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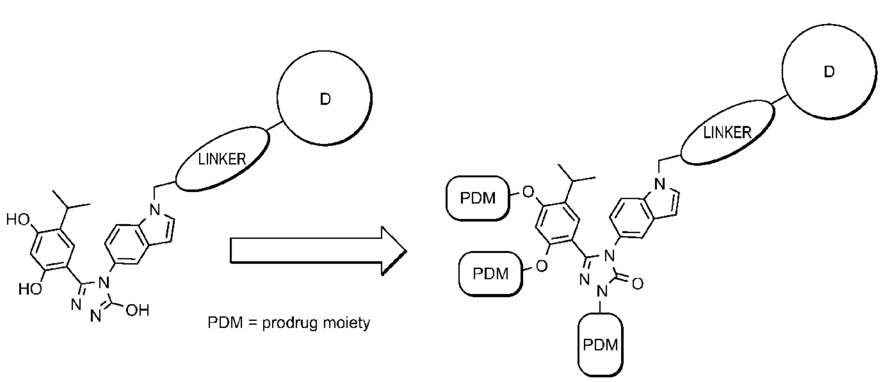

FIG. 1

(57) **Abstract**: The present invention provides pharmacological compounds including an effector moiety conjugated to a binding moiety that directs the effector moiety to a biological target of interest. Likewise, the present invention provides compositions, kits, and methods (e.g., therapeutic, diagnostic, and imaging) including the compounds. The compounds can be described as a protein interacting binding moiety-drug conjugate (SDC-TRAP) compounds, which include a protein interacting binding moiety and an effector moiety. For example, in certain embodiments directed to treating cancer, the SDC-TRAP can include an Hsp90 inhibitor conjugated to a cytotoxic agent as the effector moiety.

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TARGETED THERAPEUTICS

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 61/876,044, filed on September 10, 2013. The contents of this application are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates to pharmacological compounds including an effector moiety conjugated to a binding moiety that directs the effector moiety to a biological target of interest. The compounds have broad pharmacological applications, including therapeutics, diagnostics, and imaging. For example, the compounds can specifically direct therapeutic effector moieties to target cells or tissue of interest, for targeted chemotherapeutic treatment of conditions such as cancer.

BACKGROUND OF THE INVENTION

[0003] Although tremendous advances have been made in chemotherapy, currently available therapeutics and therapies remain unsatisfactory and the prognosis for the majority of patients diagnosed with chemotherapeutically treated diseases (*e.g.*, cancer) remains poor. Often, the applicability and/or effectiveness of chemotherapy, as well as other therapies and diagnostics employing potentially toxic moieties, is limited by undesired side effects.Many disease and disorders are characterized by the presence of high levels of certain proteins in specific types of cells. In some cases, the presence of these high levels of protein is caused by overexpression. Historically, some of these proteins have been useful targets for therapeutic molecules or used as biomarkers for the detection of disease. One class of overexpressed intracellular protein that has been recognized as a useful therapeutic target is known as the heat shock proteins.

[0004] Heat shock proteins (HSPs) are a class of proteins that are up-regulated in response to elevated temperature and other environmental stresses, such as ultraviolet light, nutrient deprivation, and oxygen deprivation. HSPs have many known functions, including acting as chaperones to other cellular proteins (called client proteins) to facilitate their proper folding and repair, and to aid in the refolding of misfolded client proteins. There are several known families of HSPs, each having its own set of client proteins. Hsp90 is one of the most abundant

HSP families, accounting for about 1-2% of proteins in a cell that is not under stress and increasing to about 4-6% in a cell under stress.

[0005] Inhibition of Hsp90 results in degradation of its client proteins via the ubiquitin proteasome pathway. Unlike other chaperone proteins, the client proteins of Hsp90 are mostly protein kinases or transcription factors involved in signal transduction, and a number of its client proteins have been shown to be involved in the progression of cancer. Hsp90 has been shown by mutational analysis to be necessary for the survival of normal eukaryotic cells. However, Hsp90 is overexpressed in many tumor types, indicating that it may play a significant role in the survival of cancer cells and that cancer cells may be more sensitive to inhibition of Hsp90 than normal cells. For example, cancer cells typically have a large number of mutated and overexpressed oncoproteins that are dependent on Hsp90 for folding. In addition, because the environment of a tumor is typically hostile due to hypoxia, nutrient deprivation, acidosis, etc., tumor cells may be especially dependent on Hsp90 for survival. Moreover, inhibition of Hsp90 causes simultaneous inhibition of a number of oncoproteins, as well as hormone receptors and transcription factors, making it an attractive target for an anti-cancer agent. In view of the above, Hsp90 has been an attractive target of drug development, including such Hsp90 inhibitor (Hsp90i) compounds as ganetespib, AUY-922, and IPI-504. At the same time, the advancement of certain of these compounds which showed early promise, *e.g.*, geldanamycin, has been slowed by those compounds' toxicity profile. Hsp90i compounds developed to date are believed to show great promise as cancer drugs, but other ways the ubiquity of Hsp90 in cancer cells might be leveraged have heretofore remained unexplored until now. Accordingly, the need exists for therapeutic molecules that selectively target proteins, such as Hsp90, that are overexpressed in cells associated with particular diseases or disorders.

SUMMARY OF THE INVENTION

[0006] The present invention provides pharmacological molecules ("SDC-TRAPs") including an effector moiety conjugated to a binding moiety, which directs the effector moiety into a target cell of interest in a manner that traps the molecule in the target cell. In a specific embodiment, the effector moiety is conjugated via a cleavable bond or linker to the binding moiety, such that the cleavable bond or linker is preferentially cleaved after the SDC-TRAP enters the target cell. The inventors of the instant application have discovered that the SDC-TRAP molecules of the invention can be used to selectively deliver an effector moiety to a specific type of cell in order to increase the intracellular level of the effector moiety in the target cell as compared to other cells. The inventors have demonstrated that certain SDC-TRAP molecules of the invention enter target cells by passive diffusion and are selectively retained in the target cells. Specifically, the inventors have shown that certain SDC-TRAP molecules of the invention are selectively retained only in cells that overexpress or otherwise have a high intracellular level of the protein to which the binding moiety binds. There are numerous advantages to these SDC-TRAP molecules and to methods of using these molecules that are described herein.

[0007] Specifically, the invention provides SDC-TRAP molecules that are targeted to cells of interest and trapped intracellularly for a sufficient period of time such that the effector moiety has the desired biological effect. In one embodiment, these SDC-TRAPs allow for the targeting of an effector moiety to a particular type of cell based on the overexpression of an intracellular protein that is characteristic of a particular disease or disorder. Accordingly, the present invention provides compositions, kits, and methods (*e.g.*, therapeutic, diagnostic, and imaging) including the compounds.

[0008] In a specific embodiment, the application exemplifies the use of Hsp90 interacting moieties, *e.g.,* inhibitors, as the binding moiety in the SDC-TRAPs. However, the invention is intended to include other binding moieties, including those that are contemplated, listed and exemplified herein. Accordingly, in certain embodiments directed to treating cancer or inflammation, the SDC-TRAP includes an Hsp90 inhibitor moiety conjugated to an effector moiety. In certain embodiments, the effector moiety is a cytotoxic effector moiety.

[0009] In another embodiment, the SDC-TRAP includes an effector moiety that is effective while still linked to the binding moiety. In such embodiment, cleavage of the bond or linker in the target cell is not a necessary feature of the invention. In other cases, such as cytotoxic effector moieties, the effector moiety should only be effective after the linker or bond is cleaved and the effector moiety is released from the SDC-TRAP molecule inside the target cell. In either case, SDC-TRAPs that do not enter into the target cell should be rapidly cleared (*e.g.,* from the plasma or other non-target cells or tissues).

[0010] In another embodiment, the binding moiety of the SDC-TRAP binds a protein within the target cell, which may itself produce a desired biological effect (*e.g.,* such as inhibiting Hsp90 within the target cell). In one embodiment, the binding moiety can contribute to the overall efficacy of the SDC-TRAP by not only binding an intracellular protein present in the target cell but by also conveying a particular desired biological effect. For example, if the binding moiety is an Hsp90 inhibitor and the target cell is a cancer cell, than the overall activity of the SDC-TRAP may not only result from the effector moiety, but also from the biological activity of the Hsp90 inhibitor.

[0011] Alternatively, interaction of the binding moiety with its protein target may not impart a biological effect, but rather only serve to attract and retain the SDC-TRAP within the target cell. In this embodiment, the binding moiety may reversibly bind to the intracellular target protein and create an intracellular equilibrium between free and bound SDC-TRAP molecules. This equilibrium may allow for cleavage of the SDC-TRAP and more effective delivery of the effector moiety, *e.g.,* release of the effector moiety from the binding moiety by, for example, enzymatic cleavage, hydrolysis or degradation. In some cases, the effector moiety may be inactive until such release occurs.

[0012] In various aspects and embodiments, the present invention provides numerous advantages. For example, the SDC-TRAP can provide for targeted therapy, maximizing efficacy and/or minimizing undesired side effects. The SDC-TRAP can provide for targeted use of an effector moiety that would otherwise be unsuitable for administration alone due to toxicity and/or undesired systemic effects. The SDC-TRAP can facilitate targeting such effector moieties to intracellular targets – that is, due to its size and chemical properties, the SDC-TRAP can passively diffuse (or in some cases be actively transported) into a cell having an intracellular target of interest. Alternatively, the SDC-TRAP can deliver in a selective manner a cytotoxic molecule to destroy a target cell, such as a cancer or inflammatory cell.

[0013] In various aspects and embodiments, the SDC-TRAP can exhibit decreased and/or minimized toxicity concurrently with increased efficacy (*e.g.*, as compared to that of the effector moiety when used alone). Decreasing and/or minimizing toxicity can encompass reducing toxicity to a predetermined level (*e.g.*, a regulatory guideline or suggested level, for example promulgated by the US Food and Drug Administration “FDA”). Increasing efficacy can encompass increasing efficacy to a predetermined level (*e.g.*, a regulatory guideline or suggested level, for example promulgated by the US FDA). Similarly, decreasing and/or minimizing toxicity concurrently with increasing efficacy can encompass achieving a predetermined therapeutic ratio (*e.g.*, a regulatory guideline or suggested value, for example promulgated by the US FDA).

[0014] Decreasing and/or minimizing toxicity can encompass, for example, reducing toxicity by 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 %, or more. Increasing efficacy can encompass, for example, increasing efficacy by 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 250, 300, 400, 500%, or more. Decreasing and/or minimizing toxicity concurrently with increasing efficacy can encompass, for example: essentially the same efficacy with decreased toxicity; essentially the same toxicity with increased efficacy; or decreased toxicity and increased efficacy. Similarly, decreasing and/or minimizing toxicity concurrently with increasing efficacy can encompass, for example, scenarios such as: increased efficacy enabling a lower dose (*e.g.*, lower dose of effector moiety with a correspondingly lower net toxicity) and decreased toxicity enabling a higher dose (*e.g.*, higher dose of effector moiety without a correspondingly higher net toxicity).

[0015] Additional advantages are discussed in detail below.

[0016] These and other advantages of the present invention are of particular interest, for example, in chemotherapy where despite tremendous recent advances, currently available therapeutics and therapies remains unsatisfactory and the prognosis for the majority of patients diagnosed with diseases such as cancer remains poor. However, while many of the illustrative embodiments and examples are presented in the context of cancer, a person of ordinary skill in the art would understand that the present invention has applications across therapeutic, diagnostic, and imaging applications that require, or would benefit from, targeting of an effector moiety.

[0017] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety and an effector moiety.

[0018] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety and an effector moiety, wherein the SDC-TRAP is able to enter a cell by active transport.

[0019] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety and an effector moiety, wherein the SDC-TRAP has a molecular weight of less than about 1600 Daltons.

[0020] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety and an effector moiety, wherein the binding moiety has a molecular weight of less than about 800 Daltons.

[0021] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety and an effector moiety, wherein the effector moiety has a molecular weight of less than 800 Daltons.

[0022] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety and an effector moiety, wherein the binding moiety and the effector moiety are approximately equal in size.

[0023] In various aspects, the invention provides an SDC-TRAP comprising an Hsp90 binding moiety and an effector moiety, wherein the Hsp90 binding moiety interacts with the N-terminal domain of Hsp90.

[0024] In various aspects, the invention provides an SDC-TRAP comprising an Hsp90 binding moiety and an effector moiety, wherein the Hsp90 binding moiety interacts with the C-terminal domain of Hsp90.

[0025] In various aspects, the invention provides an SDC-TRAP comprising an Hsp90 binding moiety and an effector moiety, wherein the Hsp90 binding moiety interacts with the middle domain of Hsp90.

[0026] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety and an effector moiety, wherein the binding moiety interacts with a predetermined domain of a multidomain target protein molecule.

[0027] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, an Hsp90 binding moiety) and an effector moiety, wherein the binding moiety (*e.g.*, Hsp90 binding moiety) has a K_d of 100 nM or higher (*e.g.*, for a predetermined target molecule, for example, Hsp90).

[0028] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein when administered to a subject, the SDC-TRAP is present at a ratio of 2:1 in target (*e.g.*, tumor) cells compared to plasma. In another embodiment, the invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein when administered to a subject the SDC-TRAP present at a ratio of 2:1 in target (*e.g.*, tumor) cells compared to normal cells.

[0029] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the SDC-TRAP is present in target (*e.g.*, cancer) cells for at least 24 hours.

[0030] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the effector moiety is released for a period of at least 6 hours (*e.g.*, within a target cell and/or tissue).

[0031] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the effector moiety is selectively released inside a target (*e.g.*, cancer) cell.

[0032] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the SDC-TRAP allows for the use of an effector moiety that is toxic or otherwise unfit for administration to a subject.

[0033] In various aspects, the invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the Hsp90 is an inhibitor (*e.g.*, Hsp90 inhibitor) that is ineffective as a therapeutic agent when administered alone.

[0034] In various aspects, the invention provides an SDC-TRAP comprising an Hsp90 binding moiety and an effector moiety.

[0035] In various aspects, the invention provides pharmaceutical compositions comprising a therapeutically effective amount of at least one SDC-TRAP, and at least one pharmaceutical excipient.

[0036] In various aspects, the invention provides methods for treating a subject in need thereof comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the subject.

[0037] In various aspects, the invention provides methods for imaging, diagnosing, and/or selecting a subject comprising administering an effective amount of at least one SDC-TRAP to the subject, thereby imaging, diagnosing, and/or selecting the subject.

[0038] In various aspects, the invention provides kits for treating a subject in need thereof comprising at least one SDC-TRAP and instruction for administering a therapeutically effective amount of the at least one SDC-TRAP to the subject, thereby treating the subject.

[0039] In various aspects, the invention provides kits for imaging, diagnosing, and/or selecting a subject comprising at least one SDC-TRAP and instruction for administering an effective amount of at least one SDC-TRAP to the subject, thereby imaging, diagnosing, and/or selecting the subject.

[0040] In various embodiments, the invention can include any one or more of the aspects disclosed herein having any one or more of the features disclosed herein.

[0041] In various embodiments, the binding moiety interacts with a protein that is overexpressed in cancerous cells compared to normal cells.

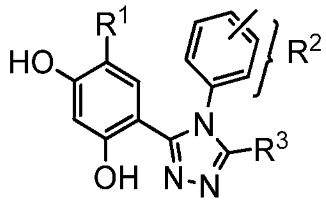
[0042] In various embodiments, the protein is a chaperonin protein. The chaperonin can be, for example, Hsp90.

[0043] In various embodiments, the chaperonin is an Hsp90 binding moiety.

[0044] In various embodiments, the binding moiety is an Hsp90 ligand or a prodrug thereof. The Hsp90 ligand can be, for example, an Hsp90 inhibitor. An Hsp90 inhibitor can be selected from the group consisting of geldanamycins, macbecins, tripterins, tanespimycins, and radicicols.

[0045] In various embodiments, the binding moiety can be an Hsp90-targeting moiety, for example a triazole/resorcinol-based compound that binds Hsp90, or a resorcinol amide-based compound that binds Hsp90, *e.g.*, ganetespib, AUY-922, or AT-13387.

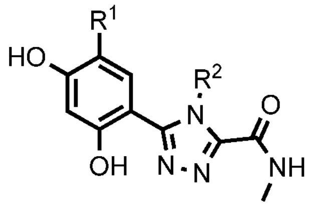
[0046] In various embodiments, the binding moiety can be an Hsp90-binding compound of

formula (I): 

, wherein

[0047] R^1 may be alkyl, aryl, halide, carboxamide or sulfonamide; R^2 may be alkyl, cycloalkyl, aryl or heteroaryl, wherein when R^2 is a six-membered aryl or heteroaryl, R^2 is substituted at the 3- and 4-positions relative to the connection point on the triazole ring, through which a linker L is attached; and R^3 may be SH, OH, -CONHR^4, aryl or heteroaryl, wherein when R^3 is a six-membered aryl or heteroaryl, R^3 is substituted at the 3 or 4 position.

[0048] In various embodiments, the binding moiety can be an Hsp90-binding compound of

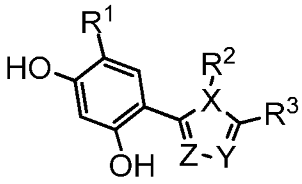
formula (II): 

wherein

[0049] R^1 may be alkyl, aryl, halo, carboxamido, sulfonamido; and R^2 may be optionally substituted alkyl, cycloalkyl, aryl or heteroaryl. Examples of such compounds include

5-(2,4-dihydroxy-5-isopropylphenyl)-N-(2-morpholinoethyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide and
5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(4-methylpiperazin-1-yl)phenyl)-N-(2,2,2-trifluoroethyl)-4H-1,2,4-triazole-3-carboxamide.

[0050] In various embodiments, the binding moiety can be an Hsp90-binding compound of formula (III):



wherein

[0051] X, Y, and Z may independently be CH, N, O or S (with appropriate substitutions and satisfying the valency of the corresponding atoms and aromaticity of the ring); R^1 may be alkyl, aryl, halide, carboxamido or sulfonamido; R^2 may be substituted alkyl, cycloalkyl, aryl or heteroaryl, where a linker L is connected directly or to the extended substitutions on these rings; R^3 may be SH, OH, NR^4R^5 AND -$CONHR^6$, to which an effector moiety may be connected; R^4 and R^5 may independently be H, alkyl, aryl, or heteroaryl; and R^6 may be alkyl, aryl, or heteroaryl, having a minimum of one functional group to which an effector moiety may be connected.

[0052] As used herein, the term "alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms. Representative saturated straight chain alkyls include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; while saturated branched alkyls include isopropyl, *sec*-butyl, isobutyl, *tert*-butyl, isopentyl, 2-methylbutyl, 3-methylbutyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 2,3-dimethylbutyl, 2,3-dimethylpentyl, 2,4-dimethylpentyl, 2,3-dimethylhexyl, 2,4-dimethylhexyl, 2,5-dimethylhexyl, 2,2-dimethylpentyl, 2,2-dimethylhexyl, 3,3-dimtheylpentyl, 3,3-dimethylhexyl, 4,4-dimethylhexyl, 2-ethylpentyl, 3-ethylpentyl, 2-ethylhexyl, 3-ethylhexyl, 4-ethylhexyl, 2-methyl-2-ethylpentyl, 2-methyl-3-ethylpentyl, 2-methyl-4-ethylpentyl, 2-methyl-2-ethylhexyl, 2-methyl-3-ethylhexyl, 2-methyl-4-ethylhexyl, 2,2-diethylpentyl, 3,3-diethylhexyl, 2,2-diethylhexyl, 3,3-diethylhexyl and the like. The term "(C_1-C_6)alkyl" means a saturated straight chain or branched non-cyclic hydrocarbon having from 1 to 6 carbon atoms. Representative (C_1-C_6)alkyl groups are those shown above having from 1 to 6 carbon atoms. Alkyl groups included in compounds of this invention may be optionally substituted with one or more substituents.

[0053] As used herein, the term “alkenyl” means a saturated straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and having at least one carbon-carbon double bond. Representative straight chain and branched (C_2-C_{10})alkenyls include vinyl, allyl, 1-butenyl, 2-butenyl, isobutylenyl, 1-pentenyl, 2-pentenyl, 3-methyl-1-butenyl, 2-methyl-2-butenyl, 2,3-dimethyl-2-butenyl, 1-hexenyl, 2-hexenyl, 3-hexenyl, 1-heptenyl, 2-heptenyl, 3-heptenyl, 1-octenyl, 2-octenyl, 3-octenyl, 1-nonenyl, 2-nonenyl, 3-nonenyl, 1-decenyl, 2-decenyl, 3-decenyl and the like. Alkenyl groups may be optionally substituted with one or more substituents.

[0054] As used herein, the term “alkynyl” means a saturated straight chain or branched non-cyclic hydrocarbon having from 2 to 10 carbon atoms and having at least one carbon-carbon triple bond. Representative straight chain and branched alkynyls include acetylenyl, propynyl, 1-butynyl, 2-butynyl, 1-pentynyl, 2-pentynyl, 3-methyl-1-butynyl, 4-pentynyl, 1-hexynyl, 2-hexynyl, 5-hexynyl, 1-heptynyl, 2-heptynyl, 6-heptynyl, 1-octynyl, 2-octynyl, 7-octynyl, 1-nonynyl, 2-nonynyl, 8-nonynyl, 1-decynyl, 2-decynyl, 9-decynyl, and the like. Alkynyl groups may be optionally substituted with one or more substituents.

[0055] As used herein, the term “cycloalkyl” means a saturated, mono- or polycyclic alkyl radical having from 3 to 20 carbon atoms. Representative cycloalkyls include cyclopropyl, 1-methylcyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, –cyclodecyl, octahydro-pentalenyl, and the like. Cycloalkyl groups may be optionally substituted with one or more substituents.

[0056] As used herein, the term “cycloalkenyl” means a mono- or poly- cyclic non-aromatic alkyl radical having at least one carbon-carbon double bond in the cyclic system and from 3 to 20 carbon atoms. Representative cycloalkenyls include cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, cycloheptenyl, cycloheptadienyl, cycloheptatrienyl, cyclooctenyl, cyclooctadienyl, cyclooctatrienyl, cyclooctatetraenyl, cyclononenyl, cyclononadienyl, cyclodecenyl, cyclodecadienyl, 1,2,3,4,5,8-hexahydronaphthalenyl and the like. Cycloalkenyl groups may be optionally substituted with one or more substituents.

[0057] As used herein, the term “haloalkyl” means and alkyl group in which one or more (including all) the hydrogen radicals are replaced by a halo group, wherein each halo group is independently selected from –F, -Cl, -Br, and -I. The term “halomethyl” means a methyl in which one to three hydrogen radical(s) have been replaced by a halo group. Representative haloalkyl groups include trifluoromethyl, bromomethyl, 1,2-dichloroethyl, 4-iodobutyl, 2-fluoropentyl, and the like.

[0058] As used herein, an “alkoxy” is an alkyl group which is attached to another moiety via an oxygen linker.

[0059] As used herein, an “haloalkoxy” is an haloalkyl group which is attached to another moiety via an oxygen linker.

[0060] As used herein, the term an “aromatic ring” or “aryl” means a hydrocarbon monocyclic or polycyclic radical in which at least one ring is aromatic. Examples of such aryl groups include, but are not limited to, phenyl, tolyl, anthracenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. Aryl groups may be optionally substituted with one or more substituents. In one embodiment, the aryl group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as “(C_6)aryl.”

[0061] As used herein, the term “aralkyl” means an aryl group that is attached to another group by a $(C_1$-$C_6)$alkylene group. Representative aralkyl groups include benzyl, 2-phenyl-ethyl, naphth-3-yl-methyl and the like. Aralkyl groups may be optionally substituted with one or more substituents.

[0062] As used herein, the term “alkylene” refers to an alkyl group that has two points of attachment. The term “$(C_1$-$C_6)$alkylene” refers to an alkylene group that has from one to six carbon atoms. Straight chain $(C_1$-$C_6)$alkylene groups are preferred. Non-limiting examples of alkylene groups include methylene ($-CH_2-$), ethylene ($-CH_2CH_2-$), n-propylene ($-CH_2CH_2CH_2-$), isopropylene ($-CH_2CH(CH_3)-$), and the like. Alkylene groups may be optionally substituted with one or more substituents.

[0063] As used herein, the term "heterocyclyl” means a monocyclic (typically having 3- to 10-members) or a polycyclic (typically having 7- to 20-members) heterocyclic ring system which is either a saturated ring or a unsaturated non-aromatic ring. A 3- to 10-membered heterocycle can contain up to 5 heteroatoms; and a 7- to 20-membered heterocycle can contain up to 7 heteroatoms. Typically, a heterocycle has at least on carbon atom ring member. Each heteroatom is independently selected from nitrogen, which can be oxidized (*e.g.*, N(O)) or quaternized; oxygen; and sulfur, including sulfoxide and sulfone. The heterocycle may be attached via any heteroatom or carbon atom. Representative heterocycles include morpholinyl, thiomorpholinyl, pyrrolidinonyl, pyrrolidinyl, piperidinyl, piperazinyl, hydantoinyl, valerolactamyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyrindinyl, tetrahydropyrimidinyl, tetrahydrothiophenyl, tetrahydrothiopyranyl, and the like. A heteroatom may be substituted with a protecting group known to those of ordinary skill in the art, for example, the hydrogen on a nitrogen may be substituted with a tert-butoxycarbonyl group. Furthermore, the heterocyclyl may be optionally substituted with one or more substituents. Only stable isomers of such substituted heterocyclic groups are contemplated in this definition.

[0064] As used herein, the term “heteroaromatic”, “heteroaryl” or like terms means a monocyclic or polycyclic heteroaromatic ring comprising carbon atom ring members and one or more heteroatom ring members. Each heteroatom is independently selected from nitrogen, which can be oxidized (*e.g.,* N(O)) or quaternized; oxygen; and sulfur, including sulfoxide and sulfone. Representative heteroaryl groups include pyridyl, 1-oxo-pyridyl, furanyl, benzo[1,3]dioxolyl, benzo[1,4]dioxinyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, a isoxazolyl, quinolinyl, pyrazolyl, isothiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl, triazolyl, thiadiazolyl, isoquinolinyl, indazolyl, benzoxazolyl, benzofuryl, indolizinyl, imidazopyridyl, tetrazolyl, benzimidazolyl, benzothiazolyl, benzothiadiazolyl, benzoxadiazolyl, indolyl, tetrahydroindolyl, azaindolyl, imidazopyridyl, quinazolinyl, purinyl, pyrrolo[2,3]pyrimidinyl, pyrazolo[3,4]pyrimidinyl, imidazo[1,2-a]pyridyl, and benzothienyl. In one embodiment, the heteroaromatic ring is selected from 5-8 membered monocyclic heteroaryl rings. The point of attachment of a heteroaromatic or heteroaryl ring to another group may be at either a carbon atom or a heteroatom of the heteroaromatic or heteroaryl rings. Heteroaryl groups may be optionally substituted with one or more substituents.

[0065] As used herein, the term “(C_5)heteroaryl” means an aromatic heterocyclic ring of 5 members, wherein at least one carbon atom of the ring is replaced with a heteroatom such as, for example, oxygen, sulfur or nitrogen. Representative (C_5)heteroaryls include furanyl, thienyl, pyrrolyl, oxazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, pyrazinyl, triazolyl, thiadiazolyl, and the like.

[0066] As used herein, the term “(C_6)heteroaryl” means an aromatic heterocyclic ring of 6 members, wherein at least one carbon atom of the ring is replaced with a heteroatom such as, for example, oxygen, nitrogen or sulfur. Representative (C_6)heteroaryls include pyridyl, pyridazinyl, pyrazinyl, triazinyl, tetrazinyl and the like.

[0067] As used herein, the term “heteroaralkyl” means a heteroaryl group that is attached to another group by a $(C_1\text{-}C_6)$alkylene. Representative heteroaralkyls include 2-(pyridin-4-yl)-propyl, 2-(thien-3-yl)-ethyl, imidazol-4-yl-methyl and the like. Heteroaralkyl groups may be optionally substituted with one or more substituents.

[0068] As used herein, the term “halogen” or “halo” means -F, -Cl, -Br or -I.

[0069] Suitable substituents for an alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroaralkyl groups include any substituent which will form a stable compound of the invention. Examples of substituents for an alkyl, alkylene, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocyclyl, aryl, aralkyl, heteroaryl, and heteroarylalkyl include an optionally substituted alkyl, an optionally substituted alkenyl, an optionally substituted alkynyl, an optionally substituted cycloalkyl, an optionally substituted cycloalkenyl, an optionally substituted heterocyclyl, an optionally substituted aryl, an optionally substituted heteroaryl, an optionally substituted aralkyl, an optionally substituted heteraralkyl, or a haloalkyl.

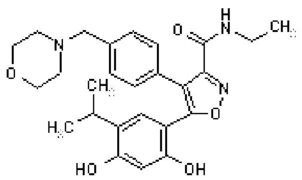
[0070] In addition, alkyl, cycloalkyl, alkylene, a heterocyclyl, and any saturated portion of a alkenyl, cycloalkenyl, alkynyl, aralkyl, and heteroaralkyl groups, may also be substituted with =O, or =S.

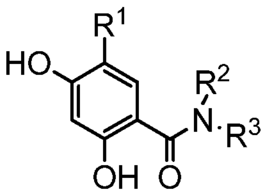
[0071] When a heterocyclyl, heteroaryl, or heteroaralkyl group contains a nitrogen atom, it may be substituted or unsubstituted. When a nitrogen atom in the aromatic ring of a heteroaryl group has a substituent the nitrogen may be a quaternary nitrogen.

[0072] As used herein, the term “lower” refers to a group having up to four atoms. For example, a “lower alkyl” refers to an alkyl radical having from 1 to 4 carbon atoms, “lower alkoxy” refers to “–O-$(C_1\text{-}C_4)$alkyl and a “lower alkenyl” or “lower alkynyl” refers to an alkenyl or alkynyl radical having from 2 to 4 carbon atoms, respectively.

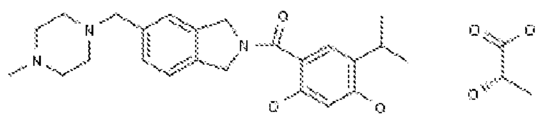
[0073] Unless indicated otherwise, the compounds of the invention containing reactive functional groups (such as (without limitation) carboxy, hydroxy, thiol, and amino moieties) also include protected derivatives thereof. “Protected derivatives” are those compounds in which a reactive site or sites are blocked with one or more protecting groups. Examples of suitable protecting groups for hydroxyl groups include benzyl, methoxymethyl, allyl, trimethylsilyl, tert-butyldimethylsilyl, acetate, and the like. Examples of suitable amine protecting groups include benzyloxycarbonyl, tert-butoxycarbonyl, tert-butyl, benzyl and fluorenylmethyloxy-carbonyl (Fmoc). Examples of suitable thiol protecting groups include benzyl, tert-butyl, acetyl, methoxymethyl and the like. Other suitable protecting groups are well known to those of ordinary skill in the art and include those found in T. W. Greene, Protecting Groups in Organic Synthesis, John Wiley & Sons, Inc. 1981.

[0074] Exemplary Hsp90 inhibitors include those disclosed in U.S. Patent Nos. 8,362,055 and 7,825,148. Examples of such compounds include AUY-922:

[0075] 

[0076] In various embodiments, the binding moiety can be an Hsp90-binding compound of formula (IV):  wherein

[0077] R^1 may be alkyl, aryl, halo, carboxamido or sulfonamido; R^2 and R^3 are independently C_1-C_5 hydrocarbyl groups optionally substituted with one or more of hydroxy, halogen, C_1-C_2 alkoxy, amino, mono- and di-C_1-C_2 alkylamino; 5- to 12- membered aryl or heteroaryl groups; or, R^2 and R^3, taken together with the nitrogen atom to which they are attached, form a 4- to 8-membered monocyclic heterocyclic group, of which up to 5 ring members are selected from O, N and S. Examples of such compounds include AT-13387: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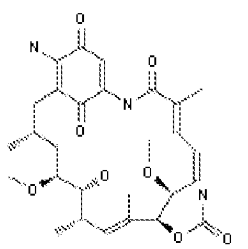
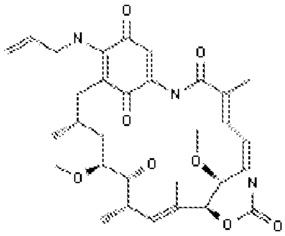
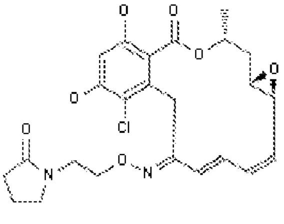
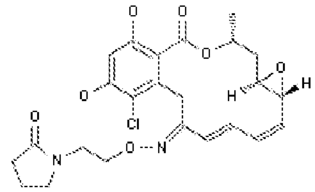
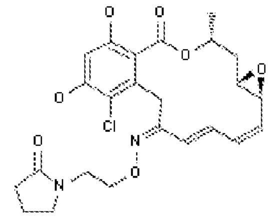
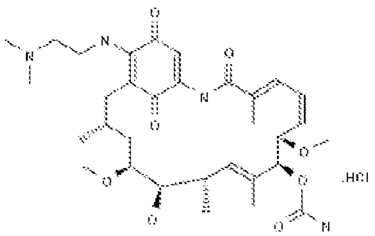
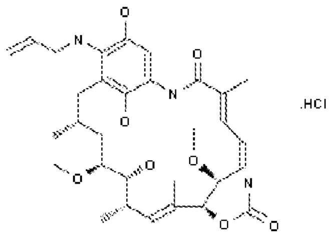
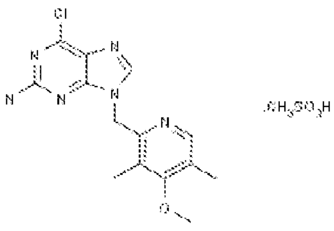
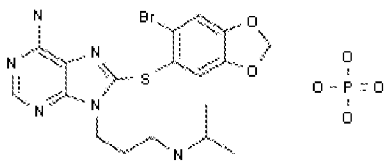
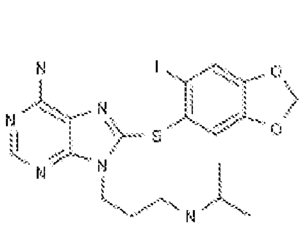
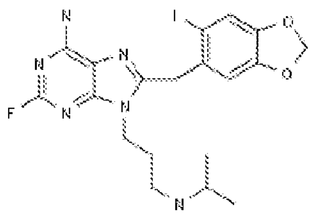
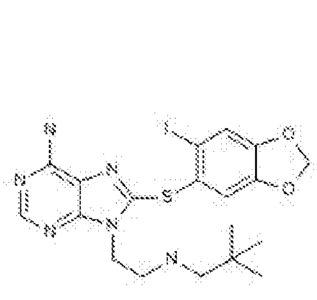
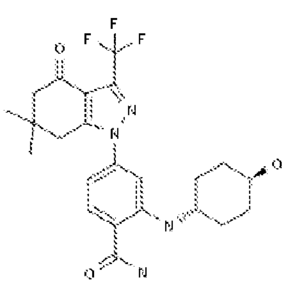
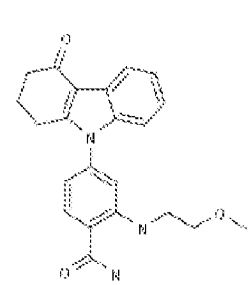
[0078] In various embodiments, the binding moiety includes an Hsp90-targeting moiety, for example one or more geldanamycins, *e.g.*, IPI-493 , macbecins, tripterins, tanespimycins, *e.g.*, 17-AAG , KF-55823 ,

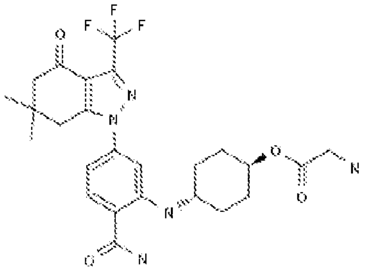
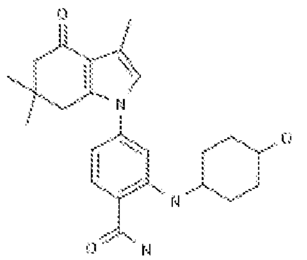
radicicols, KF-58333 , KF-58332 , 17-DMAG

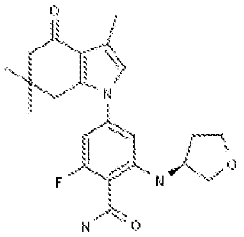
, IPI-504 , BIIB-021

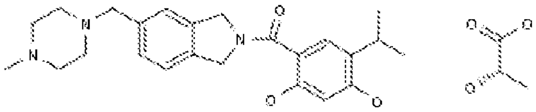
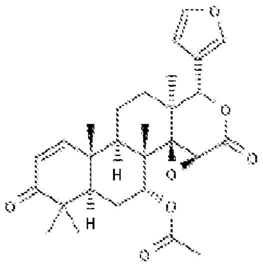
, BIIB-028, PU-H64 , PU-H71

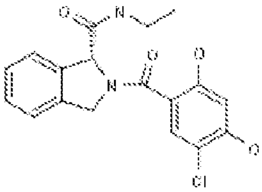
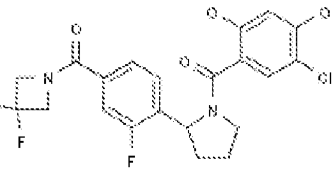
, PU-DZ8 , PU-HZ151

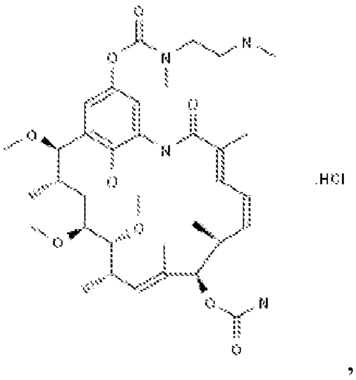
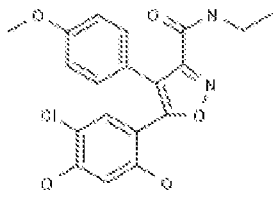
, SNX-2112 , SNX-2321 ,

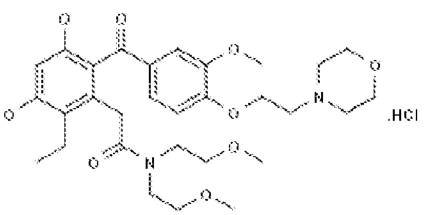
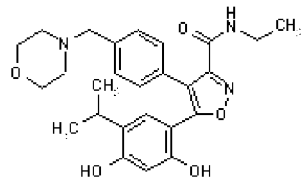
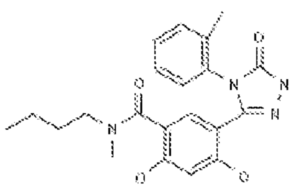
SNX-5422 , SNX-7081 , SNX-8891,

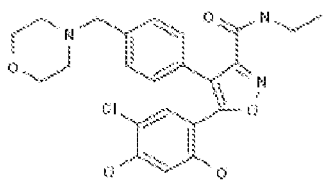
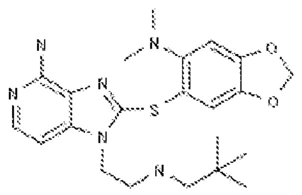
SNX-0723 , SAR-567530, ABI-287, ABI-328, AT-13387

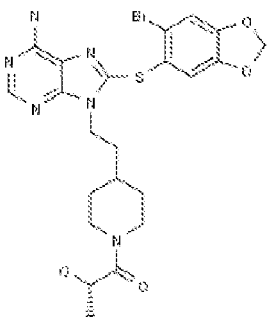
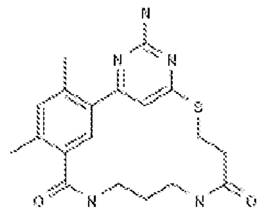
, NSC-113497 , PF-3823863

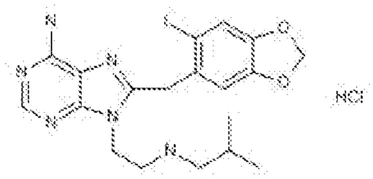
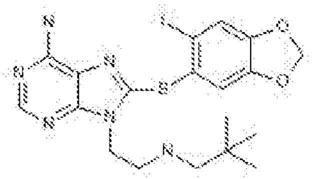
, PF-4470296 , EC-102, EC-154,

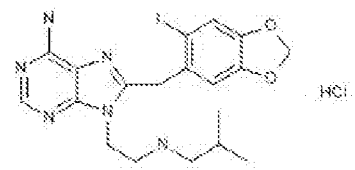
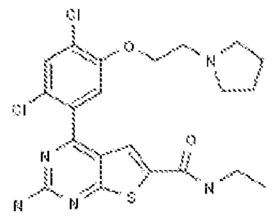
ARQ-250-RP, BC-274 , VER-50589 ,

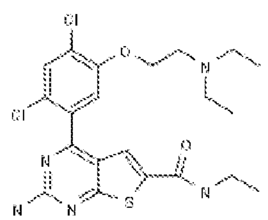
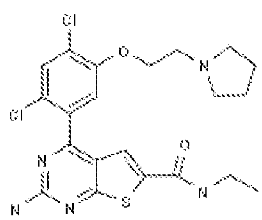
KW-2478 , BHI-001, AUY-922 , EMD-614684 , EMD-683671, XL-888, VER-51047

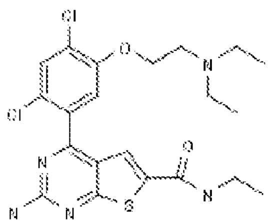
, KOS-2484, KOS-2539, CUDC-305 ,

MPC-3100 , CH-5164840 , PU-DZ13

, PU-HZ151 , PU-DZ13

, VER-82576 , VER-82160

, VER-82576 , VER-82160



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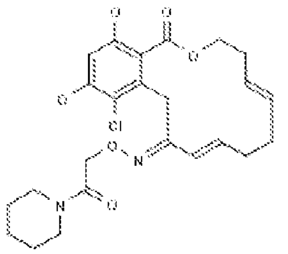

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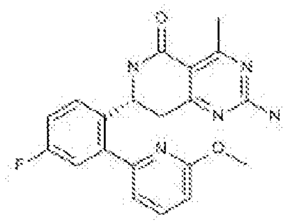

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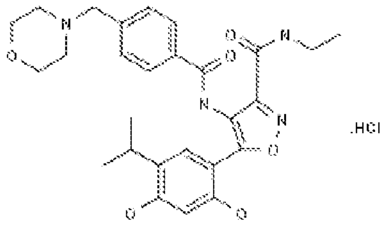

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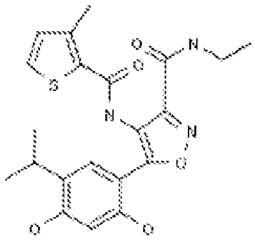

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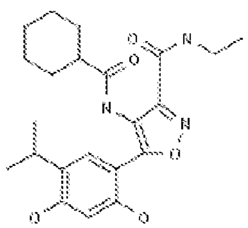

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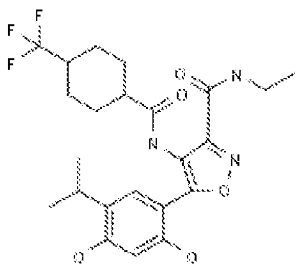
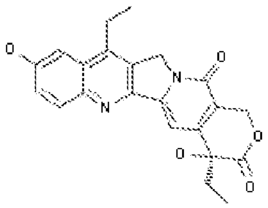


, novobiocin (a C-terminal Hsp90i.)

