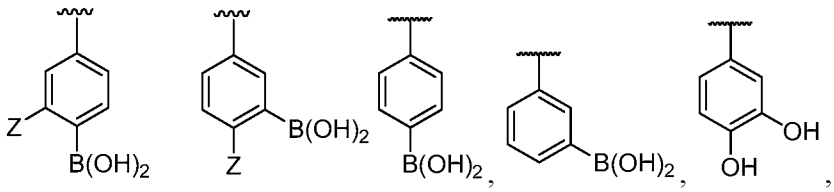
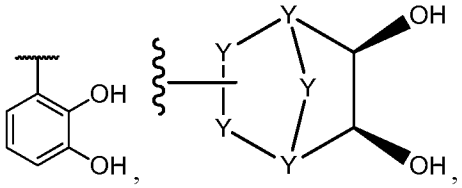



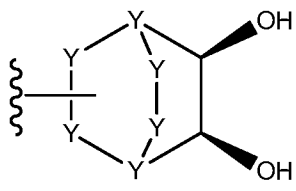
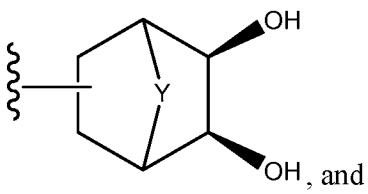




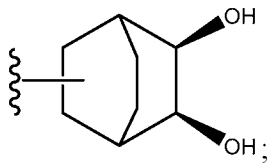
and wherein the phenyl and/or an alkyl group of the first monomer may be optionally substituted by one or more halogens (e.g., fluorine), and pharmaceutically acceptable salts thereof, wherein:

R is selected from the group consisting of:







and



X is independently selected for each occurrence from S, O, NH and N-C_{1-6}alkyl;

Z is selected from the group consisting of H, halo, CF_3, O-C_{1-6}alkyl, hydroxyl, and C_{1-6}alkyl;

Y is NR''', O or CR''$_{1-2}$, wherein R'' is independently selected from the group consisting of H, methyl, O, NH, and N-C_{1-6}alkyl; R''' is independently selected from the group consisting of H, C1-6alkyl, phenyl, optionally substituted with 1-3 halogen, nitrile, C1-3alkyl or haloalkyl; and

n is 1, 2, or 3.

17. A first monomer selected from the group consisting of:

(*Z*)-(3-((5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)methyl)phenyl)boronic acid;

(*Z*)-(3-(3-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)propyl)phenyl)boronic acid;

(*Z*)-3-(3,4-Dihydroxyphenethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione;

(*Z*)-3-(2,3-Dihydroxyphenethyl)-5-(4-ethylbenzylidene)thiazolidine-2,-dione;

(*Z*)-3-(3-(3,4-Dihydroxyphenyl)propyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione;

(*Z*)-3-(3-(2,3-Dihydroxyphenyl)propyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione;

3,4-Dihydroxy-*N*-(2-(4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)benzamide;

2,3-Dihydroxy-*N*-(2-(4-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)benzamide;

(4-((2-(4-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamoyl)phenyl)boronic acid;

(3-((2-(4-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamoyl)phenyl)boronic acid;

2,3-Dihydroxy-*N*-(2-(2-((7-nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)benzamide;

(4-((2-(2-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamoyl)phenyl)boronic acid;

(3-((2-(2-((7-Nitrobenzo[*c*][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)carbamoyl)phenyl)boronic acid;

(3-((2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid;

(4-((2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid;

(3-((4-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid;

(3-((4-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)methyl)phenyl)boronic acid;

4-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzene-1,2-diol;

3-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzene-1,2-diol;

(*Z*)-*N*-(2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)-3,4-dihydroxybenzamide;

(*Z*)-*N*-(2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)-2,3-dihydroxybenzamide;

(*Z*)-(3-((2-(5-(4-ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamoyl)phenyl)boronic acid;

N-(3,4-Dihydroxybenzyl)-2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide;

(*Z*)-*N*-(2-(2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethoxy)ethyl)-3,4-dihydroxybenzamide;

(*Z*)-*N*-(2-(2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethoxy)ethyl)-2,3-dihydroxybenzamide;

(*Z*)-(3-((2-(2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethoxy)ethyl)carbamoyl)phenyl)boronic acid;

(2'-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)-[1,1'-biphenyl]-4-yl)boronic acid;

2'-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)-[1,1'-biphenyl]-3,4-diol;

2'-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)-[1,1'-biphenyl]-2,3-diol;

N-(3,4-Dihydroxybenzyl)-4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide;

3,4-Dihydroxy-*N*-(2-(2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamido)ethyl)benzamide;

N-(2,3-Dihydroxybenzyl)-2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide;

N-(2,3-Dihydroxybenzyl)-4-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide;

(2-((7-Nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)phenyl)boronic acid;

(*Z*)-3-(3,4-Dihydroxybenzyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione;

(*Z*)-3-(2,3-Dihydroxybenzyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione;

(*Z*)-3-(2-((1*S*,2*S*,4S,5*R*,6*S*)- 5,6-Dihydroxybicyclo[2.2.1]heptane-2-yl)ethyl)-5-(4-ethylbenzylidene)thiazolidine-2,4-dione;

(1*R*,2*R*,4*S*,5*S*,6*R*)-*N*-(2-((*Z*)-5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxamide;

(1R,2S,4S,5R,6S)-N-(4-(2-(Furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)phenyl)-5,6-dihydroxy-7-oxabicyclo[2.2.1]heptane-2-carboxamide;

(4-(2-(Furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)phenyl)boronic acid;

(2-((4-(2-(Furan-2-yl)-6-(4-nitrophenyl)pyridin-4-yl)benzamido)methyl)phenyl)boronic acid;

(Z)-(4-((2-(5-(4-Ethylbenzylidene)-2,4-dioxothiazolidin-3-yl)ethyl)carbamoyl)phenyl) boronic acid;

N-(((1R,2S,4R,5S,6R)-5,6-Dihydroxybicyclo[2.2.1]heptan-2-yl)methyl)-2-((7-nitrobenzo[c][1,2,5]oxadiazol-4-yl)amino)benzamide;

and pharmaceutically acceptable salts thereof.

18. A pharmaceutically acceptable composition comprising a first monomer of any one of claims 1-17 and a pharmaceutically acceptable carrier.

19. A therapeutic multimer compound formed from the multimerization in an aqueous media of a first monomer represented by:

X^1-Y^1-Z^1 (Formula I)

and a second monomer represented by

X^2-Y^2-Z^2 (Formula II),

wherein

X^1 is a first ligand moiety capable of modulating a first c-Myc binding site;

Y^1 is absent or is a connector moiety covalently bound to X^1 and Z^1;

Z^1 is a first linker capable of binding to Z^2 to form the multimer;

X^2 is a second ligand moiety capable of modulating a second c-Myc binding site;

Y^2 is absent or is a connector moiety covalently bound to X^2 and Z^2; and

Z^2 is a second linker moiety capable of binding with the Z^1 moiety of Formula I to form the multimer; and

pharmaceutically acceptable salts, stereoisomers, metabolites, tautomers, cocrystalates, solvates, and hydrates thereof.

20. A pharmaceutically acceptable composition comprising a therapeutic multimer of claim 19 and a pharmaceutically acceptable carrier.

21. A method of treating a disease associated with c-Myc in a patient in need thereof comprising:

administering to said patient a first monomer of any one of claims 1-18; and

administering to said patient a second monomer represented by:

X^2-Y^2-Z^2 (Formula II), wherein

X^2 is a second ligand moiety capable of modulating a second c-Myc binding site,

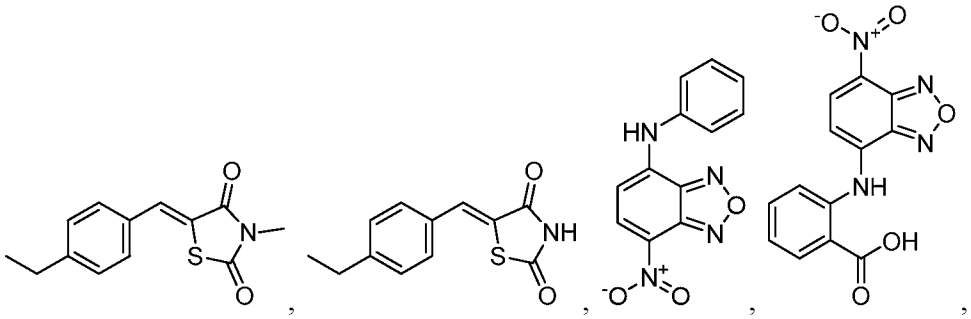
Y^2 is absent or is a connector moiety covalently bound to X^2 and Z^2; and

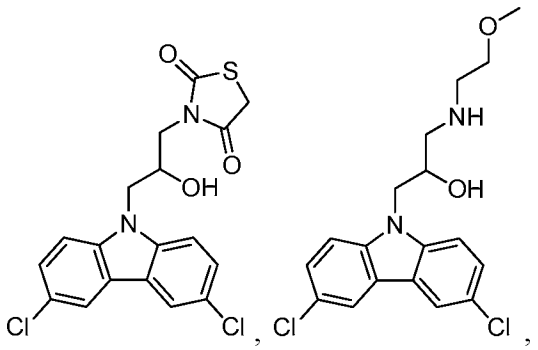
Z^2 is a second linker capable of binding to the first monomer through Z^1;

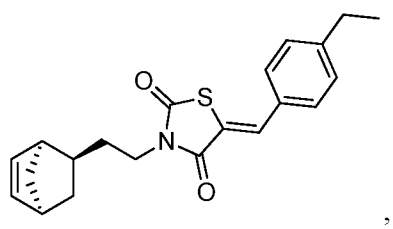
wherein upon administration, said first monomer and said second monomer form a multimer *in vivo* that binds to the first and the second c-Myc binding sites.

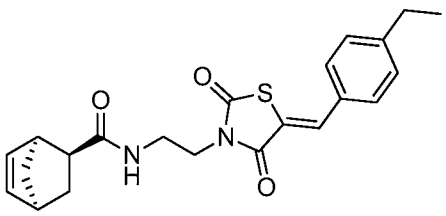
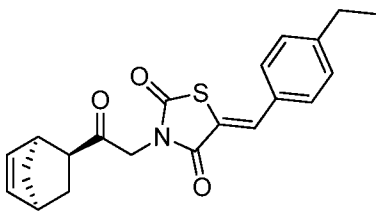
22. The method of claim 21, wherein the disease is cancer.

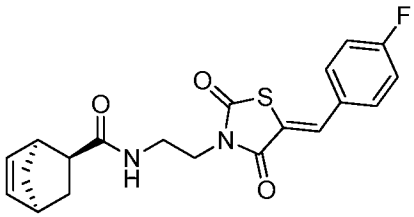
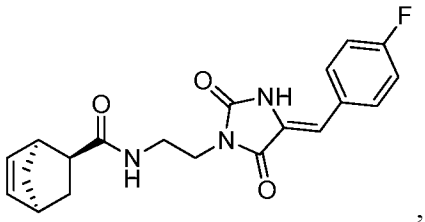
23. A method of treating a disease associated with c-Myc in a patient in need thereof, comprising administering to the patient a compound selected from the group consisting of:

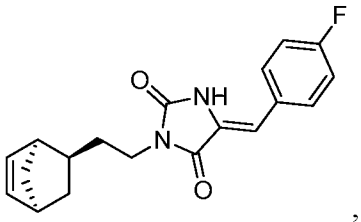
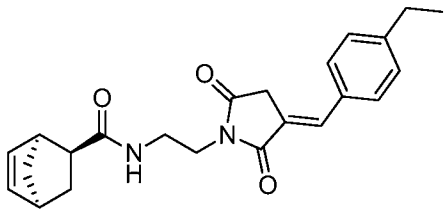


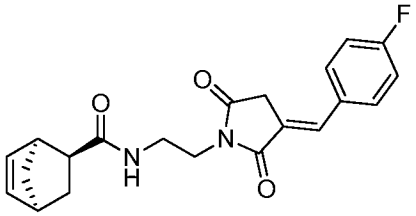
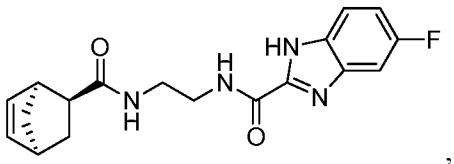


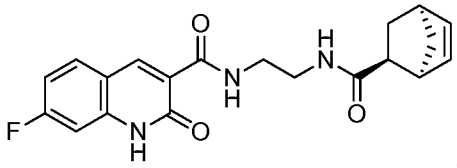
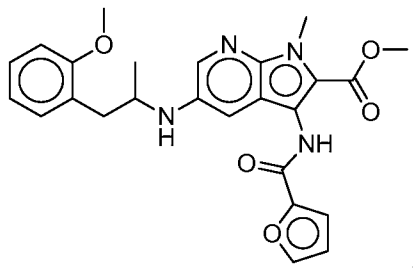


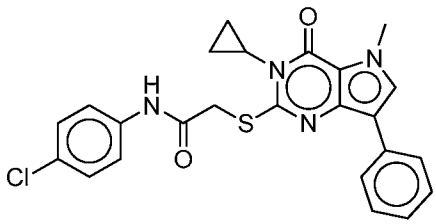
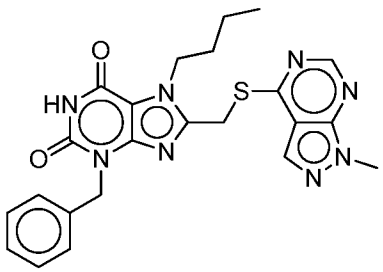
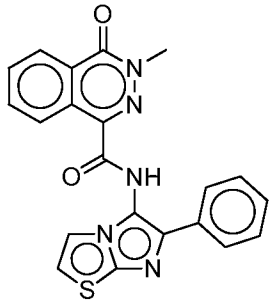



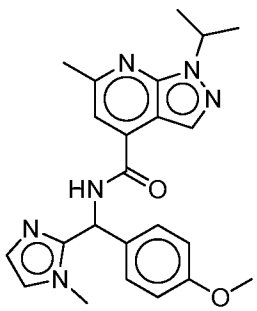
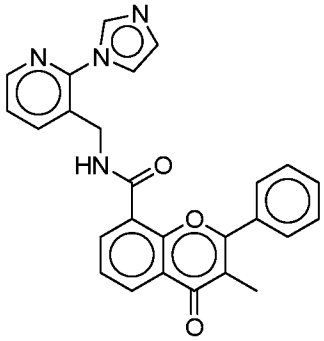
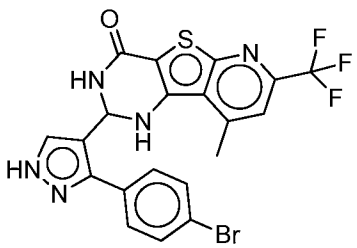



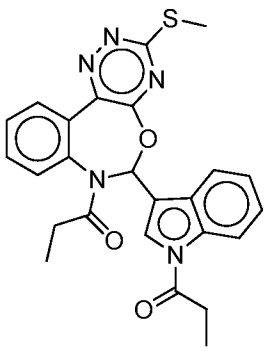
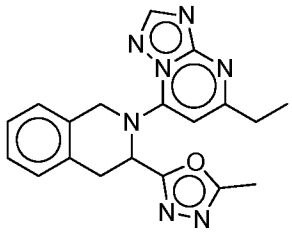
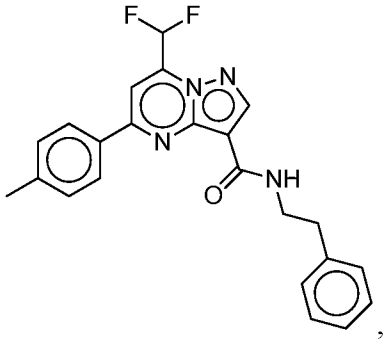
7  ,  ,

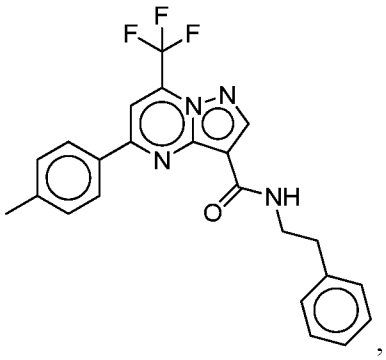
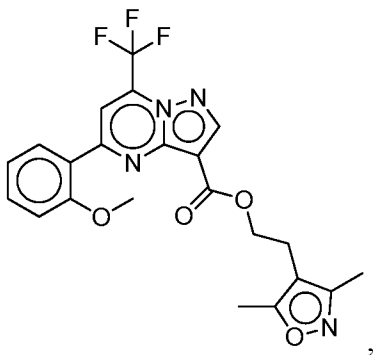
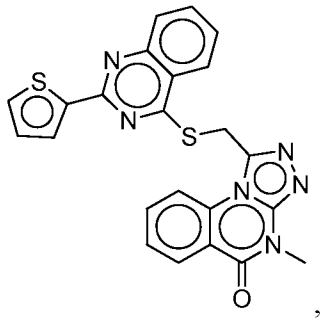
8  ,  ,

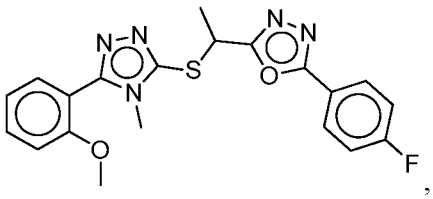
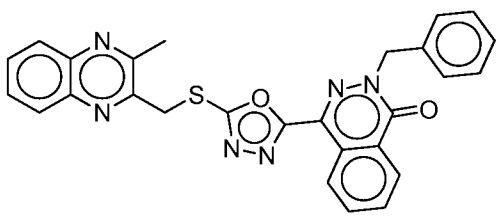
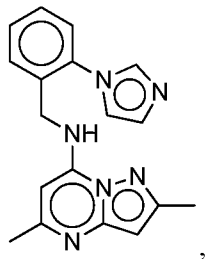
9  ,  ,

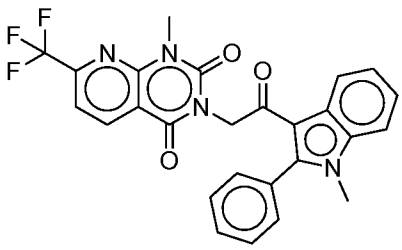
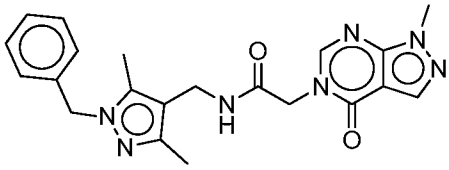
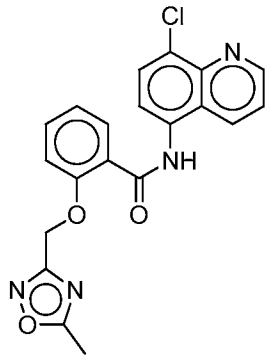
10  ,  ,  ,

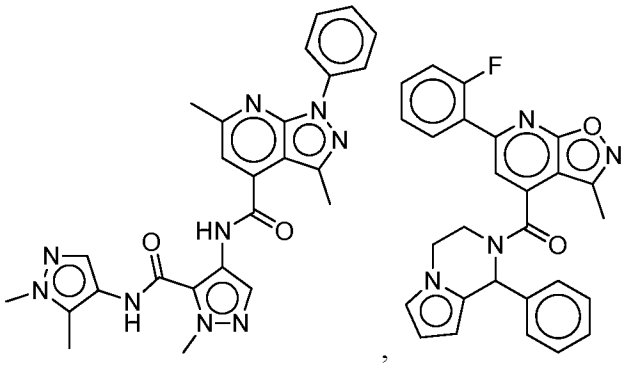
11  ,  ,  ,

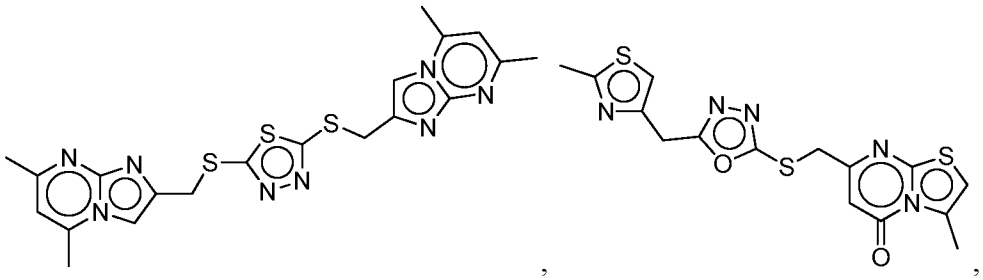
12  ,  ,  ,

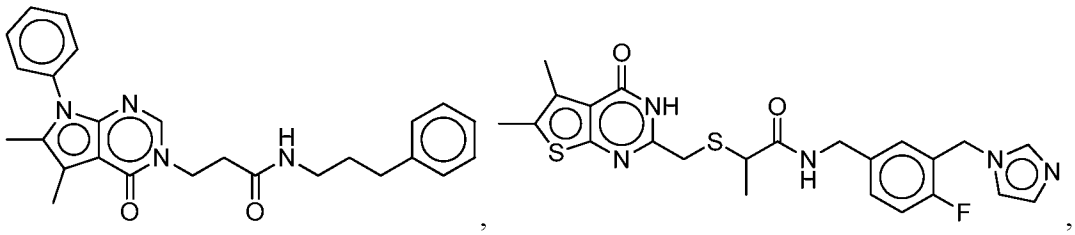
13  ,  ,  ,

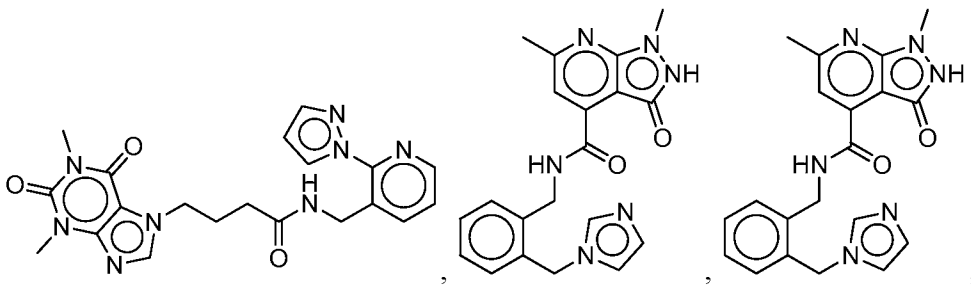
14  ,  ,  ,

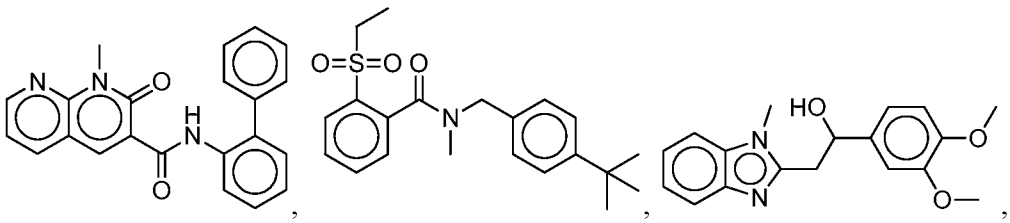
15  ,  ,  ,

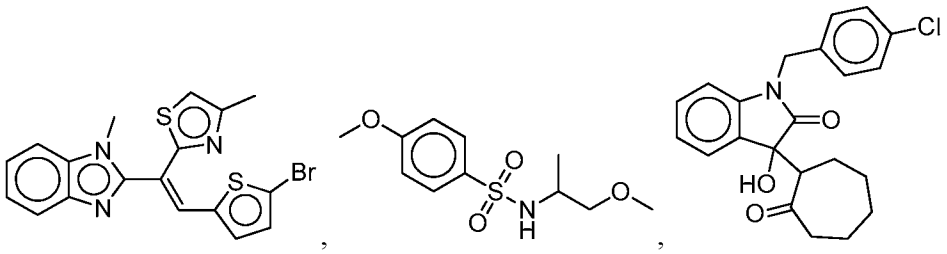
16 

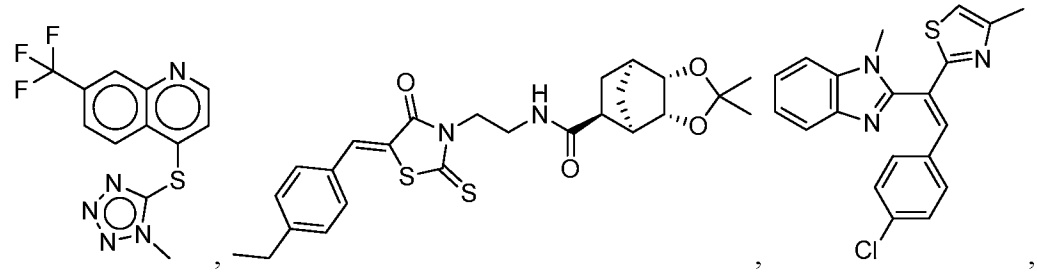
17 

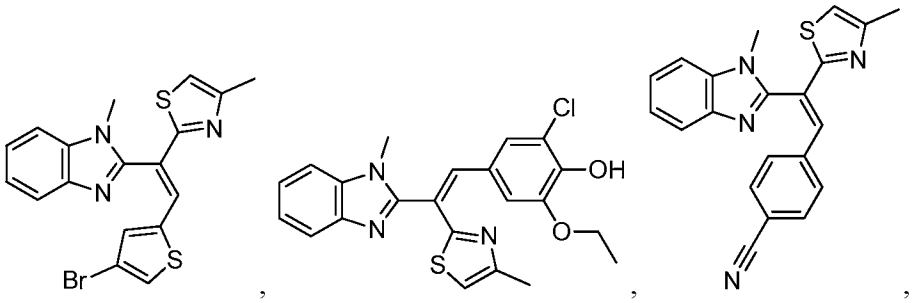
18 

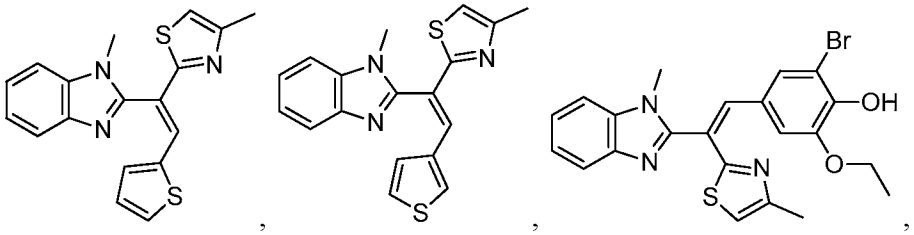
19 

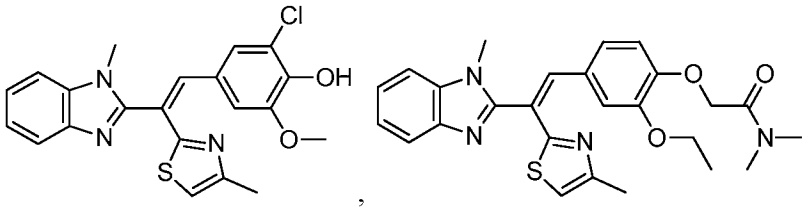
20 

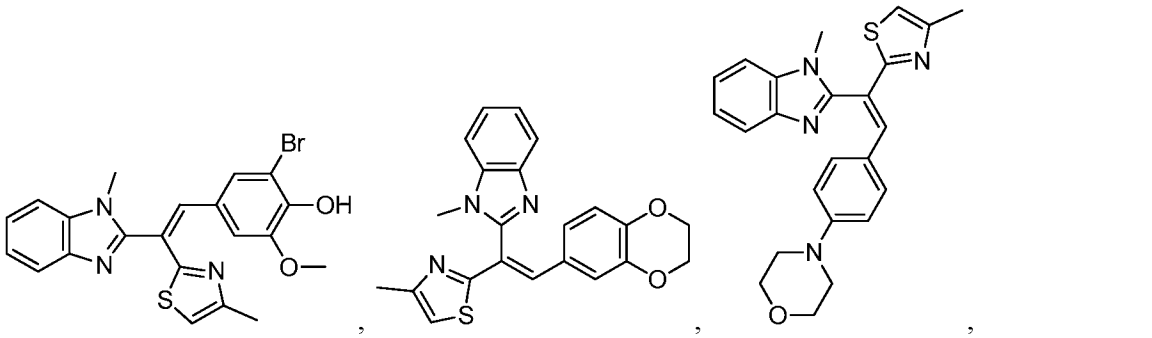
21 

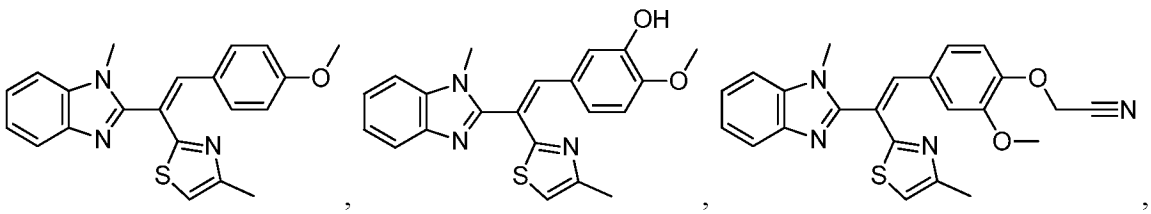
22 

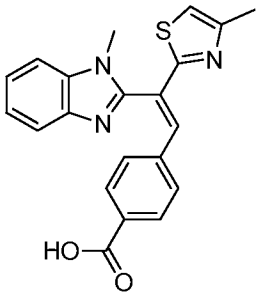
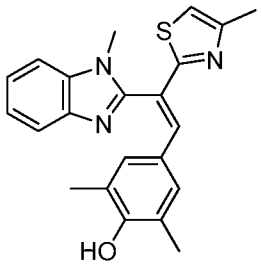
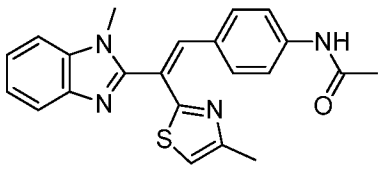
23 

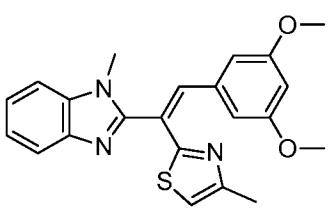
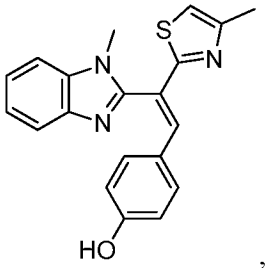
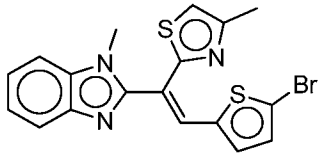
24 

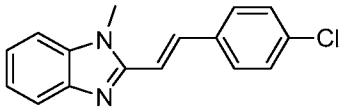
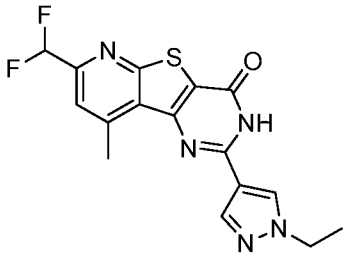
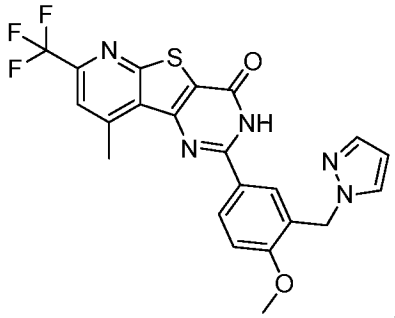
25 

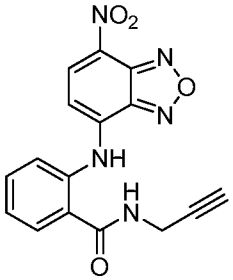
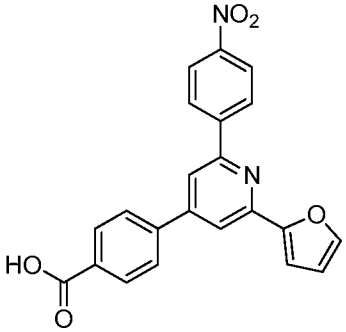
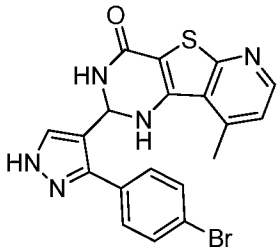
26 

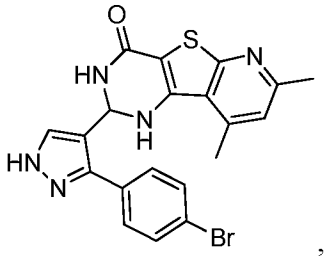
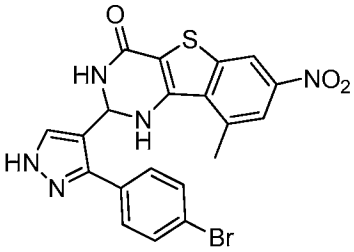
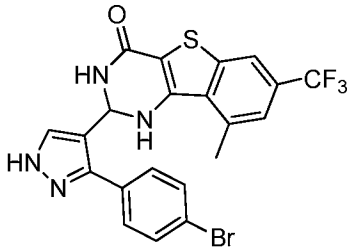
27 

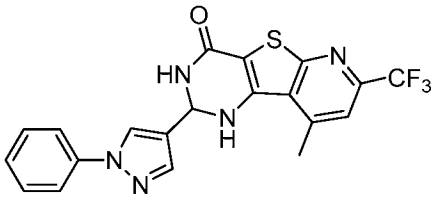
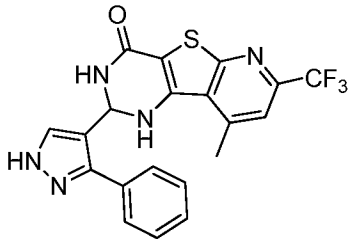
28  ,  ,  ,

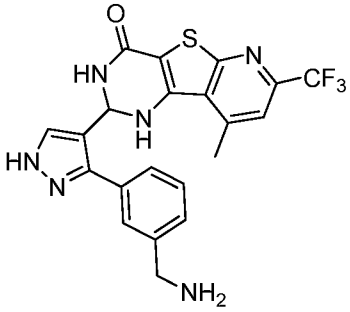
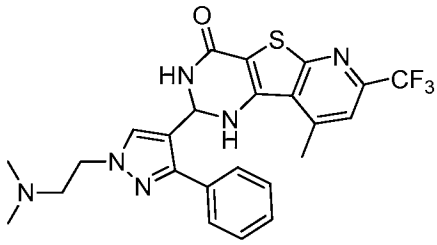
29  ,  ,  ,

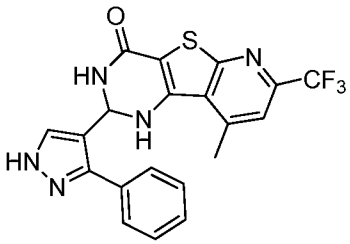
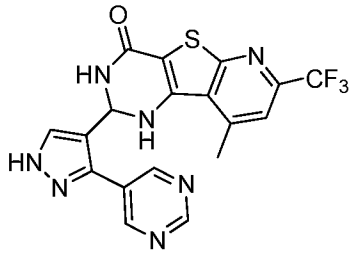
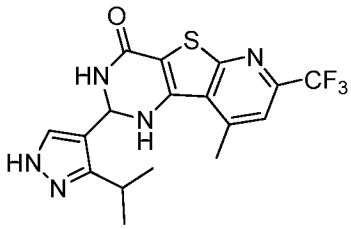
30  ,  ,  ,

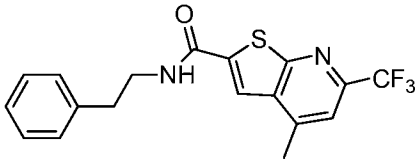
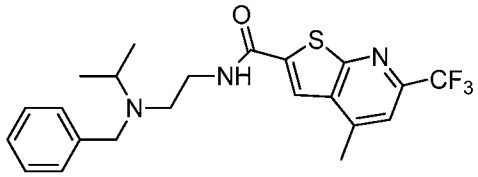
31  ,  ,  ,

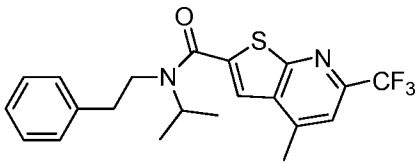
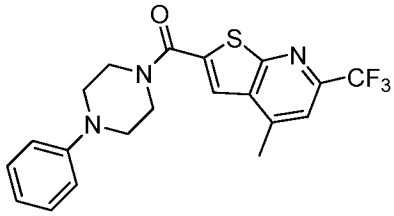
32  ,  ,  ,

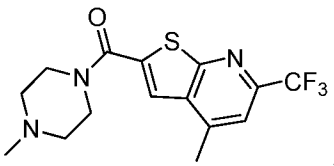
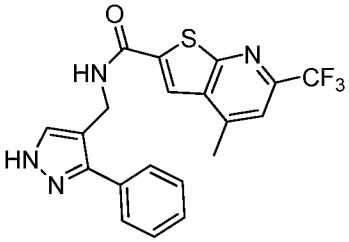
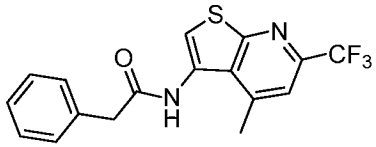
33  ,  ,

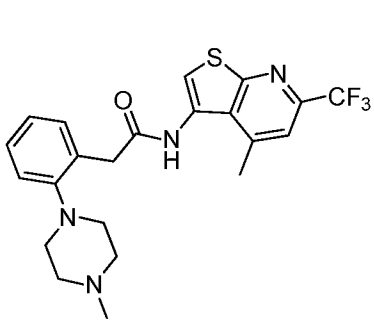
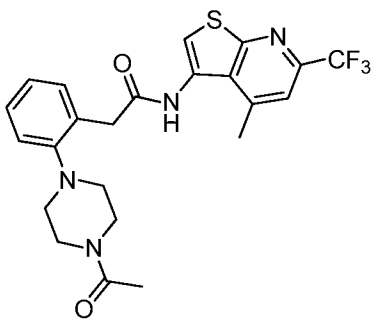
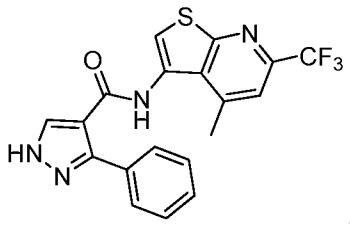
34  ,  ,