[0079] In various embodiments, the effector moiety is a therapeutic moiety. The therapeutic moiety can be, for example, a cytotoxic moiety. A cytotoxic moiety can be SN-38, bendamustine, a VDA, doxorubicin, pemetrexed, vorinostat, lenalidomide, irinotecan, ganetespib, docetaxel, 17-AAG, 5-FU, abiraterone, crizotinib, KW-2189, BUMB2, DC1, CC-1065, adozelesin, or (a) fragment(s) thereof.

[0080] In various embodiments, the effector moiety is an antifolate or fragments thereof (*e.g.*, temozolamide, mitozolamide, nitrogen mustards, estramustine, or chloromethine).

[0081] In various embodiments, the effector moiety includes one or more: peptidyl-prolyl isomerase ligands, *e.g.*, FK506 (tacrolimus); rapamycin, cyclosporin A; steroid hormone receptor ligands, *e.g.*, naturally occurring steroid hormones, such as estrogen, progestin, testosterone, as well as synthetic derivatives and mimetics thereof; small molecules that bind to cytoskeletal proteins, *e.g.*, antimitotic agents, such as taxanes, colchicine, colcemid, nocadozole, vinblastine, and vincristine, actin binding agents, such as cytochalasin, latrunculin, phalloidin; lenalidomide, pomalidomide, camptothecins including SN-38



, topotecan, combretastatins, capecitabine, gemcitabine, vinca alkaloids, platinum-containing compounds, metformin, HDAC inhibitors (*e.g.*, suberoylanilidehydroxamic acid (SAHA)), thymidylate synthase inhibitors such as methotrexate, pemetrexed, and raltitrexed; nitrogen mustards such as bendamustine and melphalan; 5-fluorouracil (5-FU) and its derivatives; and agents used in ADC drugs, such as vedotin and DM1.

[0082] In various embodiments, the effector moiety is derived from one or more: central nervous system depressants, *e.g.*, general anesthetics (barbiturates, benzodiazepines, steroids, cyclohexanone derivatives, and miscellaneous agents), sedative-hypnotics (benzodiazepines, barbiturates, piperidinediones and triones, quinazoline derivatives, carbamates, aldehydes and derivatives, amides, acyclic ureides, benzazepines and related drugs, phenothiazines), central voluntary muscle tone modifying drugs (anticonvulsants, such as hydantoins, barbiturates, oxazolidinediones, succinimides, acylureides, glutarimides, benzodiazepines, secondary and tertiary alcohols, dibenzazepine derivatives, valproic acid and derivatives, GABA analogs), analgesics (morphine and derivatives, oripavine derivatives, morphinan derivatives, phenylpiperidines, 2,6-methane-3-benzazocaine derivatives, diphenylpropylamines and isosteres, salicylates, *p*-aminophenol derivatives, 5-pyrazolone derivatives, arylacetic acid derivatives, fenamates and isosteres) and antiemetics (anticholinergics, antihistamines, antidopaminergics); central nervous system stimulants, *e.g.*, analeptics (respiratory stimulants, convulsant stimulants, psychomotor stimulants), narcotic antagonists (morphine derivatives, oripavine derivatives, 2,6-methane-3-benzoxacine derivatives, morphinan derivatives) nootropics; psychopharmacological/psychotropics, *e.g.*, anxiolytic sedatives (benzodiazepines, propanediol carbamates) antipsychotics (phenothiazine derivatives, thioxanthine derivatives, other tricyclic compounds, butyrophenone derivatives and isosteres, diphenylbutylamine derivatives, substituted benzamides, arylpiperazine derivatives, indole derivatives), antidepressants (tricyclic compounds, MAO inhibitors).

[0083] In various embodiments, the effector moiety is derived from one or more: respiratory tract drugs, *e.g.*, central antitussives (opium alkaloids and their derivatives); immunosuppressive agents; pharmacodynamic agents, such as peripheral nervous system drugs, *e.g.*, local anesthetics (ester derivatives, amide derivatives); drugs acting at synaptic or neuroeffector junctional sites, *e.g.*, cholinergic agents, cholinergic blocking agents, neuromuscular blocking agents, adrenergic agents, antiadrenergic agents; smooth muscle active drugs, *e.g.*, spasmolytics (anticholinergics, musculotropic spasmolytics), vasodilators, smooth muscle stimulants; histamines and antihistamines, *e.g.*, histamine and derivative thereof (betazole), antihistamines (H_1-antagonists, H_2-antagonists), histamine metabolism drugs; cardiovascular drugs, *e.g.*, cardiotonics (plant extracts, butenolides, pentadienolids, alkaloids from erythrophleum species, ionophores, adrenoceptor stimulants), antiarrhythmic drugs, antihypertensive agents, antilipidemic agents (clofibric acid derivatives, nicotinic acid derivatives, hormones and analogs, antibiotics, salicylic acid and derivatives), antivaricose drugs, hemostyptics; chemotherapeutic agents, such as anti-infective agents, *e.g.*, ectoparasiticides (chlorinated hydrocarbons, pyrethins, sulfurated compounds), anthelmintics, antiprotozoal agents, antimalarial agents, antiamebic agents, antileiscmanial drugs, antitrichomonal agents, antitrypanosomal agents, sulfonamides, antimycobacterial drugs, antiviral chemotherapeutics, and cytostatics, *i.e.*, antineoplastic agents or cytotoxic drugs, such as alkylating agents, *e.g.*, mechlorethamine hydrochloride (nitrogen mustard, mustargen, HN2), cyclophosphamide (Cytovan, Endoxana), ifosfamide (IFEX), chlorambucil (Leukeran), Melphalan (phenylalanine mustard, L-sarcolysin, Alkeran, L-PAM), busulfan (Myleran), Thiotepa (triethylenethiophosphoramide), carmustine (BiCNU, BCNU), lomustine (CeeNU, CCNU), streptozocin (Zanosar); plant alkaloids, *e.g.*, vincristine (Oncovin), vinblastine (Velban, Velbe), paclitaxel (Taxol); antimetabolites, *e.g.*, methotrexate (MTX) , mercaptopurine (Purinethol, 6-MP), thioguanine (6-TG), fluorouracil (5-FU), cytarabine (Cytosar-U, Ara-C), azacitidine (Mylosar, 5-AZA); antibiotics, *e.g.*, dactinomycin (Actinomycin D, Cosmegen), doxorubicin (Adriamycin), daunorubicin (duanomycin, Cerubidine), idarubicin (Idamycin), bleomycin (Blenoxane), picamycin (Mithramycin, Mithracin), mitomycin (Mutamycin), and other anticellular proliferative agents, *e.g.*, hydroxyurea (Hydrea), procarbazine (Mutalane), dacarbazine (DTIC-Dome), cisplatin (Platinol) carboplatin (Paraplatin), asparaginase (Elspar), etoposide (VePesid, VP-16-213), amsarcrine (AMSA, m-AMSA), mitotane (Lysodren), or mitoxantrone (Novatrone).

[0084] In various embodiments, the effector moiety is derived from one or more: anti-inflammatory agents; antibiotics, such as: aminoglycosides, *e.g.*, amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin, gentamicin, isepamicin, kanamycin, micronomcin, neomycin, netilmicin, paromycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin; amphenicols, *e.g.*, azidamfenicol, chloramphenicol, florfenicol, and theimaphenicol; ansamycins, *e.g.*, rifamide, rifampin, rifamycin, rifapentine, rifaximin; β-lactams, *e.g.*, carbacephems, carbapenems, cephalosporins, cehpamycins, monobactams, oxaphems, penicillins; lincosamides, *e.g.*, clinamycin, lincomycin; macrolides, *e.g.*, clarithromycin, dirthromycin, erythromycin; polypeptides, *e.g.*, amphomycin, bacitracin, capreomycin; tetracyclines, *e.g.*, apicycline, chlortetracycline, clomocycline; synthetic antibacterial agents, such as 2,4-diaminopyrimidines, nitrofurans, quinolones and analogs thereof, sulfonamides, or sulfones.

[0085] In various embodiments, the effector moiety is derived from one or more: antifungal agents, such as: polyenes, *e.g.*, amphotericin B, candicidin, dermostatin, filipin, fungichromin, hachimycin, hamycin, lucensomycin, mepartricin, natamycin, nystatin, pecilocin, perimycin; synthetic antifungals, such as allylamines, *e.g.*, butenafine, naftifine, terbinafine; imidazoles, *e.g.*, bifonazole, butoconazole, chlordantoin, chlormidazole, thiocarbamates, *e.g.*, tolciclate, triazoles, *e.g.*, fluconazole, itraconazole, or terconazole.

[0086] In various embodiments, the effector moiety is derived from one or more: anthelmintics, such as: arecoline, aspidin, aspidinol, dichlorophene, embelin, kosin, naphthalene, niclosamide, pelletierine, quinacrine, alantolactone, amocarzine, amoscanate, ascaridole, bephenium, bitoscanate, carbon tetrachloride, carvacrol, cyclobendazole, or diethylcarbamazine.

[0087] In various embodiments, the effector moiety is derived from one or more: antimalarials, such as: acedapsone, amodiaquin, arteether, artemether, artemisinin, artesunate, atovaquone, bebeerine, berberine, chirata, chlorguanide, chloroquine, chlorprogaunil, cinchona, cinchonidine, cinchonine, cycloguanil, gentiopicrin, halofantrine, hydroxychloroquine, mefloquine hydrochloride, 3-methylarsacetin, pamaquine, plasmocid, primaquine, pyrimethamine, quinacrine, quinidine, quinine, quinocide, quinoline, or dibasic sodium arsenate.

[0088] In various embodiments, the effector moiety is derived from one or more: antiprotozoan agents, such as: acranil, tinidazole, ipronidazole, ethylstibamine, pentamidine, acetarsone, aminitrozole, anisomycin, nifuratel, tinidazole, benzidazole, or suramin.

[0089] In various embodiments, the effector moiety includes one or more of: docetaxel or paclitaxel; BEZ235; temsirolimus; PLX4032; cisplatin; AZD8055; and crizotinib.

[0090] In various embodiments, the effector moiety includes a topotecan or irinotecan.

[0091] In various embodiments, the cytotoxic moiety is not suitable for administration alone. The cytotoxic moiety can be unsuitable for administration alone due to toxicity. The cytotoxic moiety can be unsuitable for administration alone due to undesired targeting or a lack of targeting.

[0092] In various embodiments, the binding moiety and the effector moiety are covalently attached. The binding moiety and the effector moiety can be covalently attached, for example by a linker. The linker can comprise a cleavable linker. The cleavable linker can comprise an enzymatically cleavable linker. The linker can be selected from the group consisting of disulfide, carbamate, amide, ester, and ether linkers.

[0093] In various embodiments, the SDC-TRAP has a molecular weight of less than about 1600 Dalton. For example, the SDC-TRAP molecular weight can be less than about 1600, 1550, 1500, 1450, 1400, 1350, 1300, 1250, 1200, 1150, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, or 200 Dalton.

[0094] In various embodiments, the binding moiety has a molecular weight of less than about 800 Dalton. For example, the binding moiety molecular weight can be less than about 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, or 100 Dalton.

[0095] In various embodiments, the effector moiety has a molecular weight of less than about 800 Dalton. For example, the effector moiety molecular weight can be less than about 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, or 100 Dalton.

[0096] In various embodiments, the binding moiety and the effector moiety are approximately equal in size. For example, the binding moiety and the effector moiety can have less than about a 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, or 400 Dalton difference in molecular weight.

[0097] In various embodiments, the binding moiety has a high affinity for a molecular target. For example, the binding moiety has a high affinity for a molecular target that is a K_d of 50, 100, 150, 200, 250, 300, 350, 400 nM or higher.

[0098] In various embodiments, when administered to a subject, the SDC-TRAP is present at a ratio of about 2:1, 5:1, 10:1, 25:1, 50:1, 75:1, 100:1, 150:1, 200:1, 250:1, 300:1, 400:1, 500:1, 600:1, 700:1, 800:1, 900:1, 1000:1, or greater. The ratio can be, for example, at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, or more hours from administration.

[0099] In various embodiments, the SDC-TRAP is present in target cells and/or tissue for at least 24 hours. The SDC-TRAP can be present in cancer cells for longer, for example, for at least 48, 72, 96, or 120 hours.

[00100] In various embodiments, the effector moiety is released for a period of at least 6 hours. The effector moiety can be released for a longer period, for example, for at least 12, 24, 48, 72, 96, or 120 hours.

[00101] In various embodiments, the effector moiety is selectively released inside a target cell and/or tissue.

[00102] In various embodiments, the present invention provides SDC-TRAP molecules comprising a binding moiety is an inhibitor of a target protein but that is ineffective as a therapeutic agent when administered alone. In these, and in other embodiments, the SDC-TRAP may facilitate an additive or synergistic effect between the binding moiety and effector moiety.

[00103] In various embodiments, the present invention provides method for treating a subject having a cancer comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the cancer.

[00104] In various embodiments, the present invention provides a method for treating a subject having a colon cancer comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the colon cancer.

[00105] In various embodiments, the present invention provides a method for treating a subject having a breast cancer comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the breast cancer.

[00106] In various embodiments, the present invention provides a method for treating a subject having an ovarian cancer comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the ovarian cancer.

[00107] In various embodiments, the present invention provides a method for treating a subject having a lung cancer comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the lung cancer. The lung cancer can comprise small cell lung cancer.

[00108] In various embodiments, the present invention provides a method for treating a subject having a skin cancer comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the skin cancer.

[00109] In various embodiments, the present invention provides a method for treating a subject having chronic bronchitis comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the chronic bronchitis.

[00110] In various embodiments, the present invention provides a method for treating a subject having asthma comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the asthma.

[00111] In various embodiments, the present invention provides a method for treating a subject having actinic keratosis comprising administering a therapeutically effective amount of at least one SDC-TRAP to the subject, thereby treating the actinic keratosis.

[00112] The present invention is described in further detail by the figures and examples below, which are used only for illustration purposes and are not limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

[00113] **FIG. 1** shows how an illustrative Hsp90-targeting moiety may be suitably modified at one or more positions to enhance the physical, pharmacokinetic, or pharmacodynamic properties of the conjugate.

[00114] **FIG. 2** illustrates an embodiment of a pharmaceutical conjugate having two effector moieties.

[00115] **FIG. 3** illustrates an example where the mean concentration of ganetespib in plasma is about 10 times higher than that in RBC at 5 min time point.

[00116] **FIG. 4** shows the change in tumor volume following treatment with SDC-TRAP-0063, compared to effector moiety irinotecan and vehicle control in an HCT-116 colon cancer model.

[00117] **FIG. 5** shows the change in animal body weight following treatment with SDC-TRAP-0063, compared to effector moiety irinotecan and vehicle control in an HCT-116 colon cancer model.

[00118] **FIG. 6** shows the change in tumor volume following treatment with SDC-TRAP-0063, compared to effector moiety irinotecan and vehicle control in an MCF-7 breast cancer model.

[00119] **FIG. 7** shows the change in animal body weight following treatment with SDC-TRAP-0063, compared to effector moiety irinotecan and vehicle control in an MCF-7 breast cancer model.

[00120] **FIG. 8** demonstrates a dose-dependent decrease in tumor volume compared to binding moiety or effector moiety alone.

[00121] **FIGS. 9, 10**, and **11** show that following SDC-TRAP intravenous injection, binding moiety and effector moiety accumulate and persist in tumor, but rapidly diminish in plasma and heart in three mouse strains.

[00122] **FIG. 12** illustrates the stability of seven SDC-TRAP species in mouse plasma.

[00123] **FIG. 13** illustrates the stability of five additional SDC-TRAP species plus effector moiety SN-38 in mouse plasma and cell culture media.

[00124] **FIG. 14** depicts the stability of SDC-TRAP-0063 and SN-38 alone.

[00125] **FIGS. 15 A-C** depict the tissue distribution of SDC-TRAP-0063, and its degradation products DP-1 and SN-38, respectively in plasma, tumor and heart.

[00126] **FIG. 16** illustrates the kinetic solubility of an SDC-TRAP-0063 in ganetespib placebo formulation (35% v/v tween 80, 40% v/v PEG-300, 25% v/v dehydrated alcohol).

[00127] **FIG. 17** illustrates the physical appearance of an SDC-TRAP-0063 stock solution prepared in DMSO and after addition of Tween 80.

[00128] **FIG. 18** depicts a physical observations of an infusion solution prepared using different diluents.

[00129] **FIG. 19** illustrates the antitumor activity of SDC-TRAP-0063, irinotecan, and ganetespib + irinotecan in human SCLC tumor xenografts. %T/C values for day 60 are used. 1/8 mice in irinotecan group was found dead on day 46.

[00130] **FIG. 20 (A & B)** illustrates the expression of indicated analytes from HCT-116 xenografts. (A): Expression of indicated analytes from HCT-116 xenografts treated as indicated. (B): Expression of indicated analytes from HCT-116 tumor bearing animals 24 hr post drug.

[00131] **FIG. 21** illustrates the expression of the indicated analytes in SCLC xenograft tumors 24 hrs after drug exposure.

[00132] **FIG. 22** illustrates the expression of the indicated analytes in SCLC xenograft tumors 24, 72, and 96 hrs after drug exposure.

[00133] **FIG. 23** illustrates the antitumor activity of SDC-TRAP-0063, irinotecan and ganetespib + irinotecan in HCT-116 human colorectal xenografts. %T/C values for day 35 are used.

[00134] **FIG. 24** illustrates the antitumor activity of SDC-TRAP-0063, irinotecan and ganetespib + irinotecan in MCF-7 human xenografts. %T/C values for day 66 are used.

[00135] **FIG. 25** illustrates the antitumor activity of SDC-TRAP-0063, irinotecan and ganetespib + irinotecan in SK-OV-3 xenografts in female Balb/c nude mice. %T/C values for day 38 are used.

[00136] Other features and advantages of the instant invention will be apparent from the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

[00137] The present invention provides molecules including an effector moiety conjugated to a binding moiety that directs the effector moiety to a biological target of interest. The molecules of the invention allow for selective targeting of an effector moiety by trapping the molecules of the invention in a desired cell, *e.g.*, a cancer cell. The molecules can be described as Small molecule Drug Conjugates that are TRAPped intracellularly (SDC-TRAP), due to their selective binding to high concentration intracellular proteins. In order for the molecules of the invention to be trapped within the cells of interest, the binding moieties that are part of the SDC-TRAP molecules interact with proteins that are overexpressed in targeted cells. In

exemplary embodiments, the proteins that are overexpressed are characteristic of a particular disease or disorder. Accordingly, the present invention provides compositions, kits, and methods (*e.g.*, therapeutic, diagnostic, and imaging) that include the molecules of the invention.

[00138] In one embodiment of the invention, SDC-TRAPs allow for the delivery of a effector molecule that would otherwise be unsuitable for administration alone due to toxicity and/or undesired systemic effects. Using the targeted delivery molecules described herein (SDC-TRAPs) allows for effector moieties that are too toxic to administer by current methods to be dosed at lower levels thereby allowing the toxic effector to be targeted to specific diseased cells at sub-toxic levels.

[00139] In various exemplary aspects and embodiments, the present invention provides compounds for treating cancer. For example, an SDC-TRAP can comprise an Hsp90 binding moiety (*i.e.*, targeting Hsp90, which is overexpressed in cancer cells compared to normal cells) and an effector moiety (*e.g.*, the Hsp90 binding moiety can be an Hsp90 inhibitor that is conjugated to a cytotoxic agent). As indicated above, the invention is exemplified herein in terms of Hsp90-targeted binding moieties and cytotoxic agents. Other binding moieties that are contemplated, mentioned or described herein are intended to be included within the scope of the invention.

[00140] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a binding moiety and an effector moiety, wherein the SDC-TRAP molecule is able to enter a cell by passive transport. The ability of an SDC-TRAP to enter a cell by passive transport can be a result of one or more unique chemical properties of the SDC-TRAP (*e.g.*, size, weight, charge, polarity, hydrophobicity, etc.) and can facilitate the delivery and/or action of the SDC-TRAP. The ability of an SDC-TRAP to enter a cell by passive transport is a functional property, which along with its physico-chemical properties, differentiates SDC-TRAPs from other targeted molecules such as antibody-drug conjugates.

[00141] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a binding moiety and an effector moiety, wherein SDC-TRAP molecule is able to enter a cell by active transport. The ability of an SDC-TRAP to enter a cell by active transport can be a result of one or more unique chemical properties of the SDC-TRAP and can facilitate the delivery and/or action of the SDC-TRAP. Example of SDC-TRAP active transport can include, for example, endocytosis, phagocytosis, pinocytosis, and exocytosis.

[00142] In various aspects and embodiments, the present invention provides an SDC-TRAP having a molecular weight of less than about 1600 Dalton (*e.g.*, less than about 1600, 1550, 1500, 1450, 1400, 1350, 1300, 1250, 1200, 1150, 1100, 1050, 1000, 950, 900, 850, 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, etc.). Similarly, in various aspects and embodiments, the present invention provides a binding moiety having a molecular weight of less than about 800 Dalton (*e.g.*, less than about 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100, etc.) and/or an effector moiety having a molecular weight of less than about 800 Dalton (*e.g.*, less than about 800, 750, 700, 650, 600, 550, 500, 450, 400, 350, 300, 250, 200, 150, 100, etc.). The overall molecular weight of an SDC-TRAP, and the individual weights of a binding moiety, effector moiety, and any linking moiety, can affect transport of the SDC-TRAP. In various examples, it has been observed that lower molecular weights can facilitate delivery and/or activity of an SDC-TRAP.

[00143] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising an Hsp90 binding moiety and an effector moiety, wherein the Hsp90 binding moiety and the effector moiety are approximately equal in size (*e.g.*, the Hsp90 binding moiety and the effector moiety have less than about a 25, 50, 75, 100, 125, 150, 175, 200, 225, 250, 275, 300, 325, 350, 375, 400, etc. Dalton difference in molecular weight.) In various examples, it has been observed that lower differences in molecular weight can facilitate delivery and/or activity of an SDC-TRAP.

[00144] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a target protein-interacting binding moiety. A target protein-interacting binding moiety can selectively interact with any one or more domains of a target protein. For example, where a target protein is Hsp90, the binding moiety can be an Hsp90 binding moiety that interacts with the N-terminal domain of Hsp90, the C-terminal domain of Hsp90, and/or the middle domain of Hsp90. Selective interaction with any one or more domains of a target protein can advantageously increase specificity and/or increase the concentration of molecular targets within a target tissue and/or cell.

[00145] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a binding moiety having a high affinity for a molecular target (*e.g.*, a K_d of 50, 100, 150, 200, 250, 300, 350, 400 nM or higher). For example, where a binding moiety is an Hsp90 binding moiety, the Hsp90 binding moiety can have a K_d of 50, 100, 150, 200, 250, 300, 350, 400 nM or higher. A binding moiety having a high affinity for a molecular target can advantageously improve targeting and/or increase the resonance time of the SDC-TRAP in a target cell and/or tissue.

[00146] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein when administered to a subject the SDC-TRAP is present at a ratio of about 2:1 in tumor cells compared to plasma. The ratio can be higher, for example, about 5:1, 10:1, 25:1, 50:1, 75:1, 100:1, 150:1, 200:1, 250:1, 300:1, 400:1, 500:1, 600:1, 700:1, 800:1, 900:1, 1000:1, or greater. In various aspects and embodiments, the ratio is at 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, or more hours from administration. The effectiveness of targeting can be reflected in the ratio of SDC-TRAP in a target cell and/or tissue compared to plasma.

[00147] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the SDC-TRAP is present in target (*e.g.*, cancer) cells for at least 24 hours. The SDC-TRAP can be present in cancer cells for longer, for example, for at least 48, 72, 96, or 120 hours. It can be advantageous for an SDC-TRAP to be present in target cells for longer periods of time to increase the therapeutic effect of a given dose of SDC-TRAP and/or increase an interval between administrations of SDC-TRAP.

[00148] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the effector moiety is released for a period of at least 6 hours. The effector moiety can be released for a longer period, for example, for at least 12, 24, 48, 72, 96, or 120 hours. Selective release can be used to control, delay, and/or extend the period of release of an effector moiety and, therefore, increase the therapeutic effect of a given dose of SDC-TRAP, decrease the undesired side effects of a given dose of SDC-TRAP, and/or increase an interval between administrations of SDC-TRAP.

[00149] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising an Hsp90 binding moiety and an effector moiety, wherein the effector moiety is selectively released inside a target (*e.g.*, cancer) cell. Selective release can be achieved, for example, by a cleavable linker (*e.g.*, an enzymatically cleavable linker). Selective release can be used to decrease undesired toxicity and/or unwanted side effects. For example, an SDC-TRAP can be designed where an effector moiety such is inactive (or relatively inactive) in a conjugated form, but active (or more active) after it is selectively released inside a target (*e.g.*, cancer) cell.

[00150] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the SDC-TRAP allows for the use of an effector moiety that is otherwise toxic or unfit for administration to a subject. The effector moiety can be unfit for administration to a subject because of undesired toxicity. In such cases, a strategy such as selective release may be used to address the undesired toxicity. The effector moiety can be unfit for administration to a subject because of undesired targeting or a lack of targeting. Targeting can address such problems, for example, by minimizing systemic toxicity while maximizing local toxicity at a target (*e.g.*, a tumor).

[00151] In various aspects and embodiments, the SDC-TRAP can exhibit decreased and/or minimized toxicity concurrently with increased efficacy (*e.g.*, as compared to that of the effector moiety when used alone). Decreasing and/or minimizing toxicity can encompass reducing toxicity to a predetermined level (*e.g.*, a regulatory guideline or suggested level, for example promulgated by the US Food and Drug Administration "FDA"). Increasing efficacy can encompass increasing efficacy to a predetermined level (*e.g.*, a regulatory guideline or suggested level, for example promulgated by the US FDA). Similarly, decreasing and/or minimizing toxicity concurrently with increasing efficacy can encompass achieving a predetermined therapeutic ratio (*e.g.*, a regulatory guideline or suggested value, for example promulgated by the US FDA).

[00152] Decreasing and/or minimizing toxicity can encompass, for example, reducing toxicity by 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 %, or more. Increasing efficacy can encompass, for example, increasing efficacy by 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 125, 150, 175, 200, 250, 300, 400, 500%, or more. Decreasing and/or minimizing toxicity concurrently with increasing efficacy can encompass, for example: essentially the same efficacy with decreased toxicity; essentially the same toxicity with increased efficacy; or decreased toxicity and increased efficacy. Similarly, decreasing and/or minimizing toxicity concurrently with increasing efficacy can encompass, for example, scenarios such as: increased efficacy enabling a lower dose (*e.g.*, lower dose of effector moiety with a correspondingly lower net toxicity) and decreased toxicity enabling a higher dose (*e.g.*, higher dose of effector moiety without a correspondingly higher net toxicity).

[00153] In various aspects and embodiments, the present invention provides an SDC-TRAP comprising a binding moiety (*e.g.*, Hsp90 binding moiety) and an effector moiety, wherein the binding moiety is an inhibitor (*e.g.*, Hsp90 inhibitor) that is ineffective as a therapeutic agent when administered alone. In such cases, the SDC-TRAP may facilitate an additive or synergistic effect between the binding moiety and effector moiety, thereby advantageously improving the efficacy and/or reducing the side effects of a therapy.

[00154] In order that the present invention may be more readily understood, certain terms are first defined. In addition, it should be noted that whenever a value or range of values of a parameter are recited, it is intended that values and ranges intermediate to the recited values are also intended to be part of this invention. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention belongs. It is also to be understood that the terminology employed is for the purpose of describing particular embodiments, and is not intended to be limiting.

[00155] Definitions

[00156] The articles "a," "an," and "the" are used herein to refer to one or to more than one (*i.e.* to at least one) of the grammatical object of the article unless otherwise clearly indicated by contrast. By way of example, "an element" means one element or more than one element.

[00157] The term "including" is used herein to mean, and is used interchangeably with, the phrase "including but not limited to."

[00158] The term "or" is used herein to mean, and is used interchangeably with, the term "and/or," unless context clearly indicates otherwise.

[00159] The term "such as" is used herein to mean, and is used interchangeably, with the phrase "such as but not limited to."

[00160] Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1 %, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein can be modified by the term about.

[00161] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 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, or 50.

[00162] The recitation of a listing of chemical group(s) in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[00163] Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

[00164] As used herein, the term "subject" refers to human and non-human animals, including veterinary subjects. The term "non-human animal" includes all vertebrates, *e.g.*, mammals and non-mammals, such as non-human primates, mice, rabbits, sheep, dog, cat, horse, cow, chickens, amphibians, and reptiles. In a preferred embodiment, the subject is a human and may be referred to as a patient.

[00165] As used herein, the terms "treat," "treating" or "treatment" refer, preferably, to an action to obtain a beneficial or desired clinical result including, but not limited to, alleviation or amelioration of one or more signs or symptoms of a disease or condition, diminishing the extent of disease, stability (*i.e.*, not worsening) state of disease, amelioration or palliation of the disease state, diminishing rate of or time to progression, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival in the absence of treatment. Treatment does not need to be curative.

[00166] A "therapeutically effective amount" is that amount sufficient to treat a disease in a subject. A therapeutically effective amount can be administered in one or more administrations.

[00167] By "diagnosing" and the like, as used herein, refers to a clinical or other assessment of the condition of a subject based on observation, testing, or circumstances for identifying a subject having a disease, disorder, or condition based on the presence of at least one indicator, such as a sign or symptom of the disease, disorder, or condition. Typically, diagnosing using the method of the invention includes the observation of the subject for multiple indicators of the disease, disorder, or condition in conjunction with the methods provided herein. Diagnostic methods provide an indicator that a disease is or is not present. A single diagnostic test typically does not provide a definitive conclusion regarding the disease state of the subject being tested.

[00168] The terms "administer," "administering" or "administration" include any method of delivery of a pharmaceutical composition or agent into a subject's system or to a particular region in or on a subject. In certain embodiments of the invention, an agent is administered intravenously, intramuscularly, subcutaneously, intradermally, intranasally, orally, transcutaneously, or mucosally. In a preferred embodiment, an agent is administered intravenously. Administering an agent can be performed by a number of people working in concert. Administering an agent includes, for example, prescribing an agent to be administered to a subject and/or providing instructions, directly or through another, to take a specific agent, either by self-delivery, *e.g.*, as by oral delivery, subcutaneous delivery, intravenous delivery through a central line, etc.; or for delivery by a trained professional, *e.g.*, intravenous delivery, intramuscular delivery, intratumoral delivery, etc.

[00169] As used herein, the term "survival" refers to the continuation of life of a subject which has been treated for a disease or condition, *e.g.*, cancer. The time of survival can be defined from an arbitrary point such as time of entry into a clinical trial, time from completion or failure or an earlier treatment regimen, time from diagnosis, etc.

[00170] As used herein, the term "recur" refers to the re-growth of tumor or cancerous cells in a subject in whom primary treatment for the tumor has been administered. The tumor may recur in the original site or in another part of the body. In one embodiment, a tumor that recurs is of the same type as the original tumor for which the subject was treated. For example, if a subject had an ovarian cancer tumor, was treated and subsequently developed another ovarian cancer tumor, the tumor has recurred. In addition, a cancer can recur in or metastasize to a different organ or tissue than the one where it originally occurred.

[00171] As used herein, the terms "identify" or "select" refer to a choice in preference to another. In other words, to identify a subject or select a subject is to perform the active step of picking out that particular subject from a group and confirming the identity of the subject by name or other distinguishing feature.

[00172] As used herein, the term "benefit" refers to something that is advantageous or good, or an advantage. Similarly, the term "benefiting," as used herein, refers to something that improves or advantages. For example, a subject will benefit from treatment if they exhibit a decrease in at least one sign or symptom of a disease or condition (*e.g.*, tumor shrinkage, decrease in tumor burden, inhibition or decrease of metastasis, improving quality of life ("QOL"), if there is a delay of time to progression ("TTP"), if there is an increase of overall survival ("OS"), etc.), or if there is a slowing or stopping of disease progression (*e.g.*, halting tumor growth or metastasis, or slowing the rate of tumor growth or metastasis). A benefit can also include an improvement in quality of life, or an increase in survival time or progression free survival.

[00173] The terms "cancer" or "tumor" are well known in the art and refer to the presence, *e.g.*, in a subject, of cells possessing characteristics typical of cancer-causing cells, such as uncontrolled proliferation, immortality, metastatic potential, rapid growth and proliferation rate, decreased cell death/apoptosis, and certain characteristic morphological features. Cancer cells are often in the form of a solid tumor. However, cancer also includes non-solid tumors, *e.g.*, blood tumors, *e.g.*, leukemia, wherein the cancer cells are derived from bone marrow. As used herein, the term "cancer" includes pre-malignant as well as malignant cancers. Cancers include, but are not limited to, acoustic neuroma, acute leukemia, acute lymphocytic leukemia, acute myelocytic leukemia (monocytic, myeloblastic, adenocarcinoma, angiosarcoma, astrocytoma, myelomonocytic and promyelocytic), acute T-cell leukemia, basal cell carcinoma, bile duct carcinoma, bladder cancer, brain cancer, breast cancer, bronchogenic carcinoma, cervical cancer, chondrosarcoma, chordoma, choriocarcinoma, chronic leukemia, chronic lymphocytic leukemia, chronic myelocytic (granulocytic) leukemia, chronic myelogenous leukemia, colon cancer, colorectal cancer, craniopharyngioma, cystadenocarcinoma, diffuse large B-cell lymphoma, Burkitt's lymphoma, dysproliferative changes (dysplasias and metaplasias), embryonal carcinoma, endometrial cancer, endotheliosarcoma, ependymoma, epithelial carcinoma, erythroleukemia, esophageal cancer, estrogen-receptor positive breast cancer, essential thrombocythemia, Ewing's tumor, fibrosarcoma, follicular lymphoma, germ cell testicular cancer, glioma, heavy chain disease, hemangioblastoma, hepatoma, hepatocellular cancer, hormone insensitive prostate cancer, leiomyosarcoma, liposarcoma, lung cancer, lymphagioendotheliosarcoma, lymphangiosarcoma, lymphoblastic leukemia, lymphoma (Hodgkin's and non-Hodgkin's), malignancies and hyperproliferative disorders of the bladder, breast, colon, lung, ovaries, pancreas, prostate, skin, and uterus, lymphoid malignancies of T-cell or B-cell origin, leukemia, lymphoma, medullary carcinoma, medulloblastoma, melanoma, meningioma, mesothelioma, multiple myeloma, myelogenous leukemia, myeloma, myxosarcoma, neuroblastoma, non-small cell lung cancer, oligodendroglioma, oral cancer, osteogenic sarcoma, ovarian cancer, pancreatic cancer, papillary adenocarcinomas, papillary carcinoma, pinealoma, polycythemia vera, prostate cancer, rectal cancer, renal cell carcinoma, retinoblastoma, rhabdomyosarcoma, sarcoma, sebaceous gland carcinoma, seminoma, skin cancer, small cell lung carcinoma, solid tumors (carcinomas and sarcomas), small cell lung cancer, stomach cancer, squamous cell carcinoma, synovioma, sweat gland carcinoma, thyroid cancer, Waldenstrom's macroglobulinemia, testicular tumors, uterine cancer, and Wilms' tumor. Other cancers include primary cancer, metastatic cancer, oropharyngeal cancer, hypopharyngeal cancer, liver cancer, gall bladder cancer, bile duct cancer, small intestine cancer, urinary tract cancer, kidney cancer, urothelium cancer, female genital tract cancer, uterine cancer, gestational trophoblastic disease, male genital tract cancer, seminal vesicle cancer, testicular cancer, germ cell tumors, endocrine gland tumors, thyroid cancer, adrenal cancer, pituitary gland cancer, hemangioma, sarcoma arising from bone and soft tissues, Kaposi's sarcoma, nerve cancer, ocular cancer, meningial cancer, glioblastomas, neuromas, neuroblastomas, Schwannomas, solid tumors arising from hematopoietic malignancies such as leukemias, metastatic melanoma, recurrent or persistent ovarian epithelial cancer, fallopian tube cancer, primary peritoneal cancer, gastrointestinal stromal tumors, colorectal cancer, gastric cancer, melanoma, glioblastoma multiforme, non-squamous non-small-cell lung cancer, malignant glioma, epithelial ovarian cancer, primary peritoneal serous cancer, metastatic liver cancer, neuroendocrine carcinoma, refractory malignancy, triple negative breast cancer, HER2- amplified breast cancer, nasopharageal cancer, oral cancer, biliary tract, hepatocellular carcinoma, squamous cell carcinomas of the head and neck (SCCHN), non-medullary thyroid carcinoma, recurrent glioblastoma multiforme, neurofibromatosis type 1, CNS cancer, liposarcoma, leiomyosarcoma, salivary gland cancer, mucosal melanoma, acral/ lentiginous melanoma, paraganglioma, pheochromocytoma, advanced metastatic cancer, solid tumor, triple negative breast cancer, colorectal cancer, sarcoma, melanoma, renal carcinoma, endometrial cancer, thyroid cancer, rhabdomysarcoma, multiple myeloma, ovarian cancer, glioblastoma, gastrointestinal stromal tumor, mantle cell lymphoma, and refractory malignancy.