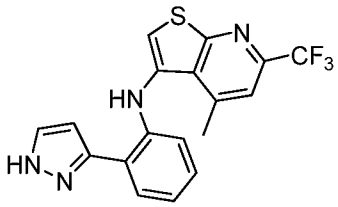
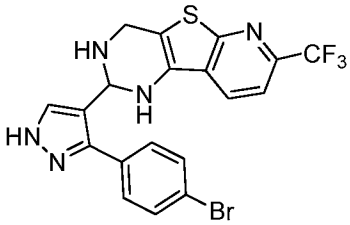
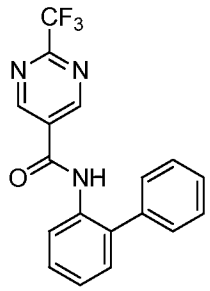
35  ,  ,  ,

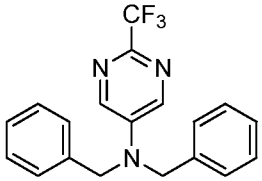
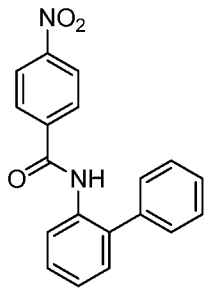
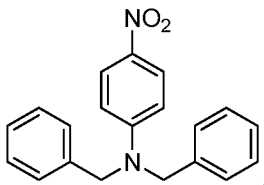
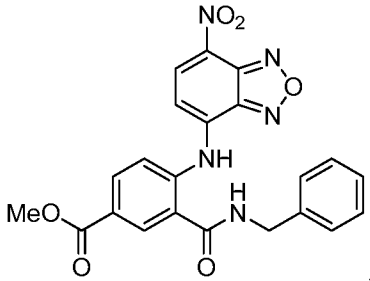
36  ,  ,

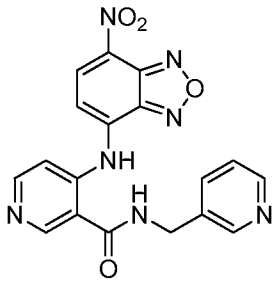
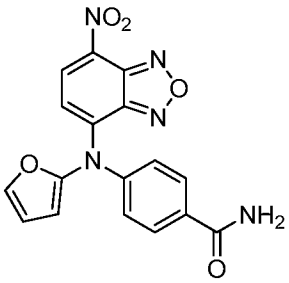
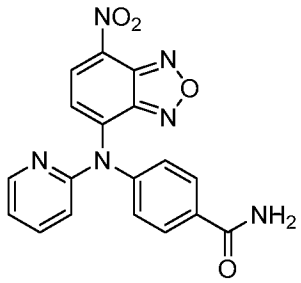
37  ,  ,

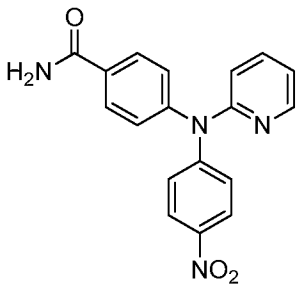
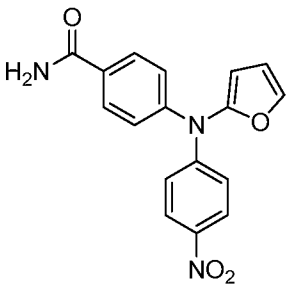
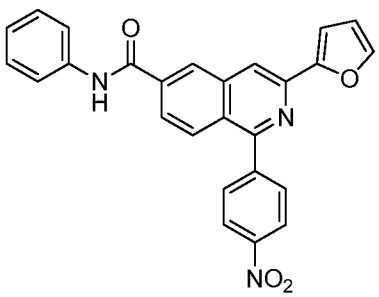
38  ,  ,  ,

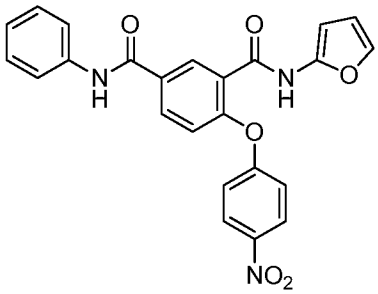
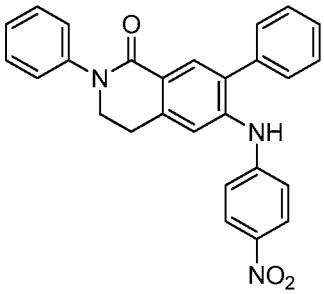
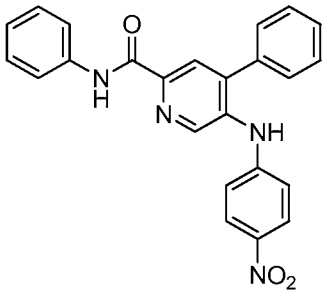
39  ,  ,  ,

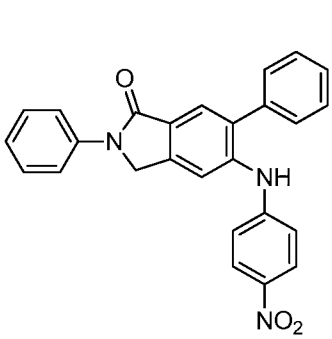
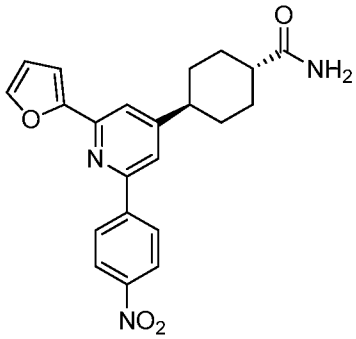
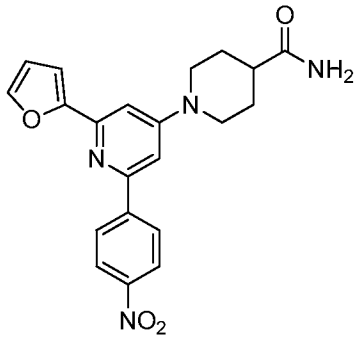
40  ,  ,  ,

41  ,  ,  ,  ,

42  ,  ,  ,

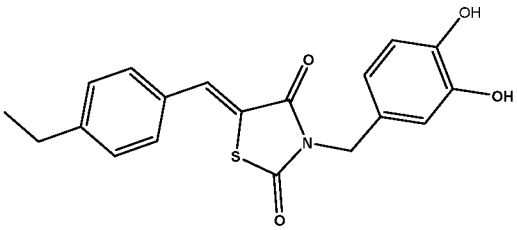
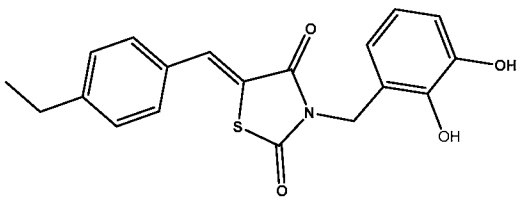
43  ,  ,  ,

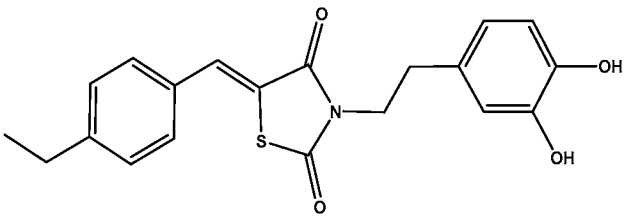




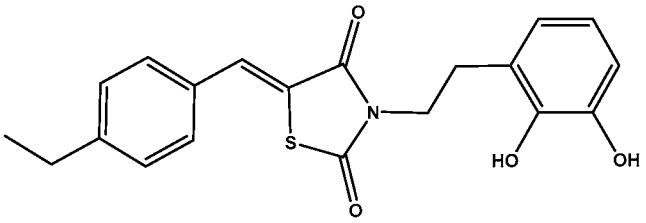




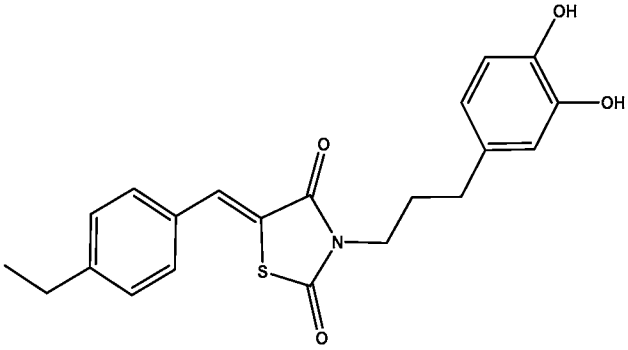
, and pharmaceutically acceptable salts thereof.

24. A first monomer selected from:





5 

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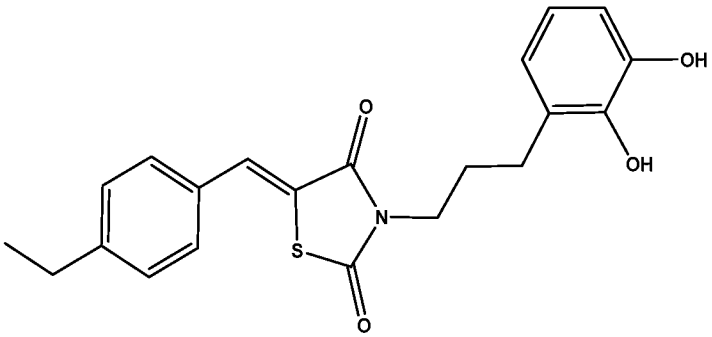
6 

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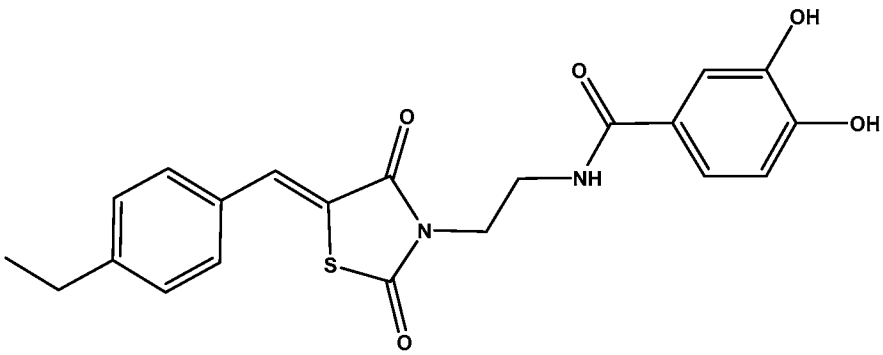
7 

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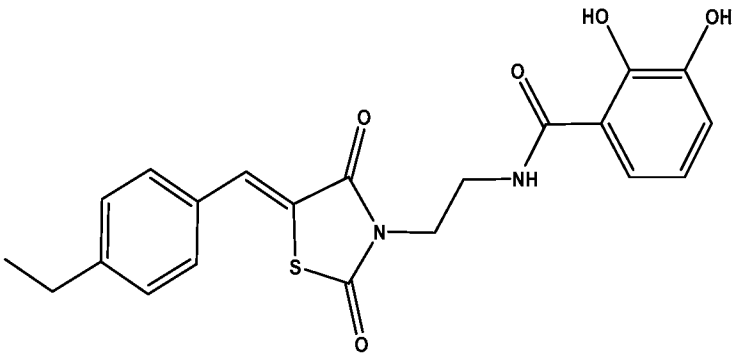
8 

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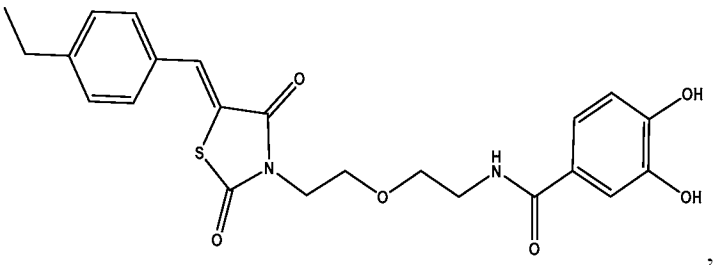
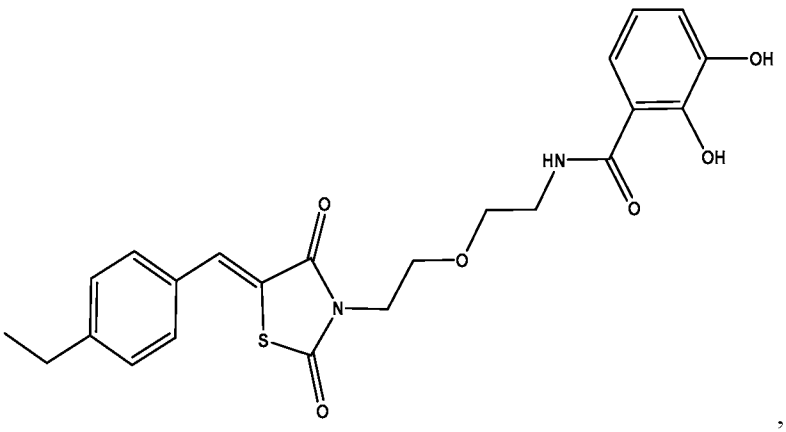
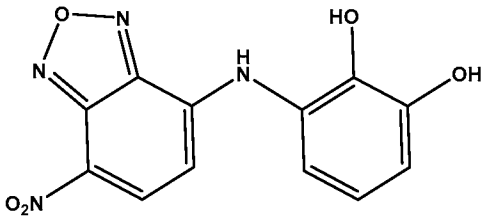
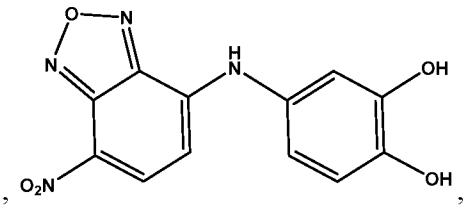
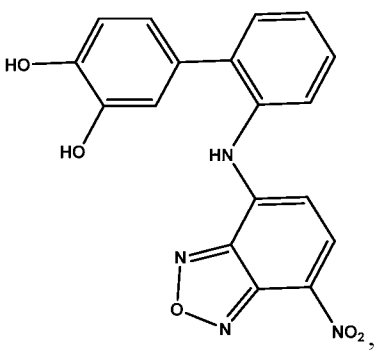
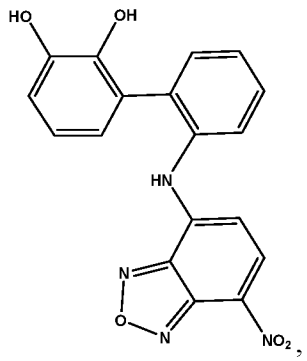
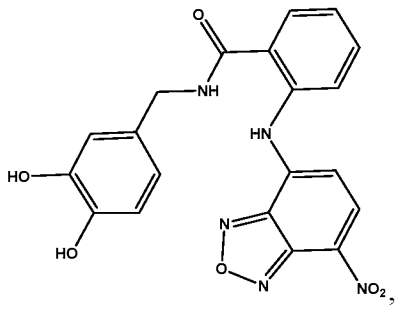
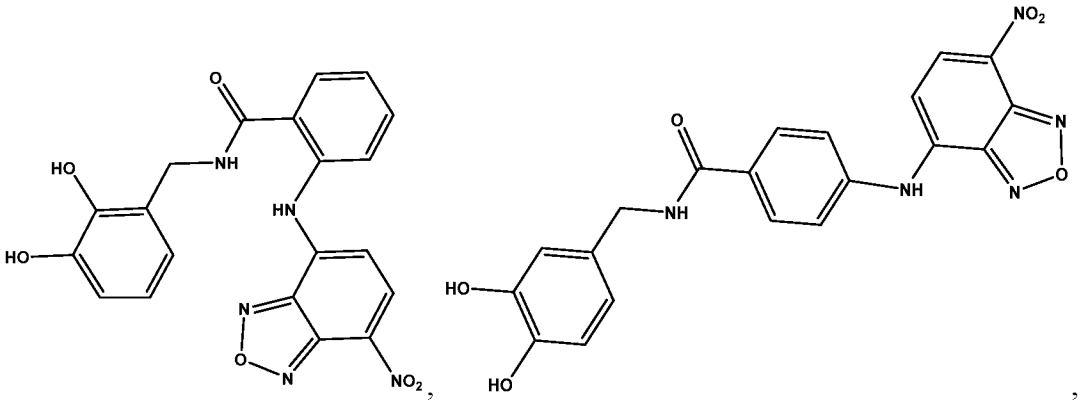
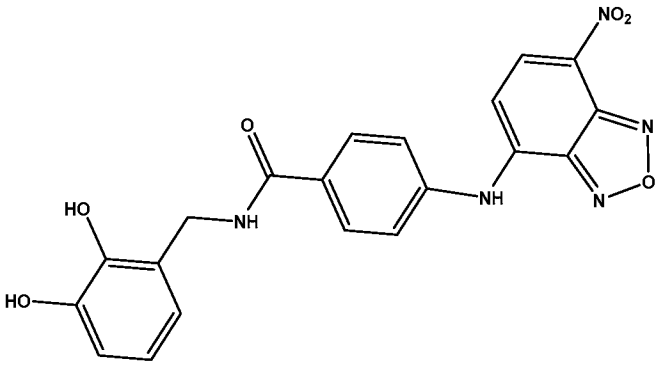
9  ,

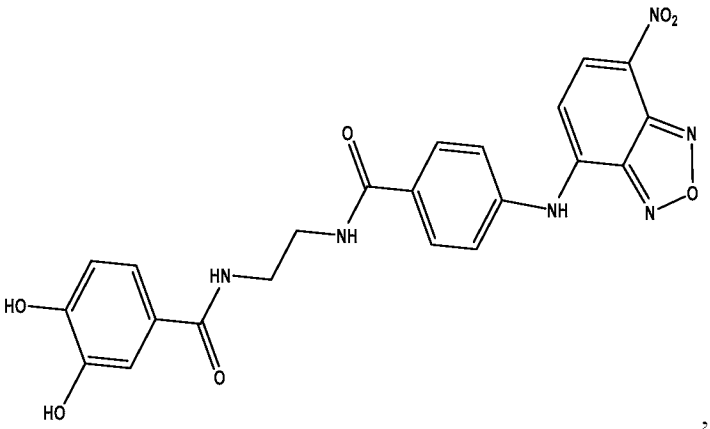
10  ,

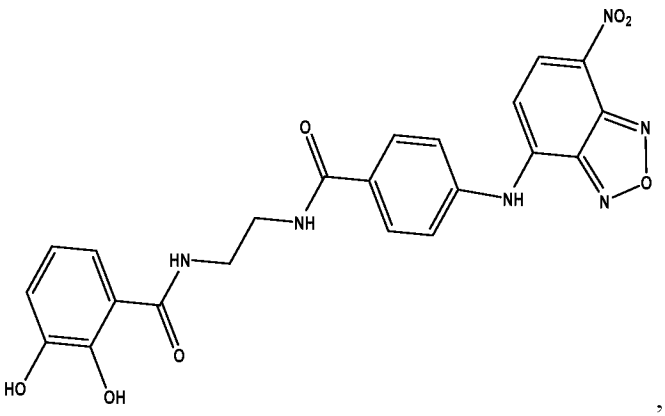
11  ,  ,

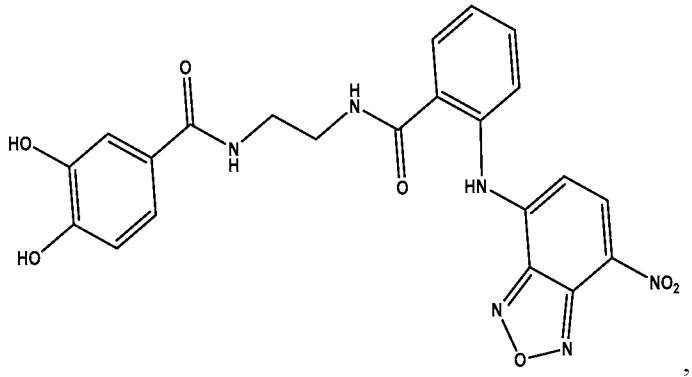
12  ,  ,  ,

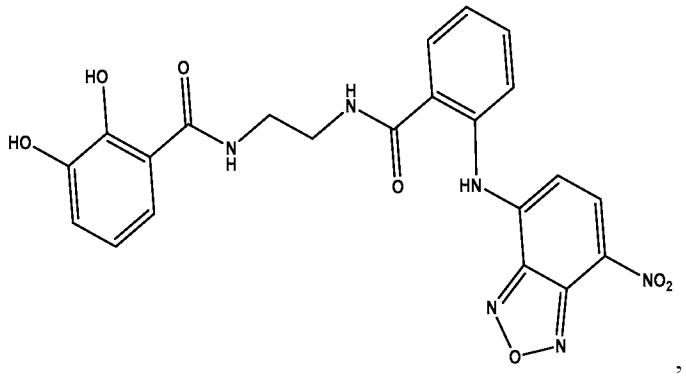
13 

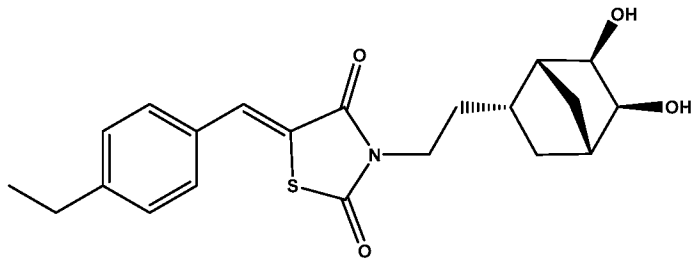
14 

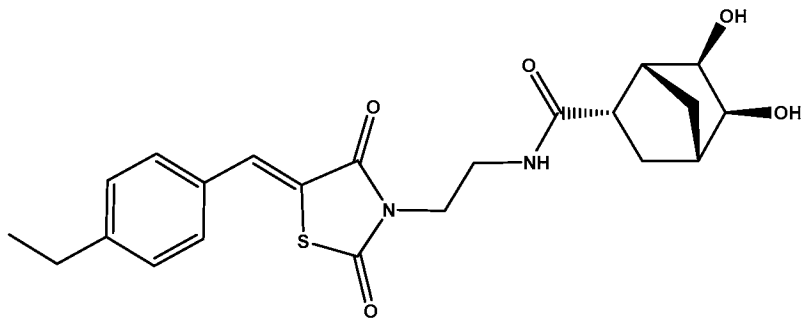
15 

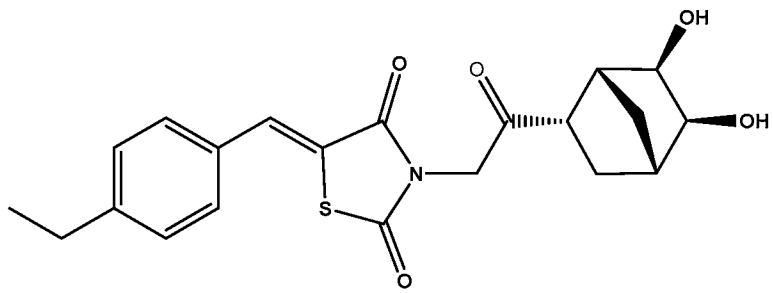
16 

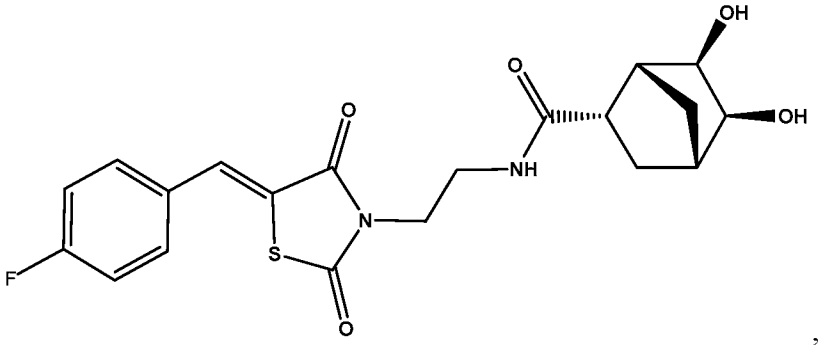
17  ,

18  ,

19  ,

20  ,

21  ,

22 
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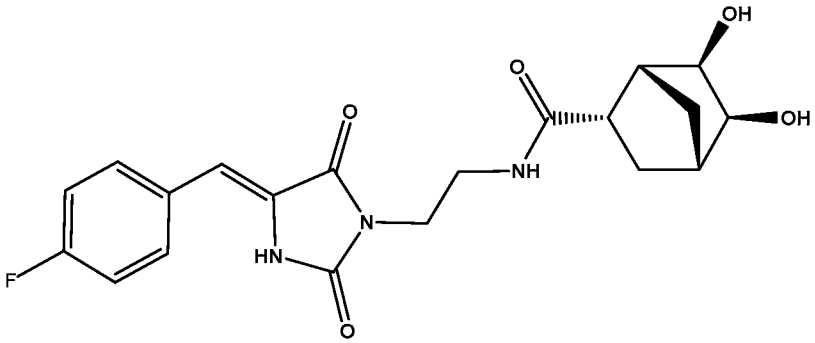
23 
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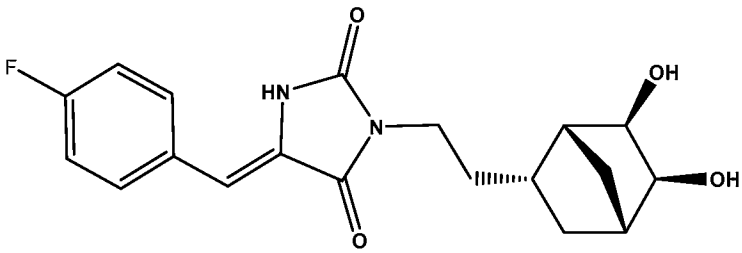
24 
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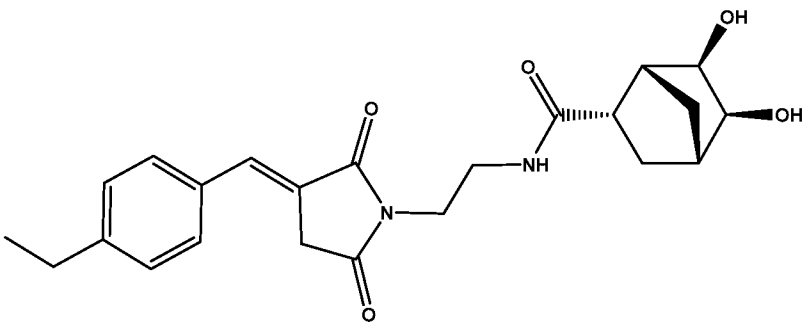
25 
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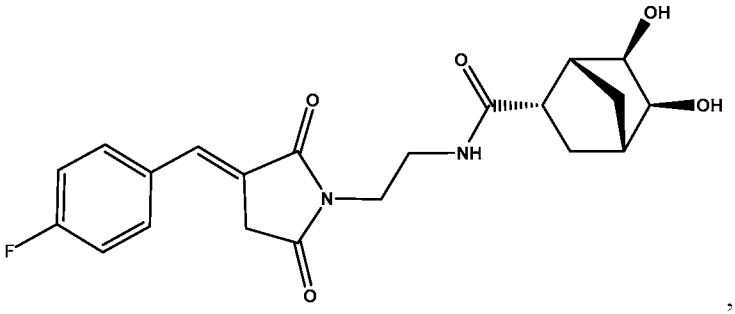
26 
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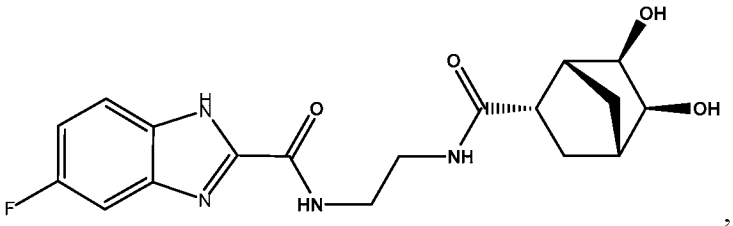
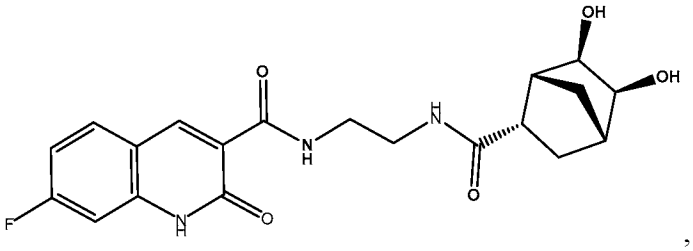
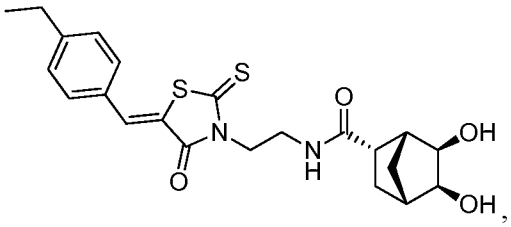
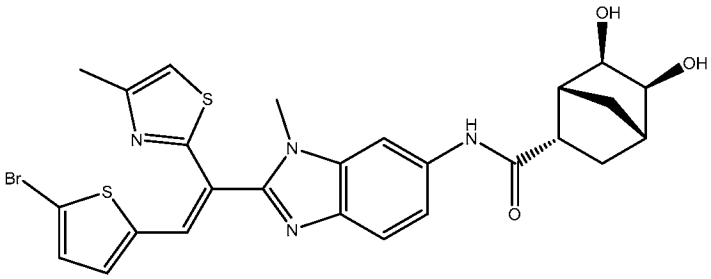
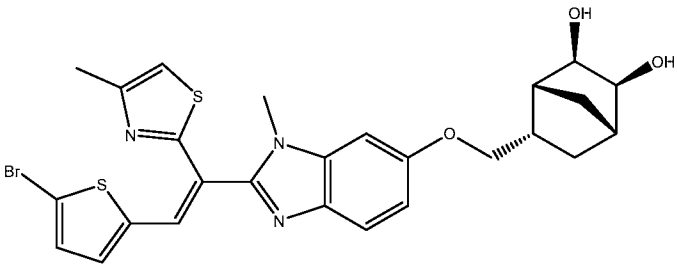
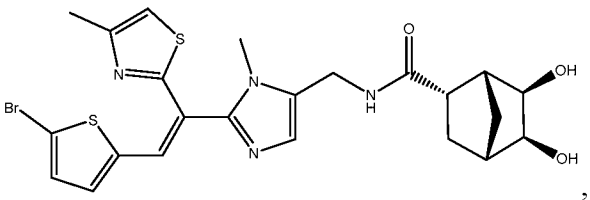
27  ,

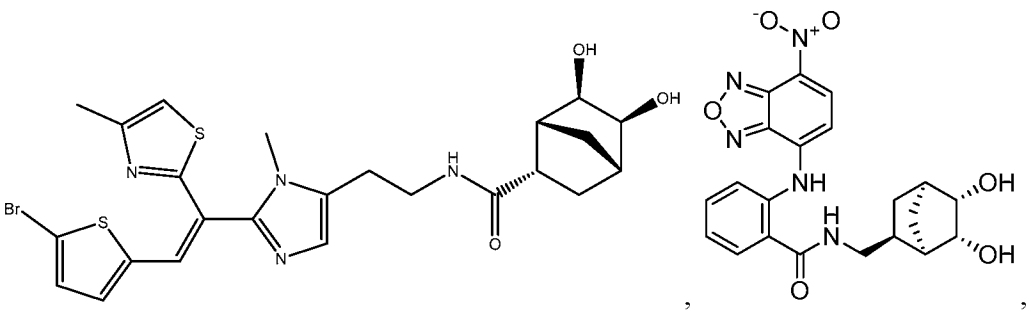
28  ,

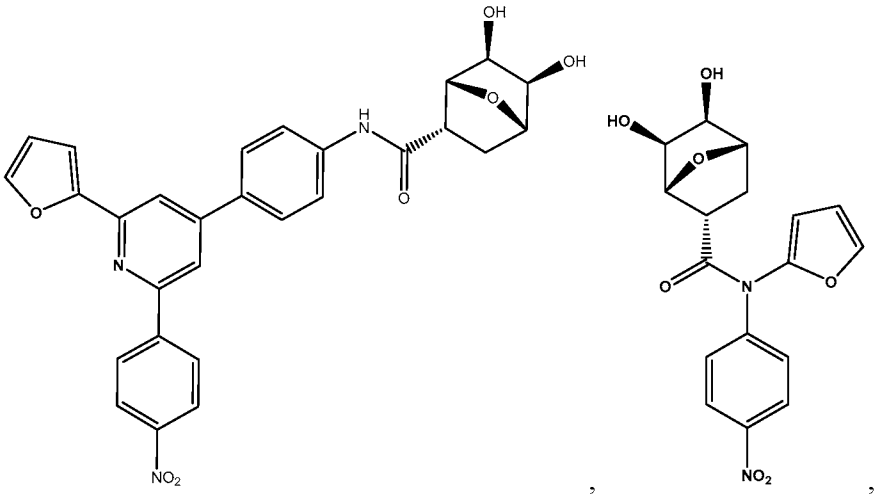
29  ,

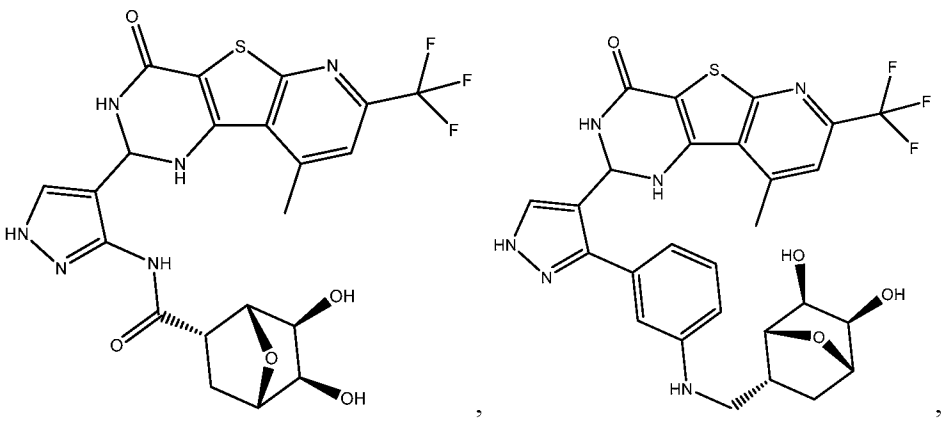
30  ,

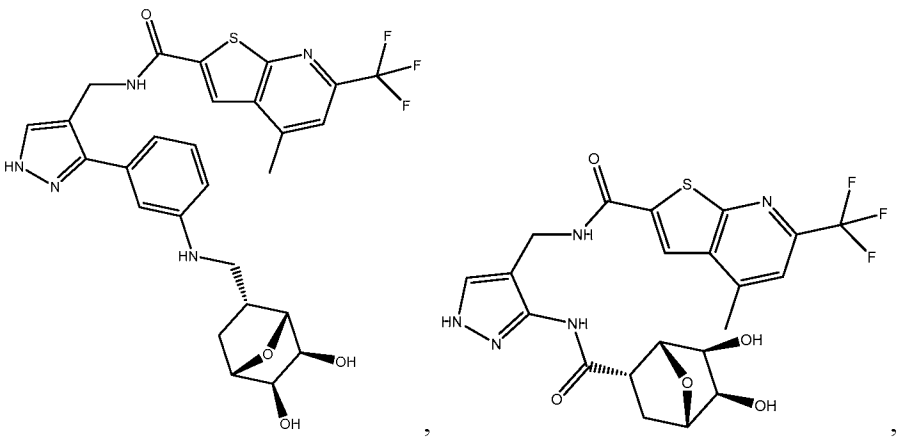
31  ,

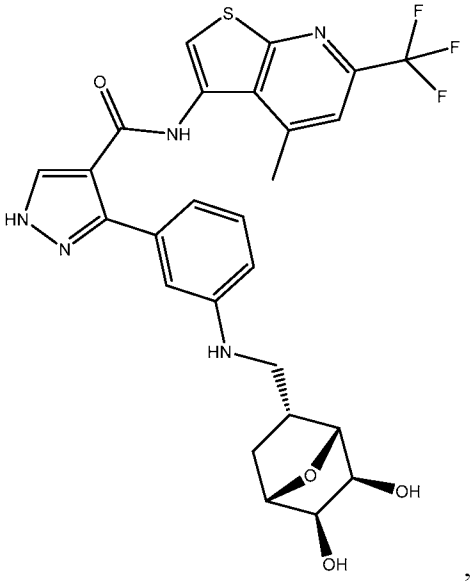
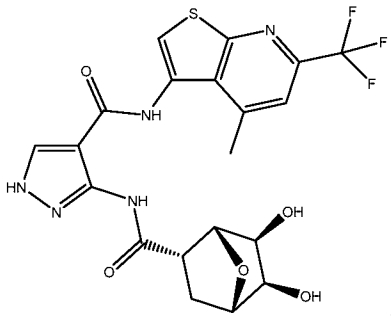
32  ,

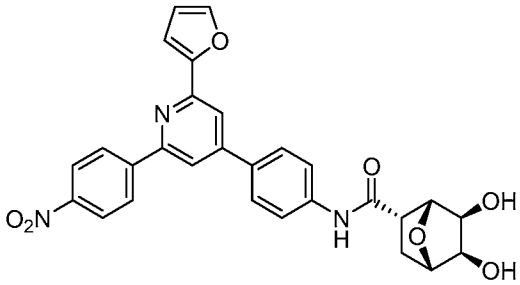
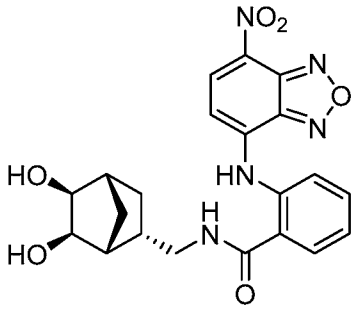
33 

34 

35 

36 

37  ,  ,

38  ,  and pharmaceutically

39 acceptable salts thereof.