[00174] "Solid tumor," as used herein, is understood as any pathogenic tumor that can be palpated or detected using imaging methods as an abnormal growth having three dimensions. A solid tumor is differentiated from a blood tumor such as leukemia. However, cells of a blood tumor are derived from bone marrow; therefore, the tissue producing the cancer cells is a solid tissue that can be hypoxic.

[00175] "Tumor tissue" is understood as cells, extracellular matrix, and other naturally occurring components associated with the solid tumor.

[00176] As used herein, the term "isolated" refers to a preparation that is substantially free (*e.g.*, 50%, 60%, 70%, 80%, 90% or more, by weight) from other proteins, nucleic acids, or compounds associated with the tissue from which the preparation is obtained.

[00177] The term "sample" as used herein refers to a collection of similar fluids, cells, or tissues isolated from a subject. The term "sample" includes any body fluid (*e.g.*, urine, serum, blood fluids, lymph, gynecological fluids, cystic fluid, ascetic fluid, ocular fluids, and fluids collected by bronchial lavage and/or peritoneal rinsing), ascites, tissue samples (*e.g.*, tumor samples) or a cell from a subject. Other subject samples include tear drops, serum, cerebrospinal fluid, feces, sputum, and cell extracts. In one embodiment, the sample is removed from the subject. In a particular embodiment, the sample is urine or serum. In another embodiment, the sample does not include ascites or is not an ascites sample. In another embodiment, the sample does not include peritoneal fluid or is not peritoneal fluid. In one embodiment, the sample comprises cells. In another embodiment, the sample does not comprise cells. Samples are typically removed from the subject prior to analysis. However, tumor samples can be analyzed in the subject, for example, using imaging or other detection methods.

[00178] The term "control sample," as used herein, refers to any clinically relevant comparative sample, including, for example, a sample from a healthy subject not afflicted with cancer, a sample from a subject having a less severe or slower progressing cancer than the subject to be assessed, a sample from a subject having some other type of cancer or disease, a sample from a subject prior to treatment, a sample of non-diseased tissue (*e.g.*, non-tumor tissue), a sample from the same origin and close to the tumor site, and the like. A control sample can be a purified sample, protein, and/or nucleic acid provided with a kit. Such control samples can be diluted, for example, in a dilution series to allow for quantitative measurement of analytes in test samples. A control sample may include a sample derived from one or more subjects. A control sample may also be a sample made at an earlier time point from the subject to be assessed. For example, the control sample could be a sample taken from the subject to be assessed before the onset of the cancer, at an earlier stage of disease, or before the administration of treatment or of a portion of treatment. The control sample may also be a sample from an animal model, or from a tissue or cell lines derived from the animal model, of the cancer. The level in a control sample that consists of a group of measurements may be determined, *e.g.*, based on any appropriate statistical measure, such as, for example, measures of central tendency including average, median, or modal values.

[00179] As used herein, the term "obtaining" is understood herein as manufacturing, purchasing, or otherwise coming into possession of.

[00180] As used herein, the term "identical" or "identity" is used herein in relation to amino acid or nucleic acid sequences refers to any gene or protein sequence that bears at least 30% identity, more preferably 40%, 50%, 60%, 70%, 75%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, and most preferably 95%, 96%, 97%, 98%, 99% or more identity to a known gene or protein sequence over the length of the comparison sequence. Protein or nucleic acid sequences with high levels of identity throughout the sequence can be said to be homologous. A "homologous" protein can also have at least one biological activity of the comparison protein. In general, for proteins, the length of comparison sequences will be at least 10 amino acids, preferably 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 150, 175, 200, 250, or at least 300 amino acids or more. For nucleic acids, the length of comparison sequences will generally be at least 25, 50, 100, 125, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 800, or at least 850 nucleotides or more.

[00181] As used herein, "detecting," "detection" and the like are understood that an assay performed for identification of a specific analyte in a sample. The amount of analyte or activity detected in the sample can be none or below the level of detection of the assay or method.

[00182] The terms "modulate" or "modulation" refer to upregulation (*i.e.*, activation or stimulation), downregulation (*i.e.*, inhibition or suppression) of a level, or the two in combination or apart. A "modulator" is a compound or molecule that modulates, and may be, *e.g.*, an agonist, antagonist, activator, stimulator, suppressor, or inhibitor.

[00183] The term "expression" is used herein to mean the process by which a polypeptide is produced from DNA. The process involves the transcription of the gene into mRNA and the translation of this mRNA into a polypeptide. Depending on the context in which used, "expression" may refer to the production of RNA, or protein, or both.

[00184] The terms "level of expression of a gene" or "gene expression level" refer to the level of mRNA, as well as pre-mRNA nascent transcript(s), transcript processing intermediates, mature mRNA(s) and degradation products, or the level of protein, encoded by the gene in the cell.

[00185] As used herein, "level of activity" is understood as the amount of protein activity, typically enzymatic activity, as determined by a quantitative, semi-quantitative, or qualitative assay. Activity is typically determined by monitoring the amount of product produced in an assay using a substrate that produces a readily detectable product, *e.g.*, colored product, fluorescent product, or radioactive product.

[00186] As used herein, "changed as compared to a control" sample or subject is understood as having a level of the analyte or diagnostic or therapeutic indicator (*e.g.*, marker) to be detected at a level that is statistically different than a sample from a normal, untreated, or control sample control samples include, for example, cells in culture, one or more laboratory test animals, or one or more human subjects. Methods to select and test control samples are within the ability of those in the art. An analyte can be a naturally occurring substance that is characteristically expressed or produced by the cell or organism (*e.g.*, an antibody, a protein) or a substance produced by a reporter construct (*e.g.*, β-galactosidase or luciferase). Depending on the method used for detection the amount and measurement of the change can vary. Changed as compared to a control reference sample can also include a change in one or more signs or symptoms associated with or diagnostic of disease, *e.g.*, cancer. Determination of statistical significance is within the ability of those skilled in the art, *e.g.*, the number of standard deviations from the mean that constitute a positive result.

[00187] "Elevated" or "lower" refers to a patient's value of a marker relative to the upper limit of normal ("ULN") or the lower limit of normal ("LLN") which are based on historical normal control samples. As the level of the marker present in the subject will be a result of the disease, and not a result of treatment, typically a control sample obtained from the patient prior to onset of the disease will not likely be available. Because different labs may have different absolute results, values are presented relative to that lab's upper limit of normal value (ULN).

[00188] The "normal" level of expression of a marker is the level of expression of the marker in cells of a subject or patient not afflicted with cancer. In one embodiment, a "normal" level of expression refers to the level of expression of the marker under normoxic conditions.

[00189] An "over-expression" or "high level of expression" of a marker refers to an expression level in a test sample that is greater than the standard error of the assay employed to assess expression, and is preferably at least 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, 4, 5, 6, 7, 8, 9, or 10 times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subject not having the marker associated disease, *i.e.*, cancer). In one embodiment, expression of a marker is compared to an average expression level of the marker in several control samples.

[00190] A "low level of expression" or "under-expression" of a marker refers to an expression level in a test sample that is less than at least 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0. 1 times the expression level of the marker in a control sample (*e.g.*, sample from a healthy subject not having the marker associated disease, *i.e.*, cancer). In one embodiment, expression of a marker is compared to an average expression level of the marker in several control samples.

[00191] As used herein, "binding" is understood as having at least a 10^2 or more, 10^3 or more, preferably 10^4 or more, preferably 10^5 or more, preferably 10^6 or more preference for binding to a specific binding partner as compared to a non-specific binding partner (*e.g.*, binding an antigen to a sample known to contain the cognate antibody).

[00192] "Determining" as used herein is understood as performing an assay or using a diagnostic method to ascertain the state of someone or something, *e.g.*, the presence, absence, level, or degree of a certain condition, biomarker, disease state, or physiological condition.

[00193] "Prescribing" as used herein is understood as indicating a specific agent or agents for administration to a subject.

[00194] As used herein, the terms "respond" or "response" are understood as having a positive response to treatment with a therapeutic agent, wherein a positive response is understood as having a decrease in at least one sign or symptom of a disease or condition (*e.g.*, tumor shrinkage, decrease in tumor burden, inhibition or decrease of metastasis, improving quality of life ("QOL"), delay of time to progression ("TTP"), increase of overall survival ("OS"), etc.), or slowing or stopping of disease progression (*e.g.*, halting tumor growth or metastasis, or slowing the rate of tumor growth or metastasis). A response can also include an improvement in quality of life, or an increase in survival time or progression free survival.

[00195] The terms "administer," "administering" or "administration" can include any method of delivery of a pharmaceutical composition or agent into a subject's system or to a particular region in or on a subject. In certain embodiments of the invention, an Hsp90 inhibitor is administered intravenously, intramuscularly, subcutaneously, intradermally, intranasally, orally, transcutaneously, or mucosally. In a preferred embodiment, an agent is administered intravenously. Administering can be performed by a number of people working in concert. Administering an agent includes, for example, prescribing an agent to be administered to a subject and/or providing instructions, directly or through another, to take a specific agent, either by self-delivery, *e.g.,* as by oral delivery, subcutaneous delivery, intravenous delivery through a central line, etc.; or for delivery by a trained professional, *e.g.,* intravenous delivery, intramuscular delivery, intratumoral delivery, etc.

[00196] As used herein, the term "high concentration" refers to the concentration of SDC-TRAP that accumulates in target cells of the invention due to the selective binding of the binding moiety of the SDC-TRAP to the target protein. In one embodiment, the concentration is higher than in similar cells that do not overexpress the target protein, *e.g.*, lung cancer cells as compared to non-cancerous lung cells. In another embodiment, the concentration is higher in target cells compared to cells that do not express, or overexpress, the target protein. In exemplary embodiments, the high concentration is 1.5, 2, 3, 4, 5, 10, 15, 20, 50, 100, 1000 times or more than cells that are not targeted by the SDC-TRAP molecules of the invention.

[00197] The term "moiety" refers generally to a portion of a molecule, which may be a functional group, a set of functional groups, and/or a specific group of atoms within a molecule, that is responsible for a characteristic chemical, biological, and/or medicinal property of the molecule.

[00198] The term "binding moiety" refers to low molecular weight (*e.g.*, less than about 800, 700, 600, 500, 400, 300, 200, or 100 etc. Dalton) organic compounds, which may serve as a therapeutic or a regulator of a biological process. Binding moieties include molecules that can bind to a biopolymer such as protein, nucleic acid, or polysaccharide and acts as an effector, altering the activity or function of the biopolymer. Binding moieties can have a variety of biological functions, serving as cell signaling molecules, as tools in molecular biology, as drugs in medicine, as pesticides in farming, and in many other roles. These compounds can be natural (such as secondary metabolites) or artificial (such as antiviral drugs); they may have a beneficial effect against a disease (such as drugs) or may be detrimental (such as teratogens and carcinogens). Biopolymers such as nucleic acids, proteins, and polysaccharides (such as starch or cellulose) are not binding moieties, although their constituent monomers – ribo- or deoxyribo-nucleotides, amino acids, and monosaccharides, respectively – are often considered to be. Small oligomers are also usually considered binding moieties, such as dinucleotides, peptides such as the antioxidant glutathione, and disaccharides such as sucrose.

[00199] As used herein, a "protein interacting binding moiety" or "binding moiety" refers to a binding moiety, or portion thereof, that interacts with a predetermined target. The interaction is achieved through some degree of specificity and/or affinity for the target. Both specificity and affinity is generally desirable, although in certain cases higher specificity may compensate for lower affinity and higher affinity may compensate for lower specificity. Affinity and specificity requirements will vary depending upon various factors including, but not limited to, absolute concentration of the target, relative concentration of the target (*e.g.*, in cancer vs. normal cells), potency and toxicity, route of administration, and/or diffusion or transport into a target cell. The target can be a molecule of interest and/or localized in an area of interest. For example, the target can be a therapeutic target and/or localized in an area targeted for a therapy (*e.g.*, a protein that is overexpressed in cancerous cells, as compared to normal cells). In one particular example, a target can be a chaperonin protein such as Hsp90 and the binding moiety can be an Hsp90 binding moiety (*e.g.*, therapeutic, cytotoxic, or imaging moiety). Preferentially, the binding moiety will enhance, be compatible with, or not substantially reduce, passive transport of a conjugate including the binding moiety into a cell, *e.g.*, a cell comprising a target protein.

[00200] The term "effector moiety" refers to a molecule, or portion thereof, that has an effect on a target and/or proximally to the target. In various preferred embodiments, the effector moiety is a binding moiety, or portion thereof. An effect can include, but is not limited to, a therapeutic effect, an imaging effect, and/or a cytotoxic effect. At a molecular or cellular level, an effect can include, but is not limited to, promotion or inhibition of the target's activity, labeling of the target, and/or cell death. Preferentially, the effector moiety will enhance, be compatible with, or not substantially reduce, passive transport of a conjugate including the effector moiety into a cell comprising a target. Different effector moieties can be used together and therapeutics in accordance with the present invention may include more than one effector moiety (*e.g.*, two or more different (or same) effector moieties in a single therapeutic in accordance with the present invention, two or more different therapeutics in accordance with the present invention including different effector moieties).

[00201] In some embodiments, the effector moiety is selected from the group consisting of peptidyl-prolyl isomerase ligands; rapamycin, cyclosporin A; steroid hormone receptor ligands, antimitotic agents, actin binding agents, camptothecins, topotecan, combretastatins, capecitabine, gemcitabine, vinca alkaloids, platinum-containing compounds, metformin, HDAC inhibitors, thymidylate synthase inhibitors; nitrogen mustards; 5-fluorouracil (5-FU) and its derivatives, or a combination thereof.

[00202] In some embodiments, the effector moiety is selected from the group consisting of FK506; rapamycin, cyclosporin A, estrogen, progestin, testosterone, taxanes, colchicine, colcemid, nocadozole, vinblastine, vincristine, cytochalasin, latrunculin, phalloidin, lenalidomide, pomalidomide, SN-38, topotecan, combretastatins, capecitabine, gemcitabine, vinca alkaloids, metformin, suberoylanilidehydroxamic acid (SAHA), methotrexate, pemetrexed, raltitrexed, bendamustine, melphalan; 5-fluorouracil (5-FU), vedotin and DM1, or a combination thereof.

[00203] The term “small molecule drug conjugate that is trapped intracellularly” or “binding moiety drug conjugate that is trapped intracellularly” or “SDC-TRAP” refers to a binding moiety and effector moiety joined to one another, or acting as if joined to one another. A binding moiety and effector moiety can be joined through essentially any chemical or physical force, either directly (*e.g.*, binding moiety and effector moiety viewed as two moieties on the same molecule, or a single moiety having both functions) or through an intermediate (*e.g.*, linker). For example, a binding moiety and effector moiety can be joined by one or more covalent bonds, ionic bonds, hydrogen bonds, the hydrophobic effect, dipole–dipole forces, ion–dipole forces, dipole-induced dipole forces, instantaneous dipole-induced dipole forces, and/or combinations thereof. Preferentially, the SDC-TRAP will be capable of passive and/or active transport into a cell comprising a target. Moreover, SDC-TRAP molecules of the invention may comprise multiple effector molecules conjugated to the binding moiety.

[00204] The term “linker” or “linking moiety,” as used herein in the context of binding moiety, effector moieties, and/or SDC-TRAPs refers to a chemical moiety that joins two other moieties (*e.g.*, a binding moiety and an effector moiety). A linker can covalently join a binding moiety and an effector moiety. A linker can include a cleavable linker, for example an enzymatically cleavable linker. A linker can include a disulfide, carbamate, amide, ester, and/or ether linkers.

[00205] In some embodiments, the linker or linking moiety of an SDC-TRAP can be advantageous when compared to the limited linking chemistry of antibody-drug conjugates (ADC). For example, unlike ADCs that are limited by the need to maintain the structure and/or stability of an antibody, SDC-TRAPs can use a wider range of linking chemistries and/or solvents (*e.g.*, that can alter, distort, or denature an antibody).

[00206] As used herein, a "ligand" is a substance (*e.g.*, a binding moiety) that can form a complex with a biomolecule. The ligand and/or formation of the ligand-biomolecule complex can have a biological or chemical effect, such as a therapeutic effect, cytotoxic effect, and/or imaging effect.

[00207] As used herein, a "prodrug" is a pharmacological substance that is administered in an inactive or less than fully active form and that is subsequently converted to an active pharmacological agent (*i.e.*, the drug) through a metabolic processes. Prodrugs can be used to improve how the intended drug is absorbed, distributed, metabolized, and/or excreted. A prodrug may also be used to improve how selectively the intended drug interacts with cells or processes that are not its intended target (*e.g.*, to reduce adverse or unintended effects of the intended drug, for example a chemotherapy drug).

[00208] The phrase "Hsp90 ligand or a prodrug thereof" refers generally to molecules that bind to and in some cases effect Hsp90, and inactive forms (*i.e.*, prodrugs) thereof. An Hsp90 ligand can be an "Hsp90 inhibitor," which is understood as a therapeutic agent that reduces the activity of Hsp90 either by directly interacting with Hsp90 or by, for example, preventing the formation of the Hsp90/CDC37 complex such that the expression and proper folding of at least one client protein of Hsp90 is inhibited. "Hsp90" includes each member of the family of heat shock proteins having a mass of about 90-kilodaltons. For example, in humans the highly conserved Hsp90 family includes cytosolic Hsp90□ and Hsp90□ isoforms, as well as GRP94, which is found in the endoplasmic reticulum, and HSP75/TRAP1, which is found in the mitochondrial matrix. As used herein, Hsp90 inhibitors include, but are not limited to ganetespib, geldanamycin (tanespimycin), *e.g.*, IPI-493, macbecins, tripterins, tanespimycins, *e.g.*, 17-AAG (alvespimycin), KF-55823, radicicols, KF-58333, KF-58332, 17-DMAG, IPI-504, BIIB-021, BIIB-028, PU-H64, PU-H71, PU-DZ8, PU-HZ151, SNX-2112, SNX-2321, SNX-5422, SNX-7081, SNX-8891, SNX-0723, SAR-567530, ABI-287, ABI-328, AT-13387, NSC-113497, PF-3823863, PF-4470296, EC-102, EC-154, ARQ-250-RP, BC-274, VER-50589, KW-2478, BHI-001, AUY-922, EMD-614684, EMD-683671, XL-888, VER-51047, KOS-2484, KOS-2539, CUDC-305, MPC-3100, CH-5164840, PU-DZ13, PU-HZ151, PU-DZ13, VER-82576, VER-82160, VER-82576, VER-82160, NXD-30001, NVP-HSP990, SST-0201CL1, SST-0115AA1, SST-0221AA1, SST-0223AA1, novobiocin (a C-terminal Hsp90i, herbinmycin A, radicicol, CCT018059, PU-H71, or celastrol.

[00209] The term “therapeutic moiety” refers to molecule, compound, or fragment thereof that is used for the treatment of a disease or for improving the well-being of an organism or that otherwise exhibit healing power (*e.g.*, pharmaceuticals, drugs, and the like). A therapeutic moiety can be a chemical, or fragment thereof, of natural or synthetic origin used for its specific action against disease, for example cancer. Therapeutic agents used for treating cancer may be called chemotherapeutic agents. As described herein, a therapeutic moiety is preferentially a small molecule. Exemplary small molecule therapeutics include those that are less than 800 Daltons, 700 Daltons, 600 Daltons, 500 Daltons, 400 Daltons, or 300 Daltons.

[00210] The term “cytotoxic moiety” refers to molecule, compound, or fragment thereof that has a toxic or poisonous effect on cells, or that kills cells. Chemotherapy and radiotherapy are forms of cytotoxic therapy. Treating cells with a cytotoxic moiety can produce a variety of results – cells may undergo necrosis, stop actively growing and dividing, or activate a genetic program of controlled cell death (*i.e.*, apoptosis). Examples of cytotoxic moieties include, but are not limited to, SN-38, bendamustine, VDA, doxorubicin, pemetrexed, vorinostat, lenalidomide, irinotecan, ganetespib, docetaxel, 17-AAG, 5-FU, abiraterone, crizotinib, KW-2189, BUMB2, DC1, CC-1065, adozelesin,, or fragment(s) thereof.

[00211] The term “imaging moiety” refers to a molecule, compound, or fragment thereof that facilitates a technique and/or process used to create images or take measurements of a cell, tissue, and/or organism (or parts or functions thereof) for clinical and/or research purposes. An imaging moiety can produce, for example, a signal through emission and/or interaction with electromagnetic, nuclear, and/or mechanical (*e.g.*, acoustic as in ultrasound) energy. An imaging moiety can be used, for example, in various radiology, nuclear medicine, endoscopy, thermography, photography, spectroscopy, and microscopy methods.

[00212] “Pharmaceutical conjugate” refers to a non-naturally occurring molecule that includes a binding moiety (*e.g.*, an Hsp90-targeting moiety) associated with an effector moiety, where these two components may also be covalently bonded to each other either directly or through a linking group.

[00213] The term “drug” refers to any active agent that affects any biological process. Active agents that are considered drugs for purposes of this application are agents that exhibit a pharmacological activity. Examples of drugs include active agents that are used in the prevention, diagnosis, alleviation, treatment or cure of a disease condition.

[00214] By "pharmacologic activity" is meant an activity that modulates or alters a biological process so as to result in a phenotypic change, *e.g.*, cell death, cell proliferation etc.

[00215] By "pharmacokinetic property" is meant a parameter that describes the disposition of an active agent in an organism or host.

[00216] By "half-life" is meant the time for one-half of an administered drug to be eliminated through biological processes, *e.g.*, metabolism, excretion, etc.

[00217] The term "efficacy" refers to the effectiveness of a particular active agent for its intended purpose, *i.e.*, the ability of a given active agent to cause its desired pharmacologic effect.

[00218] Binding Moiety-Effector Moiety Drug Conjugates that are Trapped Intracellularly (SDC-TRAPs)

[00219] The present invention provides SDC-TRAPs, as well as SDC-TRAP compositions, kits, and methods of use thereof. SDC-TRAPs include a binding moiety (*e.g.*, a binding moiety such as a ligand) conjugated to an effector moiety (*e.g.*, a pharmacological agent such as a drug or imaging agent). These two moieties can be joined by a linker, *e.g.*, a covalently-bonded linking group. SDC-TRAPs are useful in a variety of therapeutic, imaging, diagnostic, and/or research applications. In one illustrative example of cancer therapy, an SDC-TRAP can be a pharmaceutical conjugate of an Hsp90-binding moiety such as an Hsp90 ligand or inhibitor associated with an effector moiety such as a therapeutic or cytotoxic agent.

[00220] In various embodiments, an SDC-TRAP can be further characterized in that the binding moiety (*e.g.*, targeting moiety) and effector moiety are different, such that the pharmaceutical conjugate may be viewed as a heterodimeric compound produced by the joining of two different moieties. In terms of function, SDC-TRAP molecules have a targeting functionality and effector functionality (*e.g.*, therapeutic, imaging, diagnostic). These functions are provided by corresponding chemical moieties that can be different (or, in some cases, the same). SDC-TRAPs can include any one or more binding moieties conjugated to any one or more effector moieties. In some embodiments, a composition or method can include a combination of two or more binding moieties and/or two or more effector moieties (*e.g.*, a combination therapy and/or multi target therapy) embodied in one or more different types of SDC-TRAPs.

[00221] In various embodiments, an SDC-TRAP is further characterized by its ability to passively diffuse and/or be actively transported into a target cell of interest. The diffusion and/or transport properties of the SDC-TRAP can be derived, at least in part, from ionic, polar, and/or hydrophobic properties of the SDC-TRAP. In preferred embodiments, the SDC-TRAP enter cells primarily by passive diffusion. The diffusion and/or transport properties of the SDC-TRAP can be derived, at least in part, from the molecular weight of the SDC-TRAP, the binding moiety, the effector moiety, and/or the similarity in weight between the binding moiety and the effector moiety. SDC-TRAPs are desirably small, such as in comparison to antibody-drug conjugates ("ADCs"). For example, the molecular weight of an SDC-TRAP can be less than about 1600, 1500, 1400, 1300, 1200, 1100, 1000, 900, 800, 700, 600, 500, or 400 Daltons. A binding moiety and an effector moiety can each be less than about 1000, 900, 800, 700, 600, 500, 400, 300, or 200 Daltons. A binding moiety and an effector moiety can be approximately equal in size (*e.g.*, differ in weight by less than 400, 350, 300, 250, 200, 150, 100, or 50 Daltons).

[00222] Delivery of an effector molecule by an SDC-TRAP can result in greater potency compared to administering an untargeted drug comprising the same effector moiety, for example, because the SDC-TRAP can be localized at a desired target for an extended period of time through the association of a binding moiety and its target. Such localization can cause an effector moiety to be active and/or released in a target cell and/or tissue over an extended period of time. This resonance time can be selected through deliberate design of a linker moiety. In contrast, administration of the drug by itself *in vivo* can be more apt to have a shorter resonance time in a given target cell and/or tissue – if it traverses into the cell at all – due to the lack of an "anchor" within the cell.

[00223] SDC-TRAPs, in part because they comprise a targeting moiety and are relatively small in size, can be efficiently taken up or internalized by a target cell. Conversely, uptake or internalization is relatively inefficient for ADCs, which must deal with limited antigen expression and relatively inefficient internalization mechanisms for the antibody portion of the molecule. Hsp90 provides a good illustrative example of a difference between SDC-TRAPs and conventional ADCs. By way of comparison, the localization rate of radiolabeled monoclonal antibodies at a tumor in patients is low, on the order of 0.003–0.08% of the injected dose/g tumor. In contrast, a much higher accumulation rate (15–20% injected dose/g tumor) has been measured for SDC-TRAPs in mouse tumor xenografts.

[00224] SDC-TRAP pharmaceutical conjugates in accordance with the present invention can represent a significant advance over the state of the art in targeted drugs. SDC-TRAPs have broad application in many therapeutic, imaging, and diagnostic application. As discussed above, SDC-TRAPs are advantageously small in comparison to ADCs, enabling better penetration of solid tumors and more rapid clearance from normal tissues (*e.g.*, reduced toxicity). The design of SDC-TRAPs (*e.g.*, a structure-property relationship) can be established using methods and rationales within the grasp of those of ordinary skill in the art, and companion imaging diagnostics for targeted therapies may also easily be provided, in view of the simpler chemistry involved.

[00225] SDC-TRAPs of the invention are characterized by selective targeting of SDC-TRAPs to target cells in which a target protein is overexpressed. This leads to high intracellular concentrations of SDC-TRAP molecules in target cells as compared to non-targeted cells. Likewise, SDC-TRAPs of the invention are characterized by low concentrations of SDC-TRAP in non-targeted cells.

[00226] One illustrative embodiment involves a conjugate of an Hsp90 binding moiety linked to a chelator (*i.e.*, the effector moiety, for metals such as In or Gd, which conjugate may function as an imaging agent for the cells/tissues targeted by the conjugate). Another, illustrative embodiment involves a conjugate of an Hsp90 binding moiety linked to a chemotherapeutic (*i.e.*, the effector moiety, for example, SN-38). Alternatively, an illustrative SDC-TRAP is contemplated wherein an Hsp90 targeting moiety bearing radiolabeled halogen (*e.g.*, such as an iodine isotope) can serve to image the cells/tissues targeted by the conjugate, and the effector moiety can be drug to treat the targeted cells/tissues. The progression of treatment may therefore be determined by imaging the tissues being treated and reviewing the images for the presence or absence of the labeled conjugate. Such embodiments are readily adaptable to essentially any cancer, or other chemotherapeutic target. Molecular targets (*e.g.*, interacting with a binding moiety) used to target a particular cell or tissue can be selected based upon their presence in the target cell or tissue and/or their relative abundance in the target cell or tissue (*e.g.*, disease-related versus normal cells).

[00227] SDC-TRAP molecules of the present invention represent a new class of drugs. One particular advantage of SDC-TRAPs is that they can be designed to selectively deliver an effector moiety (*e.g.*, a chemotherapeutic drug) into a targeted cell because of the relative overexpression or presence of a binding moiety's molecular target in the cell. After the binding moiety binds the molecular target, the effector moiety is thereafter available (*e.g.*, through cleavage of a linker moiety joining the binding moiety and the effector moiety) to act upon the cell. Accordingly, SDC-TRAPs employ a different mechanism from strategies currently used in the art, for example delivering an Hsp90 inhibitor to a cell using HPMA copolymer-Hsp90i conjugates, Hsp90i prodrugs, nanoparticle-Hsp90i conjugates, or micellar methodologies.

[00228] SDC-TRAPs can also described by the formula:

Binding moiety-L-E

[00229] Where "binding moiety" is a protein interacting binding moiety; L is a conjugation or linking moiety (*e.g.*, a bond or a linking group); and E is an effector moiety. These elements are discussed in the context of additional illustrative examples below. However, while features of each element may be discussed separately, design and selection of an SDC-TRAP can involve the interplay and/or cumulative effect of features of each element (*e.g.*, diffusion, binding, and effect).

[00230] Once SDC-TRAP molecules of the invention enter a target cell the effector molecule is released from the SDC-TRAP. In one embodiment, the effector molecule has no activity until it is released from the SDC-TRAP. Accordingly, once the SDC-TRAP molecules enter a target cell an equilibrium exists between free and bound SDC-TRAP molecules. In one embodiment, the effector moiety is only released from the SDC-TRAP when the SDC-TRAP is not associated with the target protein. For example, when an SDC-TRAP molecule is not bound intracellular enzymes can access the linker region thereby freeing the effector moiety. Alternatively, when free SDC-TRAP molecules may be able to release effector molecules through, for example, hydrolysis of the bond or linker that connects the binding moiety and effector moiety.

[00231] Accordingly, the rate of effector molecule release and the amount of effector molecule released can be controlled by using binding moieties that bind to the target protein with different affinities. For example, binding moieties that bind to the target protein with lower affinity will be free, resulting in higher concentrations of unbound intracellular SDC-TRAP, and thereby resulting in higher concentrations of free effector molecule. Therefore, in at least one embodiment, irreversibly-binding binding moieties are incompatible with certain aspects of the invention, *e.g.*, those embodiments where effector molecule release is based on free intracellular SDC-TRAP molecules.

[00232] In one embodiment, SDC-TRAPs have favorable safety profiles, for example, when compared to, for example, the binding moiety or effector molecule alone. One reason for the increased safety profile is the rapid clearance of SDC-TRAP molecules that do not enter into a target cell.

[00233] A number of exemplary SDC-TRAP molecules are set forth in the examples. Specifically a number of Hsp90-specific SDC-TRAP molecules are described and used to demonstrate the efficacy of SDC-TRAP molecules.

[00234] Binding Moieties

[00235] A primary role of a binding moiety is to ensure that the SDC-TRAP delivers its payload – the effector moiety – to its target by binding to a molecular target in or on a target cell or tissue. In this respect, it is not necessary that the binding moiety also have an effect on the target (*e.g.*, in the case of an Hsp90-targeting moiety, to inhibit Hsp90 in the manner that Hsp90is are known to do, that is, exhibit pharmacological activity or interfere with its function), but in some embodiments, the binding moiety does have an effect on the target. Accordingly, in various embodiments, an activity of the SDC-TRAP is due solely to the effector moiety exerting a pharmacological effect on the target cell(s), which has been better facilitated by the pharmaceutical conjugate targeting the target cell(s). In other embodiments, an activity of the SDC-TRAP is due in part to the binding moiety – that is, the binding moiety can have an effect beyond targeting.

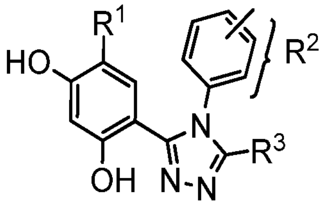
[00236] The molecular target of a binding moiety may or may not be part of a complex or structure of a plurality of biological molecules, *e.g.*, lipids, where the complexes or structures may include lipoproteins, lipid bilayers, and the like. However, in many embodiments, the molecular target to which the binding moiety binds will be free (*e.g.*, cytoplasmic globular protein and/or not be part of a macromolecular assembly or aggregation). The present invention can exploit the selectively high presence of a molecular target in locations of high physiological activity (*e.g.*, Hsp90 in oncological processes). For example, where a drug target is an intracellular drug target, a corresponding molecular target (*e.g.*, Hsp90) can be present in the cell. Likewise, where a drug target is an extracellular drug target, a corresponding molecular target (*e.g.*, Hsp90) can be extracellular, proximal, or associated with the extracellular cell membrane of the target cell or tissue.

[00237] In various embodiments, a binding moiety can effect a target cell or tissue (*e.g.*, in the case of an Hsp90-targeting moiety that in fact inhibits Hsp90, for example, Hsp90i). In such embodiments, a pharmacological activity of the binding moiety contributes to, complements, or augments, the pharmacological activity of the effector moiety. Such embodiments go beyond the advantages combination therapies (*e.g.*, a cancer combination therapy of Hsp90i and a second drug such as ganetespib or crizotinib) by providing a therapy that can be carried out by administration of a single SDC-TRAP that realizes both the benefits of the combination therapy and targeting. Other examples of such SDC-TRAPs include conjugates of an Hsp90i (such as ganetespib) and a second cancer drug such as docetaxel or paclitaxel (*e.g.*, in NSCLC); BEZ235 (*e.g.*, in melanoma, prostate and/or NSCLC); temsirolimus (*e.g.*, renal cell carcinoma (RCC), colon, breast and/or NSCLC); PLX4032 (*e.g.*, in melanoma); cisplatin (*e.g.*, colon, breast cancer); AZD8055 (*e.g.*, in NSCLC); and crizotinib (*e.g.*, ALK^+ NSCLC).

[00238] A range of pharmaceutical activities can be achieved by judicious selection of a binding moiety and an effector moiety. For example, for treating solid tumors, *e.g.*, colon cancer, high continuous doses of antimetabolites such as capecitabine or gemcitabine tend to be required in combination with other drugs. A conjugate having an Hsp90-targeting moiety with lower binding affinity or inhibitory activity to Hsp90, *e.g.*, as determined by a HER2 degradation assay, can be designed to meet this need. Such a conjugate can comprise an effector moiety that is a strong, potent antimetabolite such as 5-FU, to afford a high dose of the conjugate that may be dosed relatively frequently. Such an approach not only achieves the aim of providing a high dose of an antimetabolite fragment at the tumor, but also lowers the toxicity of administering the drug on its own, owing to the plasma stability of SDC-TRAPs of the invention, and the ability of the Hsp90-targeting moiety to deliver the antimetabolite to the desired cells or tissues.

[00239] In embodiments where solid tumors such as SCLC or colorectal cancer are to be treated with drugs such as topotecan or irinotecan, only low doses of the drug may be dosed. Due to the very high intrinsic activity of these drugs, an SDC-TRAP should be designed to provide a low dose of such drugs at the target tissue. In this scenario, for example, an Hsp90-targeting moiety having a higher binding affinity or inhibitory activity to Hsp90 (*e.g.*, as determined by a HER2 degradation assay) can sufficiently maintain the presence of the drug in the tissue at a very high level, to ensure that enough of the drug reaches and is retained by the desired target tissue due to the low dosing.

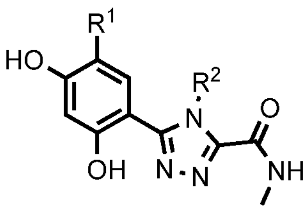
[00240] In various illustrative embodiments where a molecular target of a binding moiety is Hsp90, the binding moiety can be an Hsp90-targeting moiety, for example a triazole/resorcinol-based compound that binds Hsp90, or a resorcinol amide-based compound that binds Hsp90, *e.g.*, ganetespib, AUY-922 or AT-13387. In another embodiment, the binding moiety may advantageously be an Hsp90-binding compound of formula (I):



wherein

[00241] R^1 may be alkyl, aryl, halide, carboxamide or sulfonamide; R^2 may be alkyl, cycloalkyl, aryl or heteroaryl, wherein when R^2 is a 6 membered aryl or heteroaryl, R^2 is substituted at the 3- and 4-positions relative to the connection point on the triazole ring, through which a linker L is attached; and R^3 may be SH, OH, -CONHR^4, aryl or heteroaryl, wherein when R^3 is a 6 membered aryl or heteroaryl, R^3 is substituted at the 3 or 4 position.

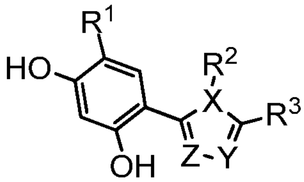
[00242] In another embodiment, the binding moiety may advantageously be an Hsp90-binding compound of formula (II):



wherein

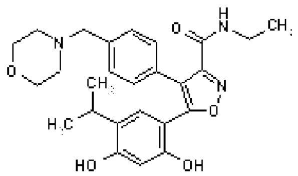
[00243] R^1 may be alkyl, aryl, halo, carboxamido, sulfonamido; and R^2 may be optionally substituted alkyl, cycloalkyl, aryl or heteroaryl. Examples of such compounds include 5-(2,4-dihydroxy-5-isopropylphenyl)-N-(2-morpholinoethyl)-4-(4-(morpholinomethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide and 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(4-methylpiperazin-1-yl)phenyl)-N-(2,2,2-trifluoroethyl)-4H-1,2,4-triazole-3-carboxamide.