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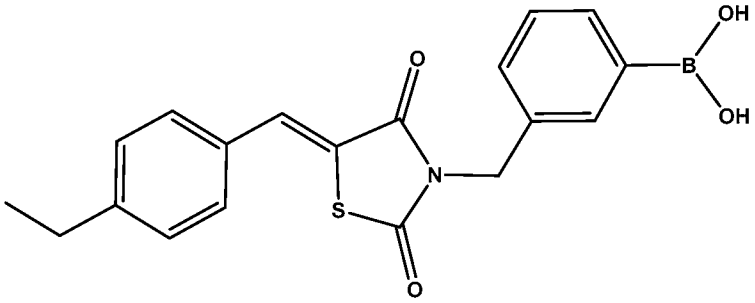
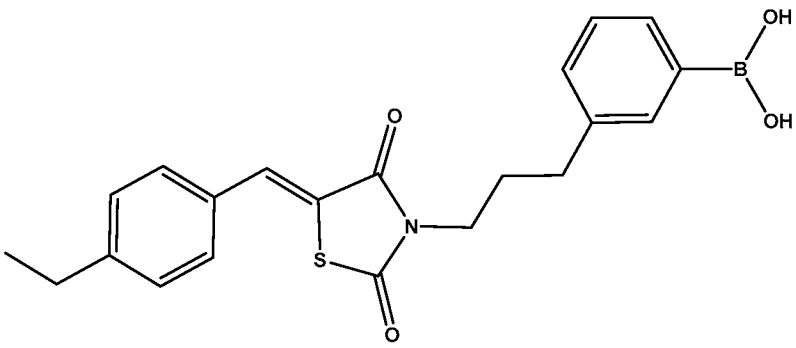
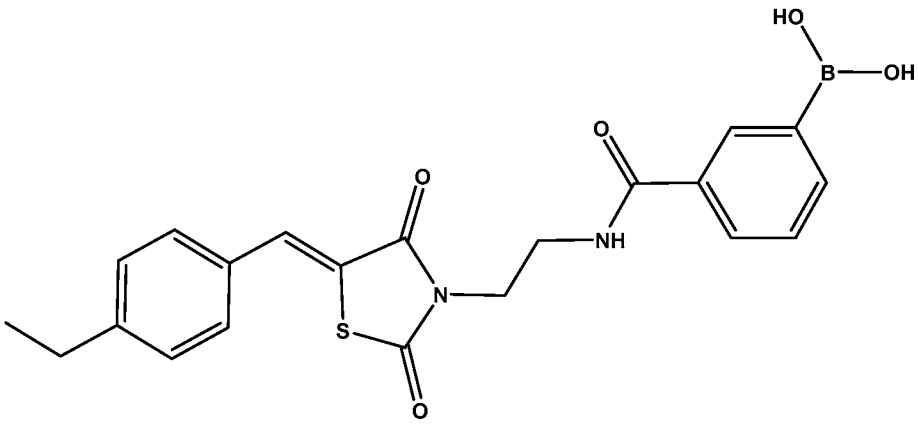
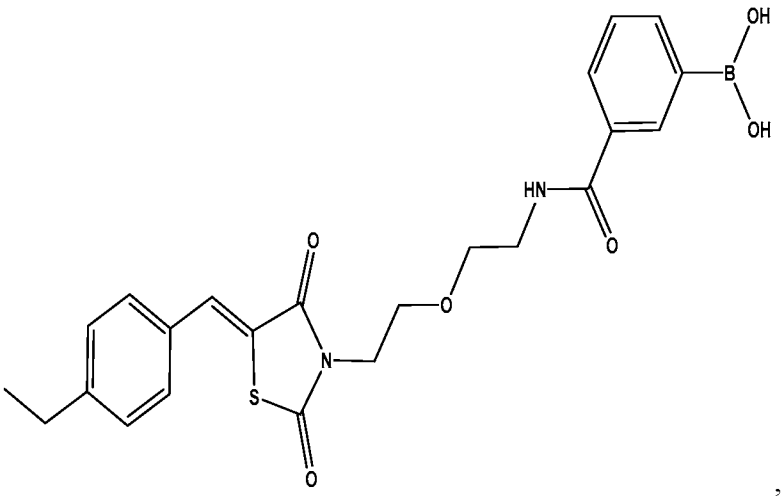
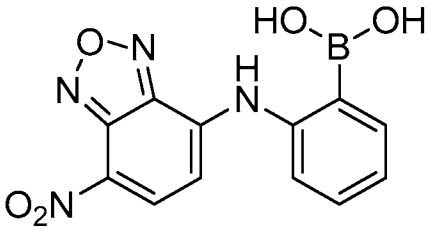
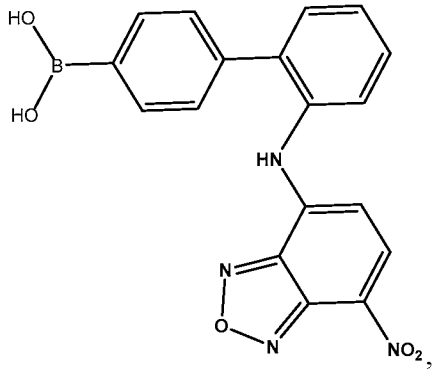
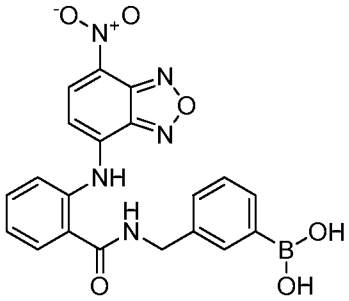
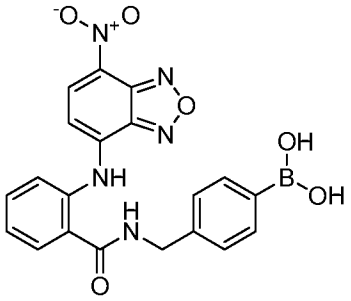
2  ,

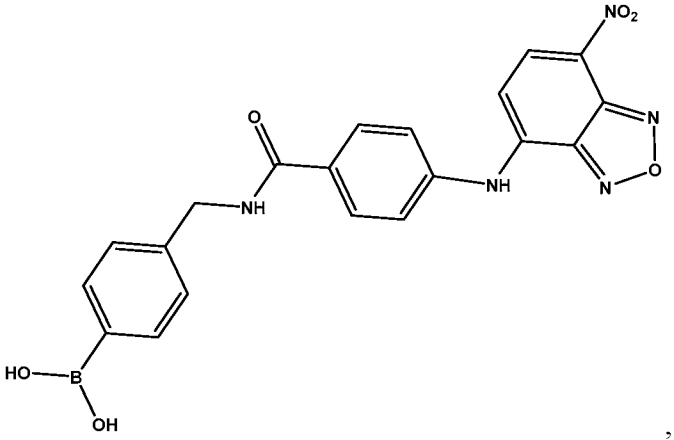
3  ,

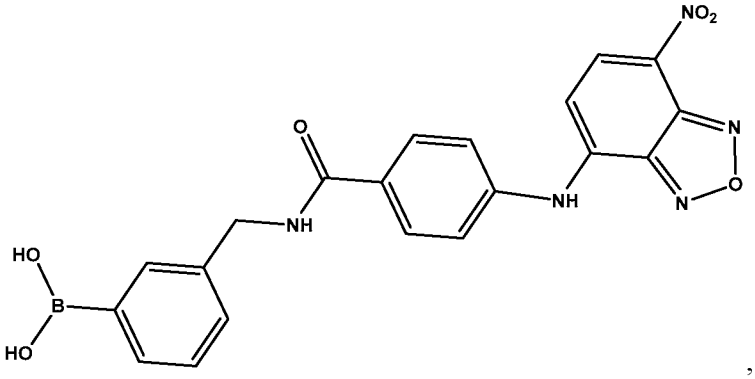
4  ,

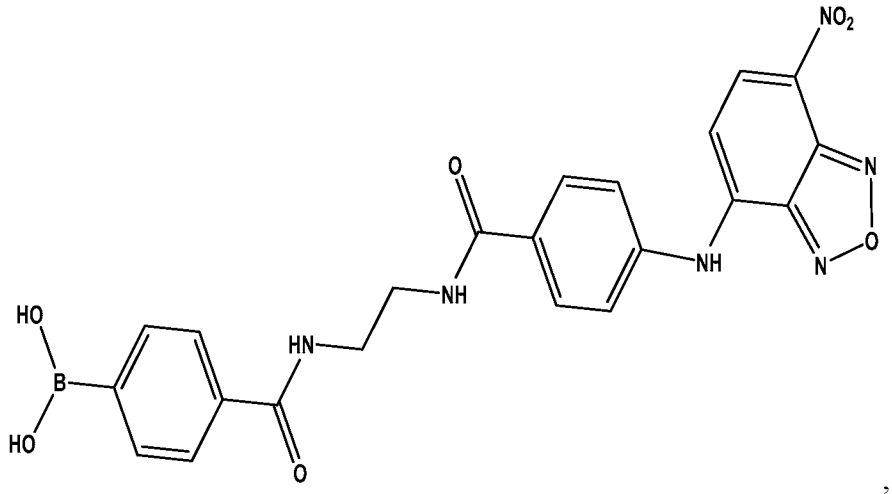
5  ,

6  ,  ,

7  ,  ,

8  ,

9  ,

10 
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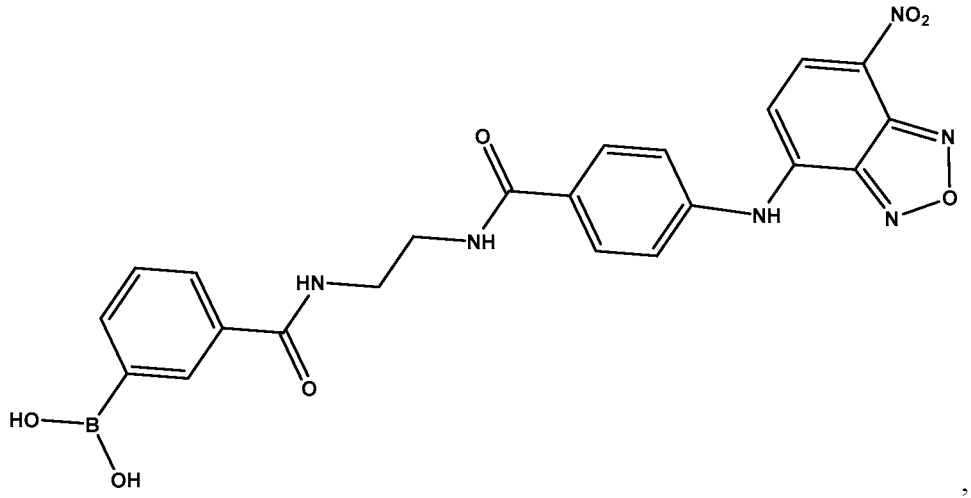
11 
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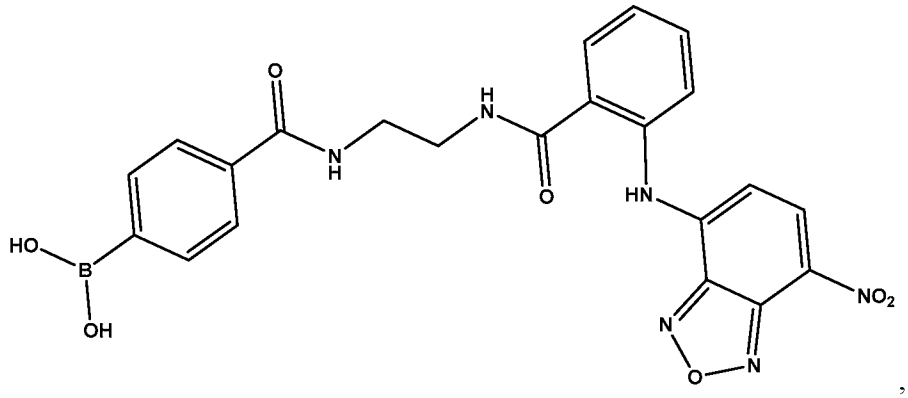
12 
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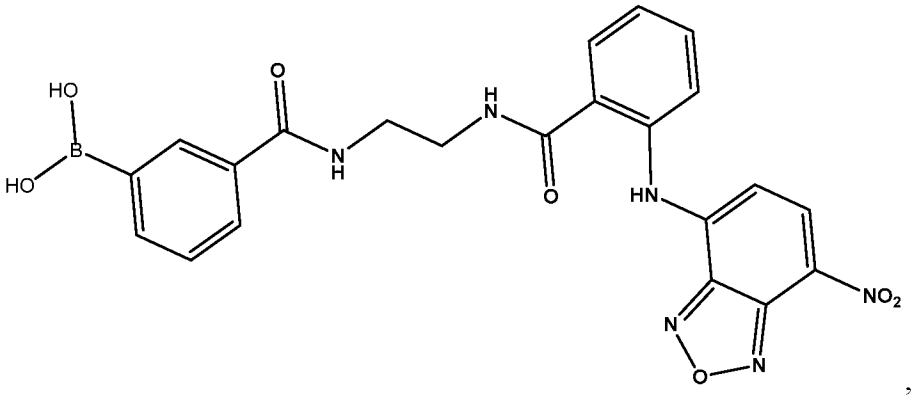
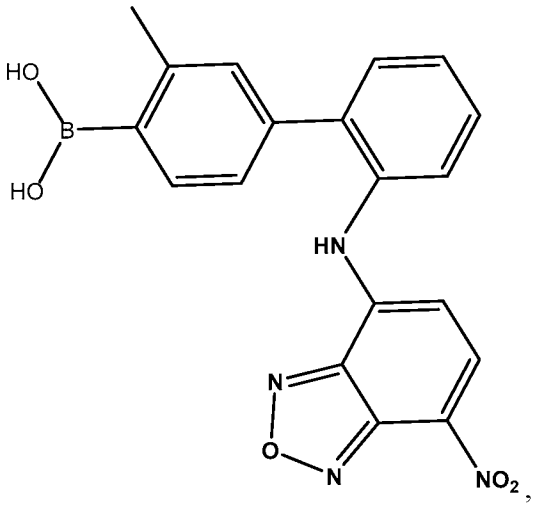
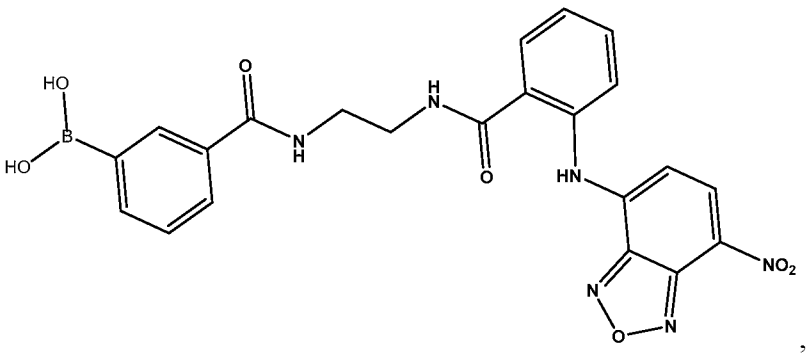
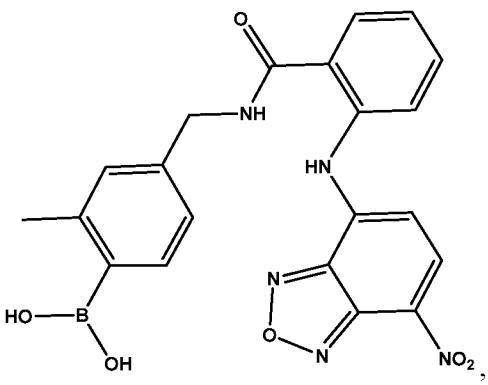
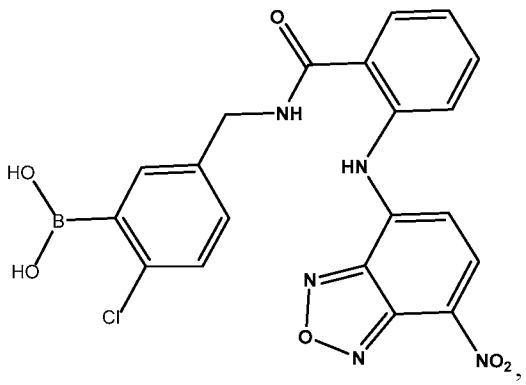
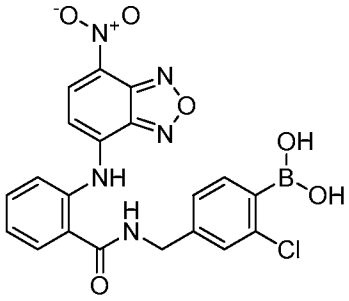
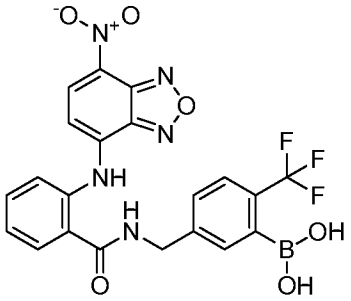
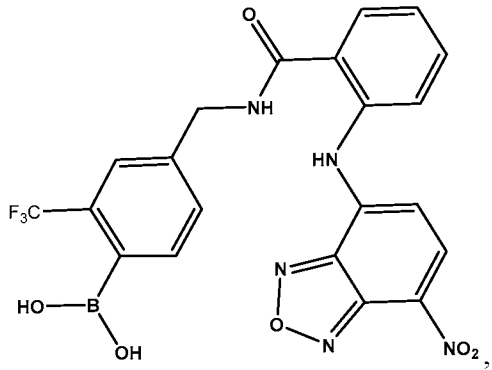
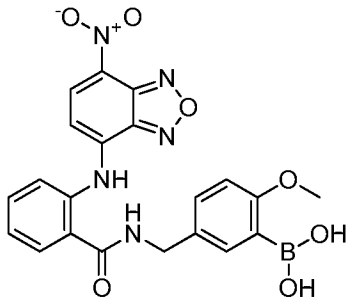
13  ,

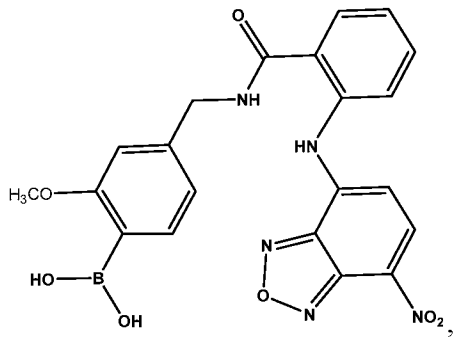
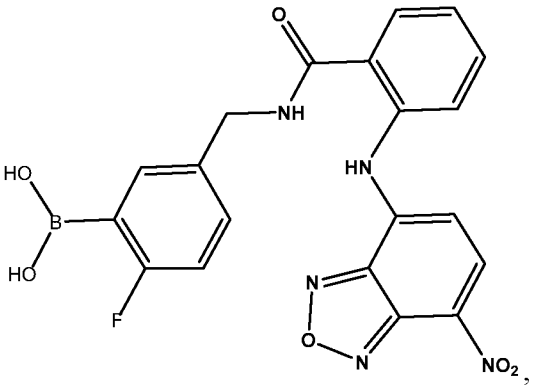
14  ,

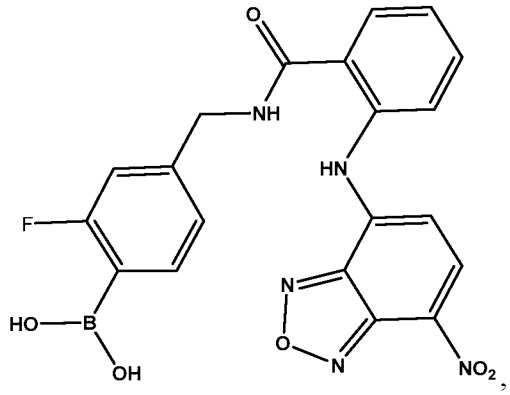
15  ,

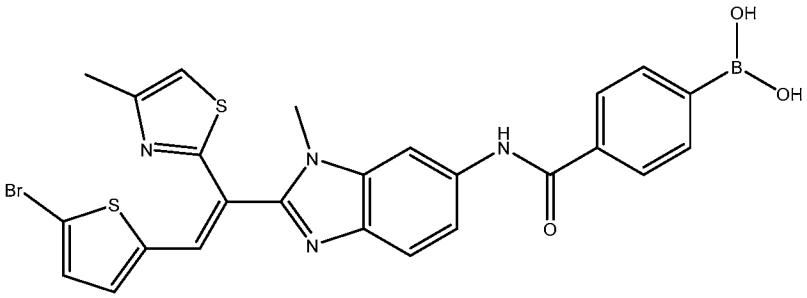
16  ,  ,

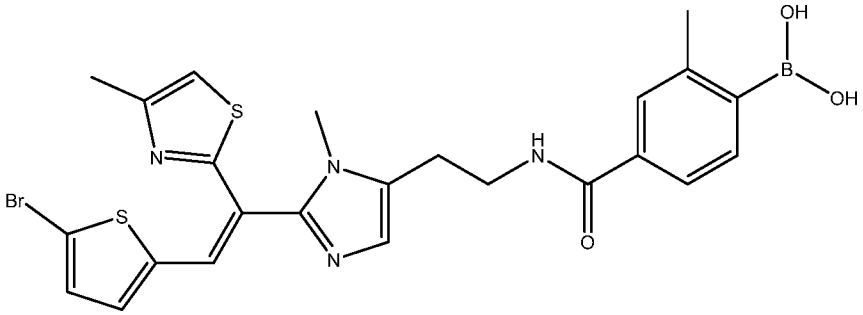
17  ,  ,

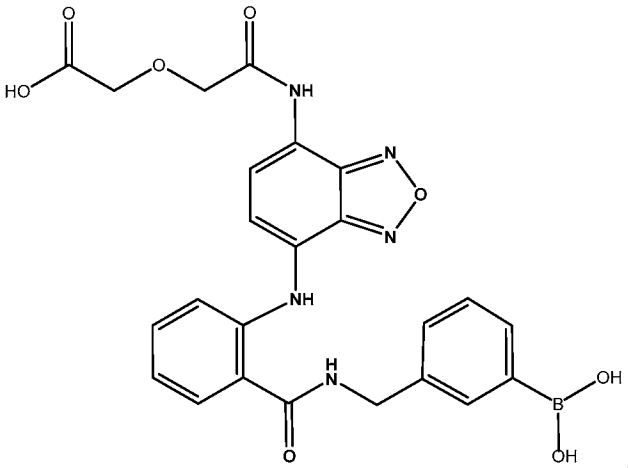
18  ,  ,

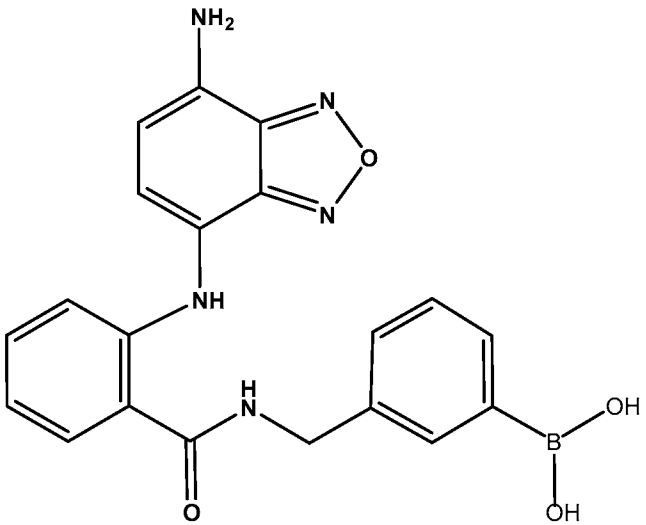
19  ,  ,

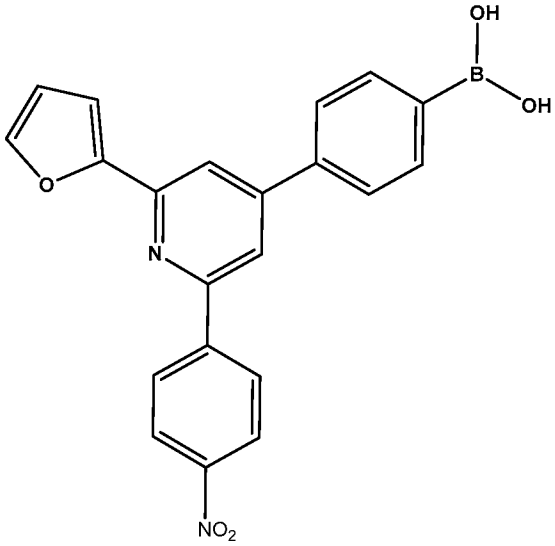
20  ,

21  ,

22  ,

23  ,

24  ,

25 
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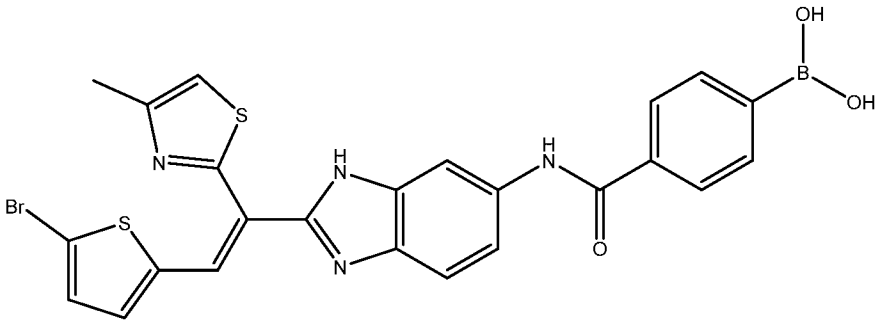
B
OH
O
N
NO2
,

26 
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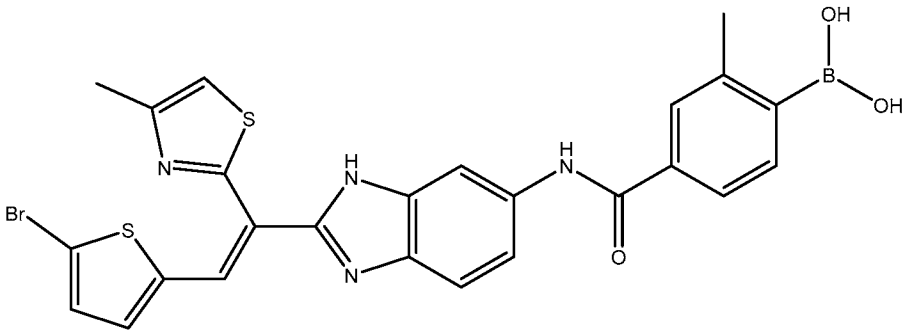
OH
S
N
H
N
Br
S
H
N
O
N
,

27 
OH
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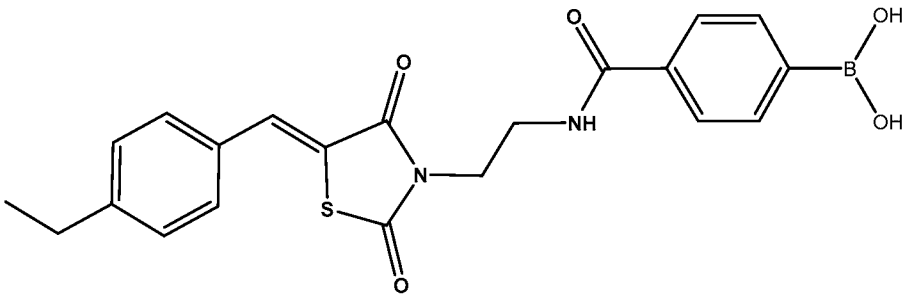
OH
S
N
H
N
Br
S
H
N
O
N
,

28 
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NH
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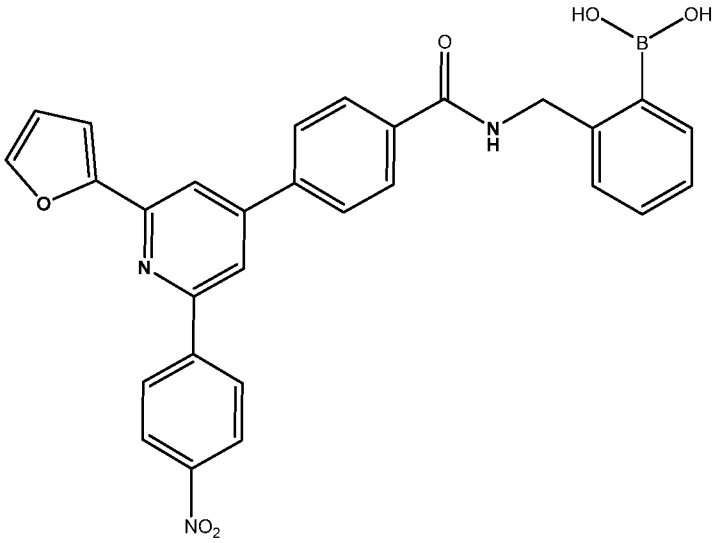
N
S
O
,

29 

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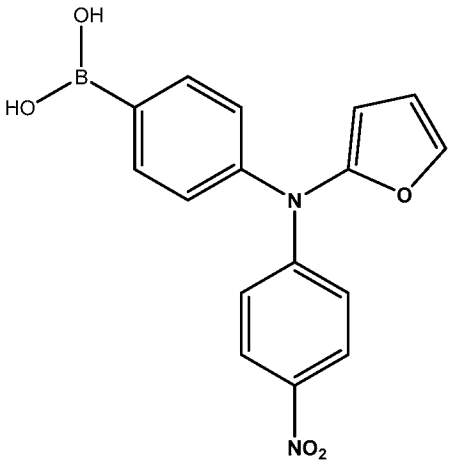
30 

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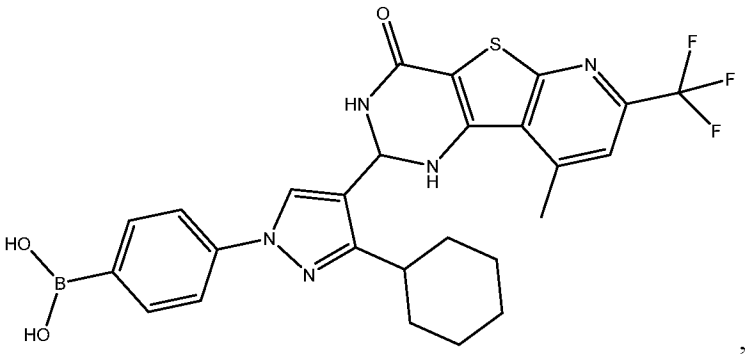
31 

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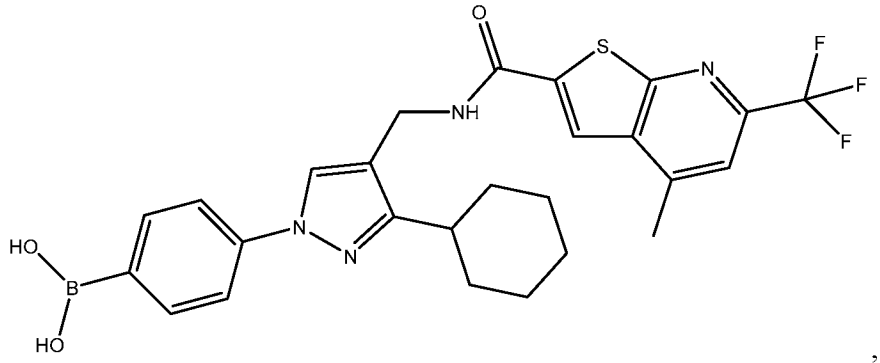
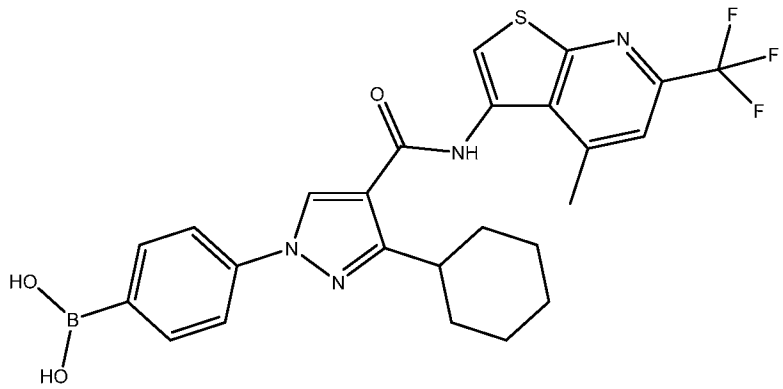
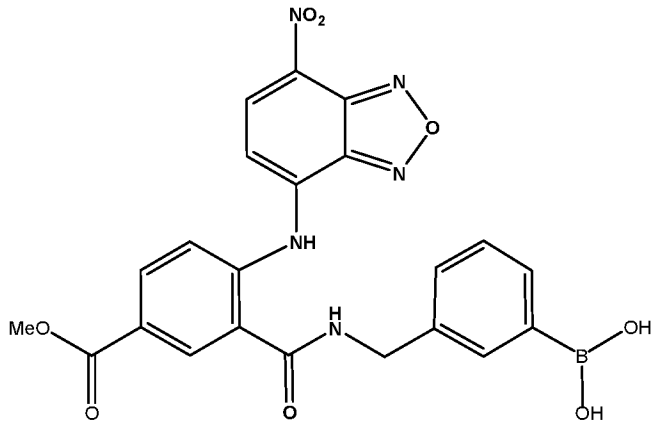
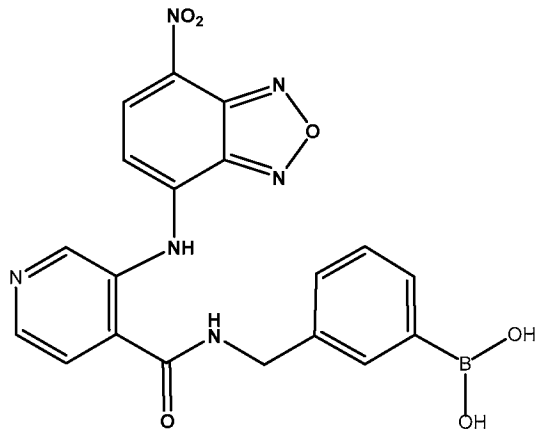
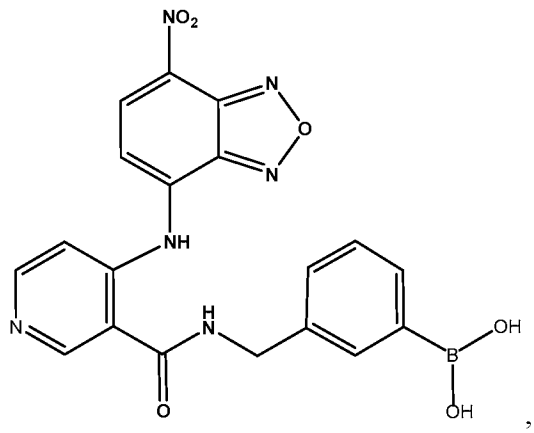
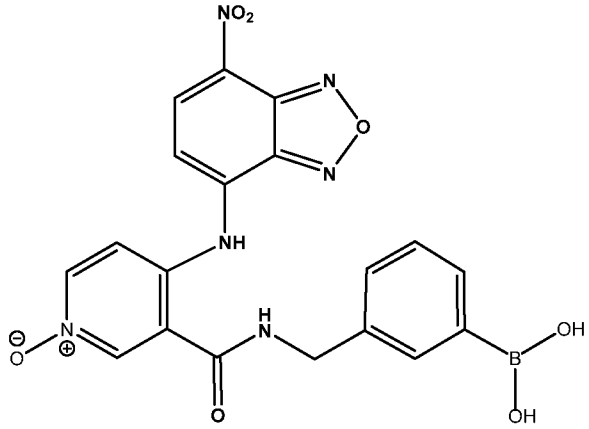
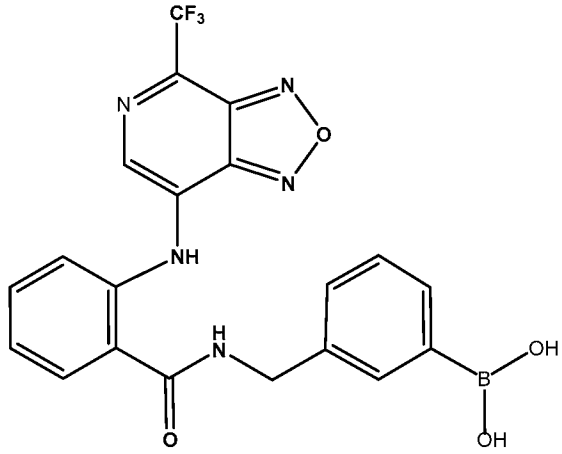
32  ,