[00244] In another embodiment, the binding moiety may advantageously be an Hsp90-binding compound of formula (III):

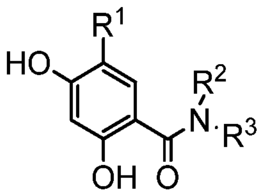


wherein

[00245] X, Y, and Z may independently be CH, N, O or S (with appropriate substitutions and satisfying the valency of the corresponding atoms and aromaticity of the ring); R^1 may be alkyl, aryl, halide, carboxamido or sulfonamido; R^2 may be substituted alkyl, cycloalkyl, aryl or heteroaryl, where a linker L is connected directly or to the extended substitutions on these rings; R^3 may be SH, OH, NR^4R^5 and -$CONHR^6$, to which an effector moiety may be connected; R^4 and R^5 may independently be H, alkyl, aryl, or heteroaryl; and R^6 may be alkyl, aryl, or heteroaryl, having a minimum of one functional group to which an effector moiety may be connected. Examples of such compounds include AUY-922:

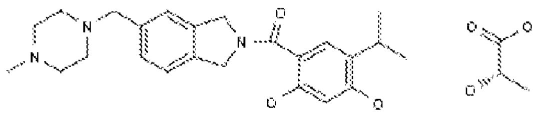


[00246] In another embodiment, the binding moiety may advantageously be an Hsp90-binding compound of formula (IV):

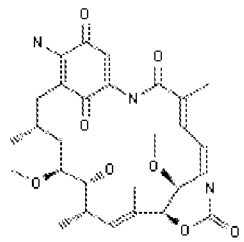
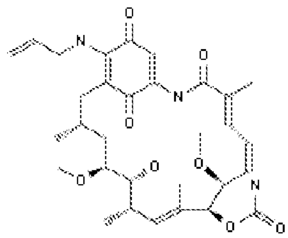
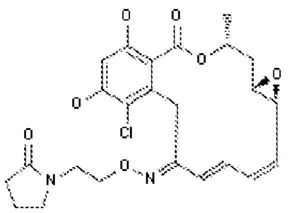
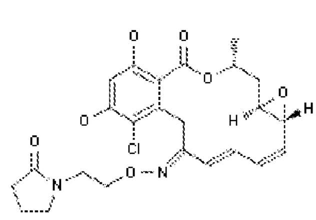
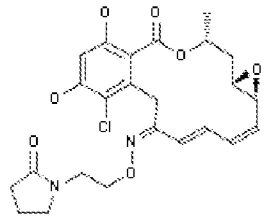
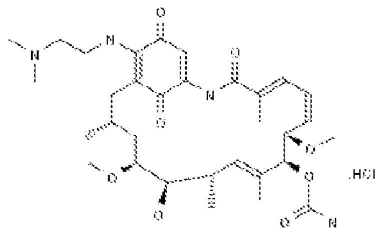
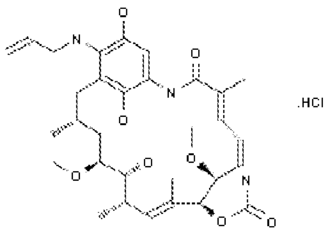


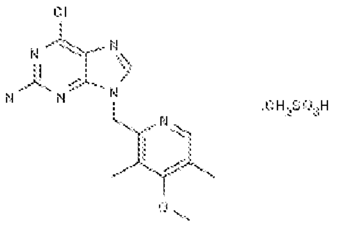
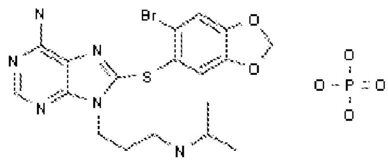
wherein

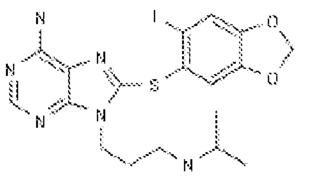
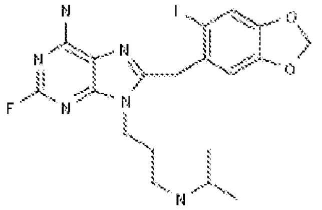
[00247] R^1 may be alkyl, aryl, halo, carboxamido or sulfonamido; R^2 and R^3 are independently C_1-C_5 hydrocarbyl groups optionally substituted with one or more of hydroxy, halogen, C_1-C_2 alkoxy, amino, mono- and di-C_1-C_2 alkylamino; 5- to 12- membered aryl or heteroaryl groups; or, R^2 and R^3, taken together with the nitrogen atom to which they are attached, form a 4- to 8- membered monocyclic heterocyclic group, of which up to 5 ring members are selected from O, N and S. Examples of such compounds include AT-13387:

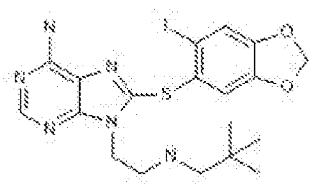
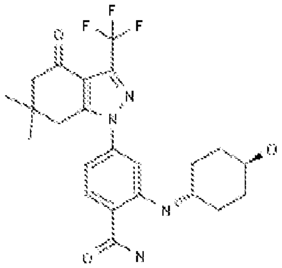
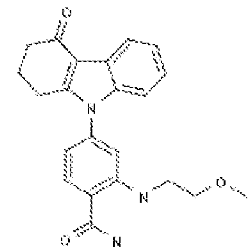
.

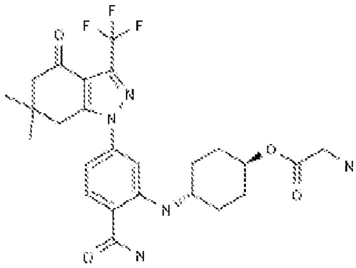
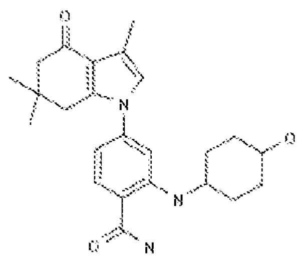
[00248] In certain embodiments, to enhance the bioavailability or delivery of the pharmaceutical conjugate, the binding moiety may be a prodrug of the Hsp90-binding compound. FIG. 1 shows how the illustrated Hsp90-targeting moiety may be suitably modified at one or more positions to enhance the physical, pharmacokinetic or pharmacodynamic properties of the conjugate.

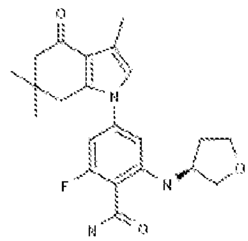
[00249] Specific examples of suitable Hsp90-targeting moieties include geldanamycins, *e.g.*, IPI-493 , macbecins, tripterins, tanespimycins, *e.g.*, 17-AAG , KF-55823 , radicicols, KF-58333 , KF-58332 , 17-DMAG , IPI-504 , BIIB-021

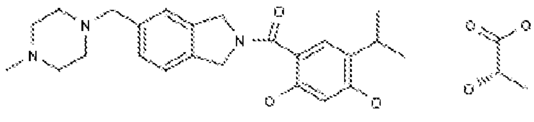
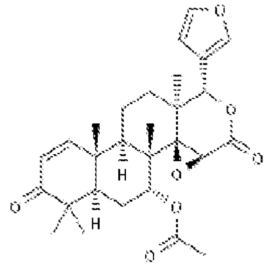
 , BIIB-028, PU-H64  , PU-H71

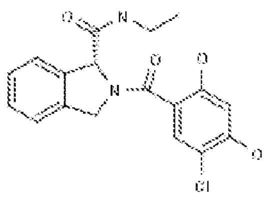
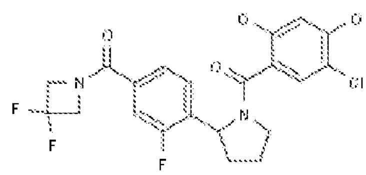
 , PU-DZ8  , PU-HZ151

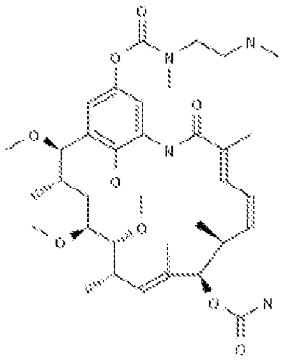
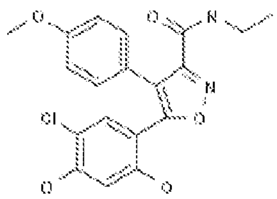
 , SNX-2112  , SNX-2321  ,

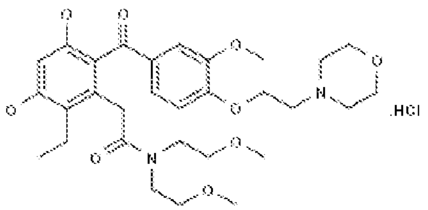
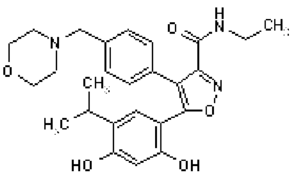
SNX-5422  , SNX-7081  , SNX-8891,

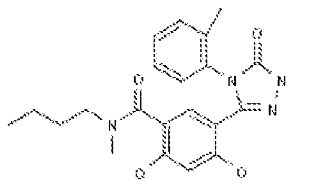
SNX-0723  , SAR-567530, ABI-287, ABI-328, AT-13387

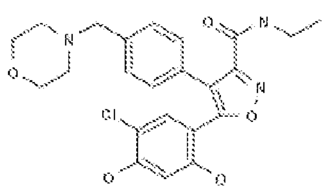
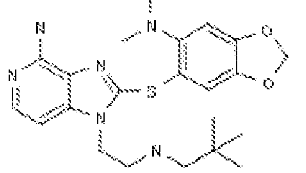
 , NSC-113497  , PF-3823863

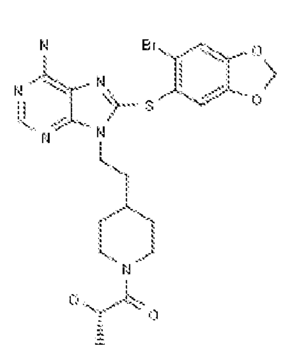
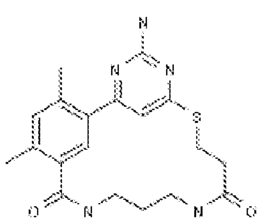
 , PF-4470296  , EC-102, EC-154,

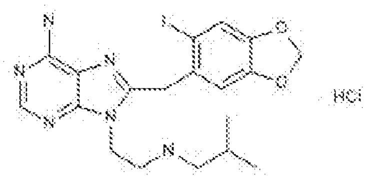
ARQ-250-RP, BC-274  , VER-50589  ,

KW-2478  , BHI-001, AUY-922  ,

EMD-614684  , EMD-683671, XL-888, VER-51047

 , KOS-2484, KOS-2539, CUDC-305  ,

MPC-3100  , CH-5164840  , PU-DZ13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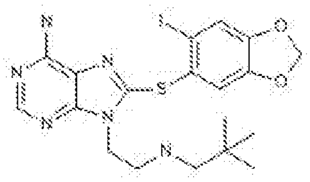
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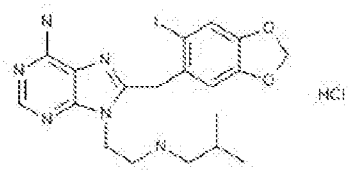
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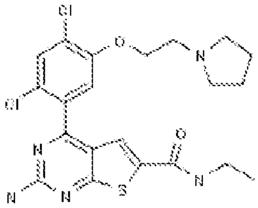
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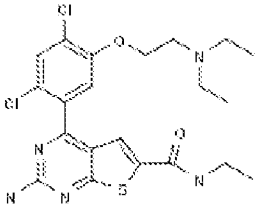
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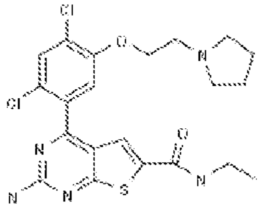
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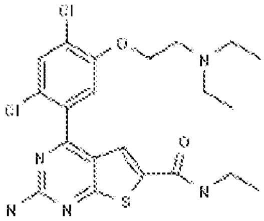
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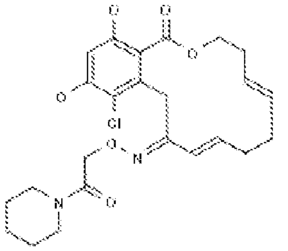
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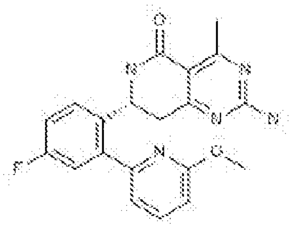
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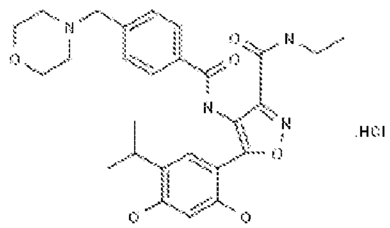
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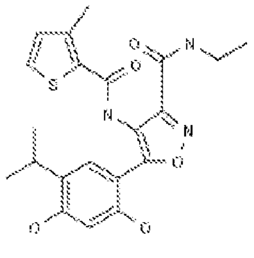
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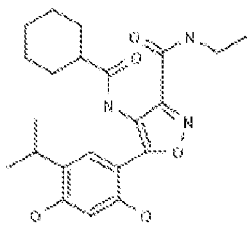
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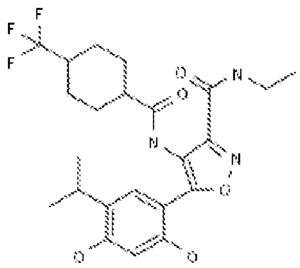


, novobiocin (a C-terminal Hsp90i.) The selection of other Hsp90-targeting moieties will be within the grasp of one of ordinary skill in the art. Likewise, the selection of binding moieties suitable for other molecular targets and/or other applications will be within the ability of one of ordinary skill in the art.

[00250] Additionally Hsp90 targeting moieties can be used to construct SDC-TRAP molecules for the treatment of inflammation. For example, binding moieties comprising the compounds shown in Tables 5, 6, and 7 of U.S. Patent Publication 2010/0280032, which is incorporated herein by reference in its entirety, or compounds of any formula therein, or tautomers, pharmaceutically acceptable salts, solvates, clathrates, hydrates, polymorphs or prodrugs thereof, inhibit the activity of Hsp90 and, thereby cause the degradation of Hsp90 client proteins. Any of these compounds may be coupled to an effector molecule to form an SDC-TRAP. The glucocorticoid receptor is a client protein of Hsp90 and binds to Hsp90 when it is in the conformation that is able to bind glucocorticoid ligands such as cortisol. Once a glucocorticoid binds to GR, the receptor disassociates with Hsp90 and translocates to the nucleus where it modulates gene expression to reduce inflammatory responses such as proinflammatory cytokine production. Thus, glucocorticoids may be given to patients in need of immunosuppression and patients with inflammatory and autoimmune disorders. Unfortunately, although glucocorticoids are effective at relieving inflammation, they have a number of severe side effects including osteoporosis, muscle wasting, hypertension, insulin resistance, truncal obesity and fat redistribution, and inhibition of wound repair. Inhibition of Hsp90 causes changes in GR activity which results in reduction of inflammatory responses similar to those seen for glucocorticoids. However, since the mechanism for reducing inflammation is different than that of glucocorticoids, it is expected that some or all of the side effects of glucocorticoid treatment will be reduced or eliminated.

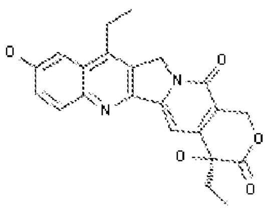
[00251] Effector Moieties

[00252] An effector moiety can be any therapeutic or imaging agent that can be conjugated to a binding moiety and, in a thus conjugated state, delivered to a molecular target of the binding moiety. An effector molecule can, in some cases, require a linking moiety for conjugation (*e.g.*, cannot be directly conjugated to a binding moiety). Similarly, an effector molecule can, in some cases, impede or reduce the ability of the binding moiety and/or SDC-TRAP to reach a target as long as the SDC-TRAP can still effect the target. However, in preferred embodiments, an effector moiety is readily conjugatable and may benefits delivery to, and effecting, of the target.

[00253] In various embodiments, an SDC-TRAP, *via* an effector moiety, can have other ways of cell penetration than simple passive diffusion. Such an example is an SDC-TRAP including an antifolate or fragments thereof (*e.g.*, temozolamide, mitozolamide, nitrogen mustards, estramustine, or chloromethine) as the effector moiety. In this case, a conjugate of a binding moiety (*e.g.*, Hsp90 inhibitor) with pemetrexed (or its folate-recognizing fragment) can undergo folate receptor mediated endocytosis rather than passive diffusion. Once in a target cell, the SDC-TRAP can bind the molecular target (*e.g.*, Hsp90 protein) via its binding moiety (*e.g.*, Hsp90 inhibitor).

[00254] As described in greater detail below, an effector moiety can comprise a region that can be modified and/or participate in covalent linkage to a binding moiety without substantially adversely affecting the binding moiety's ability to bind to its target. An effector moiety can be a pharmaceutical molecule or a derivative thereof, which essentially retains activity while conjugated to a binding moiety. It will be appreciated that drugs with otherwise good and desirable activity can prove challenging to administer conventionally (*e.g.*, due to poor bioavailability or undesirable side-effects *in vivo* prior to reaching their target) – such drugs can be "reclaimed" for use as effector moieties in the SDC-TRAPs of the present invention.

[00255] Examples of effector moieties include: peptidyl-prolyl isomerase ligands, *e.g.*, FK506; rapamycin, cyclosporin A and the like; steroid hormone receptor ligands, *e.g.*, naturally occurring steroid hormones, such as estrogen, progestin, testosterone, and the like, as well as synthetic derivatives and mimetics thereof; binding moieties that bind to cytoskeletal proteins, *e.g.*, antimitotic agents, such as taxanes, colchicine, colcemid, nocadozole, vinblastine, and vincristine, actin binding agents, such as cytochalasin, latrunculin, phalloidin, and the like; lenalidomide, pomalidomide, camptothecins including SN-38

, topotecan, combretastatins, capecitabine, gemcitabine, vinca alkaloids, platinum-containing compounds, metformin, HDAC inhibitors (*e.g.*, suberoylanilidehydroxamic acid (SAHA)), thymidylate synthase inhibitors such as methotrexate, pemetrexed, and raltitrexed; nitrogen mustards such as bendamustine and melphalan; 5-fluorouracil (5-FU) and its derivatives; and agents used in ADC drugs, such as vedotin and DM1.

[00256] The effector moiety may be obtained from a library of naturally occurring or synthetic molecules, including a library of compounds produced through combinatorial means, *i.e.*, a compound diversity combinatorial library. When obtained from such libraries, the effector moiety employed will have demonstrated some desirable activity in an appropriate screening assay for the activity. It is contemplated that in other embodiments, the pharmaceutical conjugate may include more than one effector moiety(ies), providing the medicinal chemist with more flexibility. The number of effector moieties linked to the binding moiety (*e.g.*, Hsp90-targeting moiety) will generally only be limited by the number of sites on the binding moiety (*e.g.*, Hsp90-targeting moiety) and/or any linking moiety available for linking to an effector moiety; the steric considerations, *e.g.*, the number of effector moieties than can actually be linked to the binding moiety (*e.g.*, Hsp90-targeting moiety); and that the ability of the pharmaceutical conjugate to bind to the molecular target (*e.g.*, Hsp90 protein) is preserved. An example of a two-effector moiety pharmaceutical conjugate can be seen in **FIG. 2**.

[00257] Specific drugs from which the effector moiety may be derived include: psychopharmacological agents, such as central nervous system depressants, *e.g.*, general anesthetics (barbiturates, benzodiazepines, steroids, cyclohexanone derivatives, and miscellaneous agents), sedative-hypnotics (benzodiazepines, barbiturates, piperidinediones and triones, quinazoline derivatives, carbamates, aldehydes and derivatives, amides, acyclic ureides, benzazepines and related drugs, phenothiazines, etc.), central voluntary muscle tone modifying drugs (anticonvulsants, such as hydantoins, barbiturates, oxazolidinediones, succinimides, acylureides, glutarimides, benzodiazepines, secondary and tertiary alcohols, dibenzazepine derivatives, valproic acid and derivatives, GABA analogs, etc.), analgesics (morphine and derivatives, oripavine derivatives, morphinan derivatives, phenylpiperidines, 2,6-methane-3-benzazocaine derivatives, diphenylpropylamines and isosteres, salicylates, *p*-aminophenol derivatives, 5-pyrazolone derivatives, arylacetic acid derivatives, fenamates and isosteres, etc.) and antiemetics (anticholinergics, antihistamines, antidopaminergics, etc.); central nervous system stimulants, *e.g.*, analeptics (respiratory stimulants, convulsant stimulants, psychomotor stimulants), narcotic antagonists (morphine derivatives, oripavine derivatives, 2,6-methane-3-benzoxacine derivatives, morphinan derivatives) nootropics; psychopharmacological/psychotropics, *e.g.*, anxiolytic sedatives (benzodiazepines, propanediol carbamates) antipsychotics (phenothiazine derivatives, thioxanthine derivatives, other tricyclic compounds, butyrophenone derivatives and isosteres, diphenylbutylamine derivatives, substituted benzamides, arylpiperazine derivatives, indole derivatives, etc.), antidepressants (tricyclic compounds, MAO inhibitors, etc.);

[00258] respiratory tract drugs, *e.g.*, central antitussives (opium alkaloids and their derivatives); immunosuppressive agents; pharmacodynamic agents, such as peripheral nervous system drugs, *e.g.*, local anesthetics (ester derivatives, amide derivatives); drugs acting at synaptic or neuroeffector junctional sites, *e.g.*, cholinergic agents, cholinergic blocking agents, neuromuscular blocking agents, adrenergic agents, antiadrenergic agents; smooth muscle active drugs, *e.g.*, spasmolytics (anticholinergics, musculotropic spasmolytics), vasodilators, smooth muscle stimulants; histamines and antihistamines, *e.g.*, histamine and derivative thereof (betazole), antihistamines (H_1-antagonists, H_2-antagonists), histamine metabolism drugs; cardiovascular drugs, *e.g.*, cardiotonics (plant extracts, butenolides, pentadienolids, alkaloids from erythrophleum species, ionophores,-adrenoceptor stimulants, etc.), antiarrhythmic drugs, antihypertensive agents, antilipidemic agents (clofibric acid derivatives, nicotinic acid derivatives, hormones and analogs, antibiotics, salicylic acid and derivatives), antivaricose drugs, hemostyptics; chemotherapeutic agents, such as anti-infective agents, *e.g.*, ectoparasiticides (chlorinated hydrocarbons, pyrethins, sulfurated compounds), anthelmintics, antiprotozoal agents, antimalarial agents, antiamebic agents, antileiscmanial drugs, antitrichomonal agents, antitrypanosomal agents, sulfonamides, antimycobacterial drugs, antiviral chemotherapeutics, etc., and cytostatics, *i.e.*, antineoplastic agents or cytotoxic drugs, such as alkylating agents, *e.g.*, Mechlorethamine hydrochloride (Nitrogen Mustard, Mustargen, HN2), Cyclophosphamide (Cytovan, Endoxana), Ifosfamide (IFEX), Chlorambucil (Leukeran), Melphalan (Phenylalanine Mustard, L-sarcolysin, Alkeran, L-PAM), Busulfan (Myleran), Thiotepa (Triethylenethiophosphoramide), Carmustine

(BiCNU, BCNU), Lomustine (CeeNU, CCNU), Streptozocin (Zanosar) and the like; plant alkaloids, *e.g.*, Vincristine (Oncovin), Vinblastine (Velban, Velbe), Paclitaxel (Taxol), and the like; antimetabolites, *e.g.*, Methotrexate (MTX) , Mercaptopurine (Purinethol, 6-MP), Thioguanine (6-TG), Fluorouracil (5-FU), Cytarabine (Cytosar-U, Ara-C), Azacitidine (Mylosar, 5-AZA) and the like; antibiotics, *e.g.*, Dactinomycin (Actinomycin D, Cosmegen), Doxorubicin (Adriamycin), Daunorubicin (duanomycin, Cerubidine), Idarubicin (Idamycin), Bleomycin (Blenoxane), Picamycin (Mithramycin, Mithracin), Mitomycin (Mutamycin) and the like, and other anticellular proliferative agents, *e.g.*, Hydroxyurea (Hydrea), Procarbazine (Mutalane), Dacarbazine (DTIC-Dome), Cisplatin (Platinol) Carboplatin (Paraplatin), Asparaginase (Elspar) Etoposide (VePesid, VP-16-213), Amsarcrine (AMSA, m-AMSA), Mitotane (Lysodren), Mitoxantrone (Novatrone), and the like;

[00259] anti-inflammatory agents; antibiotics, such as: aminoglycosides, *e.g.*, amikacin, apramycin, arbekacin, bambermycins, butirosin, dibekacin, dihydrostreptomycin, fortimicin, gentamicin, isepamicin, kanamycin, micronomcin, neomycin, netilmicin, paromycin, ribostamycin, sisomicin, spectinomycin, streptomycin, tobramycin, trospectomycin; amphenicols, *e.g.*, azidamfenicol, chloramphenicol, florfenicol, and theimaphenicol; ansamycins, *e.g.*, rifamide, rifampin, rifamycin, rifapentine, rifaximin; β-lactams, *e.g.*, carbacephems, carbapenems, cephalosporins, cehpamycins, monobactams, oxaphems, penicillins; lincosamides, *e.g.*, clinamycin, lincomycin; macrolides, *e.g.*, clarithromycin, dirthromycin, erythromycin, etc.; polypeptides, *e.g.*, amphomycin, bacitracin, capreomycin, etc.; tetracyclines, *e.g.*, apicycline, chlortetracycline, clomocycline, etc.; synthetic antibacterial agents, such as 2,4-diaminopyrimidines, nitrofurans, quinolones and analogs thereof, sulfonamides, sulfones;

[00260] antifungal agents, such as: polyenes, *e.g.*, amphotericin B, candicidin, dermostatin, filipin, fungichromin, hachimycin, hamycin, lucensomycin, mepartricin, natamycin, nystatin, pecilocin, perimycin; synthetic antifungals, such as allylamines, *e.g.*, butenafine, naftifine, terbinafine; imidazoles, *e.g.*, bifonazole, butoconazole, chlordantoin, chlormidazole, etc., thiocarbamates, *e.g.*, tolciclate, triazoles, *e.g.*, fluconazole, itraconazole, terconazole;

[00261] anthelmintics, such as: arecoline, aspidin, aspidinol, dichlorophene, embelin, kosin, naphthalene, niclosamide, pelletierine, quinacrine, alantolactone, amocarzine, amoscanate, ascaridole, bephenium, bitoscanate, carbon tetrachloride, carvacrol, cyclobendazole, diethylcarbamazine, etc.;

[00262] antimalarials, such as: acedapsone, amodiaquin, arteether, artemether, artemisinin, artesunate, atovaquone, bebeerine, berberine, chirata, chlorguanide, chloroquine, chlorprogaunil, cinchona, cinchonidine, cinchonine, cycloguanil, gentiopicrin, halofantrine, hydroxychloroquine, mefloquine hydrochloride, 3-methylarsacetin, pamaquine, plasmocid, primaquine, pyrimethamine, quinacrine, quinidine, quinine, quinocide, quinoline, dibasic sodium arsenate; and

[00263] antiprotozoan agents, such as: acranil, tinidazole, ipronidazole, ethylstibamine, pentamidine, acetarsone, aminitrozole, anisomycin, nifuratel, tinidazole, benzidazole, suramin, and the like.

[00264] Conjugation and Linking Moieties

[00265] Binding moieties and effector moieties of the present invention can be conjugated, for example, through a linker or linking moiety L, where L may be either a bond or a linking group. For example, in various embodiments, a binding moiety and an effector moiety are bound directly or are parts of a single molecule. Alternatively, a linking moiety can provide a covalent attachment between a binding moiety and effector moiety. A linking moiety, as with a direct bond, can achieve a desired structural relationship between a binding moiety and effector moiety and or an SDC-TRAP and its molecular target. A linking moiety can be inert, for example, with respect to the targeting of a binding moiety and biological activity of an effector moiety.

[00266] Appropriate linking moieties can be identified using the affinity, specificity, and/or selectivity assays described herein. Linking moieties can be selected based on size, for example, to provide an SDC-TRAP with size characteristics as described above. In various embodiments, a linking moiety can be selected, or derived from, known chemical linkers. Linking moieties can comprise a spacer group terminated at either end with a reactive functionality capable of covalently bonding to the drug or ligand moieties. Spacer groups of interest include aliphatic and unsaturated hydrocarbon chains, spacers containing heteroatoms such as oxygen (ethers such as polyethylene glycol) or nitrogen (polyamines), peptides, carbohydrates, cyclic or acyclic systems that may possibly contain heteroatoms. Spacer groups may also be comprised of ligands that bind to metals such that the presence of a metal ion coordinates two or more ligands to form a complex. Specific spacer elements include: 1,4-diaminohexane, xylylenediamine, terephthalic acid, 3,6-dioxaoctanedioic acid,

ethylenediamine-N,N-diacetic acid, 1,1'-ethylenebis(5-oxo-3-pyrrolidinecarboxylic acid), 4,4'-ethylenedipiperidine. Potential reactive functionalities include nucleophilic functional groups (amines, alcohols, thiols, hydrazides), electrophilic functional groups (aldehydes, esters, vinyl ketones, epoxides, isocyanates, maleimides), functional groups capable of cycloaddition reactions, forming disulfide bonds, or binding to metals. Specific examples include primary and secondary amines, hydroxamic acids, N-hydroxysuccinimidyl esters, N-hydroxysuccinimidyl carbonates, oxycarbonylimidazoles, nitrophenylesters, trifluoroethyl esters, glycidyl ethers, vinylsulfones, and maleimides. Specific linking moieties that may find use in the SDC-TRAPs include disulfides and stable thioether moieties.

[00267] In some embodiments, the linker or linking moiety of an SDC-TRAP can be advantageous when compared to the limited linking chemistry of antibody-drug conjugates (ADC). For example, unlike ADCs that are limited by the need to maintain the structure and/or stability of an antibody, SDC-TRAPs can use a wider range of linking chemistries and/or solvents (*e.g.*, that can alter, distort, or denature an antibody).

[00268] In various embodiments, a linking moiety is cleavable, for example enzymatically cleavable. A cleavable linker can be used to release an effector moiety inside a target cell after the SDC-TRAP is internalized. The susceptibility of a linking moiety to cleavage can be used to control delivery of an effector molecule. For example, a linking moiety can be selected to provide extended or prolonged release of an effector moiety in a target cell over time (*e.g.*, a carbamate linking moiety may be subject to enzymatic cleavage by a carboxylesterase via the same cellular process used to cleave other carbamate prodrugs like capecitabine or irinotecan). In these, and various other embodiments, a linking moiety can exhibit sufficient stability to ensure good target specificity and low systemic toxicity, but not so much stability that it results in lowering the potency and efficacy of the SDC-TRAP.

[00269] Exemplary linkers are described in U.S. Pat. No. 6,214,345 (Bristol-Myers Squibb), U.S. Pat. Appl. 2003/0096743 and U.S. Pat. Appl. 2003/0130189 (both to Seattle Genetics), de Groot et al., J. Med. Chem. 42, 5277 (1999); de Groot et al. J. Org. Chem. 43, 3093 (2000); de Groot et al., J. Med. Chem. 66, 8815, (2001); WO 02/083180 (Syntarga); Carl et al., J. Med. Chem. Lett. 24, 479, (1981); Dubowchik et al., Bioorg & Med. Chem. Lett. 8, 3347 (1998) and Doronina et al. BioConjug Chem. 2006; Doronina et al. Nat Biotech 2003.

[00270] Identification and Selection of Targets and Corresponding SDC-TRAPs

[00271] The present invention provides for a broad class of pharmacological compounds including an effector moiety conjugated to an binding moiety directing the effector moiety to a biological target of interest. While treating cancer using an Hsp90 inhibitor binding moiety conjugated to a cytotoxic agent effector moiety is one illustrative example of the present invention, SDC-TRAPs are fundamentally broader in terms of their compositions and uses.

[00272] In various embodiments, the broad class of SDC-TRAP pharmacological compounds that are directed to biological targets have the following properties:

[00273] the biological target (a cell and/or tissue target of interest, *e.g.*, a tumor) should be effectible by an effector moiety, and the effector moiety should be known or developed for the biological target (*e.g.*, chemotherapeutic agent for the tumor); the biological target should be associated with a molecular target (*e.g.*, biomolecule, capable of being specifically bound, that is uniquely represented in the biological target) that specifically interacts with a binding moiety, and the binding moiety should be known or developed for the molecular target (*e.g.*, ligand for the biomolecule); and the effector moiety and binding moiety should be amenable to coupling and should essentially retain their respective activity after coupling. Furthermore, the conjugate should be capable of reaching and interacting with the molecular target, and in clinical applications should be suitable for administration to a subject (*e.g.*, a subject can tolerate a therapeutically effective dose).

[00274] Examples of therapeutic molecular targets (*i.e.*, binding moiety binding partners) for various conditions/disease states are presented in the table below. A suitable binding moiety can be selected based upon a given molecular target and/or a suitable effector moiety can be selected based upon a given condition/disease. In some cases, an FDA approved therapeutic agent can be used as an effector moiety (*i.e.*, where the FDA approved therapeutic agent is an effector moiety as described herein, for example, a binding moiety and not an antibody).

Condition/Disease State	**Molecular target(s)**	**FDA Approved Therapeutic Agent**
Acute allograft rejection (renal transplant)	CD3E	Muromonab
Acromegaly	somatostatin receptor 1	Octreotide
Actinic Keratosis	toll-like receptor 7	Imiquimod
Acute Coronary Syndrome	P2Y12 ADP-receptor	Brilinta
Acute Myocardial Infarction	plasminogen	Reteplase

Condition/Disease State	Molecular target(s)	FDA Approved Therapeutic Agent
$alpha_1$-proteinase inhibitor (A_1-PI) deficiency	elastase, neutrophil expressed	Alpha-1 proteinase inhibitor
Alzheimer's Disease	BACE1	
Alzheimer's Disease	soluble APP α and APP β	
Anemia	erythropoietin receptor	Epoetin alfa
Angina, chronic stable	calcium channel, voltage-dependent, L type, alpha 1C subunit	Nicardipine
Angina, unstable	P2Y12 ADP-receptor	Brilinta
Angioedema, hereditary	kallikrein 1	Ecallantide
Angioedema, acute hereditary	bradykinin B2 receptor	Firazyr
Ankylosing spondylitis	tumor necrosis factor	Infliximab
Anticoagulant	serpin peptidase inhibitor, clade D (heparin cofactor), member 1	Ardeparin (withdrawn)
Arrhythmia (ventricular)	potassium voltage-gated channel, subfamily H (eag-related), member 2	Propafenone
Arrhythmia	calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	Bepridil
Arthritis / rheumatic disorders	dihydroorotate dehydrogenase (quinone)	Leflunomide
Arthritis / rheumatic disorders	interleukin 1 receptor, type I	Anakinra
Asthma	cysteinyl leukotriene receptor 1	Nedocromil
Asthma	IgE antibodies	Omalizumab
Atypical hemolytic uremic syndrome (aHUS)	complement component 5	Eculizumab
Baldness	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	Finasteride
Benign prostatic hyperplasia	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	Finasteride
Bone / vertebral fracture prevention	TGF-beta activated kinase 1/MAP3K7 binding protein 2	-
Breast Cancer	ER (estrogen receptor)	
Breast Cancer	HER-2/neu	Trastuzumab (HER-2)
Breast Cancer	tubulin, beta 1 class VI	Paclitaxel
Breast Cancer	chromodomain helicase DNA binding protein 1	Epirubicin
Breast Cancer	Tubulin	Halaven
Breast / Ovarian Cancer	BRCA genes	
Bronchitis, chronic	phosphodiesterase 4 (PDE4) inhibitors	Daliresp
Cardiac Ischemic Conditions	integrin, beta 3 (platelet glycoprotein IIIa, antigen CD61)	Abciximab
Cancer	CD74; Trop-2; CEACAM6	
Cancer	EGFR	
Cardiovascular disease	Matrix Metalloproteinases	
Cardiovascular disease	VKORC1	
Cardiovascular disease	LDL	
Cervical Dystonia	vesicle-associated membrane protein 1 (synaptobrevin 1)	Botulinum toxin type B
Chemoprotectant	alkaline phosphatase, placental-like 2	Amifostine

Condition/Disease State	Molecular target(s)	FDA Approved Therapeutic Agent
Chronic myelogenous leukemia	interferon (alpha, beta and omega) receptor 1	Interferon alfa-2a
Chronic Obstructive Pulmonary Disorder	phosphodiesterase 4 (PDE4) inhibitors	Daliresp
Chronic spasticity due to upper motor disorders	ryanodine receptor 1 (skeletal)	Dantrolene
Colon Cancer	guanylate cyclase 2C	
Colorectal Cancer	EGFR	
Colorectal Cancer	KRAS	
Colorectal Cancer	CEA	
Congestive Heart Failure	B-type natriuretic peptide	
Congestive Heart Failure	plasminogen	Reteplase
Crohn's Disease	integrin, alpha 4 (antigen CD49D, alpha 4 subunit of VLA-4 receptor)	Natalizumab
Cryopyrin-associated periodic syndromes	interleukin 1, beta	Canakinumab
Cryopyrin-associated periodic syndromes	interleukin 1, alpha	Rilonacept
Depression	5HT1A receptor (a serotonin reuptake inhibitor)	Viibryd
Diabetes	dipeptidyl peptidase-4 (DPP-4) enzyme	Tradjenta
Diabetes	protein kinase, AMP-activated, beta 1 non-catalytic subunit	Metformin
Diabetes	amylase, alpha 2A (pancreatic)	Acarbose
Diabetes	peroxisome proliferator-activated receptor gamma	Troglitazone (withdrawn)
Diabetes	glucagon-like peptide 1 receptor	Exenatide
Diabetes	receptor (G protein-coupled) activity modifying protein 1	Pramlintide
Diabetes	dipeptidyl-peptidase 4	Sitagliptin
Edema	potassium voltage-gated channel, Isk-related family, member 1	Indapamide
Edema	solute carrier family 12 (sodium/potassium/chloride transporters), member 2	Bumetanide
Factor XIII (FXIII) deficiency, congenital	enzyme replacement therapy (Factor XIII)	Corifact
Familial cold autoinflammatory syndrome	interleukin 1, beta	Canakinumab
Familial cold autoinflammatory syndrome	interleukin 1, alpha	Rilonacept
Gaucher Disease, type I	UDP-glucose ceramide glucosyltransferase	Miglustat
GI stromal tumors (GIST), metastatic malignant	Bcr-Abl tyrosine kinase (an abnormal tyrosine kinase)	
Glaucoma	prostaglandin F receptor (FP)	Latanoprost
Granulomatous disease, chronic	interferon gamma receptor 1	Interferon gamma-1b
Growth disorder	insulin-like growth factor 1 receptor	Mecasermin
Growth hormone deficiency	growth hormone releasing hormone receptor	Sermorelin
Hairy cell leukemia	interferon (alpha, beta and omega) receptor 1	Interferon alfa-2a
Hairy cell leukemia	adenosine deaminase	Pentostatin
Heartburn (Gastric reflux)	5-hydroxytryptamine (serotonin) receptor 4, G protein-coupled	Cisapride (withdrawn)

Condition/Disease State	Molecular target(s)	FDA Approved Therapeutic Agent
Hemophilia (prevent bleeding)	plasminogen activator, tissue	Tranexamic acid
Hepatitis C	interferon (alpha, beta and omega) receptor 1	Interferon alfa-2a
Hepatitis C (genotype 1)	hepatitis C virus non-structural protein 3 (NS3) serine protease	Victrelis
Hepatitis C (genotype 1)	hepatitis C virus non-structural protein 3 (NS3)/4A serine protease	Incivek
Hepatocellular Carcinoma	α-fetoprotein	
HIV	chemokine (C-C motif) receptor 5 (gene/pseudogene)	Maraviroc
HIV	HIV-1 reverse transcriptase	Edurant
Hyperammonemia	carbamoyl-phosphate synthase 1, mitochondrial	Carglumic acid
Hypercalcemia in patients with parathyroid carcinoma	calcium-sensing receptor	Cinacalcet
Hypercholesterolemia	3-hydroxy-3-methylglutaryl-CoA reductase	Lovastatin
Hyperlipidemia	NPC1 (Niemann-Pick disease, type C1, gene)-like 1	Ezetimibe
Hyperplasia	steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1)	Finasteride
Hypertension	adrenoceptor alpha 1D	Terazosin
Hypertension	calcium channel, voltage-dependent, P/Q type, alpha 1A subunit	Bepridil
Hypertension	calcium channel, voltage-dependent, N type, alpha 1B subunit	Amlodipine
Hypertension	angiotensin II receptor, type	Losartan
Hypertension	renin	Aliskiren
Hypertension	AT1 subtype angiotensin II receptor	Edarbi
Hypertension	membrane metallo-endopeptidase	Candoxatril
Increase bone density, prevent bone fracture	parathyroid hormone 1 receptor	Teriparatide
Infections, acute skin and skin structure	penicillin-binding proteins	Teflaro
Infections, bacterial	dipeptidase 1 (renal)	Cilastatin (adjuvant)
Infections (bone marrow transplant, etc.)	colony stimulating factor 3 receptor (granulocyte)	Filgrastim
Infections, immunomodulatory agents	colony stimulating factor 2 receptor, alpha, low-affinity (granulocyte-macrophage)	Sargramostim
Infertility	follicle stimulating hormone receptor	Urofollitropin
Inflammation	C Reactive Protein	
Interstitial cystitis, bladder pain/discomfort due to	fibroblast growth factor 1 (acidic)	Pentosan polysulfate
Irritable Bowel Syndrome	chloride channel, voltage-sensitive 2	Lubiprostone
Kaposi's sarcoma, AIDS-related	interferon (alpha, beta and omega) receptor 1	Interferon alfa-2a
Leukemia/Lymphoma	CD20 Antigen	
Leukemia/Lymphoma	CD30	
Leukemia/Lymphoma	PML/RAR alpha	
Leukemia, chronic myeloid	proto-oncogene tyrosine-protein kinase Src	Dasatinib
Leukemia, myeloid	CD33, Myeloid cell surface antigen CD33	Gemtuzumab ozogamicin (withdrawn)
Lipodystrophy	human GRF receptors	Egrifta

Condition/Disease State	Molecular target(s)	FDA Approved Therapeutic Agent
Lung Cancer	ALK	
Lung Cancer	CD98; fascin; 14-3-3 eta	
Lymphocytic leukemia, B-cell chronic	polymerase (DNA directed), alpha 1, catalytic subunit	Fludarabine
Lymphocytic leukemia, B-cell chronic	CD52 (CAMPATH-1 antigen precursor)	Alemtuzumab
Lymphocytic leukemia, chronic	membrane-spanning 4-domains, subfamily A, member 1	Rituximab
Lymphoma, Hodgkin's	chemokine (C-X-C motif) receptor 4	Plerixafor
Lymphoma, Hodgkin's	CD30	Adcetris
Lymphoma, mantle cell	proteasome (prosome, macropain) subunit, beta type, 1	Bortezomib
Lymphoma, systemic anaplastic large cell	CD30	Adcetris
Lymphocytic leukemia, T-cell	histone deacetylase 1	Vorinostat
Melanoma	S100 protein	
Melanoma, metastatic (with BRAFV600E mutation)	mutated form of BRAF that facilitates cell growth	Zelboraf
Melanoma, metastatic	CTLA-4	Yervoy
Migraine Headache	carbonic anhydrase II	Topiramate
Muckle-Wells syndrome	interleukin 1, beta	Canakinumab
Muckle-Wells syndrome	interleukin 1, alpha	Rilonacept
Multiple Sclerosis	sphingosine-1-phosphate receptor 1	Fingolimod
Myeloma, multiple	chemokine (C-X-C motif) receptor 4	Plerixafor
Myeloma, multiple	proteasome (prosome, macropain) subunit, beta type, 1	Bortezomib
Myocardial Infarction	Troponin I	
Myocardial Infarction, non-ST-elevation	P2Y12 ADP-receptor	Brilinta
Myocardial Infarction, ST-elevation	P2Y12 ADP-receptor	Brilinta
N-acetylglutamate synthase (NAGS) deficiency	carbamoyl-phosphate synthase 1, mitochondrial	Carglumic acid
Nausea/vomiting	5-hydroxytryptamine (serotonin) receptor 3A, ionotropic	Ondansetron
Nausea/vomiting	tachykinin receptor 1	Aprepitant
Nausea/vomiting (severe)	cannabinoid receptor 1 (brain)	Marinol
Non-Hodgkin's Lymphoma	membrane-spanning 4-domains, subfamily A, member 1	Rituximab
Non-small cell lung cancer	phosphoribosylglycinamide formyltransferase, phosphoribosylglycinamide synthetase, phosphoribosylaminoimidazole synthetase	Pemetrexed
Non-small cell lung cancer	epidermal growth factor receptor	Gefitinib
Non-small cell lung cancer (that is ALK-positive)	the ATP-binding pocket of target protein kinases	Xalkori
Obesity	lipase, gastric / pancreatic lipase	Orlistat
Ovarian Cancer	IGF-II; leptin; osteopontin; prolactin	
Oral mucositis	fibroblast growth factor receptor 2	Palifermin
Organ rejection prophylaxis	FK506 binding protein 1A, 12kDa	Tacrolimus
Organ rejection prophylaxis	IMP (inosine 5'-monophosphate) dehydrogenase 2	Mycophenolate mofetil
Organ rejection prophylaxis	interleukin 2 receptor, alpha	Daclizumab

Condition/Disease State	Molecular target(s)	FDA Approved Therapeutic Agent
Organ rejection prophylaxis	FK506 binding protein 12-rapamycin associated protein 1	Sirolimus
Organ rejection prophylaxis	protein phosphatase 3, regulatory subunit B, beta	Cyclosporine
Organ rejection prophylaxis	CD80 and CD86, blocks CD28 mediated costimulation of T lymphocytes	Nulojix
Osteoporosis	interferon gamma receptor 1	Interferon gamma-1b
Osteoporosis (prophylaxis)	TGF-beta activated kinase 1/MAP3K7 binding protein 2	Denosumab
Paget's Disease	farnesyl diphosphate synthase	Pamidronate
Pancreatic Cancer	CA19-9	
Parkinson's Disease	catechol-O-methyltransferase	Tolcapone (withdrawn)
Parkinson's Disease	monoamine oxidase B	Selegiline
Paroxysmal nocturnal hemoglobinuria	complement component 5	Eculizumab
Pneumonia, susceptible bacterial community-acquired	penicillin-binding proteins	Teflaro
Poisoning, ethylene glycol or methanol	alcohol dehydrogenase 1B (class I), beta polypeptide	Fomepizole
Psoriasis, plaque	interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40)	Ustekinumab
Psoriasis, plaque	integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide)	Efalizumab (withdrawn)
Psoriasis, chronic plaque	T-cell surface antigen CD2 precursor	Alefacept
Psoriatic Arthritis	tumor necrosis factor	Infliximab
Prostate Cancer	PSA (prostate specific antigen)	
Prostate hyperplasia, benign	adrenoceptor alpha 1D	Terazosin
Pulmonary embolism	Factor Xa	Xarelto
Pulmonary hypertension	endothelin receptor type B	Bosentan
Renal cell carcinoma	v-raf-1 murine leukemia viral oncogene homolog 1	Sorafenib
Renal cell carcinoma	fms-related tyrosine kinase 1 (vascular endothelial growth factor/vascular permeability factor receptor)	Sunitinib
Renal cell carcinoma	vascular endothelial growth factor A	Bevacizumab
Rheumatoid arthritis	TNF-α	
Rheumatoid arthritis	IL-6	
Rheumatoid arthritis	inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta	Auranofin
Rheumatoid arthritis	tumor necrosis factor	Infliximab
Rheumatoid arthritis	CD80 (T-lymphocyte activation antigen CD80)	Abatacept
Rheumatoid arthritis	interleukin 6 receptor	Tocilizumab
Rheumatoid arthritis	CEP-1	
Schizophrenia	CYP2D6	
Scorpion stings	venom toxins	Anascorp
Seizures	carbonic anhydrase II	Topiramate
Seizures	solute carrier family 6 (neurotransmitter transporter, GABA), member 1	Tiagabine
Seizures	4-aminobutyrate aminotransferase	Divalproex sodium
Seizures	Gamma-amino butyric acid (GABA)	
Sepsis, severe	coagulation factor VIII (Factors Va and VIIIa),	Drotrecogin alfa

Condition/Disease State	Molecular target(s)	FDA Approved Therapeutic Agent
	procoagulant component	
Small Cell Lung Cancer	topoisomerase (DNA) II alpha 170kDa	Etoposide
Small Cell Lung Cancer	topoisomerase (DNA) I	Topotecan
Stroke	thrombin	Pradaxa
Stroke	Factor Xa	Xarelto
Stroke, thrombotic	purinergic receptor P2Y, G-protein coupled, 12	Ticlopidine
Systemic embolism	Factor Xa	Xarelto
systemic embolism in non-valvular atrial fibrillation	thrombin	Pradaxa
Systemic lupus erythematosus	human B lymphocyte stimulator protein (BLyS)	Benlysta
Testicular Cancer	LDH	
Thyroid Cancer Metastasis	Thyro-globulin	
Thrombocythemia	phosphodiesterase 4B, cAMP-specific	Amrinone
Thrombocytopenia	myeloproliferative leukemia virus oncogene expression product	Romiplostim
Thrombocytopenia	interleukin 11 receptor, alpha	Oprelvekin
Thrombosis, Deep vein	Factor Xa	Xarelto
Thyroid Cancer	protein kinases of the VEGF, EGFR, and/or RET pathways	Caprelsa
Tyrosinemia type I, hereditary	4-hydroxyphenylpyruvate dioxygenase	Nitisinone
Ulcer (anti-ulcer agent)	ATPase, H+/K+ exchanging, alpha polypeptide	Omeprazole
Ulcers, diabetic neuropathic	platelet-derived growth factor receptor, beta polypeptide	Becaplermin
Urothelial Cell Carcinoma	Bladder Tumor Antigen	

[00275] Examples of imaging/diagnostic molecular targets (*i.e.*, binding moiety binding partners) for various conditions/disease states are presented in the table below. A suitable binding moiety can be selected based upon a given molecular target and/or a suitable effector moiety can be selected based upon a given condition/disease. In some cases, an FDA approved imaging/diagnostic agent can be used as an effector moiety (*i.e.*, where the FDA approved imaging/diagnostic agent is an effector moiety as described herein, for example, a binding moiety and not an antibody).

Condition/Disease State	Molecular target(s)	FDA Approved Imaging/Diagnostic
Alzheimer's disease, stroke, schizophrenia	cerebral blood flow (hemoglobin)	
Alzheimer's disease	β-amyloid protein (can be used to monitor progression of the disease)	
Diagnostic (screening test for exocrine pancreatic insufficiency and to monitor the adequacy of supplemental pancreatic therapy)	pancreatic lipase	Bentiromide
Diagnostic for bone density	parathyroid hormone 1 receptor	Teriparatide
Diagnostic/imaging	proteasome (prosome, macropain) subunit, alpha type, 6 pseudogene 1	Capromab
Diagnostic for MRI to visualize blood brain barrier / abnormal vascularity of the CNS (to diagnose disorders of the brain and spine)	Paramagnetic macrocyclic contrast agent	Gadavist
General Cognitive Decline (Dementia, Alzheimer's Disease, Parkinson's Disease, etc.)	thinning of the cerebral cortex	
Inflammation / tumor progression	(radiolabeled) 18F-fludeoxyglucose	
Osteoarthritis	cartilage (collagen and proteoglycan) degeneration	
Parkinson's syndrome	Dopamine receptors (diagnostic that detects dopamine receptors)	DaTscan
Thyroid Cancer	thyroid stimulating hormone receptor	Thyrotropin alfa

[00276] Imaging Moieties, and Diagnostic and Research Applications

[00277] In various embodiments, the effector moiety is an imaging moiety – that is, a molecule, compound, or fragment thereof that facilitates a technique and/or process used to create images or take measurements of a cell, tissue, and/or organism (or parts or functions thereof) for clinical and/or research purposes. An imaging moiety can produce, for example, a signal through emission and/or interaction with electromagnetic, nuclear, and/or mechanical (*e.g.*, acoustic as in ultrasound) energy. An imaging moiety can be used, for example, in various radiology, nuclear medicine, endoscopy, thermography, photography, spectroscopy, and microscopy methods.

[00278] Imaging studies can be used, for example, in a clinical or research setting to diagnose a subject, select a subject for therapy, select a subject for participation in a clinical trial, monitor the progression of a disease, monitor the effect of therapy, to determine if a subject should discontinue or continue therapy, to determine if a subject has reached a clinical

end point, and to determine recurrence of a disease. Imaging studies can be used, for example, to conduct research to identify effective interacting moieties and/or effector moieties and/or combinations thereof, to identify effective dosing and dose scheduling, to identify effective routes of administration, and to identify suitable targets (*e.g.*, diseases susceptible to particular treatment).

[00279] Methods of Making Pharmaceutical Conjugates

[00280] The pharmaceutical conjugates, *i.e.*, SDC-TRAPs, of the invention may be prepared using any convenient methodology. In a rational approach, the pharmaceutical conjugates are constructed from their individual components, binding moiety, in some cases a linker, and effector moiety. The components can be covalently bonded to one another through functional groups, as is known in the art, where such functional groups may be present on the components or introduced onto the components using one or more steps, *e.g.*, oxidation reactions, reduction reactions, cleavage reactions and the like. Functional groups that may be used in covalently bonding the components together to produce the pharmaceutical conjugate include: hydroxy, sulfhydryl, amino, and the like. The particular portion of the different components that are modified to provide for covalent linkage will be chosen so as not to substantially adversely interfere with that components desired binding activity, *e.g.*, for the effector moiety, a region that does not affect the target binding activity will be modified, such that a sufficient amount of the desired drug activity is preserved. Where necessary and/or desired, certain moieties on the components may be protected using blocking groups, as is known in the art, *see*, *e.g.*, Green & Wuts, Protective Groups in Organic Synthesis (John Wiley & Sons) (1991).

[00281] Alternatively, the pharmaceutical conjugate can be produced using known combinatorial methods to produce large libraries of potential pharmaceutical conjugates which may then be screened for identification of a bifunctional, molecule with the pharmacokinetic profile. Alternatively, the pharmaceutical conjugate may be produced using medicinal chemistry and known structure-activity relationships for the targeting moiety and the drug. In particular, this approach will provide insight as to where to join the two moieties to the linker.

[00282] A number of exemplary methods for preparing SDC-TRAP molecules are set forth in the examples. As one of skill in the art will understand, the exemplary methods set forth in the examples can be modified to make other SDC-TRAP molecules.

[00283] Methods of Use, Pharmaceutical Preparations, and Kits

[00284] The pharmaceutical conjugates find use in treatment of a host condition, *e.g.*, a disease condition. In these methods, an effective amount of the pharmaceutical conjugate is administered to the host, where "effective amount" means a dosage sufficient to produce the desired result, *e.g.*, an improvement in a disease condition or the symptoms associated therewith. In many embodiments, the amount of drug in the form of the pharmaceutical conjugate that need be administered to the host in order to be an effective amount will vary from that which must be administered in free drug form. The difference in amounts may vary, and in many embodiments may range from two-fold to ten-fold. In certain embodiments, *e.g.*, where the resultant modulated pharmacokinetic property or properties result(s) in enhanced activity as compared to the free drug control, the amount of drug that is an effective amount is less than the amount of corresponding free drug that needs to be administered, where the amount may be two-fold, usually about four-fold and more usually about ten-fold less than the amount of free drug that is administered.

[00285] The pharmaceutical conjugate may be administered to the host using any convenient means capable of producing the desired result. Thus, the pharmaceutical conjugate can be incorporated into a variety of formulations for therapeutic administration. More particularly, the pharmaceutical conjugate of the present invention can be formulated into pharmaceutical compositions by combination with appropriate, pharmaceutically acceptable carriers or diluents, and may be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols. As such, administration of the pharmaceutical conjugate can be achieved in various ways, including oral, buccal, rectal, parenteral, intraperitoneal, intradermal, transdermal, intracheal, etc., administration. In pharmaceutical dosage forms, the pharmaceutical conjugate may be administered alone or in combination with other pharmaceutically active compounds.

[00286] The subject methods find use in the treatment of a variety of different disease conditions. In certain embodiments, of particular interest is the use of the subject methods in

disease conditions where an active agent or drug having desired activity has been previously identified, but which active agent or drug does not bind to its target with desired affinity and/or specificity. With such active agents or drugs, the subject methods can be used to enhance the binding affinity and/or specificity of the agent for its target.

[00287] The specific disease conditions treatable by with the subject bifunctional compounds are as varied as the types of drug moieties that can be present in the pharmaceutical conjugate. Thus, disease conditions include cellular proliferative diseases, such as neoplastic diseases, autoimmune diseases, central nervous system or neurodegenerative diseases, cardiovascular diseases, hormonal abnormality diseases, infectious diseases, and the like.

[00288] By treatment is meant at least an amelioration of the symptoms associated with the disease condition afflicting the host, where amelioration is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, *e.g.*, symptom, associated with the pathological condition being treated, such as inflammation and pain associated therewith. As such, treatment also includes situations where the pathological condition, or at least symptoms associated therewith, are completely inhibited, *e.g.*, prevented from happening, or stopped, *e.g.*, terminated, such that the host no longer suffers from the pathological condition, or at least the symptoms that characterize the pathological condition.

[00289] Methods of use of the invention extend beyond strict treatment of a disease. For example, the invention includes uses in a clinical or research setting to diagnose a subject, select a subject for therapy, select a subject for participation in a clinical trial, monitor the progression of a disease, monitor the effect of therapy, to determine if a subject should discontinue or continue therapy, to determine if a subject has reached a clinical end point, and to determine recurrence of a disease. The invention also includes uses in conducting research to identify effective interacting moieties and/or effector moieties and/or combinations thereof, to identify effective dosing and dose scheduling, to identify effective routes of administration, and to identify suitable targets (*e.g.*, diseases susceptible to particular treatment).

[00290] A variety of hosts are treatable according to the subject methods. Generally such hosts are “mammals” or “mammalian,” where these terms are used broadly to describe organisms which are within the class Mammalia, including the orders carnivore (*e.g.*, dogs and cats), rodentia (*e.g.*, mice, guinea pigs, and rats), and primates (*e.g.*, humans, chimpanzees, and monkeys). In many embodiments, the hosts will be humans.

[00291] The invention provides kits for treating a subject in need thereof comprising at least one SDC-TRAP and instruction for administering a therapeutically effective amount of the at least one SDC-TRAP to the subject, thereby treating the subject. The invention also provides kits for imaging, diagnosing, and/or selecting a subject comprising at least one SDC-TRAP and instruction for administering an effective amount of at least one SDC-TRAP to the subject, thereby imaging, diagnosing, and/or selecting the subject.

[00292] Kits with unit doses of the pharmaceutical conjugate, usually in oral or injectable doses and often in a storage stable formulation, are provided. In such kits, in addition to the containers containing the unit doses, an informational package insert describing the use and attendant benefits of the drugs in treating pathological condition of interest will be included. Preferred compounds and unit doses are those described herein above.

[00293] The invention also provides methods for treatment of a disease or disorder in which the subject to be treated is selected for treatment based on the presence of, or the overexpression of, a particular protein. For example, subjects may be selected for treatment of cancer based on the presence of greater the normal levels of Hsp90. In this case, subjects would be administered an SDC-TRAP that comprises a binding moiety that selectively binds to Hsp90.

[00294] The invention provides methods of treating or preventing an inflammatory disorder in a subject, comprising administering to the subject an effective amount of a compound represented by any one of formula (I) through (LXXII), or any embodiment thereof, or a compound shown in Table 5, 6, or 7 as disclosed in U.S. Patent Publication 2010/0280032. In one embodiment, the compound or binding moiety or SDC-TRAP may be administered to a human to treat or prevent an inflammatory disorder. In another embodiment, the inflammatory disorder is selected from the group consisting of transplant rejection, skin graft rejection, arthritis, rheumatoid arthritis, osteoarthritis and bone diseases associated with increased bone resorption; inflammatory bowel disease, ileitis, ulcerative colitis, Barrett's syndrome, Crohn's disease; asthma, adult respiratory distress syndrome, chronic obstructive airway disease; corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis, endophthalmitis; gingivitis, periodontitis; tuberculosis; leprosy; uremic complications, glomerulonephritis, nephrosis; sclerodermatitis, psoriasis, eczema; chronic demyelinating diseases of the nervous system, multiple sclerosis, AIDS-related neurodegeneration, Alzheimer's disease, infectious meningitis, encephalomyelitis, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis viral or autoimmune encephalitis;

autoimmune disorders, immune-complex vasculitis, systemic lupus and erythematodes; systemic lupus erythematosus (SLE); cardiomyopathy, ischemic heart disease hypercholesterolemia, atherosclerosis, preeclampsia; chronic liver failure, brain and spinal cord trauma. In another embodiment, an SDC-TRAP, or a compound shown in Table 5, 6, or 7 as disclosed in U.S. Patent Publication 2010/0280032, is administered with an additional therapeutic agent. In another embodiment, the additional therapeutic agent may an anti-inflammatory agent.

[00295] In one embodiment, an SDC-TRAP that is administered to a subject but does not enter a target cell is rapidly cleared from the body. In this embodiment, the SDC-TRAP that does not enter a target cell is rapidly cleared in order to reduce the toxicity due to the components of the SDC-TRAP, the degradation products of the SDC-TRAP or the SDC-TRAP molecule. Clearance rate can be determined by measuring the plasma concentration of the SDC-TRAP molecule as a function of time.

[00296] Likewise, SDC-TRAP molecules that enter non-targeted cells by passive diffusion rapidly exit the non-targeted cell or tissue and are either eliminated from the subject or proceed to enter and be retained a targeted cell or tissue. For example, an SDC-TRAP that is intended to treat tumor cells and is targeted to tumor cells that overexpress, for example, Hsp90 will accumulate selectively in tumor cells that overexpress Hsp90. Accordingly, very low levels of this exemplary SDC-TRAP will be present in non-tumor tissue such as normal lung tissue, heart, kidney, and the like. In one embodiment, the safety of the SDC-TRAP molecules of the invention can be determined by their lack of accumulation in non-targeted tissue. Conversely, the safety of the SDC-TRAP molecules of the invention can be determined by their selective accumulation in the targeted cells and/or tissue.

[00297] Examples

[00298] The following examples, which are briefly summarized and then discussed in turn below, are offered by way of illustration and not by way of limitation.

[00299] Example 1 presents the synthesis of exemplary SDC-TRAPs.

[00300] Example 2 presents the targeted delivery of exemplary SDC-TRAPs.

[00301] Example 3 presents an exemplary assay for selecting binding moieties.

[00302] Example 4 presents the cytotoxicity of exemplary SDC-TRAPs.

[00303] Example 5 presents the stability of exemplary SDC-TRAPs in plasma.

[00304] Example 6 presents a detailed schematic for the synthesis of an exemplary SDC-TRAP.

[00305] Example 7 presents results of tests using the SDC-TRAP of Example 6.

[00306] Example 8 presents the synthesis and testing of a lenalidomide-based SDC-TRAP.

[00307] Examples 9 and 10 present examples of IC_{50} value determinations.

[00308] Example 11 presents an exemplary Hsp90α binding assay.

[00309] Example 12 presents an exemplary HER2 degradation assay.

[00310] Example 13 presents an exemplary cytotoxicity assay.

[00311] Example 14 presents an exemplary plasma stability protocol.

[00312] Example 15 presents an exemplary tissue distribution extraction procedure.

[00313] Example 16 presents an exemplary tissue distribution study.

[00314] Examples 17 and 18 present examples of SDC-TRAP stability in mouse plasma and cell culture media.

[00315] Examples 19-29 present synthesis and IC_{50} data for different exemplary SDC-TRAPs. Within examples 19-29, exemplary synthetic schemes are set forth. It is to be understood that the additional exemplary compounds were synthesized according to the methods described for the exemplary synthetic schemes.

[00316] Example 30 sets forth the identification and use of SDC-TRAPs for prevention and treatment of chronic bronchitis and asthma.

[00317] Example 31 sets forth the identification and use of SDC-TRAPs for prevention and treatment of skin cancers and actinic keratosis.

[00318] Example 32: SDC-TRAP-233

[00319] Example 33: SDC-TRAP-234

[00320] Example 34: Identification and Use of SDC-TRAP for Prevention and Treatment of Chronic Bronchitis and Asthma

[00321] Example 35: Identification and Use of SDC-TRAP for Prevention and Treatment of Skin Cancers and Actinic Keratosis

[00322] Example 36: Determining the Permeability of SDC-TRAP Molecules

[00323] Example 37: Physical Properties and Further Characterization of SDC-TRAP-0063.

[00324] Example 38: SDC-TRAP-0063 has superior antitumor activity compared with irinotecan in a SCLC model.

[00325] Example 39: Pharmacodynamics of SDC-TRAP-0063 in CRC xenograft tumors

[00326] Example 40: Pharmacodynamics of SDC-TRAP-0063 in SCLC xenograft tumors

[00327] Example 41: ADME/PK Data Summary for *In vitro* and *In vivo* Studies.

[00328] Example 42: SDC-TRAP-0063 has superior antitumor activity compared with irinotecan in HCT-116 model.

[00329] Example 43: SDC-TRAP-0063 has superior antitumor activity compared with irinotecan in MCF-7 xenograft model.

[00330] Example 44: SDC-TRAP-0063 exhibits superior delayed antitumor activity in SKOV-3 ovarian cancer xenografts.

[00331] Example 45: Synthesis of SDC-TRAPs comprising AUY-922.

[00332] Example 46: Synthesis of SDC-TRAPs comprising VER-82160.

[00333] Example 47: Synthesis of SDC-TRAPs comprising AT-13387AU.

[00334] Example 48: Synthesis of SDC-TRAPs comprising Geldanamycin.

[00335] Example 49: Synthesis of SDC-TRAPs comprising SNX-5422.

[00336] Example 50: Synthesis of SDC-TRAPs comprising BIIB028.

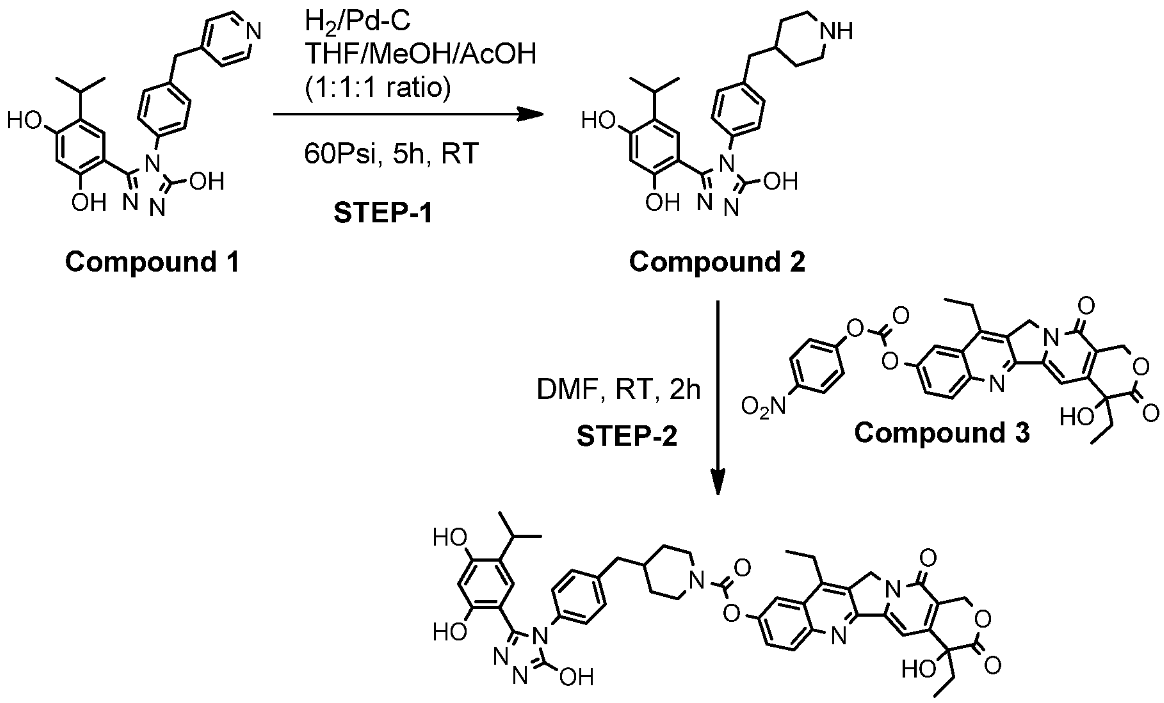
[00337] Example 51: Synthesis of SDC-TRAPs comprising MPC-3100

[00338] Example 52: General synthesis of exemplary SDC-TRAPs.

[00339] Example 53: Retention of particular SDC-TRAPs in mouse tumor tissue.

[00340] **Example 1**

[00341] SDC-TRAPs of an exemplary embodiment may be prepared in the following manner:



[00342] The synthesis of Compound 1 and Compound 3 are discussed in WO 2007/139968 and WO 2004/012661, respectively.

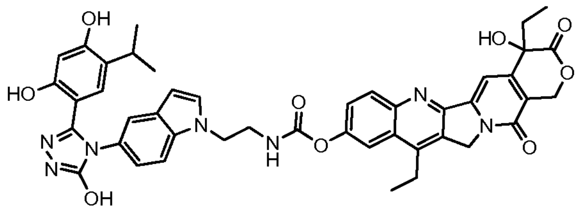
[00343] Synthesis of **Compound 2** (STEP-1): To a solution of 1.0 g (2.48 mmols) of **Compound 1** in 60 mL of 1:1:1-Methanol:Tetrahydrofuran:Acetic acid was added 75 mg of 10% Palladium on charcoal (wet Degussa type) and the contents of the flask was deoxygenated by vacuum and hydrogen purge. It was then pressurized to 60 Psi with hydrogen and stirred for 5 h at room temperature. The flask was then thoroughly flushed with argon and filtered the solids through a short pad of celite. Evaporation and recrystallization of the crude product afforded 900 mg (88%) of the **Compound 2** in pure form as an off-white solid. ESMS calculated for $C_{23}H_{28}N_4O_3$: 408.22; Found: 409.1 (M^+).

[00344] Synthesis : To a stirred solution of 0.1g (0.245mmols) of **Compound 2** in 5mL of anhydrous N,N-Dimethylformamide was added in portion 0.13g (0.245mmols) of **Compound 3** (4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3’,4’:6,7]indolizino[1,2-b]quinolin-9-yl (4-nitrophenyl) carbonate) and the mixture was stirred at room temperature for 2h. After confirming the completion of the reaction by LC-MS, 30 mL of water was added to the flask and stirred for 5 mins. The resultant precipitate was filtered, thoroughly washed with water (10 mL x 3) and dried. The solids were dissolved in 25 mL of 95:5-dichloromethane:methanol and dried over anhydrous Na_2SO_4. Evaporation followed by column chromatography afforded the conjugate 1 which was further purified by crystallization in methanol to remove minor impurities (mostly SN-38) and the procedure afforded 130 mg (65%) of the pure **Conjugate 1**. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm):11.93 (bs, 1H), 9.57 (bs, 1H), 9.45 (bs, 1H), 8.18 (d, J = 8Hz, 1H), 7.98 (s, 1H), 7.66 (dd, J = 4.0, 8.0Hz, 1H). 7.34 (s, 1H), 7.24 (d, J = 8Hz, 2H), 7.13 (d, J = 8Hz, 2H), 6.77 (s, 1H), 6.54 (bs, 1H), 6.28 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 3.21-3.18 (m, 2H), 3.10-2.96 (m, 3H), 2.59 (d, J = 8Hz, 2H), 1.91-1.76 (m, 3H), 1.67 (bs, 2H), 1.30 (t, J = 8Hz, 3H), 0.95 (d, J = 8Hz, 6H), 0.89 (d, J = 8Hz, 3H). ESMS calculated for $C_{46}H_{46}N_6O_9$: 826.33; Found: 827.3 (M^+).

[00345] Additional SDC-TRAPs made according to the general scheme noted above include the following:

[00346] Compound SDC-TRAP-0008:

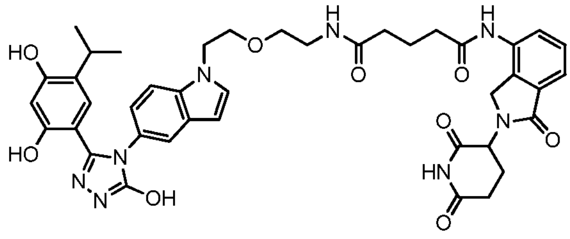
[00347] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7] indolizino[1,2-b]quinolin-9-yl (2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)carbamate:



[00348] ESMS calculated for $C_{44}H_{41}N_7O_9$: 811.30; Found: 812.3 (M^+).

[00349] SDC-TRAP-0015:

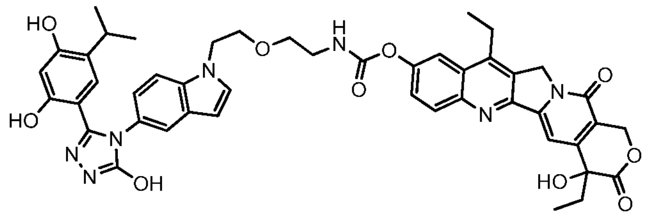
[00350] N1-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)glutaramide:



[00351] ESMS calculated for $C_{41}H_{44}N_8O_9$: 792.32; Found: 793.3 (M^+).

[00352] SDC-TRAP-0016:

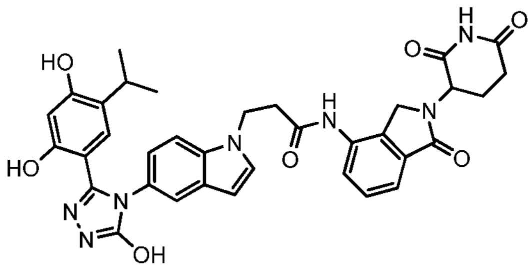
[00353] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)carbamate:



[00354] ESMS calculated for $C_{46}H_{45}N_7O_{10}$: 855.32; Found: 856.3 (M^+).

[00355] SDC-TRAP-0017:

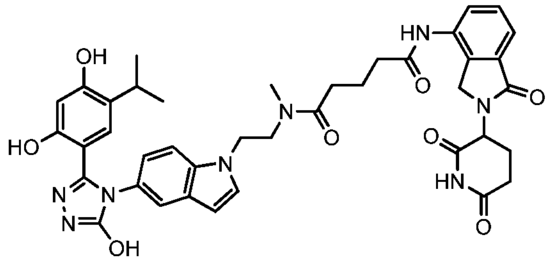
[00356] 3-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)propanamide:



[00357] ESMS calculated for $C_{35}H_{33}N_7O_7$: 663.24; Found: 664.3 (M^+).

[00358] SDC-TRAP-0018:

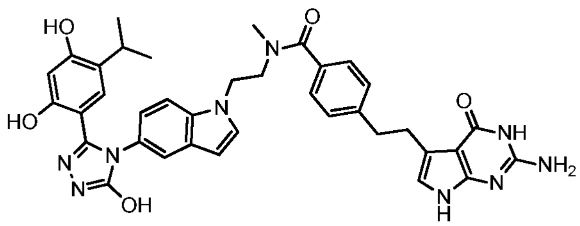
[00359] N1-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-N5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-N1-methylglutaramide:



[00360] ESMS calculated for $C_{40}H_{42}N_8O_8$: 762.31; Found: 763.3 (M^+).

[00361] SDC-TRAP-0019:

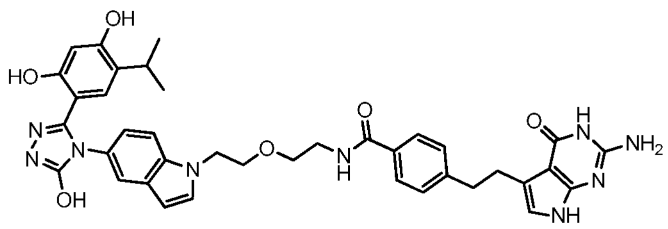
[00362] 4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)-N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-N-methylbenzamide:



[00363] ^{1}H NMR (300 MHz, DMSO-d6), d (ppm): 11.86 (s, 1H); 10.61(s, 1H); 10.14(s,1H); 9.51 (s, 1H); 9.47 (s, 1H); 7.59-7.45 (m, 2H); 7.28-6.96 (m, 5H); 6.72 (m, 2H); 6.47(s,1H); 6.32 (s, 1H); 6.24 (s, 1H); 6.00(bs, 2H); 4.46-4.28 (m, 2H);3.75-3.49(m,2H); 2.96 -2.80(m, 5H); 2.61(s, 3H); 0.81 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{37}H_{37}N_9O_5$: 687.29; Found: 688.2 (M^+).

[00364] SDC-TRAP-0020:

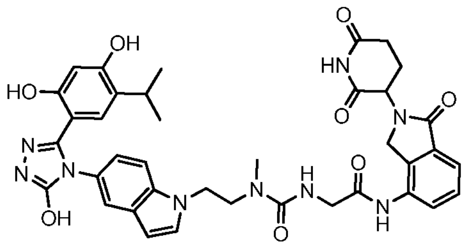
[00365] 4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)-N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)benzamide:



[00366] ESMS calculated for $C_{38}H_{39}N_9O_6$: 717.3; Found: 718.3 (M^+).

[00367] SDC-TRAP-0021:

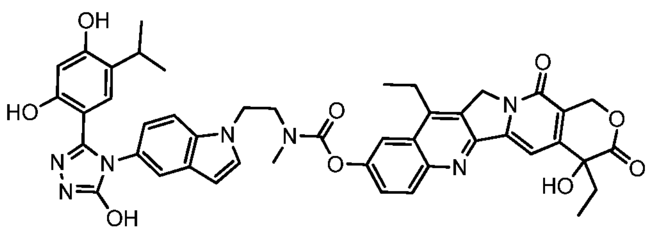
[00368] 2-(3-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-3-methylureido)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide:



[00369] ESMS calculated for $C_{38}H_{39}N_9O_8$: 749.29; Found: 750.3 (M^+).

[00370] SDC-TRAP-0022:

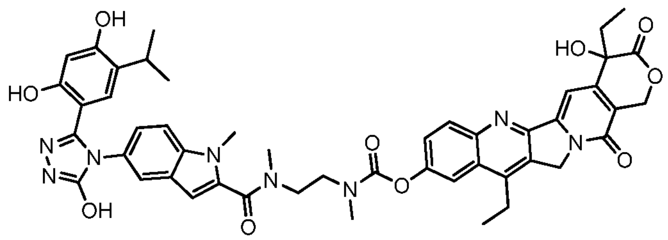
[00371] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)(methyl)carbamate:



[00372] ESMS calculated for $C_{45}H_{43}N_7O_9$: 825.31; Found: 826.3 (M^+).

[00373] SDC-TRAP-0010:

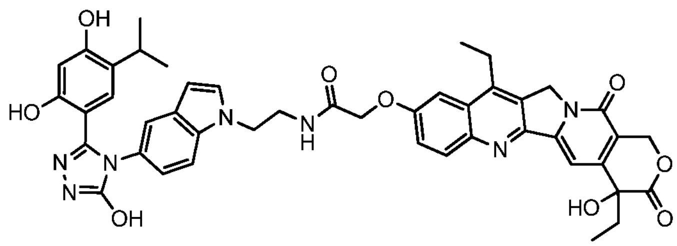
[00374] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-N,1-dimethyl-1H-indole-2-carboxamido)ethyl)(methyl)carbamate:



[00375] ESMS calculated for $C_{48}H_{48}N_8O_{10}$: 896.35; Found: 897.4 (M^+).

[00376] SDC-TRAP-0023:

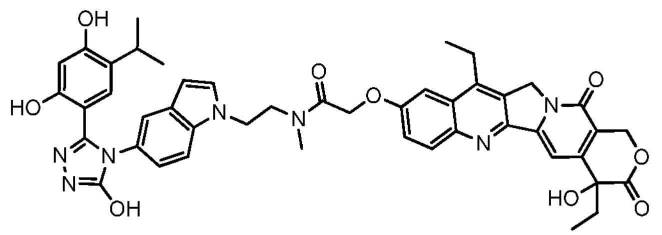
[00377] 2-((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)-N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)acetamide:



[00378] ESMS calculated for $C_{45}H_{43}N_7O_9$: 825.31; Found: 826.3 (M^+).

[00379] SDC-TRAP-0027:

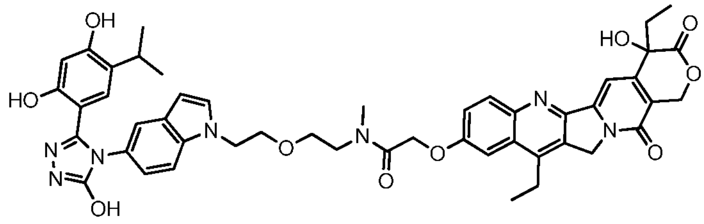
[00380] 2-((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)-N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-N-methylacetamide:



[00381] ESMS calculated for $C_{46}H_{45}N_7O_9$: 839.33; Found: 840.4 (M^+).