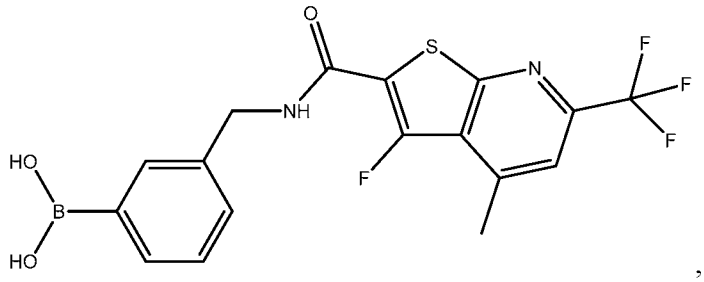
33  ,

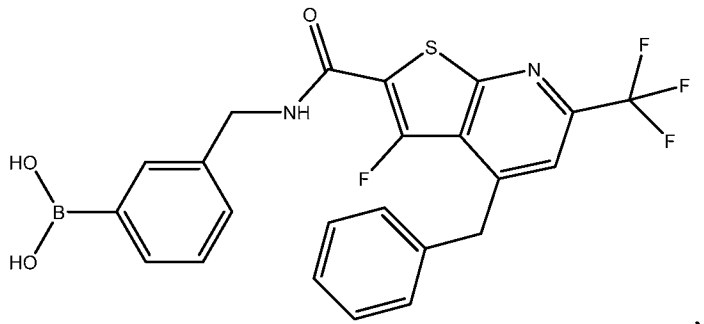
34  ,

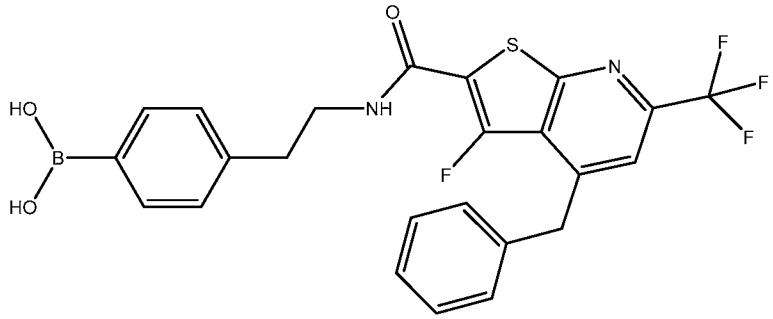
35  ,  ,

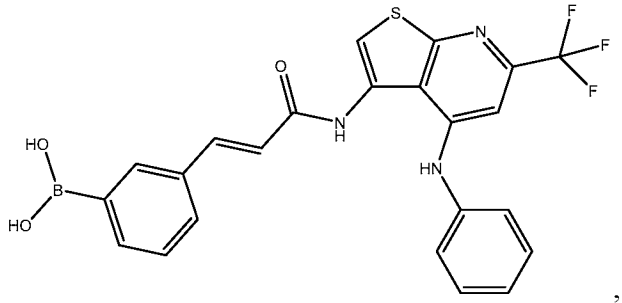
36  ,

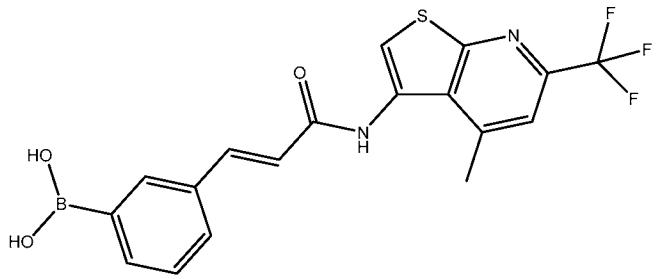
37  ,

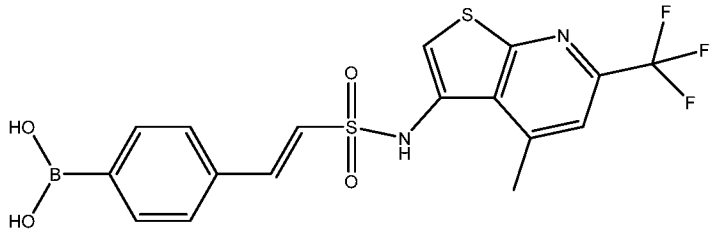
38  ,

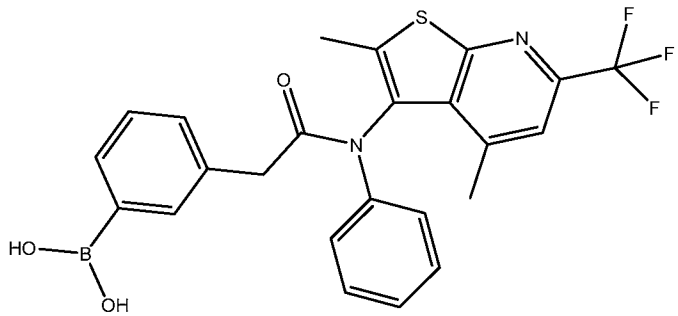
39  ,

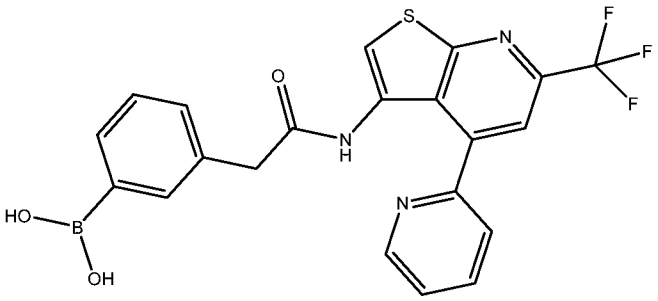
40  ,

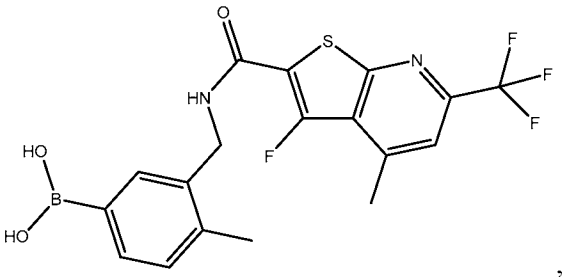
41  ,

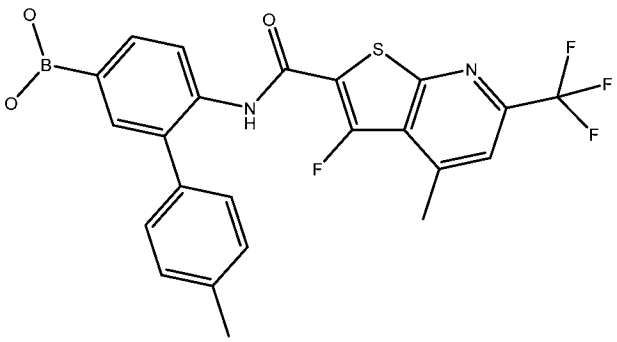
42  ,

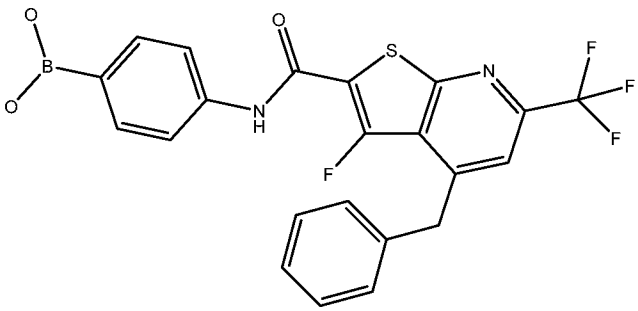
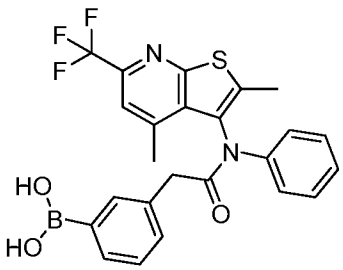
43  ,

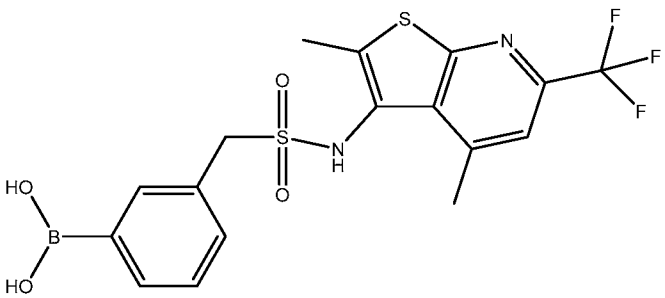
44  ,

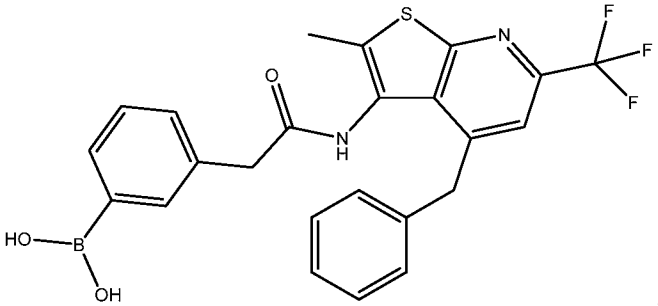
45  ,

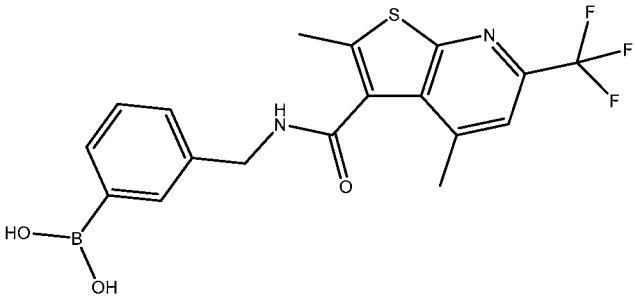
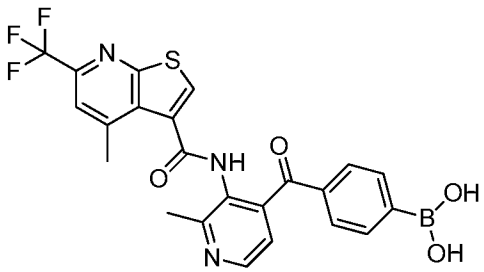
46  ,

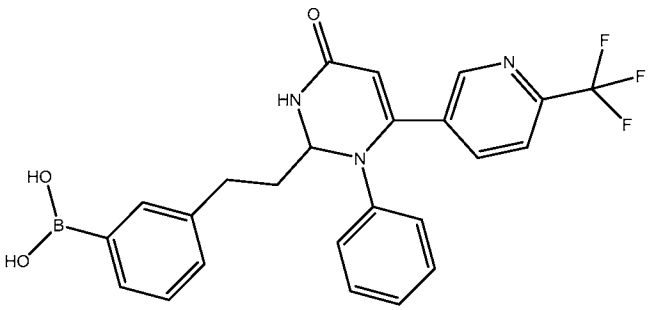
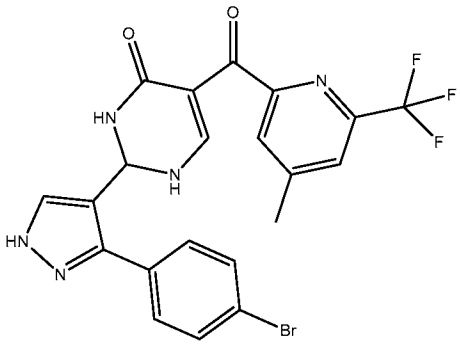
47  ,

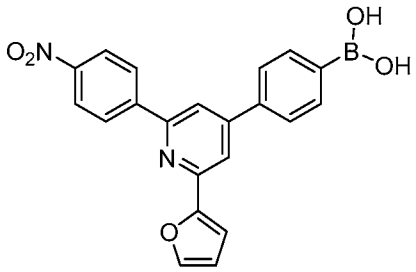
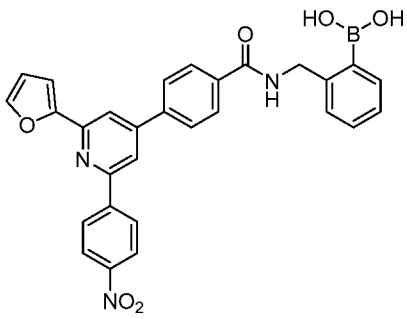
48  ,  ,

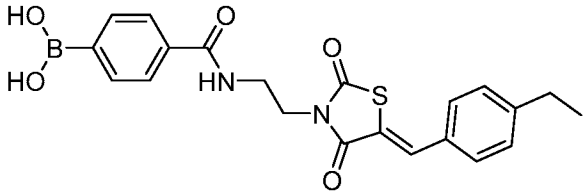
49  ,

50  ,

51  ,  ,

52  ,  ,

53  ,  ,

54  and pharmaceutically acceptable salts thereof.

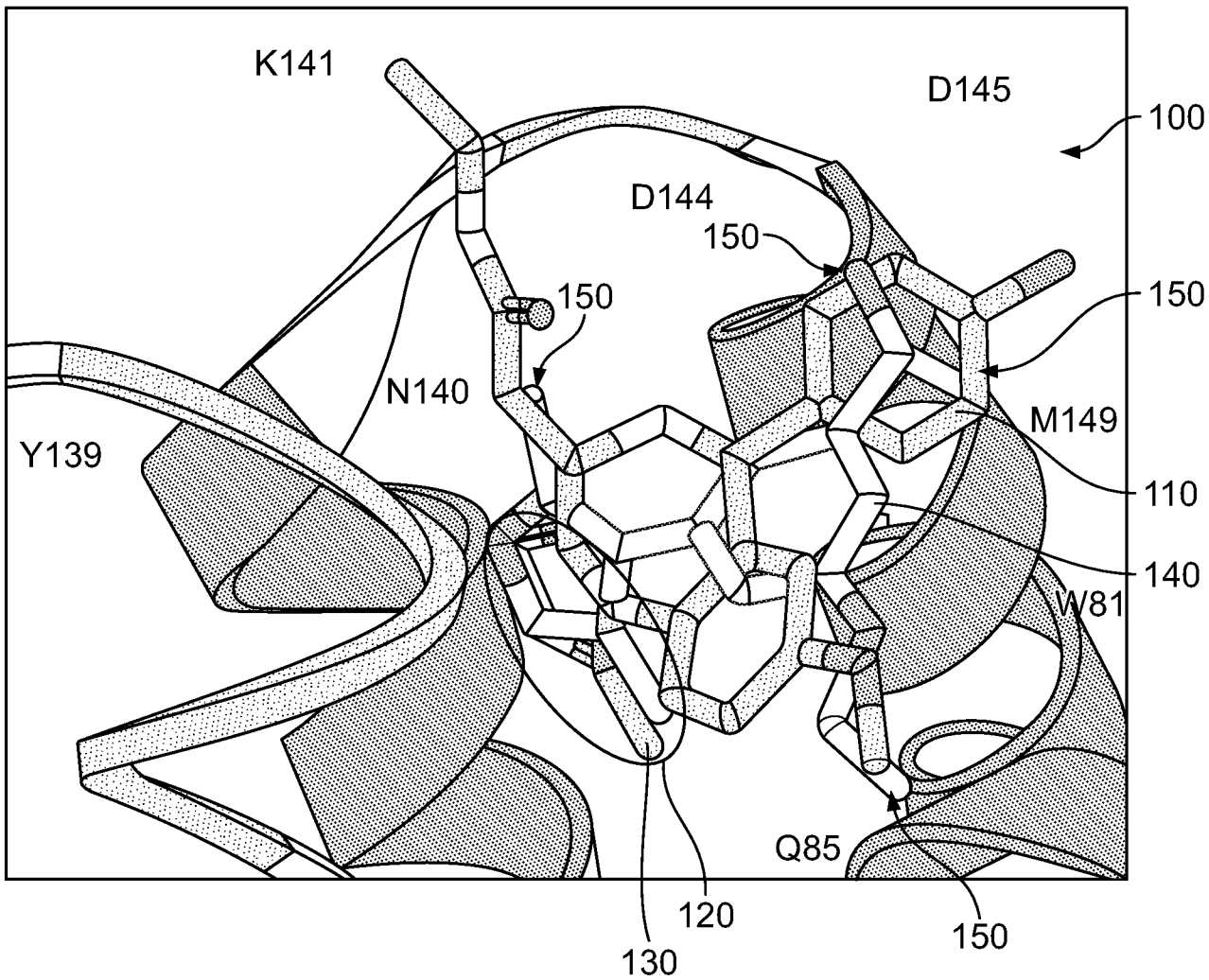

K141
D145
100
D144
150
150
150
N140
M149
Y139
110
140
W81
Q85
120
150
130

FIG. 1

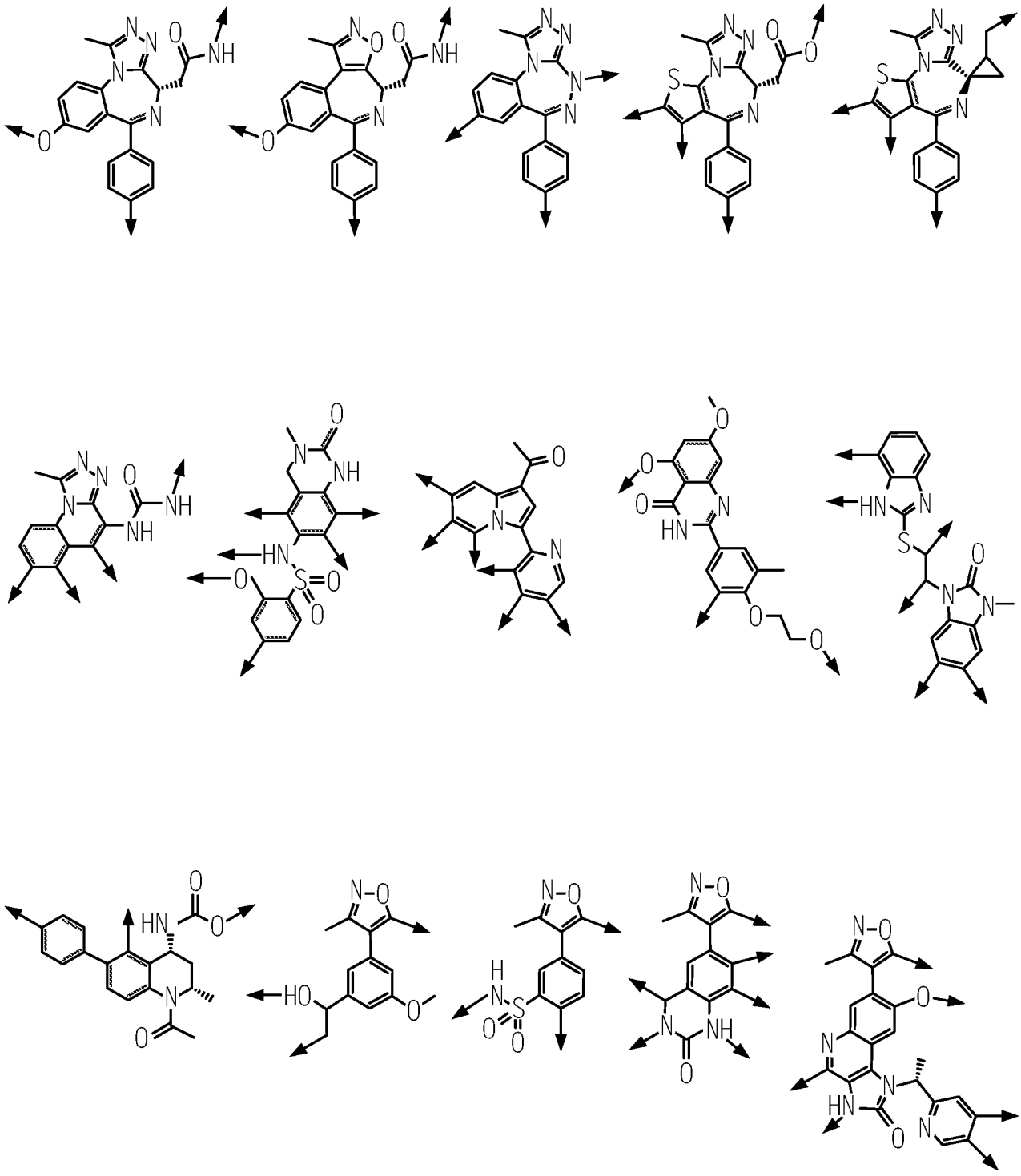
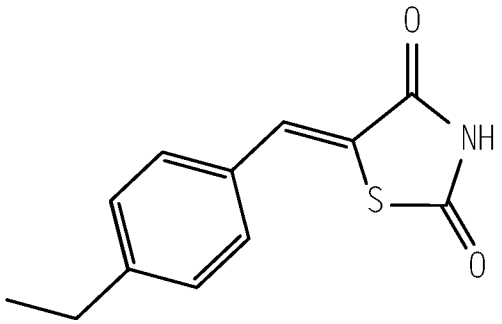
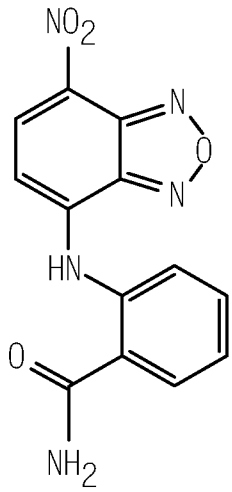