[00382] SDC-TRAP-0028:

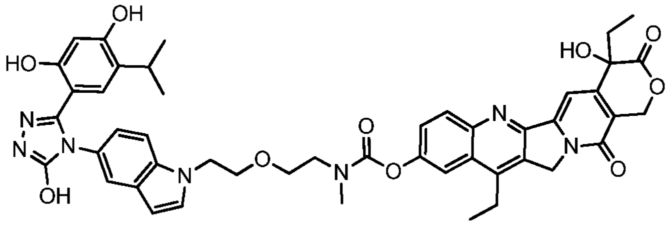
[00383] 2-((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)-N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N-methylacetamide:



[00384] ESMS calculated for $C_{48}H_{49}N_7O_{10}$: 883.35; Found: 884.4 (M^+).

[00385] SDC-TRAP-0029:

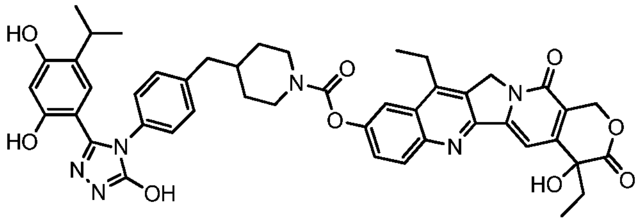
[00386] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)(methyl)carbamate:



[00387] ESMS calculated for $C_{47}H_{47}N_7O_{10}$: 869.34; Found: 870.4 (M^+).

[00388] SDC-TRAP-0031:

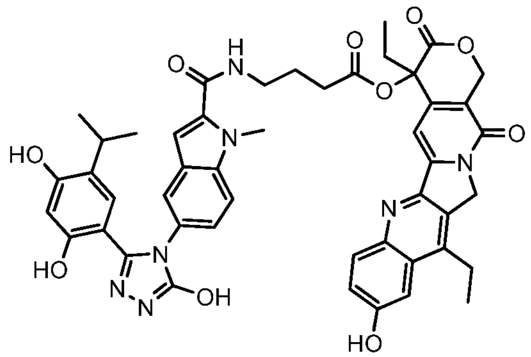
[00389] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl) -5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidine-1-carboxylate:



[00390] ^{1}H NMR (400 MHz, DMSO-d_6), d (ppm):11.93 (bs, 1H), 9.57 (bs, 1H), 9.45 (bs, 1H), 8.18 (d, *J* = 8Hz, 1H), 7.98 (s, 1H), 7.66 (dd, *J* = 4.0, 8.0Hz, 1H). 7.34 (s, 1H), 7.24 (d, *J* = 8Hz, 2H), 7.13 (d, *J* = 8Hz, 2H), 6.77 (s, 1H), 6.54 (bs, 1H), 6.28 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 3.21-3.18 (m, 2H), 3.10-2.96 (m, 3H), 2.59 (d, J = 8Hz, 2H), 1.91-1.76 (m, 3H), 1.67 (bs, 2H), 1.30 (t, J = 8Hz, 3H), 0.95 (d, J = 8Hz, 6H), 0.89 (d, J = 8Hz, 3H). ESMS calculated for $C_{46}H_{46}N_6O_9$: 826.33; Found: 827.3 (M^+).

[00391] SDC-TRAP-0024

[00392] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7] indolizino[1,2-b]quinolin-4-yl 4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy- 4H-1,2,4-triazol-4-yl)-1-methyl-1H-indole-2-carboxamido)butanoate:

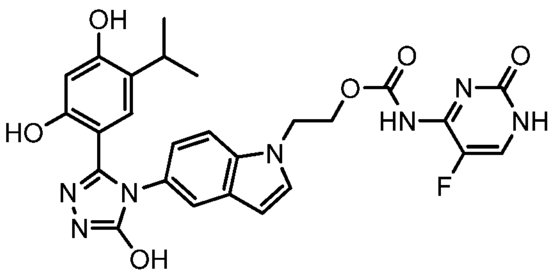


[00393] ^{1}H NMR (400 MHz, CH_3OD) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.44 (s, 1 H), 7.35-7.27 (m, 4H), 7.16-7.14 (m, 1H), 6.73 (s, 1H), 6.67 (s, 1H), 6.26 (s, 1H), 5.62 (d, J = 16 Hz, 1H), 5.44 (d, J = 16 Hz, 1H), 5.05 (d, J = 16 Hz, 1H), 3.58 (s, 3H), 3.48-3.33 (m, 3H), 3.09-3.04 (m, 1H), 2.96-2.86 (m, 2H), 2.75-2.71 (m, 2H), 2.25-2.13 (m, 2H), 2.05-1.94 (m, 2H), 1.29 (t, J =

8.0 Hz, 3H), 1.01 (t, J = 8.0 Hz, 3H), 0.78-0.72 (m, 6H); ESMS calculated for $C_{47}H_{45}N_7O_{10}$: 867.3; found: 868.3 (M+H).

[00394] SDC-TRAP-0025:

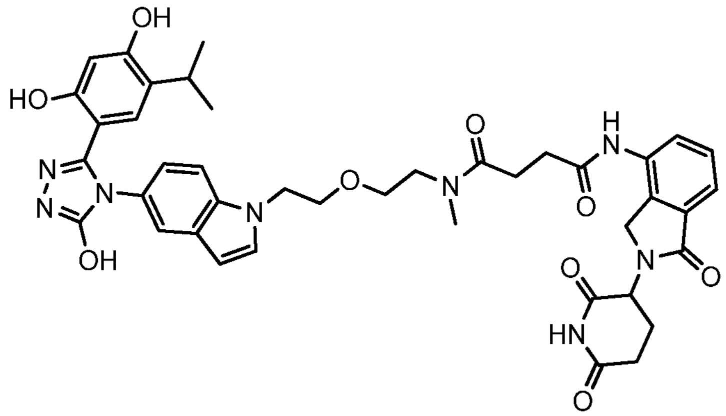
[00395] 2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl (5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl) carbamate:



[00396] ESMS calculated $C_{26}H_{24}FN_7O_6$: 549.18; found: 550.1 (M+H).

[00397] SDC-TRAP-0033:

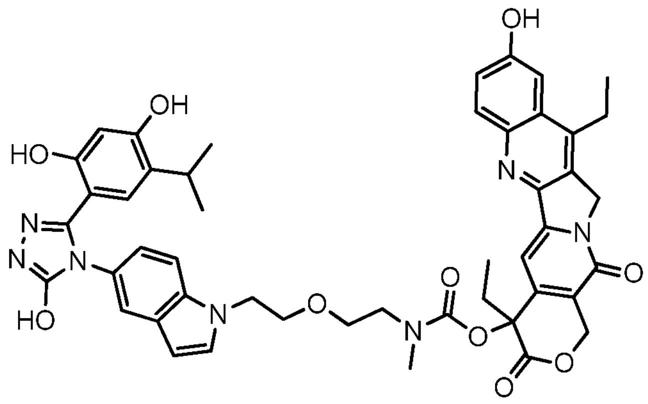
[00398] N1-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoiso indolin-4-yl)-N1-methylsuccinamide:



[00399] ESMS calculated for $C_{41}H_{44}N_8O_9$: 792.32; found: 793.3 (M+H).

[00400] SDC-TRAP-0037:

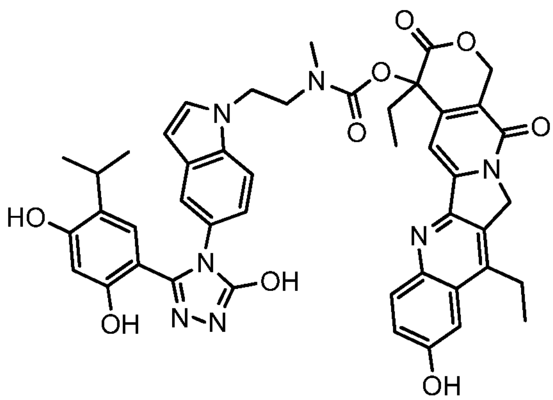
[00401] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3’,4’:6,7]indolizino[1,2-b]quinolin-4-yl (2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)(methyl)carbamate:



[00402] ESMS calculated for $C_{47}H_{47}N_7O_{10}$: 869.34; found: 870.3 (M+H).

[00403] SDC-TRAP-0038:

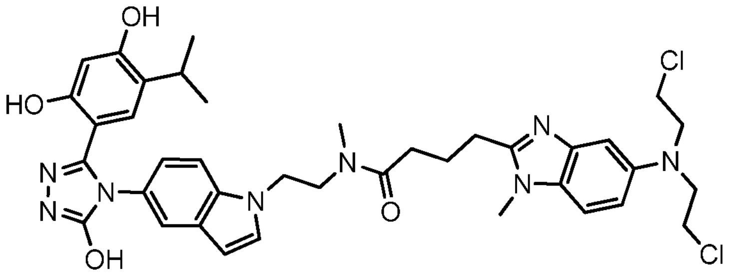
[00404] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3’,4’:6,7]indolizino[1,2-b]quinolin-4-yl (2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)(methyl)carbamate:



[00405] ESMS calculated for $C_{45}H_{43}N_7O_9$: 825.31; found: 826.3 (M+H).

[00406] SDC-TRAP-0039:

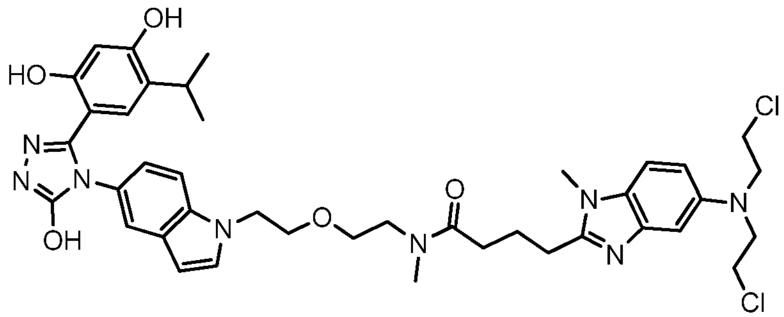
[00407] -(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl) ethyl)-N-methylbutanamide:



[00408] ESMS calculated for $C_{38}H_{44}Cl_2N_8O_4$: 746.29; found: 747.3 (M+H).

[00409] SDC-TRAP-0040:

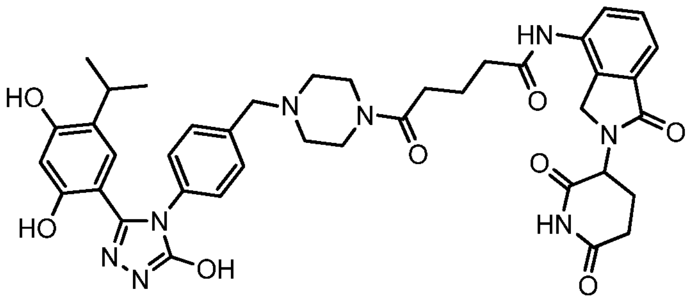
[00410] -(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N-methylbutanamide:



[00411] ESMS calculated for $C_{40}H_{48}Cl_2N_8O_5$: 790.31; found: 791.3 (M+H).

[00412] SDC-TRAP-0041:

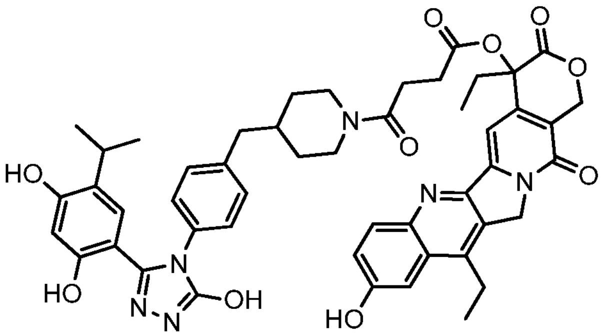
[00413] 5-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-5-oxopentanamide:



[00414] ESMS calculated for $C_{40}H_{44}N_8O_8$: 764.33; found: 765.3 (M+H).

[00415] SDC-TRAP-0042:

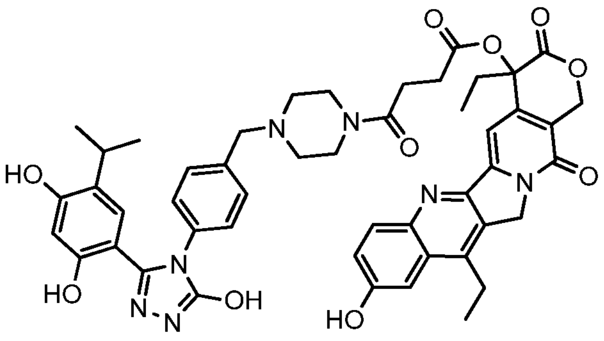
[00416] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-4-oxobutanoate:



[00417] ESMS calculated for $C_{49}H_{50}N_6O_{10}$: 882.36; found: 883.3 (M+H).

[00418] SDC-TRAP-0043:

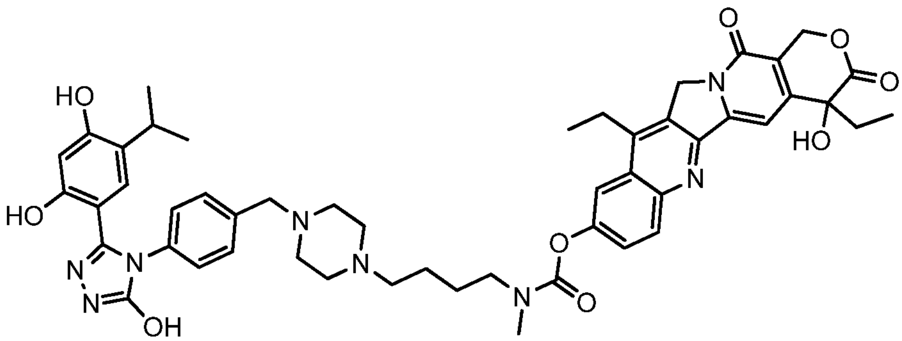
[00419] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-4-oxobutanoate:



[00420] ESMS calculated for $C_{48}H_{49}N_7O_{10}$: 883.35; found: 884.3 (M+H).

[00421] SDC-TRAP-0044:

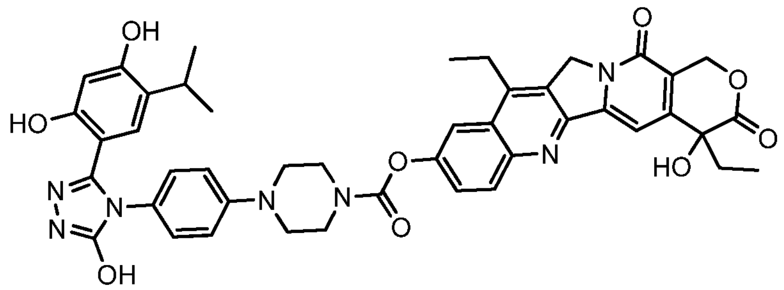
[00422] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3’,4’:6,7]indolizino[1,2-b]quinolin-9-yl (4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)butyl)(methyl)carbamate:



[00423] ESMS calculated for $C_{50}H_{56}N_8O_9$: 912.42; found: 913.4 (M+H).

[00424] SDC-TRAP-0045:

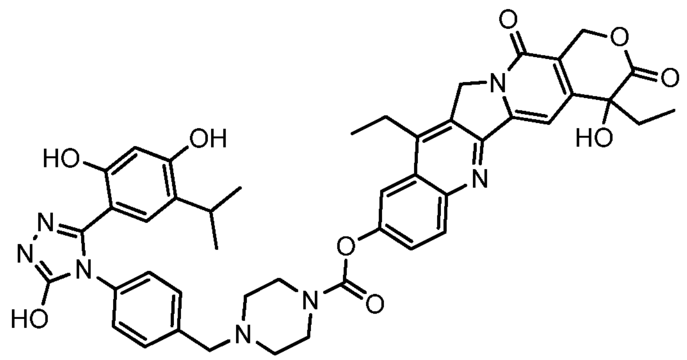
[00425] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3’,4’:6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazine-1-carboxylate:



[00426] ESMS calculated for $C_{44}H_{43}N_7O_9$: 813.31; found: 814.3 (M+H).

[00427] SDC-TRAP-0046:

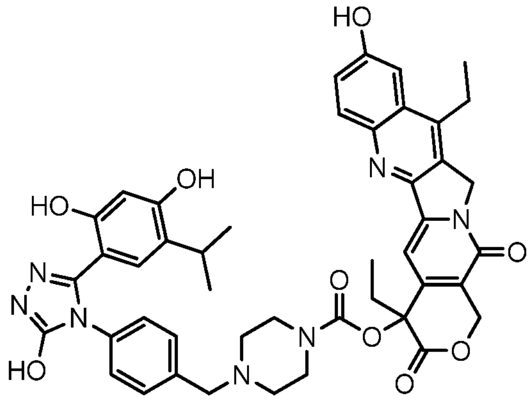
[00428] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate:



[00429] ESMS calculated for $C_{45}H_{45}N_7O_9$: 827.33; found: 828.3 (M+H).

[00430] SDC-TRAP-0047:

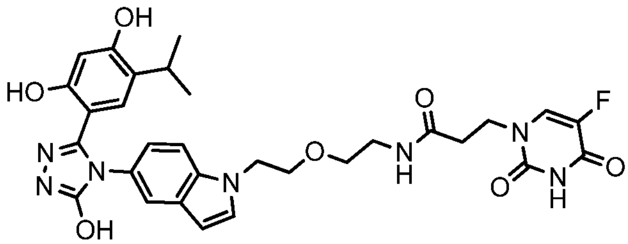
[00431] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate:



[00432] ESMS calculated for $C_{45}H_{45}N_7O_9$: 827.33; found: 828.3 (M+H).

[00433] SDC-TRAP-0048:

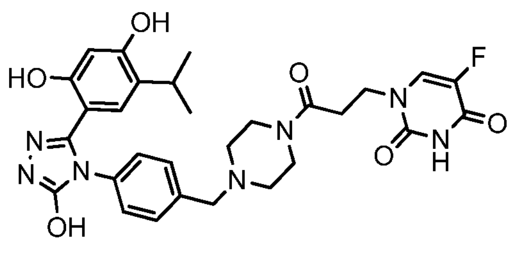
[00434] N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanamide:



[00435] ESMS calculated for $C_{30}H_{32}FN_7O_7$: 621.23; found: 622.2 (M+H).

[00436] SDC-TRAP-0049:

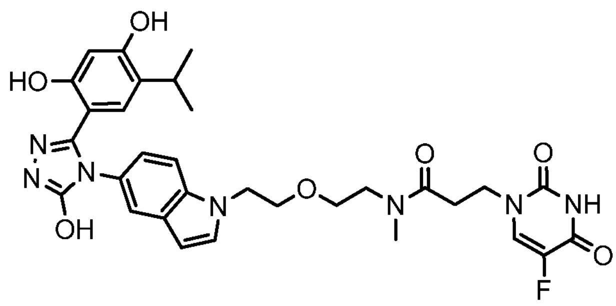
[00437] 1-(3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-3-oxopropyl)-5-fluoropyrimidine-2,4(1H,3H)-dione :



[00438] ESMS calculated for $C_{29}H_{32}FN_7O_6$: 593.24; found: 594.2 (M+H).

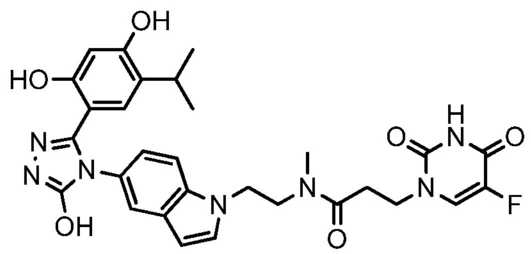
[00439] SDC-TRAP-0050:

[00440] N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-N-methylpropanamide:



[00441] ESMS calculated for $C_{31}H_{34}FN_7O_7$: 635.64; found: 636.6 (M+H).

[00442] SDC-TRAP-0051: N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-N-methylpropanamide:



[00443] ESMS calculated for $C_{29}H_{30}FN_7O_6$: 591.22; found: 592.2 (M+H).

[00444] **Example 2**

[00445] The ability of Hsp90-targeting moieties to penetrate solid tumors and exhibit rapid clearance from normal tissues for reduced toxicity is illustrated in the following tissue distribution study with a compound, ganetespib, which may be used as an Hsp90 binding moiety.

[00446] Tissue distribution of ganetespib in female CD-1 nu/nu mice bearing RERF human NSCLC xenografts

[00447] Objectives:

[00448] To confirm the distribution of ganetespib in blood, livers, kidneys, brains, hearts, lungs and tumors after IV administration of ganetespib to female CD-1 nu/nu mice bearing RERF human NSCLC xenografts, and to examine metabolic profiles of ganetespib in plasma, red blood cells, and above tissues.

[00449] Study outline:

[00450] Test Articles: ganetespib

[00451] Animals: female CD-1 nu/nu mice bearing RERF human NSCLC xenografts (N=3/group)

[00452] Route: IV

[00453] Dosage: 50 mg/kg

[00454] Dose level: 10 mL/kg

[00455] Formulation: 10% DMSO, 18% Cremophor RH40, 3.6% dextrose solution (DRD)

[00456] Bleeding time points: 5 min, 6, 24 hr

[00457] Collected tissues: blood (plasma and red blood cells (RBC)), liver, kidneys, brain, heart, lung, tumor

[00458] Method

Sample preparation

[00459] Plasma and RBC

[00460] Protein precipitation: 50 μL of 10 times diluted plasma or RBC + 150 μL ACN (10 mM NH_4OAc), vortexed and centrifuged at 10000 rpm for 8 min; 150 μL supernatant + 150 μL water (10 mM NH_4OAc)

[00461] Other tissues

[00462] Protein precipitation: 100 μL homogenized tissue (1:3 tissue: PBS buffer) + 100 μL ACN (10 mM NH_4OAc), vortexed and centrifuged at 10000 rpm for 8 min

[00463] Bioanalysis

[00464] HPLC (ChemStation)

[00465] Column: Agilent Zorbax Eclipse XDB-C18, 4.6x150 mm, 5 μm

[00466] Mobile phase: A: water containing 10 mM NH_4OAc; B: 95% ACN containing 10 mM NH_4OAc

[00467] Gradient: 95/5 A/B to 5/95 A/B in 10 min, total run time 15 min

[00468] Flow rate: 1 mL/min

[00469] Column temp.: 40 °C

[00470] Wavelength: 254 nm

[00471] Injection volume: 100 μL

[00472] Calibration curve range:

[00473] Plasma: 1-50 μM (linear regression; R^2 =0.9901); LLOQ = 1 μM

[00474] RBC: 1-50 μM (linear regression; R^2 =0.9987); LLOQ = 1 μM

[00475] Kidney: 1-100 μM (linear regression; R^2 =1.0000); LLOQ = 1 μM

[00476] Lung: 1-100 μM (linear regression; R^2 =1.0000); LLOQ = 1 μM

[00477] Heart: 1-100 μM (linear regression; R^2 =0.9998); LLOQ = 1 μM

[00478] Liver: 1-100 μM (linear regression; R^2 =1.0000); LLOQ = 1 μM

[00479] Tumor:0.1-10 μM (linear regression; R^2 =1.0000); LLOQ = 0.1 μM

[00480] LC-MS/MS (Q-Trap4000)

[00481] Polarity: positive (ESI)

[00482] Column: Phenomenex Synergi, 2.1x50 mm, 4 μm

[00483] Mobile phase: A: water containing 0.1% HCOOH; B: ACN containing 0.1% HCOOH

[00484] Gradient: 60/40 A/B to 5/95 A/B in 0.5 min, total run time 4 min

[00485] Flow rate: 0.5 mL/min

[00486] Column temp.: room temperature

[00487] Injection volume: 20 μL

[00488] Calibration curve range:

[00489] Plasma: 2.5-500 nM (linear regression; R^2 =0.9994); LLOQ = 2.5 nM

[00490] RBC: 2.5-500 nM (linear regression; R^2 =0.9998); LLOQ = 2.5 nM

[00491] Kidney: 2.5-500 nM (linear regression; R^2 =0.9993); LLOQ = 2.5 nM

[00492] Lung: 2.5-500 nM (linear regression; R^2 =0.9993); LLOQ = 2.5 nM

[00493] Heart: 2.5-500 nM (linear regression; R^2 =0.9997); LLOQ = 2.5 nM

[00494] Liver: 2.5-500 nM (linear regression; R^2 =1.0000); LLOQ = 2.5 nM

- 0.5-5 μM (linear regression; R^2 =0.9970); LLOQ = 0.5 μM

[00495] Brain: 2.5-500 nM (linear regression; R^2 =0.9998); LLOQ = 2.5 nM

- 0.5-5 μM (linear regression; R^2 =0.9992); LLOQ = 0.5 μM

[00496] Results

[00497] Formulations

[00498] The dosing solution was confirmed to have 98.1% accuracy by HPLC.

[00499] Tissue Distribution

[00500] The concentrations of ganetespib in plasma, RBC and the tissues are summarized in Fig. 1 at each time point.

[00501] The mean plasma concentration of ganetespib at 5 min after IV injection was 160 μM, highest among all the tissues studied. Thereafter, the plasma ganetespib concentration declined quickly and at 6 hr, it was 0.12 μM. At 24 hr, it was below the lower limit of quantitation (LLOQ, <2.5 nM).

[00502] After IV injection, ganetespib was widely distributed to the normal tissues analyzed. At 5 min, the highest concentration of ganetespib among the tissues was observed in kidney (57.8 μM), followed by liver (46.3 μM) and heart (36.2 μM). In brain, 0.53 μM of ganetespib was detected at 5 min, which was the lowest among the tissues. In all the normal tissues, the concentrations of ganetespib decreased quickly.

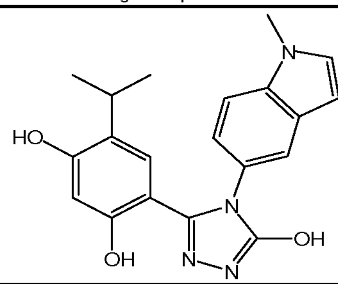
[00503] Although the concentration of ganetespib in tumor at 5 min (2.35 M) was lower than that in plasma and most of the other tissues studied, it remained relatively constant up to 24 hr (0.85 μM at 24 hr). However, the *in vitro* IC_{50} values of ganetespib are small, and the tumor concentration of ganetespib at 24 hr was significantly higher than IC_{50} of *in vitro* HER2 assays (~30 nM). Thus, the prolonged efficacy is expected even after ganetespib was cleared from the blood stream.

[00504] The mean concentration of ganetespib in plasma was about 10 times higher than that in RBC at 5 min time point, indicating that ganetespib tends to stay in plasma rather than in RBCs. See **FIG. 3**.

[00505] Conclusion

[00506] Ganetespib appeared to persist longer in tumor than in plasma or any other tissues studied. The results from this study suggest that ganetespib also has a higher binding affinity to Hsp90 from tumor cells than Hsp90 from normal cells, and that it is possible for ganetespib to modulate relative protein concentrations of Hsp90 and its client proteins selectively in tumors. The plasma concentrations of ganetespib did not correlate to the concentrations in tumor.

[00507] Table 1. Concentrations of ganetespib in tissues:

Test Articles	ganetespib							
Structure								
Species	CD-1-nu/nu female mice							
Tumor	RERF human NSCLC							
Route	IV							
Dosage	50mg/kg							
Formulation	DRD							
Time	plasma (μg/mL)	RBC (μg/mL)	tumor (μg/g)	liver (μg/g)	kidneys (μg/g)	brain (μg/g)	heart (μg/g)	lung (μg/g)
5min	58.4	6.00	0.86	16.9	21.1	0.19	13.2	9.24
6hr	0.04	No data	0.29	0.14	0.06	0.07	0.05	0.05
24hr	<LLOQ	0.003	0.31	0.005	0.01	0.04	0.00	0.00
Time	plasma (μM)	RBC (μM)	tumor (μM)	liver (μM)	kidneys (μM)	brain (μM)	heart (μM)	lung (μM)
5min	160	16.5	2.35	46.3	57.8	0.53	36.2	25.4
6hr	0.12	N/A	0.80	0.39	0.15	0.18	0.13	0.14
24hr	<LLOQ	0.007	0.85	0.01	0.02	0.12	0.00	0.005

[00508] Summary

[00509] Ganetespib was widely distributed to various tissues. The compound was accumulated in tumor relative to the plasma and other tissues, indicating the higher binding affinity of this compound to Hsp90 in tumor than Hsp90 in other tissues. The metabolite M2, which was previously thought to be human-specific, was also detected in mouse liver, kidney, heart and lung, but not in plasma. M2 does not seem to be excreted into blood stream in mice and possibly in other species as well.

[00510] Example 3

[00511] This example illustrates how a HER2 degradation assay may be used as a test to determine and select Hsp90-targeting moieties suitable for use in SDC-TRAPs of the invention, and further illustrates the ability of SDC-TRAPs to target cells preferentially expressing Hsp90. Such a test may further be used to determine the Hsp90 binding ability of SDC-TRAPs of the invention, as well as through competitive binding assays and cell-based Hsp90 client protein degradation assays known in the art.

[00512] Degradation of HER2 in Cells after Treatment with an SDC-TRAP of the invention

[00513] Method 1: BT-474 cells are treated with 0.5 μM, 2 μM, or 5 μM of 17-AAG (a positive control) or 0.5 μM, 2 μM, or 5 μM of an Hsp90-targeting moiety or conjugate of the invention overnight in DMEM medium. After treatment, each cytoplasmic sample is prepared from $1x10^6$ cells by incubation of cell lysis buffer (#9803, Cell Signaling Technology) on ice for 10 minutes. The resulting supernatant used as the cytosol fractions is dissolved with sample buffer for SDS-PAGE and run on a SDS-PAGE gel, blotted onto a nitrocellulose membrane by using semi-dry transfer. Non-specific binding to nitrocellulose is blocked with 5% skim milk in TBS with 0.5% Tween at room temperature for 1 hour, then probed with anti-HER2/ErB2 mAb (rabbit IgG, #2242, Cell Signaling) and anti-Tubulin (T9026, Sigma) as housekeeping control protein. HRP-conjugated goat anti–rabbit IgG (H+L) and HRP-conjugated horse anti–mouse IgG (H+L) are used as secondary Ab (#7074, #7076, Cell Signaling) and LumiGLO reagent, 20x Peroxide (#7003, Cell Signaling) is used for visualization. The Hsp90 client protein HER2 is degraded when cells are treated with Hsp90-targeting moieties or SDC-TRAPs of the invention. 0.5 μM of 17-AAG, a known Hsp90 inhibitor used as a positive control, causes partial degradation of HER2.

[00514] Method 2: BT-474 cells are plated in the interior 60 wells of a 96 well black clear bottom plate (20,000 cells/well) in DMEM medium, with DMEM media in the surrounding 36 wells, and incubated at 37 °C with 5% CO_2 overnight. On the second day, concentration response curve source plates are produced (10 point, 3-fold dilution of compounds in DMSO)

followed by a 1:30 dilution in an intermediate dilution plate containing DMEM. Compound is transferred from the intermediate plate to the cell plate at a dilution of 1:10. The cells are then incubated at 37 °C with 5% CO_2 for 24 hours.

[00515] Cells are then fixed in 4% phosphate-buffered paraformaldehyde for 30 minutes at room temperature and then permeabilized by washing five times with 0.1% Triton X-100 in PBS for 5 minutes at room temperature on a shaker. Cells are blocked with Odyssey Blocking Buffer (LI-COR, #927-40000) on a shaker at room temperature for 1.5 hours, followed by incubation with HER2 antibody (CST, #2165) diluted 1:400 in blocking buffer overnight on a shaker at 4 °C. Cells are washed five times with 0.1% Tween-20 in PBS for 5 minutes at room temperature on a shaker and incubated with fluorescently-labeled secondary antibody (LI-COR, #926-32211) diluted 1:1000 in blocking buffer, and DRAQ5 nuclear stain (Biostatus Limited, #DRAQ5) diluted 1:10,000, at room temperature on a shaker for 1 hour. Cells are washed 5 times with 0.1% Tween-20 in PBS for 5 minutes at room temperature on a shaker and imaged on a LI-COR Odyssey imaging station. The raw data is normalized to DRAQ5 and the HER2 EC_{50} is calculated using XLfit™.

[00516] The above procedures were utilized to generate the following HER2 degradation data, which show the ability of these exemplary SDC-TRAPs to target cells preferentially expressing Hsp90. As noted above, a potent Hsp90 inhibitor need not be necessarily used in an SDC-TRAP as the targeting moiety. A feature of SDC-TRAP molecules is their retention by the desired target cells such that the effector moiety remains in the target cell rather than in undesired areas. As such, in embodiments, it is not necessary for an Hsp90 inhibitor targeting moiety to be potent in terms of its Hsp90 inhibitory effect. Indeed, in embodiments where the effector moiety is cleaved in the target cell, the pharmacological effects would be derived from the effector moiety. In such embodiments, suitable SDC-TRAP molecules may be found to have HER2 degradation potency IC_{50} of at least about 10 μM:

HER2 (IC_{50}, nM)	SDC-TRAP
2347	SDC-TRAP-0015
>5000	SDC-TRAP-0017
>5000	SDC-TRAP-0018
4419	SDC-TRAP-0019
>5000	SDC-TRAP-0020
>5000	SDC-TRAP-0021

HER2 (IC_{50}, nM)	SDC-TRAP
>5000	SDC-TRAP-0022
>5000	SDC-TRAP-0010
4300	SDC-TRAP-0023
>5000	SDC-TRAP-0027
>5000	SDC-TRAP-0028
1603	SDC-TRAP-0029
2916	SDC-TRAP-0031
>5000	SDC-TRAP-0024
395	SDC-TRAP-0025
>5000	SDC-TRAP-0033
2112	SDC-TRAP-0037
>5000	SDC-TRAP-0038
2935	SDC-TRAP-0039
4741	SDC-TRAP-0040
>5000	SDC-TRAP-0041
1057	SDC-TRAP-0042
2135	SDC-TRAP-0043
602	SDC-TRAP-0044
464	SDC-TRAP-0045
246	SDC-TRAP-0046
875	SDC-TRAP-0047

[00517] Example 4

[00518] This example illustrates a method of assessing the cytotoxicity of SDC-TRAPs of the invention.

[00519] **Cell Lines.** Human H3122 NSCLC cells were obtained and grown in RPMI in the presence of fetal bovine serum (10%), 2 mM L-glutamine and antibiotics (100 IU/ml penicillin and 100 μg/ml streptomycin, Sigma Aldrich.) Cells were maintained at 37 °C, 5% CO_2 atmosphere.

[00520] **Cell Viability Assays.** Cell viability was measured using the CellTiter-Glo® assay (Promega). In brief, cells were plated in 96-well plates in triplicate at optimal seeding density (determined empirically) and incubated at 37 °C, 5% CO_2 atmosphere for 24 hr prior to the addition of drug or vehicle (0.3% DMSO) to the culture medium. At the end of the assay, CellTiter-Glo was added to the wells per manufacturer's recommendation, shaken for two minutes and incubated for 10 minutes at room temperature. Luminescence (0.1 sec) was measured with a Victor II microplate reader (Perkin Elmer) and the resulting data were used to calculate cell viability, normalized to vehicle control.

[00521] Cells as described above were treated with exemplary SDC-TRAPs and their viability determined as above as well. The following table illustrates the results.

SDC-TRAP Number	IC_{50} (H3122) (nM)
SDC-TRAP-0010	234
SDC-TRAP-0015	1273
SDC-TRAP-0017	> 3000
SDC-TRAP-0018	620
SDC-TRAP-0019	393
SDC-TRAP-0020	1737
SDC-TRAP-0021	717
SDC-TRAP-0022	492
SDC-TRAP-0023	137
SDC-TRAP-0024	99
SDC-TRAP-0027	1354
SDC-TRAP-0028	909
SDC-TRAP-0029	125

[00522] **Example 5**

[00523] This example illustrates a method for assessing the stability of SDC-TRAP of the invention in human and mouse plasma.

[00524] SDC-TRAP-0022 and SDC-TRAP-0028 were incubated in human and mouse plasma for 2 h at 37 °C and assayed for integrity at 0.25, 0.5, 1 and 2 h. The values reported below are the remaining of the parent compound at the end of the 2 h incubation period.

Conjugate ID	Concentration	% Remaining 2 h (37 °C)	
		HU	MO
SDC-TRAP-0022	1 µM	29%	32%
	10 µM	30%	31%
SDC-TRAP-0028	1 µM	51%	53%
	10 µM	65%	47%

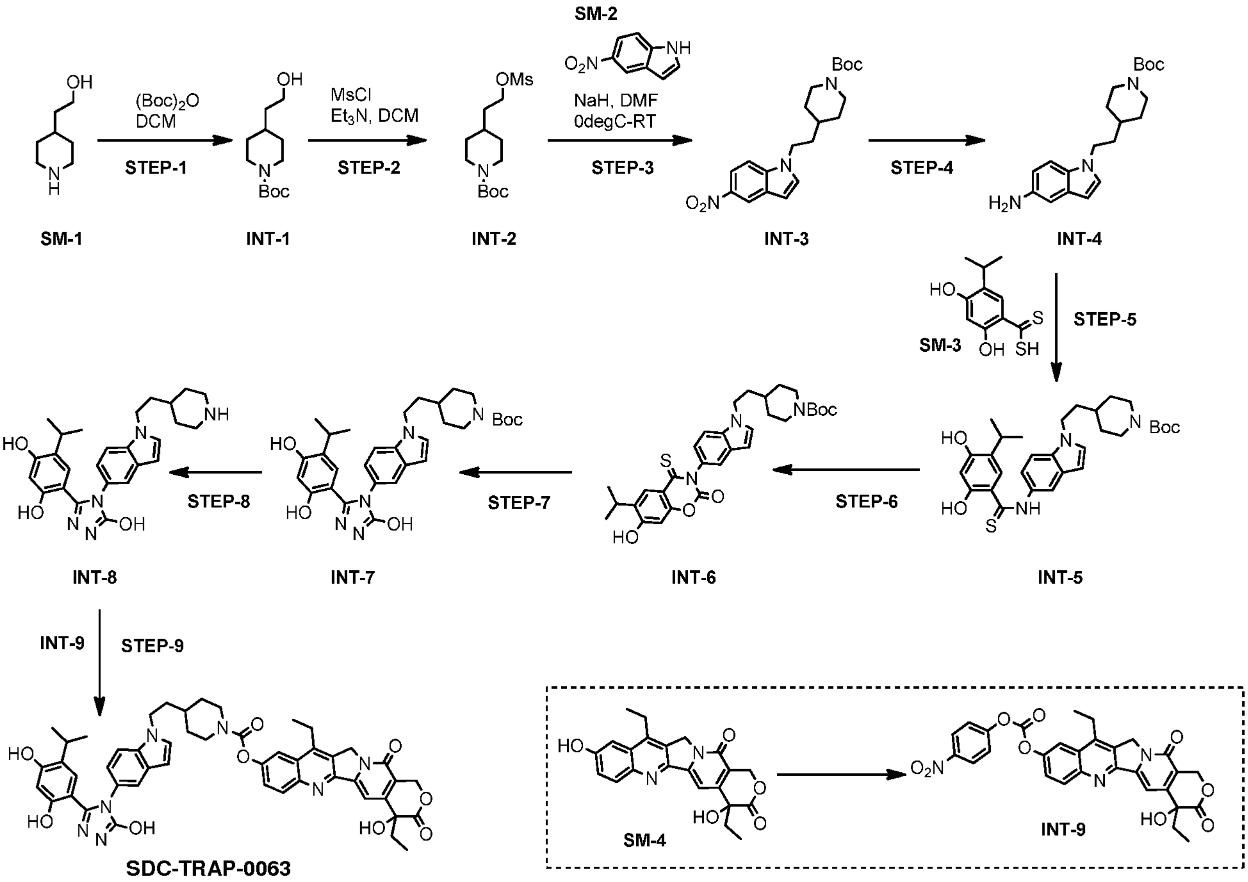
[00525] Example 6

[00526] A detailed schematic for the synthesis of SDC-TRAP-0063

[00527] A detailed scheme of the synthesis of SDC-TRAP-0063 is provided. The person of ordinary skill in the art would be able, without undue experimentation, to adapt this synthetic scheme for making other targeting molecule conjugates within the scope of the invention.

[00528] As explained hereinabove, SDC-TRAP-0063 is essentially a conjugate of the binding moiety ganetespib and the effector moiety irinotecan. SDC-TRAP-0063 is: 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate.

[00529] SDC-TRAP-0063 was synthesized according to the following scheme:



[00530] Synthesis of each of the above intermediates (INT) is detailed as follows.

[00531] Preparation of tert-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate (INT-1):

[00532] To a stirred solution of 2-(piperidin-4-yl)ethanol (30 g, 0.2322 mmol) in 1,2-dichloromethane (200 ml) was added in portions di-tert-butyl dicarbonate (53 g, 0.24 mmol) . The resultant mixture was stirred at room temperature overnight. After confirming reaction completion by thin-layer chromatography, the reaction mixture was washed with water and concentrated to yield compound INT-1 (52g).

[00533] Preparation of tert-butyl 4-(2-((methylsulfonyl)oxy)ethyl)piperidine-1-carboxylate (INT-2):

[00534] To a stirred solution of INT-1 (52 g, 0.23 mmol), 4-dimethylamino pyridine (4.2 g, 3.41mmol) and triethylamine (92g, 908 mmol) in 1,2-dichloroethane was added to methanesulfonyl chloride drop wise at 0 °C, and the mixture was stirred at room temperature overnight. After confirming reaction completion by thin-layer chromatography, the mixture was washed with water and concentrated to yield compound INT-2 (67g).

[00535] Preparation of tert-butyl 4-(2-(5-nitro-1H-indol-1-yl)ethyl)piperidine-1-carboxylate (INT-3):

[00536] To a stirred solution of 5-nitro-1H-indole (SM-2, above, 30 g, 185 mmol) in N,N-dimethylformamide (200 ml), sodium hydride (13g,325.5 mmol) was added in portions at 0 °C and the mixture was stirred at room temperature for 30 min. INT-2 (67g, 217 mmol) was added at 0 °C and the resultant mixture was stirred at room temperature overnight. The mixture was carefully poured into ice water while a yellow precipitate was observed. The mixture was extracted with ethyl acetate followed drying and concentration to afford the crude product, which was then purified by silica gel chromatography to yield INT-3 as a yellow solid (80g).

[00537] Preparation of compound tert-butyl 4-(2-(5-amino-1H-indol-1-yl)ethyl) piperidine-1-carboxylate (INT-4):

[00538] To a solution of INT-3 (80 g, 215 mmol) in a mixture of ethanol (200 ml) and tetrahydrofuran (350ml) was added Raney nickel (10 g). The resultant mixture was stirred at room temperature overnight under hydrogen atmosphere. The contents then were filtered to remove the solids and concentrated to yield INT-4 (70g).

[00539] Preparation of compound tert-butyl 4-(2-(5-(2,4-dihydroxy-5-isopropylphenylthioamido)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate (INT-5):

[00540] A mixture of 2,4-dihydroxy-5-isopropylbenzodithioic acid (SM-3, 46.5g, 204 mmol), sodium 2-chloroacetate (38g, 326.4 mmol) and sodium bicarbonate (52.0 g, 612 mmol) in N,N-dimethylformamide (350 ml) was degassed using nitrogen gas to remove oxygen. The reaction mixture then was stirred at 25 °C for 3 hours. The second reactant, INT-4 (70.0 g, 204mmol) in N,N-dimethylformamide (150ml) was added slowly to the reaction mixture through a syringe. The reaction mixture was stirred at 80 °C for 3 hours. After reaction completion, the reaction mixture was extracted with ethyl acetate, washed with water, then brine, and dried. Concentration by flash chromatography yielded INT-5 (58g).

[00541] Preparation of tert-butyl 4-(2-(5-(7-hydroxy-6-isopropyl-2-oxo-4-thioxo-2H-benzo[e][1,3]oxazin-3(4H)-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate (INT-6):

[00542] To a stirred solution of compound INT-5 (27 g, 50.86 mmol) in tetrahydrofuran (200 ml), carbonyldiimidazole (16.5 g, 101.7 mmol) was added in portions. The resulting mixture was stirred at room temperature for 3 hours under nitrogen atmosphere, then poured into water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to yield INT-6 (28 g).

[00543] Preparation of tert-butyl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate (INT-7):

[00544] To a stirred solution of compound INT-6 (28 g, 50.86 mmol) in anhydrous ethanol (200 mL) was added hydrazine hydrate (5 ml, 102.2 mmol), and the resulting mixture was stirred overnight at room temperature under argon atmosphere. The reaction product was filtered over a short pad of silica gel, followed by concentration and thorough drying yielding INT-7 (16.4 g.)

[00545] Preparation of 4-(5-hydroxy-4-(1-(2-(piperidin-4-yl)ethyl)-1H-indol-5-yl) -4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (INT-8):

[00546] To a solution of compound INT-7 (8 g,14.3 mmol) in methanol (40mL) was added a solution of 1.0 M HCl in methanol (100ml). The resulting mixture was stirred at room temperature overnight. The resultant solids were concentrated, then washed with methanol to yield INT-8 as a hydrochloride salt (4.8 g.)

[00547] To a 0 °C stirred suspension of 4-(5-hydroxy-4-(1-(2-(piperidin-4-yl)ethyl)-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol hydrochloride (INT-8, 3.0 mmol) and (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (4-nitrophenyl) carbonate (INT-9, 3.0 mmol) in dimethylformamide (40 mL) was added triethylamine (4.0 mmol) dropwise, and the mixture was stirred at 0°C for 1 hour. 50 mL water then was poured into the mixture. The yellow suspension was stirred at room temperature for 1 hour, then filtered. The filter cake was washed with water (10 mL × 2) and purified by column chromatography to yield SDC-TRAP-0063 as a white solid (2.20 g, 2.5 mmol).

[00548] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.68 (s, 1H), 7.64 – 7.56 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.24 – 7.12 (m, 2H), 6.55 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.37 (d, *J* = 4.2 Hz, 2H), 5.73 (d, *J* = 16.3 Hz, 1H), 5.36 – 5.24 (m, 3H), 4.41 (d, *J* = 13.5 Hz, 1H), 4.29 (q, *J* = 9.3, 7.5 Hz, 3H), 3.17 (q, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 12.7 Hz, 1H), 2.96 – 2.77 (m, 2H), 2.42 (s, 2H), 1.90 (dq, *J* = 14.2, 7.1 Hz, 6H), 1.45 – 1.33 (m, 5H), 1.31 – 1.22 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.50 (d, *J* = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{49}H_{49}N_7O_9$: 879.4; found: 880.2 (M + H^+).

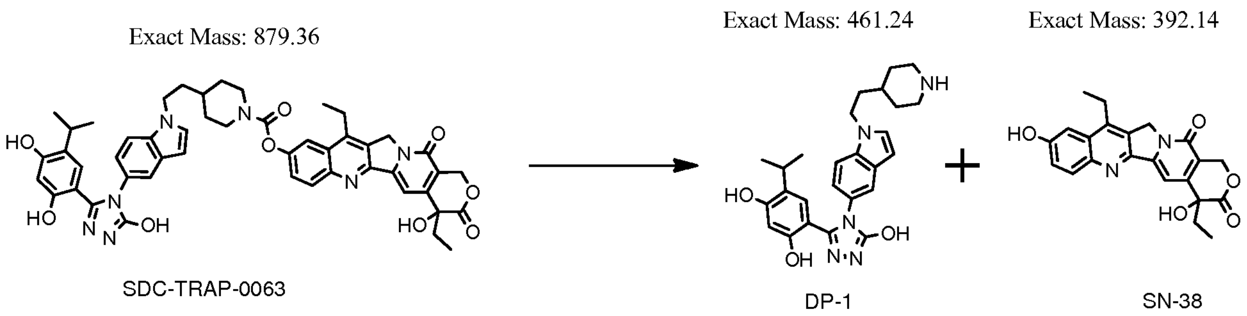
[00549] **Example 7**

[00550] The following example uses a number of assays to characterize SDC-TRAP-0063 (described in Example 6.)

[00551] *In vitro* activity as determined by the HER2 degradation and Hsp90 binding assay is set forth below. Protocols for the HER2 degradation assay and Hsp90 binding assay are provided in Examples 11 and 12, respectively.

IC_{50} (HER2 degradation assay)	EC_{50} (Hsp90 binding assay)
793nM	157nM

[00552] In order to determine the stability of SDC-TRAP-0063 in plasma, the compound was exposed to mouse plasma and the percent of the compound remaining at 1 hour was determined. After 1 hour 11.1% of SDC-TRAP-0063 remained. As shown below, SDC-TRAP-0063 breaks down into degradation product 1 (DP-1, an Hsp90 inhibitor fragment) and SN-38.



[00553] The degradation of SDC-TRAP-0063 was followed in mouse plasma. The release profile of fragment DP-1 and payload (SN-38) was determined according to the protocols provided in Examples 16-18.

	MOUSE PLASMA (MO)			
	Peak Area Ratio			
Time (h)	0	0.25	0.5	1
SDC-TRAP-0063	17.9	15.6	7.77	1.98
DP-1	0.00133	0.00268	0.0190	0.113
SN-38	0.0616	1.37	4.13	4.46

[00554] In order to determine if SDC-TRAP-0063 is targeting tumor cells selectively, the tissue distribution of SDC-TRAP-0063 and its degradation products DP-1 and SN-38 was monitored in mouse plasma, tumor and heart. Data from these experiments are presented in the table below and in Figures 15A-C. The data demonstrate that SDC-TRAP-0063 selectively targets and accumulates in tumor cells, as does the degradation products of SDC-TRAP-0063 including the chemotherapeutic SN-38.

Compound ID	SDC-TRAP-0063		
Lot	1		
Dose	50mg/10mL/kg		
Species	Female SCID Mouse (H1975)		
Route	IV		
Formulation	DRD		
Appearance	N/A		
Accuracy	N/A		
Analyte Target	SDC-TRAP-0063	DP-1	SN-38
Time (h)	**Plasma Conc. (μM)**		
0.083	526	0.0662	20.4
6	1.69	0.0397	0.0509
24	0.00675	0.0175	0.0240
48	BQL	0.00793	0.00524
Time (h)	**Tumor Conc. (nmol/g of tissue)**		
0.083	6.43	0.00758	1.47
6	1.61	0.111	0.730
24	0.203	0.404	0.618
48	0.0188	1.06	0.296
Time (h)	Heart Conc. (nmol/g of tissue)		
0.083	79.1	0.0271	0.927
6	0.536	0.207	BQL
24	BQL	0.0855	BQL
48	BQL	0.0238	BQL

[00555] Mouse xenograft efficacy data in an HCT-116 colon cancer model

[00556] A xenograft tumor model was used to evaluate the anti-tumor efficacy of SDC-TRAP-0063. The tumor model was established by transplanting HCT-116 tumor cells into mice and testing the effect of SDC-TRAP-0063 on tumor volume and change in tumor volume.

[00557] HCT 116 human colorectal adenocarcinoma tumor cells were purchased from ATCC. The cells were maintained *in vitro* as a monolayer culture in McCoy's 5a Medium. Fetal bovine serum was then be added to the medium. The final concentration of fetal bovine serum was 10%. Cells were cultured at 37°C and 5% CO_2 . The tumor cells were routinely sub-cultured twice weekly by trypsin-EDTA treatment. Cells in an exponential growth phase were harvested and counted for tumor inoculation.

[00558] 100 18-22 g, 5-7 week old, female BALB/cA nude mice were inoculated with the HCT 116 cells (2.0 x 10^6, 1:1 with Matrigel) subcutaneously on the back of each animal (0.1 mL/mouse). When the average tumor volume reached about 150-250 mm^3, 60 of the inoculated mice was selected based on tumor growth and randomly grouped into 6 treatment groups (10 mice per group) according to the following table. Mice that were not put on treatment were euthanized. Animals were sourced through Shanghai SINO-British SIPPR/BK Lab Animal Ltd, Shanghai, China. Mice were treated as set forth in the table below:

[00559] Treatment Groups

Groups	Animal Number	Treatment	Dosage (mg/kg)	Dosage Conc. (mg/mL)	Dosage Vol. (mL/kg)	Route of Adm.	Dosing Schedule
1	10	Vehicle	NA	NA	10	IV	Q7D x 3
2	10	SDC-TRAP-0063	200	20	10	IV	Q7D x 3
3	10	SDC-TRAP-0063	100	10	10	IV	Q7D x 3
4	10	SDC-TRAP-0046	94	9.4	10	IV	Q7D x 3
5	10	irinotecan	67	6.7	10	IV	Q7D x 3
6	10	irinotecan	67	6.7	10	IV	Q7D x 3
7		SYN-01	100	10	10	IV	Q7D x 3

[00560] Dose Preparation & Treatment Schedule

[00561] The dosing solutions of SDC-TRAP-0063, SDC-TRAP-0046, SYN-01(ganetespib) and irinotecan were prepared according to the DRD formulation protocol (10% dimethyl sulfoxide (DMSO), 18% Cremophor RH40, 3.6% dextrose, 68.4% sterile water and the clearly dissolved drug was added at desired concentration in DMSO). The administrations were made with 27-gauge IV needle.

[00562] Evaluation of Anti-Tumor Activity

[00563] During the treatment period, the implanted tumors were measured by caliper twice per week. The tumors were measured for the maximum width (X) and length (Y) and the tumor volumes (V) were calculated using the formula: $V = (X^2Y)/2$. The differences in the tumor volume between the control and treatment groups were analyzed for significance using the unpaired two-tailed Student's t-test. $P < 0.05$ was considered to be statistically significant. The animal body weights were also weighed and recorded twice per week. The changes in tumor volume in the days following compound treatment are shown in FIG. 4. The changes in animal body weight in the days following compound treatment are shown in FIG. 5.

[00564] Mouse xenograft efficacy data in an MCF-7 breast cancer model

[00565] A xenograft tumor model to evaluate the anti-tumor efficacy of SDC-TRAP-0063 was established by transplanting MCF-7 breast cancer cells into mice and testing the effect of SDC-TRAP-0063 on tumor volume and change in tumor volume.

[00566] MCF-7 breast cancer cells were purchased from ATCC. The cells were maintained *in vitro* as a monolayer culture in McCoy's 5a Medium. Fetal bovine serum was then added to the medium. The final concentration of fetal bovine serum was 10%. Cells were cultured at 37°C and 5% CO_2. The tumor cells were routinely sub-cultured twice weekly by trypsin-EDTA treatment. Cells in an exponential growth phase were harvested and counted for tumor inoculation.

[00567] 75 24-30g, 10-13 week old, female CD-1 nude mice were inoculated with the MCF-7 cells (5.0×10^6 /mouse) orthotopically in mammary fat pad (0.1 mL/mouse). 60 days estrogen pellets was implanted the day prior to cell implantations. When the average tumor volume reached about 100-225 mm^3, 40 of the inoculated mice were selected based on tumor growth and randomly grouped into 5 treatment groups (8 mice per group) according to the following table. Mice that were not put on treatment were euthanized. Animals were sourced through CRL (Wilmington, MA). Animals were treated as set forth in the table below.

Group	Animal Number	Treatment	Dosage (mg/kg)	Dosage Conc. (mg/mL)	Dosage Vol. (mL/kg)	Roe Adm.	Dosing Schedule
1	8	Vehicle	NA	NA	10	IV	Q7D x 3
2	8	SDC-TRAP-0063	150	15	10	IV	Q7D x 3
3	8	SDC-TRAP-0063	100	10	10	IV	Q7D x 3
5	8	Irinotecan	67	6.7	10	IV	Q7D x 3
6	8	Irinotecan	67	6.7	10	IV	Q7D x 3
		ganetespib	42	10	10	IV	Q7D x 3

[00568] Dose Preparation & Treatment Schedule

[00569] The dosing solutions of SDC-TRAP-0063, ganetespib and irinotecan were prepared in a standard DRD formulation (10% DMSO, 18% Cremophor RH40, 3.6% dextrose, 68.4% sterile water, while clearly dissolved drug substances were added in DMSO.) The administrations were made with a 27-gauge IV needle. In the combo group, irinotecan was dosed 2 hours after ganetespib.

[00570] Evaluation of Anti-Tumor Activity

[00571] During the treatment period, the implanted tumors were measured by caliper twice per week. The tumors were measured for the maximum width (X) and length (Y) and height (Z), the tumor volumes (V) were calculated using the formula: $V = 0.5236*X*Y*Z$. The differences in the tumor volume between the control and treatment groups were analyzed for significance using %T/C value. Animal body weights were also weighed and recorded 5x per week. The changes in tumor volume in the days following compound treatment are shown in FIG. 6. The changes in animal body weight in the days following compound treatment are shown in FIG. 7.

[00572] Preliminary toxicological evaluation data (TK analysis, biomarker analysis for myelosupression at various dose levels in rats):

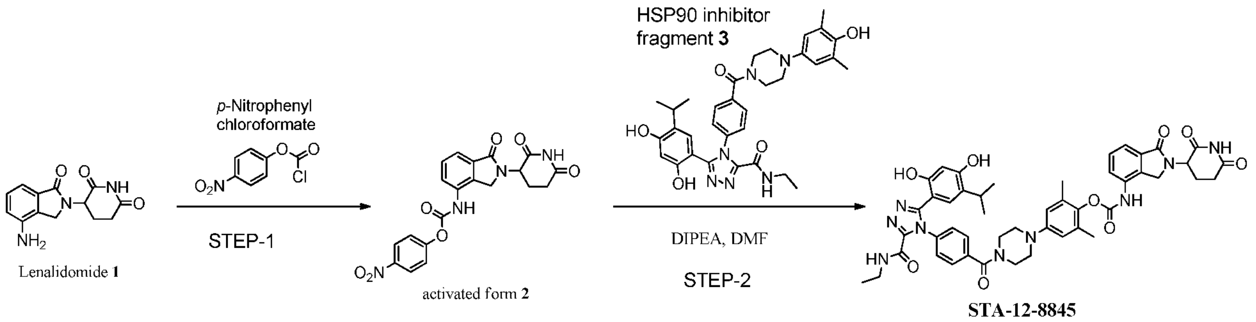
[00573] The data presented in FIG. 8 indicates that a higher dose (150mg/kg/1×wk) of conjugate SDC-TRAP-0063 appears to prolong the suppression of increase in tumor volume compared to a lower dose (100 mg/kg/1×wk). Either dose of SDC-TRAP-0063 has greater tumor growth suppression than effector moiety irinotecan alone, or unconjugated binding moiety ganetespib and effector moiety irinotecan administered together.

[00574] **Example 8**

[00575] Synthesis and Testing of Lenalidomide Conjugate SDC-TRAP-0178

[00576] Synthesis and testing of SDC-TRAP-0178, which is a conjugate of HSP90 inhibitor fragment 3 and lenalidomide, is exemplified below.

[00577] Synthesis and Structure of Lenalidomide Conjugate SDC-TRAP-0178:



[00578] STEP-1: To a stirred suspension of lenalidomide **1** (520mg, 2mmol) in dry THF (70 mL) was added 4-nitrophenylchloroformate (605mg, 3mmol). The reaction mixture was refluxed for 2h, concentrated to approximately 40mL, and triturated with ethyl acetate to yield a white precipitate. The solid was collected by filtration and washed with ethyl acetate to give carbamate 2 (650mg, 77%).

[00579] STEP-2: Diisopropylethylamine (33mg, 0.25mmol) was added to a stirred solution of Hsp90 inhibitor fragment 3 (120mg, 0.2mmol) and the activated lenalidomide **2** (86mg, 0.2mmol) in anhydrous DMF (5 mL). The reaction mixture was stirred at room temperature for 18h; then diluted with water (5 mL) and extracted with ethyl acetate (100mL). The organic phase was dried (sodium sulfate), filtered and evaporated, followed by flash chromatography (hexane-ethyl acetate 1:1 and ethyl acetate-methanol 98:2) to give SDC-TRAP-0178 (95mg, 53%) as a white solid.

[00580] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.22 (s, 1H), 10.17 (s, 1H), 9.74 (s, 1H), 9.02 (t, J = 5.9 Hz, 1H), 7.86 – 7.77 (m, 1H), 7.58 – 7.46 (m, 4H), 7.45 – 7.37 (m, 2H), 6.73 (d, J = 11.9 Hz, 3H), 6.33 (s, 1H), 5.13 (dd, J = 13.2, 5.1 Hz, 1H), 4.50 (d, J = 17.6 Hz, 1H), 4.41 (d, J = 17.6 Hz, 1H), 3.76 (s, 2H), 3.48 (s, 2H), 3.25 – 3.13 (m, 4H), 3.02 – 2.85 (m, 2H), 2.66 – 2.57 (m, 1H), 2.45 – 2.31 (m, 1H), 2.14 (s, 6H), 2.04-2.02(m, 1H), 1.06 (t, J = 7.2 Hz, 3H), 0.91 (d, J = 6.9 Hz, 6H).

[00581] ESMS calculated for $C_{47}H_{49}N_9O_9$: 883.37; Found: 884.1 $(M+H)^+$.

[00582] SDC-TRAP-0178 was tested in the HER2 degradation assays described in Example 12. These results are set forth in the table below.

[00583] SDC-TRAP-0178 HER2 Degradation Assay

SDC-TRAP#	HER2 Degradation IC50 (nM)
SDC-TRAP-0178	91 nM

[00584] SDC-TRAP-0178 Mouse Plasma Stability Assay

[00585] The percentage of a 10 μmol (μM) intravenous dose of SDC-TRAP-0178 remaining in plasma of a mouse after 1 hour was determined by the protocol set forth in Example 16:

Compound ID	% Remaining (1h, 10μM)
SDC-TRAP-0178	82.0%

[00586] SDC-TRAP-0178 Tissue Distribution

[00587] Tissue distribution of SDC-TRAP-0178 in plasma and tumor was determined following the protocol set forth in Example 14. Data therefrom are set forth in the table below:

Analyte Target	Plasma Conc. (µM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
	SDC-TRAP -0178	SDC-TRAP-0183	Lenalidomide	SDC-TRAP -0178	SDC-TRAP -0183	Lenalidomide	SDC-TRAP -0178	SDC-TRAP -0183	Lenalidomide
Time (h)									
0.083	918	N/A	1.39	16.4	0.320	0.623	0.0179	--	0.449
1	217	N/A	0.963	12.8	0.316	0.629	0.0589	--	0.653
6	4.51	N/A	0.00447	7.17	0.418	0.0532	1.59	--	11.9
24	0.0280	N/A	BQL	2.81	0.556	BQL	100	--	--
48	0.241	N/A	BQL	1.01	0.508	BQL	--	--	--

[00588] Determination of Cytotoxicity of Additional SDC-TRAP Molecules

[00589] The cytotoxicity of additional SDC-TRAP molecules was determined in BT-474, SW780 and RT-112 cancer cell lines. Cytotoxicity was determined following the protocol set forth in Example 13. Results are presented in the table below.

Compounds	Payload	Cytotoxicity (IC_{50}, nM)		
		BT-474	RT-112	SW-780
SDC-TRAP-0069	Bendamustine	914	909	1,342
SDC-TRAP-0211	Bendamustine	249	110	2,341
SDC-TRAP-0098	VDA	41	22	257
SDC-TRAP-0198	Doxorubicin	786	297	>10,000
SDC-TRAP-0199	Doxorubicin	29	29	2,299
SDC-TRAP-0219	Doxorubicin	>10,000	973	>10,000
SDC-TRAP-0200	Doxorubicin	32	16	651
SDC-TRAP-0068	Pemetrexed fragment	70	74	202
SDC-TRAP-0093	Pemetrexed fragment	1,540	1287	>10,000
SDC-TRAP-0117	Vorinostat	452	152	284
SDC-TRAP-0201	SN-38	1406	72	1,097
SDC-TRAP-0204	SN-38	8062	1314	>10,000
SDC-TRAP-0046	SN-38	205	20	489
SDC-TRAP-0063	SN-38	320	83	261
SDC-TRAP-0171	Lenalidomide	58	20	275
SDC-TRAP-0178	Lenalidomide	37	29	>10,000
SDC-TRAP-0196	Lenalidomide	17	31	>10,000
Lenalidomide		>10,000	>10,000	>10,000
(17-AAG)		42	44	161
(SN-38)		>10,000	<10	38

[00590] **Example 9**

[00591] Determination of IC_{50} by assessing the effects of various SDC-TRAPs on tumor shrinkage

[00592] H3122 cells were seeded into in 96-well plates at 7,500 cells/90 µL/well, and were incubated for 24 hours. 14 SDC-TRAPs, plus ganetespib as a control, were serially diluted in dimethylsulfoxide (DMSO) into each of six wells of each 96-well plate according to the graphic below, where each cell represents a well in the plate.

Plate #1(continuous), #2(pulse)

	3000	1000	333.3	111.1	37.0	12.3	3000	1000	333.3	111.1	37.0	12.3	
Drug	Dose (nM)						Dose (nM)						**Drug**
ganetespib													SDC-TRAP -0018
SDC-TRAP -0003													SDC-TRAP-0019
SDC-TRAP -0004													SDC-TRAP-0020
SDC-TRAP -0005													SDC-TRAP-0021
SDC-TRAP -0006													SDC-TRAP-0022
SDC-TRAP -0010													SDC-TRAP-0023
SDC-TRAP -0015													SDC-TRAP-0024
SDC-TRAP -0017													DMSO

Plate #3(continuous), #4(pulse)

	3000	1000	333.3	111.1	37.0	12.3	3000	1000	333.3	111.1	37.0	12.3	
Drug	Dose (nM)						Dose (nM)						**Drug**
ganetespib													SDC-TRAP-0036
SDC-TRAP-0027													SDC-TRAP-0224
SDC-TRAP-0028													SDC-TRAP-0225
SDC-TRAP-0029													SDC-TRAP-0226
SDC-TRAP-0030													SDC-TRAP-0227
SDC-TRAP-0032													SDC-TRAP-0228
SDC-TRAP-0034													SDC-TRAP-0223
SDC-TRAP-0035													DMSO

[00593] To each well of plates #1 and 3 (continuous plates), 145 µL of media was added, and the cells were incubated. The wells of plates #2 and 4 (pulsed plates) were incubated for 1 hour, then the wells were rinsed 2X with fresh media to remove the conjugate, and 145 µL of media was then added to each washed well. IC_{50} was determined visually under a microscope after 48 hours and 72 hours drug-exposure. Also at the 72 hour time point, 50µL of the cell culture supernatant was mixed with 50μL of CellTiter-Glo and the luminescence was determined, from which an IC_{50} for each conjugate was calculated.

[00594] The data demonstrating the tumor effect of these SDC-TRAPs are set forth in Figures 4–8.

[00595] **Example 10**

[00596] IC_{50} of continuous and pulsed exposure to SDC-TRAPs

[00597] IC_{50} toxicity was determined for 72 hour continuous exposure to 14 SDC-TRAPs run in triplicate, and for duplicate pulse exposure (1 hour "pulse" exposure to conjugate compound, followed by 72 hour incubation in conjugate-free media) using H3211 cells, according to the protocol set forth in Example 9. The experimental data are set forth in the table below.

	Compound	**72h-continuous**	**72h-continuous**	**72h-continuous**	**1h-pulse/ 71h-compound free**	**1h-pulse/ 71h-compound free**
H 3211 NSLC cells (7.5x10^3 cells/well), plate #1 (continuous), #2 (pulse), n=1	**SDC-TRAP-0223**	12 >	12 >	12 >	82	88
	SDC-TRAP-0003	> 3000	> 3000	> 3000	> 3000	> 3000
	SDC-TRAP-0004	22	60	40	624	1748
	SDC-TRAP-0005	> 3000	> 3000	> 3000	>3000	> 3000
	SDC-TRAP-0006	21	49	27	>3000	756
	SDC-TRAP-0010	144	327	232	291	>3000
	SDC-TRAP-0015	796	2227	796	>3000	>3000
	SDC-TRAP-0017	> 3000	> 3000	> 3000	>3000	>3000
	SDC-TRAP-0018	287	839	735	>3000	>3000
	SDC-TRAP-0019	209	713	258	>3000	>3000
	SDC-TRAP-0020	587	2615	2009	>3000	>3000
	SDC-TRAP-0021	431	817	902	>3000	>3000
	SDC-TRAP-0022	193	823	460	>3000	>3000
	SDC-TRAP-0023	59	239	113	> 3000	> 3000
	SDC-TRAP-0024	76	118	104	697	2211

H 3211 NSLC cells (7.5x10^3 cells/well), plate #3 (continuous), #4 (pulse), n=1	SDC-TRAP-0223	> 12	12 >	12 >	49	116
	SDC-TRAP-0027	984	1743	1335	>3000	>3000
	SDC-TRAP-0028	468	1761	499	>3000	>3000
	SDC-TRAP-0029	79	191	106	>3000	>3000
	SDC-TRAP-0030	53	38	53	>3000	>3000
	SDC-TRAP-0032	250	407	333	>3000	>3000
	SDC-TRAP-0034	587	1167	2046	>3000	>3000
	SDC-TRAP-0035	260	830	787	>3000	>3000
	SDC-TRAP-0036	139	265	96	>3000	>3000
	SDC-TRAP-0224	> 3000	> 3000	> 3000	>3000	>3000
	SDC-TRAP-0225	12 >	12 >	12 >	108	1481
	SDC-TRAP-0226	152	292	232	1089	2901
	SDC-TRAP-0227	> 3000	> 3000	> 3000	>3000	>3000
	SDC-TRAP-0228	> 3000	> 3000	> 3000	>3000	>3000
	SDC-TRAP-0223	> 12	12 >	12 >	60	111

[00598] **Example 11**

[00599] Hsp90$^{\alpha}$ Binding Assay Protocol

[00600] An Hsp90$^{\alpha}$ fluorescence assay kit from BPS Bioscience (Cat #50294) containing Hsp90 recombinant enzyme, FITC-labeled geldanamycin, assay buffer and a low binding 384-well plate was used to assay Hsp90$^{\alpha}$ binding. Dithiothreitol (DTT) (Cat #D0643) and bovine serum albumin (BSA) (Cat #A2153) were obtained from Sigma-Aldrich. Fluorescence polarization was measured using a PHERAstar microplate reader (BMG LABTECH GmbH, Ortenberg, Germany.)

[00601] The compounds were diluted to 1 mM in DMSO and loaded into a compound dilution plate to make 3-fold dilutions yielding a total of 8 concentrations. 1 □ iluted to 1 mM in DMSO and loaded into a compound dilution plate to make 3-fold dilutions yielding a total of 8 5 mL of Hsp90□ binding solution was prepared having a final concentration of 7 ng/□binding□, 5 nM FITC-labeled geldanamycin, 2 mM DTT and 0.1 mg/mL BSA. 49 µL of

binding solution was added to each microplate well, incubated at room temperature for 1 hour, then read using the PHERAstar microplate reader. The high control sample contained no compound plus Hsp90$^{\alpha}$; the low control sample contained no compound and no Hsp90$^{\alpha}$. Percent inhibition was calculated using high control as 100% and low control as 0% inhibition. The IC_{50} was calculated using GraphPad Prism 4 software.

[00602] **Example 12**

[00603] HER2 degradation assay with BT-474 cell line

[00604] HER2 has emerged as a key target for anticancer drugs due to its intrinsic involvement in the phosphatidylinositol-3-kinase-Akt/protein kinase B (PI3K-Akt) and the mitogen-activated protein kinase (MAPK) pathways, both of which suppress apoptosis and promote tumor cell survival, gene transcription, angiogenesis, cellular proliferation, migration, mitosis, and differentiation. The degradation of HER2 is a measure of efficacy of anticancer therapeutics that target Hsp90. Accordingly, the SDC-TRAP molecules of the invention that comprise a binding moiety that binds Hsp90 were tested in the following HER2 degradation assay.

[00605] BT-474 cells (human breast cancer cell line ATCC HTB-20) were obtained from ATCC and seeded into 12-well tissue culture plates at $0.2x10^6$/1.8mL/well. The cells were incubated for more than 6 hours at 37 °C in DMEM + 10% FBS, + 1% P/S, + 1.5g/L sodium bicarbonate. Each test compound was titrated in 4-fold dilutions from 5 μM to 78 nM with DMSO and 200 μL of the titration was added to each well of the cell plate. The DMSO final concentration was 0.2%. Cells were incubated overnight at 37°C in 5% CO_2.

[00606] Media was decanted from the plate, cells were washed 1× in PBS. 400 μL trypsin (EDTA) per well was added, and the cells were incubated for 2 to 3 minutes. Cells were collected into FACS tubes containing 1 ml culture medium to neutralize the trypsin and were centrifuged for 5 minutes at 1200 rpm. Supernatant was decanted and the cells were resuspended in 5 μL FITC (anti HER2/nu)/200 μL staining buffer (1x PBS + 1%FBS + 0.05% Sodium Azide)/tube. Controls were 5 μL IgG isotype control and staining buffer only. Tubes were incubated for 30 minutes in the dark at room temperature. 1 mL staining buffer was added to each tube and the tubes were centrifuged for 6 minutes at 1200 rpm. The supernatant was decanted and 300 μL staining buffer was added to each tube, which was store at 4°C fpr

FACS (cytometer) analysis. The cytometer readout was normalized and the potency of each compound is evaluated with IC_{50} calculated with XLfit™ software.

[00607] **Example 13**

[00608] Cytotoxicity assay with cancer cell lines

[00609] Cytotoxicity of SDC-TRAP molecules was determined in three cancer cell lines. 5000 cells/100 μL/well of human breast cancer cell line BT-474 (ATCC #HTB-20) and human urinary bladder cancer cell line SW780 (ATCC# CRL-2169) and 5000 cells/well of human urinary bladder cancer cell line RT-112 were seeded into 96-well flat-bottom tissue cultures plates and incubated overnight at 37 °C in 5% CO_2. BT-474 and SW780 cells were cultured in DMEM + 10% FBS, + 1% P/S, + 1.5g/L sodium bicarbonate; RT-112 cells were cultured in EMEM + 10% FBS, + 1% P/S. SDC-TRAP-0178 was titrated by 10-fold dilutions from 10 μM to 10nM and added to the plate at 10μL/well. Final concentration of DMSO in the cell plate was 0.25%. The plates were incubated for 72 hours at 37 °C in 5% CO_2. 80 μL of CellTiter-Glo was added to each well, followed by room temperature incubation in the dark for 15 minutes. Cell was determined by luminescence. $IC_{50}$was calculated using XLfit™ software.

[00610] **Example 14**

[00611] Tissue Distribution Extraction Procedure for SDC-TRAP Tumor Samples

[00612] SDC-TRAP molecules have the ability to be specifically targeted to desired cells. For example, SDC-TRAP molecules can be targeted to tumors and tumor cells in order to treat cancer. This example sets forth a protocol to extract the SDC-TRAP molecules of the invention from tumor samples.

[00613] A 150 ng/mL solution of SDC-TRAP-0002 in methanol was prepared using an internal spiking solution (500 μg/mL SDC-TRAP-0002 in DMSO). Using the 10 mM stock solutions of the SDC-TRAP molecule and its Hsp90i binding moiety and effector moiety in DMSO, spiking solutions were prepared at 0.025, 0.05, 0.1, 0.5, 1, 5, 10, 50, 100, 250, and 500 μM in DMSO. 5 μL of each spiking solution was added to a 96-deep well plate.

[00614] Quality control standards were prepared from 5 μL of 0.1, 1, and 10 μM calibration standard spiking solution added in triplicate into 96-deep well plate and adding 50 μL of matrix (plasma or homogenized tumor).

[00615] To prepare test samples, test plasma was diluted as needed using blank plasma. Tumor samples were pulverized in liquid nitrogen, weighed, and homogenized in PBS at 5× volume to sample weight. 50 µL of unknown plasma or homogenized tumor sample was mixed with 5 µL of DMSO. The samples were extracted by precipitating calibration standards, QC standards, and unknown samples with 200 µL of internal standard solution. The samples were mixed by vortex at room temperature for approximately 1.5 minutes, then centrifuge at 2-8 ºC. 150 µL of supernatant was collected and 25 µL of water added. Samples were mixed and analyzed by LC-MS/MS.

[00616] **Example 15**

[00617] SDC-TRAP-0063 Tissue Distribution Study in Mice

[00618] The following experiment was conducted in order to demonstrate the ability of SDC-TRAP molecules to specifically target desired tissues. An exemplary SDC-TRAP molecule, SDC-TRAP-0063, was administered to mice according to the protocol below and tissue samples were collected to evaluate tissue distribution.

[00619] Samples of plasma, heart and tumor were excised from a euthanized mouse, homogenized in PBS at 5 times tissue weight and diluted in 5 µL DMSO/50 µL sample. Prior to analysis, 55 µL samples and calibration standards were precipitated in 200 µL methanol in 96-well plates. Samples were mixed on a vortex mixer for 1.5 minutes at 1500 rpm at room temperature, then centrifuged at 4400 rpm for 10 minutes at 8°C. 150 µL of each supernatant was transferred to a well of a new 96-well plate, and 25 µL of water was added and mixed with the sample. The samples were analyzed by LCMS/MS using a Phenomenex Kinetex 2.6µm C18 100A, 30x2.1mm column at 0.5 mL/minute for 3.5 minutes with a TIS detector. For the analysis of samples from female SCID mice, a gradient of solvent A (water/0.1 % formic acid) and B (acetonitrile/0.1 % formic acid) was used as in Table 2 below. The solvent gradient used to analyze the tissues from male SD and CD-1 mice is shown in Table 3 below.

Table 2

Time (min)	A	B
0	80	20
1.7	5	95
2	5	95
2.1	80	20
3.5	80	20

Table 3

Time (min)	A	B
0	95	5
1.7	5	95
2	5	95
2.1	95	5
3.5	95	5

[00620] The distribution of SDC-TRAP-0063 and its expected degradants, DP-1, (ganetespib) and effector moiety SN-38 (irinotecan) in plasma, tumor and heart of female SCID mice at the illustrated time points following injection are shown in the tables below and in FIG. 9. Similar data were collected from male SD mice (FIG. 10) and male CD-1 mice (FIG. 11.) Tabular data are not shown. In each case, data collected over 48 hours post-treatment indicate that binding moiety and effector moiety accumulate and persist in tumor, but rapidly diminish in plasma and heart, demonstrating the efficacy of the SDC-TRAP molecules.

Compound ID	SDC-TRAP-0063		
Lot	1		
Dose	50mg/10mL/kg		
Species	Female SCID Mouse (H1975)		
Route	IV		
Formulation	DRD		
Appearance	N/A		
Accuracy	N/A		
Analyte Target	SDC-TRAP-0063	DP-1	SN-38
Time (h)	**Plasma Conc. (µM)**		
0.083	526	0.0662	20.4
6	1.69	0.0397	0.0509
24	0.00675	0.0175	0.0240
48	BQL	0.00793	0.00524
Time (h)	**Tumor Conc. (nmol/g of tissue)**		
0.083	6.43	0.00758	1.47
6	1.61	0.111	0.730
24	0.203	0.404	0.618
48	0.0188	1.06	0.296
Time (h)	**Heart Conc. (nmol/g of tissue)**		
0.083	79.1	0.0271	0.927
6	0.536	0.207	BQL
24	BQL	0.0855	BQL
48	BQL	0.0238	BQL

Time (h)	Tumor/Plasma Ratio		
0.083	0.0122	0.114	0.0721
6	0.958	2.79	14.3
24	30.1	23.1	25.8
48	--	134	56.4
Time (h)	**Heart/Plasma Ratio**		
0.083	0.151	0.409	0.0454
6	0.318	5.21	--
24	--	4.90	--
48	--	3.00	--

[00621] The tissue distribution of SDC-TRAP-0056 and SDC-TRAP-0052 as well as SN-38 and irinotecan was evaluated in female SCID mice as set forth above for SDC-TRAP-0063, DP-1 and SN-38. In each case, the data demonstrate that SDC-TRAP molecule and the effector moiety accumulate and persist in tumor, but rapidly diminish from the plasma, demonstrating the efficacy of the SDC-TRAP molecules. The data is shown in the table below.