FIG. 2

A

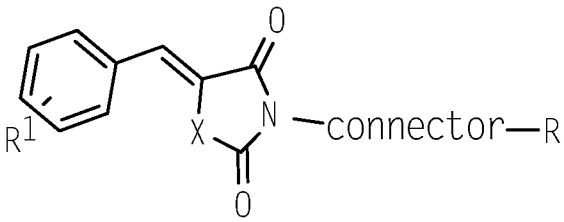


C01

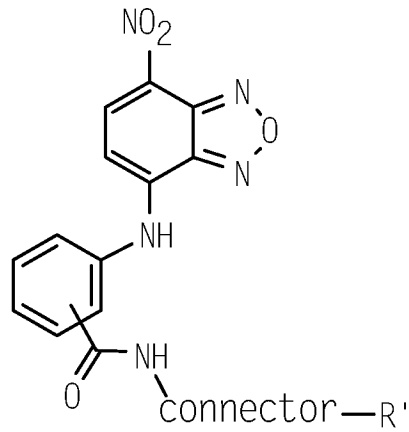


C02

B



R = Aryl$(OH)_2$,
Alkyl$(OH)_2$



R' = Aryl-B$(OH)_2$

R^1 = alkyl, halo

X = S,O,NH,N-alkyl,CH_2

FIG. 3

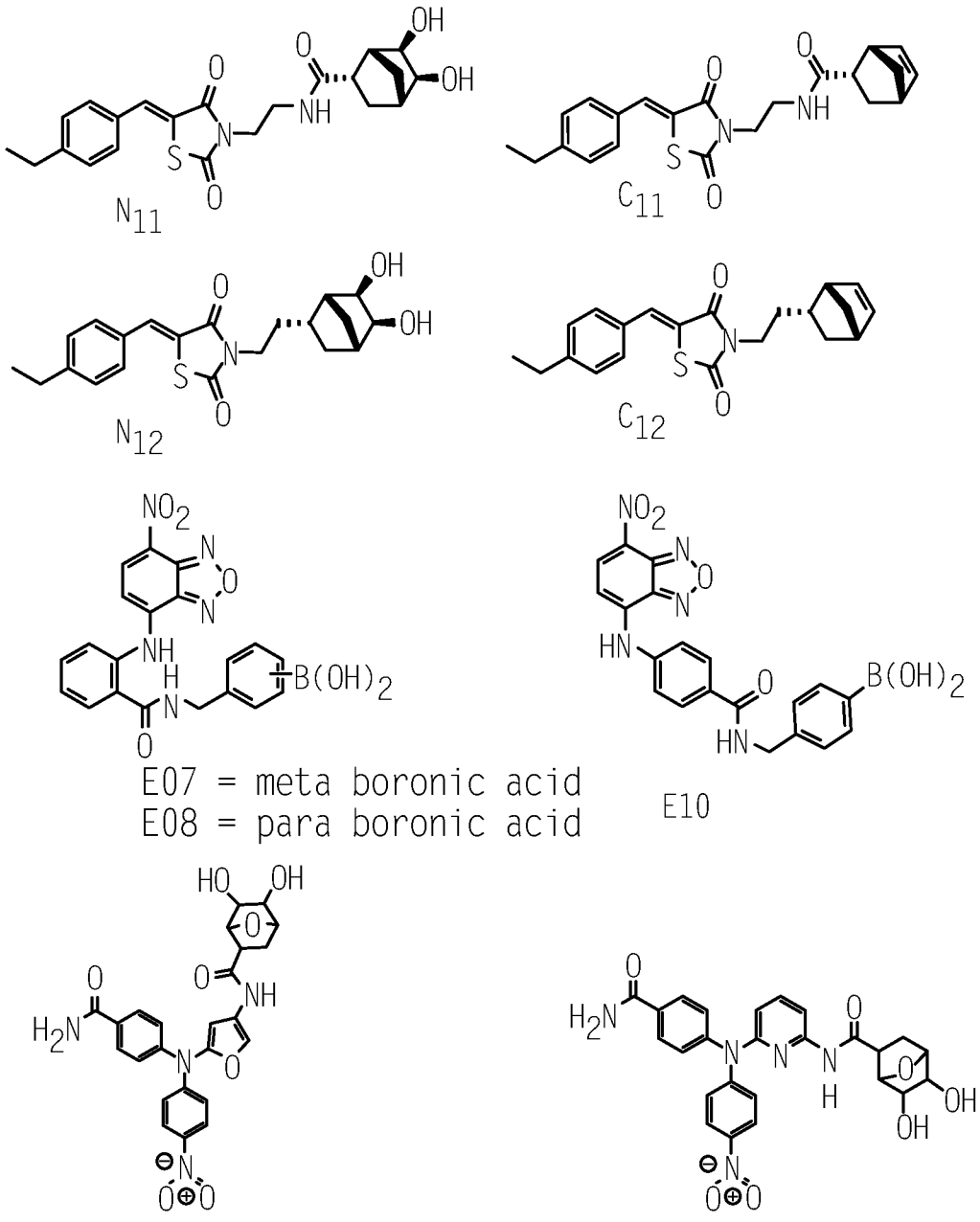

N11
C11
N12
C12
E07 = meta boronic acid
E08 = para boronic acid
E10

FIG. 4A

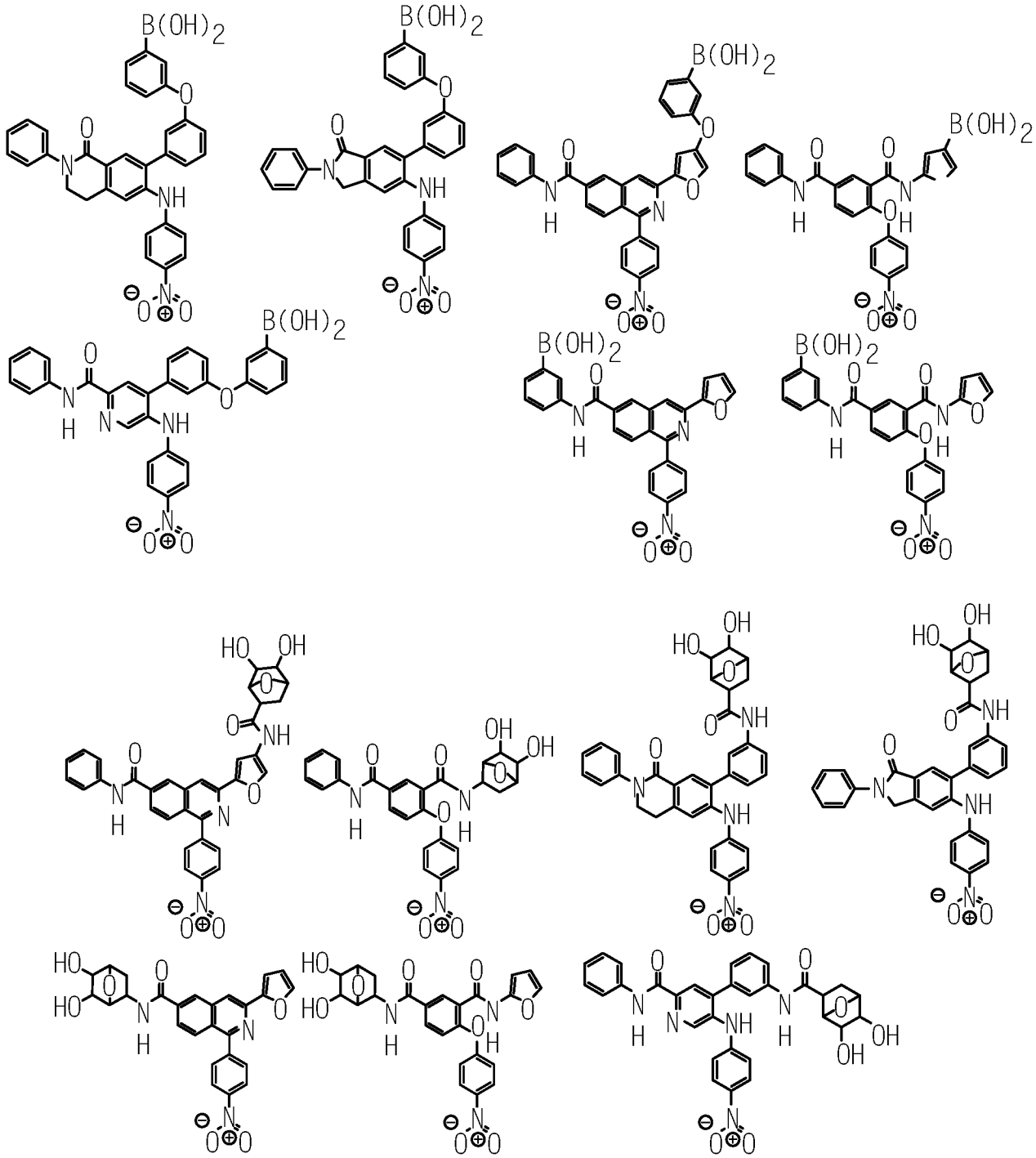


FIG. 4B

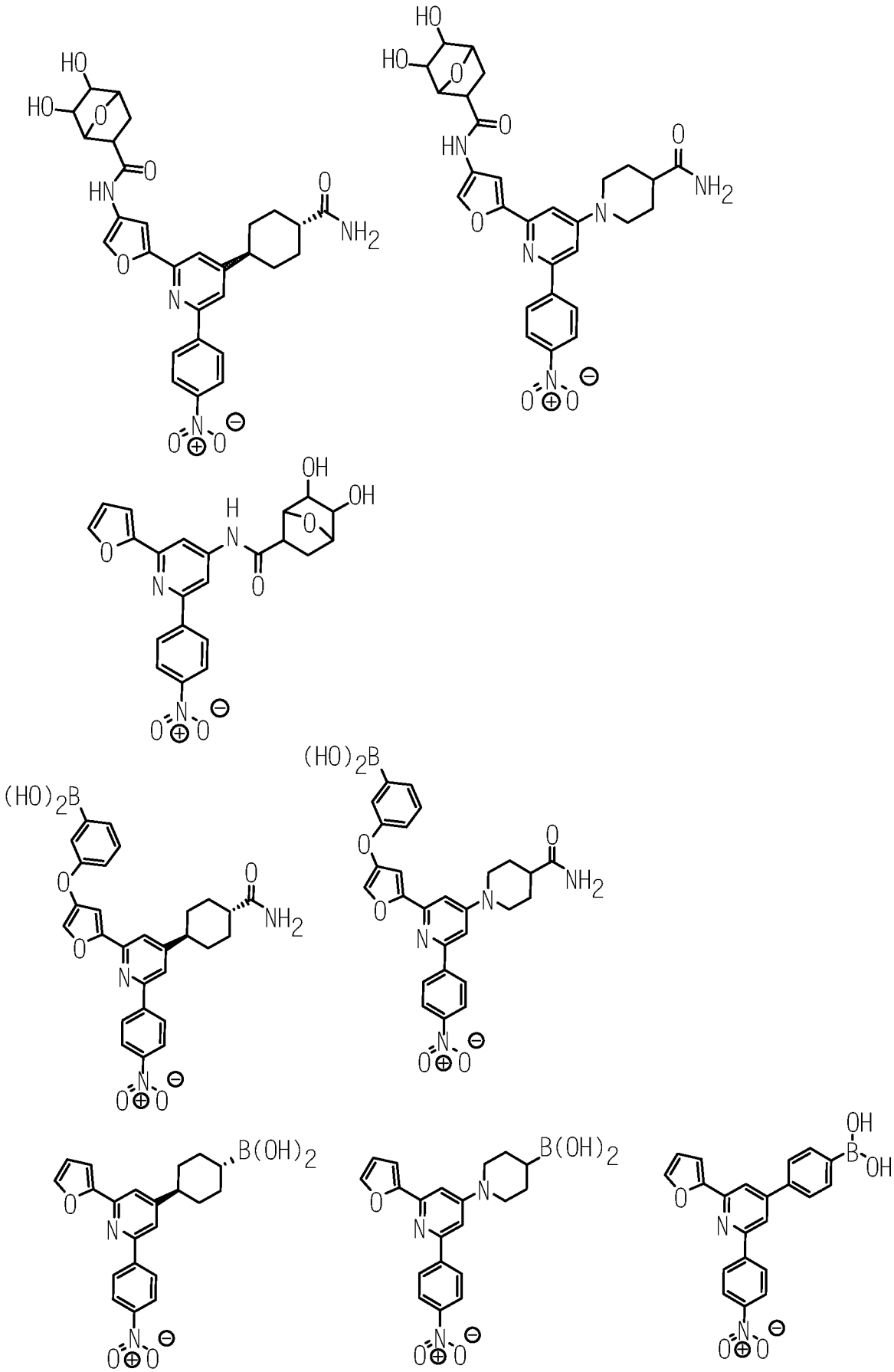


FIG. 4C

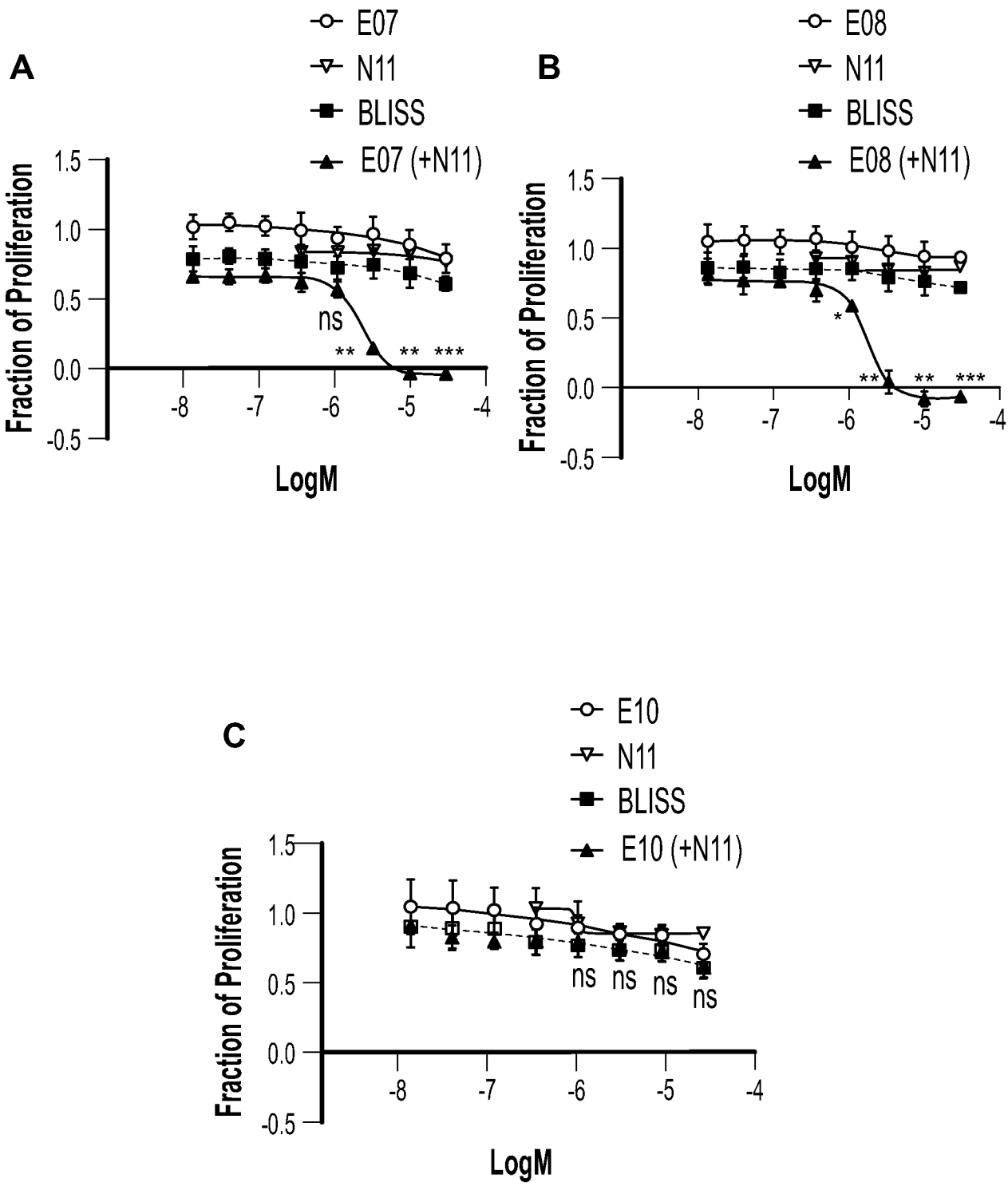
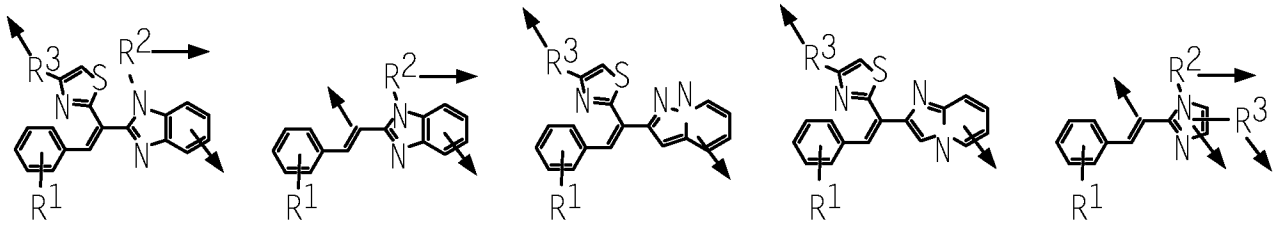

A
E07
N11
BLISS
E07 (+N11)
Fraction of Proliferation
1.5
1.0
0.5
0.0
-0.5
-8
-7
-6
-5
-4
LogM
ns
**
**
***
B
E08
N11
BLISS
E08 (+N11)
Fraction of Proliferation
LogM
*
**
**
***
C
E10
N11
BLISS
E10 (+N11)
Fraction of Proliferation
LogM
ns
ns
ns
ns

FIG. 5



R^1 = Halogens, short (linear or branched) alkyl or alkoxy, nitrile

R^2 = H, Et, i-Pr

R^3 = H, Et, i-Pr

FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/13429

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/4245; A61K 31/426; C07D 413/02 (2016.01)
CPC - C07D 277/00; C07D 413/02
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
CPC: C07D277/00; C07D413/02
IPC(8): A61K 31/4245; A61K 31/426; C07D 413/02 (2016.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/364; 548/126; 514/369 (See Search Words Below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Patbase: Full-text = AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO
Google: Scholar/Patents: c-myc multimer compound boronic Nitrobenzo[c] [l,2,5]oxadiazol-4-yl)amino)benzene-1,2-diol benzylidene dioxothiazolidine 7-nitrobenzooxadiazol-4-yl aminobenzamide dihydroxyphenyl monomer first second connector

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MCKEOWN et.al. Therapeutic Strategies to Inhibit MYC in Cold Spring Harbor Perspective Medicine, 2014, Vol 4, a014266, pp 1-17. pg 3, Col 2, para 2; pg 5, Figure 2; pg 10, Col 2, para 1	1-4;16;17;19;20;23-25
Y	US 2014/0194383 A1 (BARANY et.al.) 10 July 2014 (10.07.2014) para [0064];[0080]-[0082];[0142]-[0144];[0195]-[0199];[0241]-[0243];[0266];[0287]	1-4;16;17;19;20;23-25

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
03 March 2016 (03.03.2016)	31 MAR 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/13429

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5-15, 18 and 21-22
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.