Compound ID	SDC-TRAP-0046			SDC-TRAP-0052	Irinotecan	
Lot	2			1	RCN-102	
Dose	50mg/10mL/kg			25mg/10mL/kg	24mg/10mL/kg	
Species	Female SCID Mouse (H1975)					
Route	IV			IV	IV	
Formulation	DRD			DRD	DRD	
Appearance	Clear			Clear	Clear	
Accuracy	81.6%			97.2%	97.1%	
Analyte Target	SDC-TRAP-0046	SDC-TRAP-0052	SN-38	SDC-TRAP-0052	Irinotecan	SN-38
Time (h)	**Plasma Conc. (μM)**					
0.083	360	0.0782	2.29	--	--	--
6	5.88	0.0917	0.0773	58.7	2.24	1.42
12	2.37	0.0612	0.0389	--	--	--
24	0.0542	0.0364	0.00955	0.0223	BQL	BQL
48	BQL	0.0107	BQL	--	--	--
Time (h)	**Tumor Conc. (nmol/g of tissue)**					
0.083	6.94	BQL	0.298	--	--	--
6	4.97	0.241	0.448	13.9	13.1	1.44
12	5.21	0.407	0.344	--	--	--
24	2.19	1.71	1.01	5.33	0.0307	BQL
48	0.188	1.01	BQL	--	--	--

Time (h)	Tumor/Plasma Ratio					
0.083	0.0193	--	0.130	--	--	--
6	0.844	2.63	5.80	0.236	5.82	1.01
12	2.20	6.65	8.83	--	--	--
24	40.3	46.9	105	238	--	--
48	--	94.4	--	--	--	--

[00622] Example 16

[00623] Plasma Stability Protocol for SDC-TRAP Compounds

[00624] 150 ng/mL solution of SDC-TRAP-0002 in methanol was prepared using the internal standard spiking solution. This solution was used to precipitate all plasma samples in the study. 200 μL was pipetted into a 96 deepwell plate over dry ice. 10 μL of 1 mM stock in DMSO was added to a 1.5 mL microfuge tube, then 990 μL of plasma. Samples were mixed by vortex, then 50 μL of each sample was added in triplicate to a 96-well plate containing internal standard solution. This was designated the 0 hour time point sample. 250 μL of the remaining plasma sample was added to each of four 96 deepwell plates – one per time point. Samples were incubated at 37 ºC with gentle shaking for 0.25, 0.5, and 1 hour. After each time point, one plate of each sample was removed from the shaker and placed on wet ice for approximately 2 minutes. 50 μL plasma aliquots (in triplicate) were added to the deepwell plate containing internal standard solution. After the last time point was extracted, the 96 deepwell plate was vortexed, then centrifuged at 2-8 ºC. 150 μL of supernatant was collected and 25 μL of water was added. Samples were mixed and analyzed by LC-MS/MS.

[00625] Example 17

[00626] SDC-TRAP Stability in Mouse Plasma

[00627] The stability of seven SDC-TRAP types in mouse plasma was measured as follows. 990 μL mouse plasma aliquots from a common stock were spiked with 10 μL of 1 mM stock of one of seven SDC-TRAP samples identified in the table below. Each sample was mixed and divided into 250 μL aliquots, each representing time points 0, 15 minutes, 30 minutes or 1 hour. At the prescribed time point, 3 × 50 μL samples were each mixed with 200 μL of methanol containing internal standard and held on dry ice until all time point samples were extracted. The samples collectively were vortex mixed for 1.5 minutes at 1500 rpm, then centrifuged at 4400 rpm for 10 minutes at 8°C. 150 μL of each supernatant was transferred to a new 96-well plate, 25 μL of water added and mixed, then each sample was analyzed by

LCMS/MS as described in Example 16. The data collected at one hour are set forth in the table below.

Compound ID	% Remaining (1h)
SDC-TRAP-0063	11.1%
SDC-TRAP-0064	91.5%
SDC-TRAP-0172	74.7%
SDC-TRAP-0180	72.4%
SDC-TRAP-0184	18.0%
SDC-TRAP-0185	68.1%
SDC-TRAP-0186	57.9%

[00628] These and data taken at times 0, 15 minutes, 30 minutes and 1 hour are presented graphically in FIG. 12. As indicated in Figure 12, the SDC-TRAP molecules of the invention are stable in mouse plasma

[00629] The mouse plasma stability protocol outlined in Example 16 can, in embodiments of the invention - where the SDC-TRAP is intended to cleave gradually in the target cells, *e.g.,* tumor tissue, to provide a constant supply of the payload - be an additional indicator of selecting a suitable SDC-TRAP molecule of the invention. In a further embodiment, the mouse plasma stability protocol may be part of a two-pronged method of selecting a suitable SDC-TRAP molecule, along with determining a HER2 degradation potency IC_{50} of at least about 10 μM, such as discussed in Example 3, above. Although it is recognized that linker cleavage may be species-specific, it has been found that SDC-TRAP molecules exhibiting at least about 10% stability in mouse plasma after 1h (*i.e.,* at least 10% of the molecule remains intact) can be selected as suitable SDC-TRAP molecules.

[00630] **Example 18**

[00631] SDC-TRAP Stability in Mouse Plasma and Cell Culture Media

[00632] The stability of six SDC-TRAP molecules with a variety of binding moieties and a particular effector moiety (SN-38/irinotecan) in mouse plasma and cell culture media was assessed. Mouse plasma samples were prepared according to Example 16. 98 μL of DMEM + 10% FBS, + 1% P/S, + 1.5g/L sodium bicarbonate cell culture media was mixed with 2 μL of DMSO and aliquotted into 96-well plates at 250 μL per 0, 1, 2, and 18 hour time point. Plasma samples were mixed at 150 rpm for the required time and extracted and processed for analysis according to Example 16.

[00633] 3× 50 μL media samples in 96 were held in 96-well plates at -80 °C until the last time point was extracted. 200 μL of methanol containing IS was added and mixed by vortex at 1500 rpm for 1.5 minutes at room temperature. The samples were centrifuged at 4400 rpm for 10 minutes at 8 °C. 150 μL of supernatant was transferred to a new 96-well plate; 25 μL of water was added to each well; and mixed and the samples were analyzed according to the procedure described in Example 16.

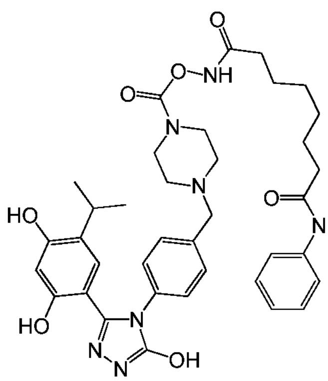
SDC-TRAP-#	Mouse (10 μM) % Remaining 1h (37°C) §	Mouse (10 μM) % Remaining 1h (37°C) *	Media (5 μM) % Remaining 1h (37°C) §	Media (5 μM) % Remaining 1h (37°C) *	Media (5 μM) % Remaining 19h (37°C)
SDC-TRAP-0029	44%	47%	43%	46%	29%
SDC-TRAP-0037	--	95%	--	67%	6%
SDC-TRAP-0044	--	61%	--	50%	41%
SDC-TRAP-0045	34%	45%	72%	77%	50%
SDC-TRAP-0046	50%	52%	62%	65%	37%
SN-38	--	64%	--	82%	52%

§ : Data from single parent peak. No double peak for SDC-TRAP-0044 plasma and media or SDC-TRAP-0037 plasma. SN-38 only integrated for double peaks.
* : Double peaks observed in parent chromatogram. Data calculated with sum of both peaks.

[00634] **Example 19: SDC-TRAPs comprising vorinostat**

[00635] SDC-TRAP-0117

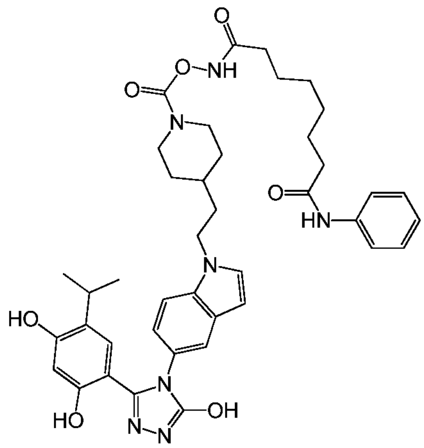
[00636] N1-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) benzyl)piperazine-1-carbonyl)oxy)-N8-phenyloctanediamide



[00637] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 11.40 (s, 1H), 9.83 (s, 1H), 9.58 (s, 1H), 9.39 (s, 1H), 7.62 – 7.54 (m, 2H), 7.35 – 7.23 (m, 4H), 7.18 – 7.10 (m, 2H), 7.05 – 6.96 (m, 1H), 6.78 (s, 1H), 6.26 (s, 1H), 3.48 (s, 2H), 3.40 (s, 4H), 2.97 (p, J = 6.9 Hz, 1H), 2.40 – 2.24 (m, 6H), 2.07 (t, J = 7.3 Hz, 2H), 1.54 (dt, J = 22.8, 7.3 Hz, 4H), 1.36 – 1.25 (m, 4H), 0.95 (d, J = 6.9 Hz, 6H); ESMS calculated for $C_{37}H_{45}N_7O_7$: 699.34; Found: 700.3 $(M+H)^+$.

[00638] SDC-TRAP-0118

[00639] N1-((4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carbonyl)oxy)-N8-phenyloctanediamide



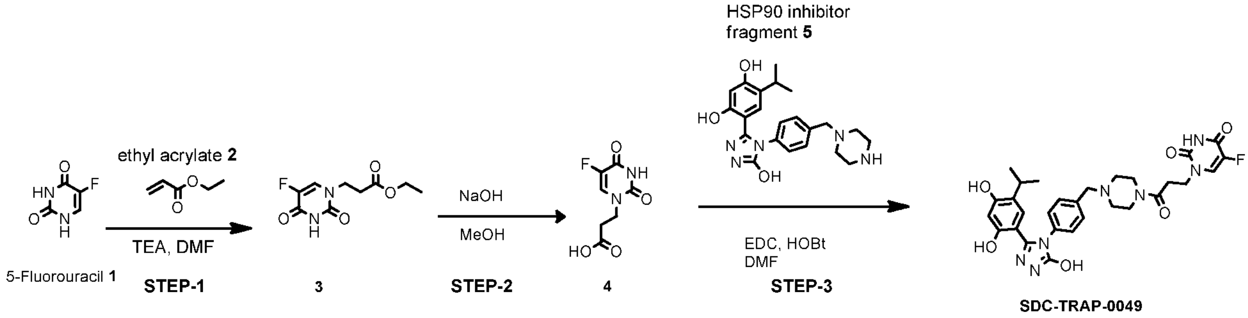
[00640] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 11.37 (s, 1H), 9.84 (s, 1H), 9.53 (d, J = 19.5 Hz, 2H), 7.58 (dt, J = 7.3, 1.0 Hz, 2H), 7.52 – 7.39 (m, 3H), 7.32 – 7.22 (m, 2H), 7.06 – 6.90 (m, 2H), 6.69 (s, 1H), 6.43 (d, J = 3.1 Hz, 1H), 6.23 (s, 1H), 4.22 (t, J = 7.1 Hz, 2H), 3.91 (s, 2H), 2.95 – 2.80 (m, 3H), 2.29 (t, J = 7.4 Hz, 2H), 2.07 (t, J = 7.3 Hz, 2H), 1.79 – 1.64 (m, 4H), 1.54 (dt, J = 24.2, 6.6 Hz, 5H), 1.43 (s, 1H), 1.37 – 1.25 (m, 4H), 1.16 (q, J = 12.3, 9.7 Hz, 4H), 0.80 (d, J = 6.8 Hz, 6H); ESMS calculated for $C_{41}H_{49}N_7O_7$: 751.37; Found: 752.3 $(M+H)^+$.

[00641] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

SDC-TRAP#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0117	1095
SDC-TRAP-0118	2352

[00642] **Example 20: SDC-TRAPs comprising 5-FU**

Exemplary Synthetic Protocol:



[00643] STEP-1: To a solution of 5-fluorouracil **1** (650mg, 5mmol) in anhydrous DMF (8mL), triethylamine (100mg, 1mmol) was added while stirring. After 5min, methyl acrylate **2** (1g, 10mmol) was added dropwise. Stirring was continued for 36h. The solvent was evaporated under reduced pressure, and the residue was purified on chromatographic column (95:5 CH_2Cl_2/ MeOH) to give compound **3** (860mg, 75%).

[00644] STEP-2: A solution of compound **3** (800mg, 3.47mmol) in a mixture of MeOH (4mL) and 2N aqueous solution NaOH (3mL) was heated for 4h at 60°C. The solvent was removed under reduced pressure, and the residue was subjected to acidification to pH2, using a solution of 10% HCl, resulting in acid **4** as white crystals. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 12.43 (s, 1H); 11.78(s, 1H); 8.06 (d, J = 7.2 Hz, 1H); 3.82 (t, J = 6.9 Hz, 2H); 2.63 (t, J = 6.9 Hz, 2H)

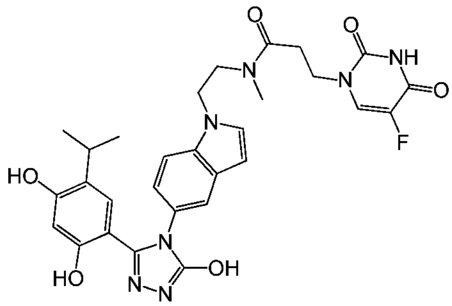
[00645] STEP-3: To a solution of acid **4** (42mg, 0.2mmol) and amine **5** (82mg, 0.2mmol) in anhydrous DMF (4 mL) was added EDC (60mg, 0.3mmol) and HOBT (27mg, 0.2mmol). The reaction mixture was stirred at room temperature for 5h. The reaction mixture was diluted with 5mL water and extracted with 100mL of ethyl acetate. The organic phase was dried with sodium sulfate, filtered and evaporated, followed by flash chromatography (hexane-ethyl acetate 1:1 and ethyl acetate-methanol 98:2) to give SDC-TRAP-0049 (95mg, 80%) as a white solid.

[00646] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 11.75 (s, 1H), 9.62 (s, 1H), 9.42 (s, 1H), 8.04 (d, J = 6.9 Hz, 1H), 7.32 – 7.30 (m, 2H), 7.15-7.12 (m, 2H), 6.77 (s, 1H), 6.27 (s, 1H), 3.82 (t, J = 6.8 Hz, 2H), 3.54 – 3.33 (m, 6H), 2.90 (ddt, J = 13.9, 9.7, 5.3 Hz, 1H), 2.73 – 2.60 (m, 2H), 2.34-2.29 (m, 4H), 0.94 (dd, J = 11.8, 6.9 Hz, 6H); ESMS calculated for $C_{29}H_{32}FN_7O_6$: 593.24; Found: 594.2 $(M+H)^+$.

[00647] The following compounds were made in the same general manner as above:

[00648] SDC-TRAP-0051

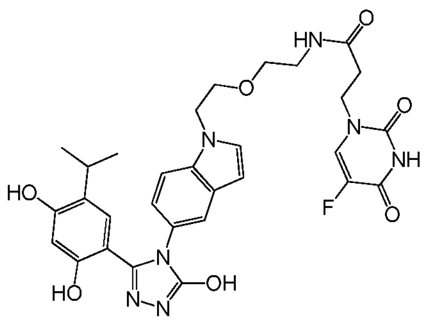
[00649] N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-N-methylpropanamide



[00650] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 11.75 (s, 1H), 9.56 (s, 1H), 9.47 (d, J = 14.3 Hz, 1H), 8.04 (d, J = 6.9 Hz, 1H), 7.54 – 7.35 (m, 3H), 6.95 (td, J = 8.9, 2.0 Hz, 1H), 6.74 (d, J = 13.6 Hz, 1H), 6.47 – 6.40 (m, 1H), 6.23 (d, J = 4.1 Hz, 1H), 4.37 (t, J = 6.0 Hz, 1H), 4.28 (t, J = 6.5 Hz, 1H), 3.82 (t, J = 6.8 Hz, 1H), 3.60 (q, J = 6.8 Hz, 3H), 3.54 – 3.33 (m, 6H), 2.90 (ddt, J = 13.9, 9.7, 5.3 Hz, 1H), 2.73 – 2.60 (m, 5H), 2.34 (t, J = 6.7 Hz, 1H), 0.84 (dd, J = 11.8, 6.9 Hz, 6H); ESMS calculated for $C_{29}H_{30}FN_7O_6$: 591.22; Found: 592.1 $(M+H)^+$.

[00651] SDC-TRAP-0048

[00652] N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanamide

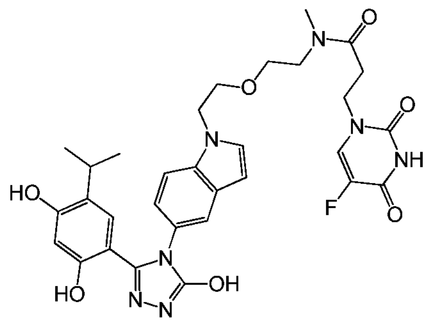


[00653] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 11.77 (s, 1H), 9.56 (s, 1H), 9.48 (s, 1H), 8.00 (t, J = 5.6 Hz, 1H), 7.93 (d, J = 6.8 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.41 (t, J = 2.1 Hz, 2H), 6.93 (dd, J = 8.6, 2.1 Hz, 1H), 6.73 (s, 1H), 6.43 (d, J = 3.2 Hz, 1H), 6.23 (s, 1H), 4.31 (t, J = 5.3 Hz, 2H), 3.81 (t, J = 6.6 Hz, 2H), 3.67 (t, J = 5.4 Hz, 2H), 3.57 (s, 1H), 3.48 – 3.31

(m, 13H), 3.15 (q, *J* = 5.6 Hz, 2H), 2.90 (p, *J* = 6.8 Hz, 1H), 2.45 (t, *J* = 6.7 Hz, 2H), 0.83 (d, *J* = 6.9 Hz, 6H); ESMS calculated for $C_{30}H_{32}FN_7O_7$: 621.23; Found: 622.2 $(M+H)^+$.

[00654] SDC-TRAP-0050

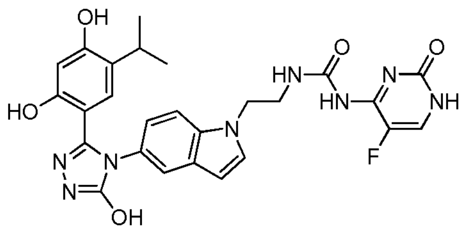
[00655] N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-N-methylpropanamide



[00656] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 11.76 (s, 1H), 9.56 (s, 1H), 9.49 (d, *J* = 3.0 Hz, 1H), 8.03 (d, *J* = 6.8 Hz, 1H), 7.49 (d, *J* = 8.7 Hz, 1H), 7.45 – 7.32 (m, 2H), 6.92 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.73 (d, *J* = 1.6 Hz, 1H), 6.41 (dd, *J* = 13.7, 3.1 Hz, 1H), 6.23 (s, 1H), 4.32 (q, *J* = 5.2 Hz, 2H), 3.88 (s, 2H), 3.80 (td, *J* = 6.9, 3.6 Hz, 2H), 3.71 – 3.63 (m, 2H), 3.47 (dd, *J* = 19.9, 8.3 Hz, 7H), 2.90 (hept, *J* = 7.0 Hz, 1H), 2.80 (s, 2H), 2.76 – 2.60 (m, 4H), 0.84 (d, *J* = 6.9 Hz, 6H); ESMS calculated for $C_{31}H_{34}FN_7O_7$: 635.25; Found: 636.2 $(M+H)^+$.

[00657] SDC-TRAP-0009

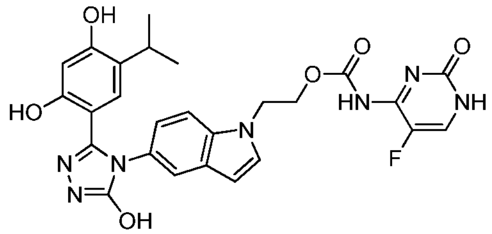
[00658] 1-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-3-(5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl)urea



[00659] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 9.52 (s, 1H), 9.46 (d, *J* = 4.8 Hz, 1H), 8.10 – 7.82 (m, 2H), 7.59 – 7.39 (m, 3H), 6.95 (t, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 9.6 Hz, 1H), 6.44 (dd, *J* = 16.8, 3.3 Hz, 1H), 6.22 (s, 1H), 4.31 (dt, *J* = 12.6, 6.4 Hz, 2H), 3.57 – 3.48 (m, 2H), 2.90 (h, J = 7.1 Hz, 1H), 0.84 (t, J = 7.8 Hz, 6H); ESMS calculated ($C_{26}H_{25}FN_8O_5$): 548.2; found: 549.1 (M+H).

[00660] SDC-TRAP-0025

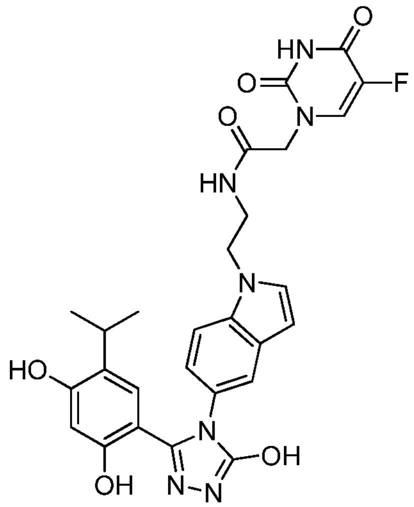
[00661] 2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)-1*H*-indol-1-yl)ethyl (5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate



[00662] [1]H NMR (400 MHz, Methanol-d_4) δ 7.77 (d, J = 5.3 Hz, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.51 (d, J = 2.0 Hz, 1H), 7.42 (t, J = 3.9 Hz, 1H), 7.07 (dd, J = 8.7, 2.1 Hz, 1H), 6.51 (q, J = 3.4 Hz, 2H), 6.26 (d, J = 2.7 Hz, 1H), 4.57-4.47 (m, 4H), 2.84 (q, J = 6.8 Hz, 1H), 0.61 (d, J = 6.8 Hz, 6H); ESMS calculated ($C_{26}H_{24}FN_7O_6$): 549.2; found: 550.2 (M+H).

[00663] SDC-TRAP-0013

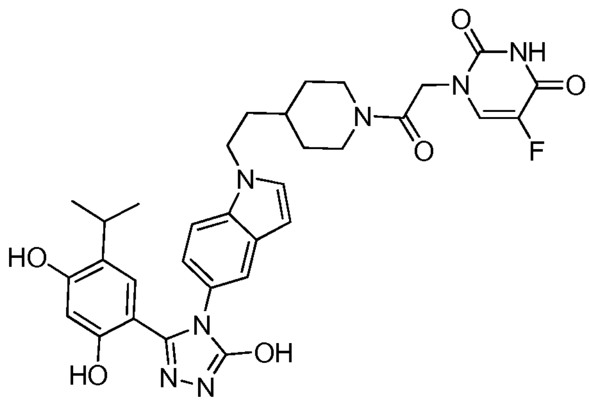
[00664] N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-2-(5-fluoro-2,4-dioxo-3,4- dihydropyrimidin-1(2H)-yl)
acetamide



[00665] [1]H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 2H), 9.53 (s, 1H), 9.45 (s, 1H), 8.34 (t, J = 5.6 Hz, 1H), 7.96 (d, J = 6.7 Hz, 1H), 7.51 – 7.38 (m, 3H), 6.95 (dd, J = 8.6, 2.1 Hz, 1H), 6.78 (s, 1H), 6.43 (d, *J* = 3.1 Hz, 1H), 6.22 (s, 1H), 4.23 (d, *J* = 7.9 Hz, 3H), 3.46 – 3.34 (m, 2H), 3.35 – 3.26 (m, 1H), 2.98 – 2.88 (m, 1H), 0.88 (d, *J* = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{27}H_{26}FN_7O_6$: 563.2; found: 563.9 (M + H^+).

[00666] SDC-TRAP-0137

[00667] 1-(2-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-2-oxoethyl)-5-fluoropyrimidine-2,4(1H,3H)-dione



[00668] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 (d, *J* = 2.4 Hz, 1H), 7.44 (dt, *J* = 6.5, 3.1 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.19 (q, *J* = 3.3 Hz, 1H), 7.12 (dq, *J* = 8.6, 3.8, 3.0 Hz, 1H), 6.52 (q, *J* = 3.3 Hz, 1H), 6.44 – 6.27 (m, 2H), 4.74 – 4.35 (m, 2H), 4.34 – 4.16 (m, 2H), 4.09 (ddt, *J* = 19.4, 7.6, 3.9 Hz, 1H), 3.43 – 3.28 (m, 1H), 3.18 – 2.96 (m, 2H), 2.84 (qd, *J* = 8.1, 5.3 Hz, 1H), 2.63 (t, *J* = 12.4 Hz, 1H), 1.93 – 1.68 (m, 4H), 1.45 – 1.06 (m, 3H), 0.48 (dt, *J* = 6.4, 3.0 Hz, 6H). ppm; ESMS calculated for $C_{32}H_{34}FN_7O_6$: 631.3; found: 632.2 (M + H^+).

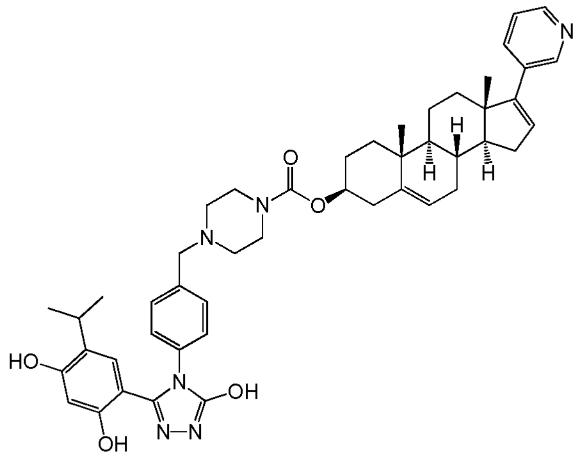
[00669] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0049	>5000
SDC-TRAP-0048	>5000
SDC-TRAP-0050	>5000
SDC-TRAP-0051	>5000
SDC-TRAP-0013	>5000
SDC-TRAP-0137	>5000

[00670] **Example 21: SDC-TRAPs comprising abiraterone**

[00671] SDC-TRAP-0150

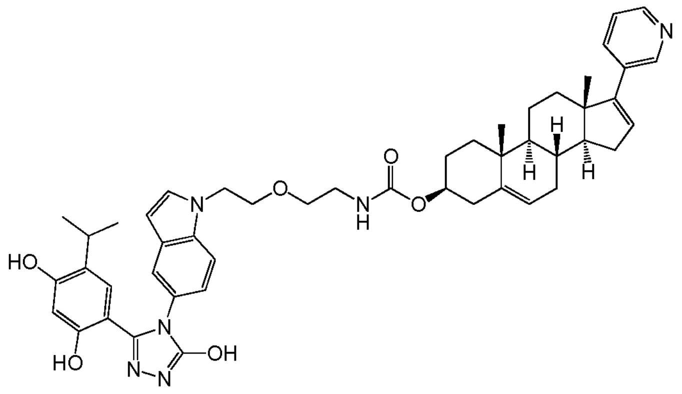
[00672] (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl) piperazine-1-carboxylate



[00673] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 9.61 (s, 1H), 9.41 (s, 1H), 8.59 (dd, J = 2.3, 0.9 Hz, 1H), 8.43 (dd, J = 4.8, 1.6 Hz, 1H), 7.76 (dt, J = 8.1, 1.9 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.18 – 7.10 (m, 2H), 6.78 (s, 1H), 6.26 (s, 1H), 6.12 (s, 1H), 5.38 (d, J = 4.9 Hz, 1H), 4.34 (tt, J = 10.8, 4.8 Hz, 1H), 3.47 (s, 2H), 2.97 (p, J = 6.9 Hz, 1H), 2.36 – 2.16 (m, 7H), 2.05 (dt, J = 15.2, 8.2 Hz, 3H), 1.82 -1.46 (m, 8H), 1.40 (td, J = 12.2, 5.0 Hz, 1H), 1.03 (d, J = 5.6 Hz, 8H), 0.95 (d, J = 6.8 Hz, 6H).; ESMS calculated for $C_{47}H_{56}N_6O_5$: 784.43; Found: 785.3 $(M+H)^+$.

[00674] SDC-TRAP-0151

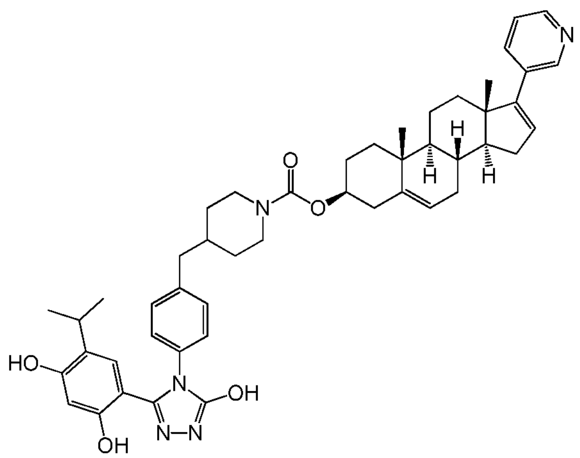
[00675] (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl (2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)carbamate



[00676] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 9.55 (s, 1H), 9.47 (s, 1H), 8.60 (d, J = 2.4 Hz, 1H), 8.44 (dd, J = 4.7, 1.6 Hz, 1H), 7.77 (dt, J = 8.2, 1.9 Hz, 1H), 7.50 (d, J = 8.7 Hz, 1H), 7.44 – 7.30 (m, 3H), 7.06 (q, J = 6.4, 5.7 Hz, 1H), 6.91 (dd, J = 8.7, 2.0 Hz, 1H), 6.73 (s, 1H), 6.40 (d, J = 3.1 Hz, 1H), 6.22 (s, 1H), 6.12 (dd, J = 3.3, 1.8 Hz, 1H), 5.38 (d, J = 4.9 Hz, 1H), 4.32 (q, J = 5.8, 5.3 Hz, 3H), 3.67 (t, J = 5.3 Hz, 2H), 3.08 (q, J = 5.8 Hz, 2H), 2.96 – 2.84 (m, 1H), 2.33 – 2.17 (m, 3H), 2.11 – 1.96 (m, 3H), 1.87 – 1.35 (m, 8H), 1.12 – 1.00 (m, 8H), 0.83 (d, J = 6.9 Hz, 6H); ESMS calculated for $C_{48}H_{56}N_6O_6$: 812.43; Found: 813.3 $(M+H)^+$.

[00677] SDC-TRAP-0153

[00678] (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl) piperidine-1-carboxylate



[00679] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 9.61 (s, 1H), 9.43 (s, 1H), 8.59 (s, 1H), 8.43 (dd, J = 4.8, 1.6 Hz, 1H), 7.76 (dt, J = 8.2, 2.0 Hz, 1H), 7.38 – 7.29 (m, 1H), 7.18 (d, J = 8.6 Hz, 2H), 7.14 – 7.06 (m, 2H), 6.75 (s, 1H), 6.27 (s, 1H), 6.12 (dd, J = 3.1, 1.7 Hz, 1H), 5.38 (s, 1H), 4.33 (tt, J = 10.9, 4.7 Hz, 1H), 3.94 (d, J = 12.6 Hz, 2H), 2.96 (p, J = 6.8 Hz, 1H), 2.67 (s, 2H), 2.37 – 2.16 (m, 3H), 2.04 (td, J = 14.7, 13.8, 4.7 Hz, 3H), 1.87 – 1.60 (m, 6H), 1.53 (d, J = 12.9 Hz, 5H), 1.40 (td, J = 12.2, 5.0 Hz, 1H), 1.13 – 0.90 (m, 15H); ESMS calculated for $C_{48}H_{57}N_5O_5$: 783.44; Found: 784.5 $(M+H)^+$.

[00680] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0150	1407
SDC-TRAP-0151	1194
SDC-TRAP-0153	6336

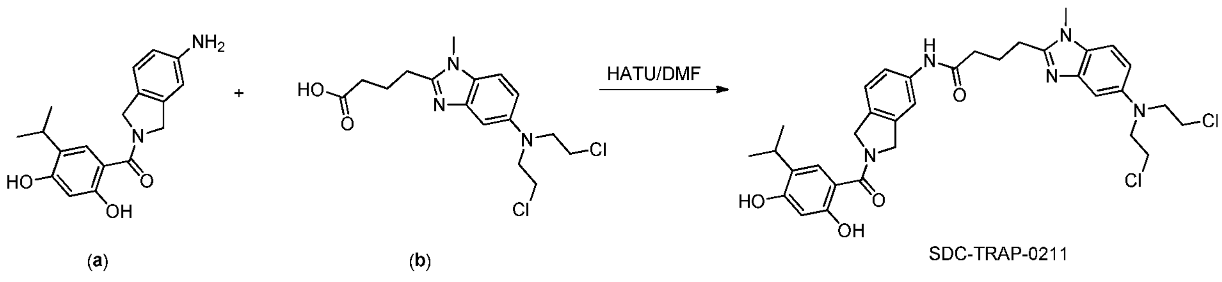
Mouse plasma stability data

SDC-TRAP-#	% Remaining (1h)
SDC-TRAP-0150	103%

[00681] Example 22: SDC-TRAPs comprising bendamustine

[00682] SDC-TRAP-0211

4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-N-(2-(2,4-dihydroxy-5-isopropylbenzoyl)isoindolin-5-yl)butanamide

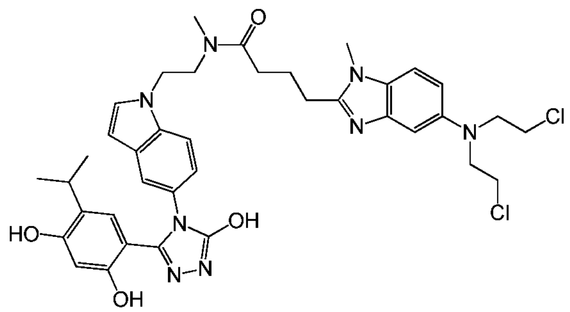


[00683] A mixture of (5-aminoisoindolin-2-yl)(2,4-dihydroxy-5-isopropylphenyl) methanone (a, 0.1 mmol), bendamustine (b, 0.1 mmol) and HATU (0.1 mmol) in DMF (2 mL) was stirred at room temperature for 16 h. The mixture was diluted with 50 mL of water and extracted with 50 mL x 2 EtOAc, and the organic layers were combined, concentrated and purified by column to yield SDC-TRAP-0211 as a white solid (25 mg, 0.04 mmol).

[00684] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 (s, 1H), 7.41 (s, 1H), 7.28 (s, 1H), 7.20 (t, *J* = 9.3 Hz, 2H), 6.96 (d, *J* = 2.3 Hz, 1H), 6.80 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 5.00 (d, *J* = 5.3 Hz, 4H), 3.77 – 3.68 (m, 6H), 3.61 (t, *J* = 6.7 Hz, 4H), 3.25 (p, *J* = 6.9 Hz, 1H), 2.97 (t, *J* = 6.8 Hz, 2H), 2.49 (d, *J* = 14.8 Hz, 4H), 2.20 (dq, *J* = 20.9, 7.1 Hz, 2H), 1.31 – 1.17 (m, 6H).; ESMS calculated for $C_{34}H_{39}Cl_2N_5O_4$: 651.2; found: 652.0 (M + H$^+$).

[00685] SDC-TRAP-0039

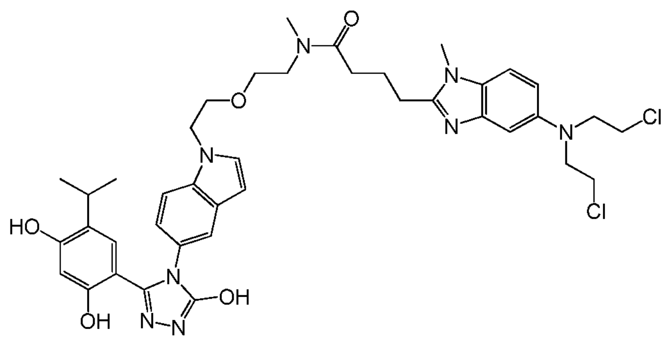
[00686] 4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-N-methylbutanamide



[00687] ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.85 (d, *J* = 1.9 Hz, 1H), 9.61 (s, 1H), 9.58 (s, 1H),7.50-7.32(m,4H), 6.92 – 6.74 (m, 4H), 6.42 (s,1H), 6.22 (d, *J* = 1.6 Hz, 1H), 4.38-4.30 (m, 2H), 3.71 – 3.58 (m, 14H), 2.95 – 2.73 (m, 3H), 2.40 - 2.35 (m, 2H), 1.90-1.98 (m, 2H), 0.84 (dd, *J* = 6.9, 4.4 Hz, 6H); ESMS calculated for $C_{38}H_{44}Cl_2N_8O_4$: 746.29; Found: 747.3 (M+H)$^+$.

[00688] SDC-TRAP-0040

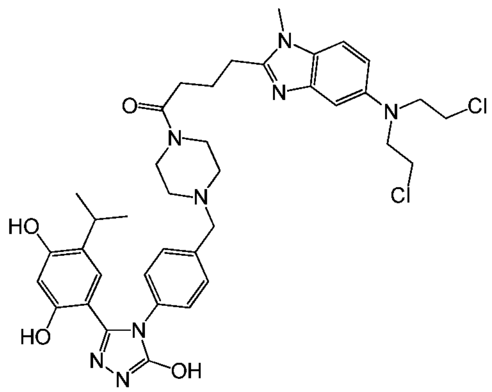
[00689] 4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N-methylbutanamide



[00690] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (d, J = 1.9 Hz, 1H), 9.60 (s, 1H), 9.55 (s, 1H),7.49-7.28(m,4H), 6.95 – 6.87 (m, 2H), 6.73 – 6.70 (m, 2H), 6.39 (s,1H), 6.24 (d, J = 1.6 Hz, 1H), 4.30 (dt, J = 16.3, 5.2 Hz, 2H), 3.73 – 3.62 (m, 13H), 2.86 – 2.73 (m, 6H), 2.41 - 2.35 (m, 2H), 1.93 (dd, J = 10.0, 5.1 Hz, 2H), 0.84 (dd, J = 6.9, 4.4 Hz, 6H); ESMS calculated for $C_{40}H_{48}Cl_2N_8O_5$: 790.31; Found: 791.3 $(M+H)^+$.

[00691] SDC-TRAP-0069

[00692] 4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl) piperazin-1-yl)butan-1-one



[00693] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 9.61 (s, 1H), 9.41 (s, 1H), 7.31 (dd, J = 8.5, 4.6 Hz, 3H), 7.18 – 7.10 (m, 2H), 6.91 (d, J = 2.3 Hz, 1H), 6.82 – 6.74 (m, 2H), 6.27 (s, 1H), 3.71-.3.68 (m,10H), 3.65 (s, 3H), 3.43 (dd, J = 12.5, 7.2 Hz, 6H), 2.96 (h, J = 6.9 Hz, 1H), 2.82 (t, J = 7.4 Hz, 2H), 2.44 (t, J = 7.2 Hz, 2H), 2.31 (dt, J = 26.0, 5.1 Hz, 4H), 1.97 (d, J = 11.4 Hz, 2H), 0.94 (d, J = 6.8 Hz, 6H); ESMS calculated for $C_{38}H_{46}Cl_2N_8O_4$: 748.30; Found: 749.1 $(M+H)^+$.

[00694] *In vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

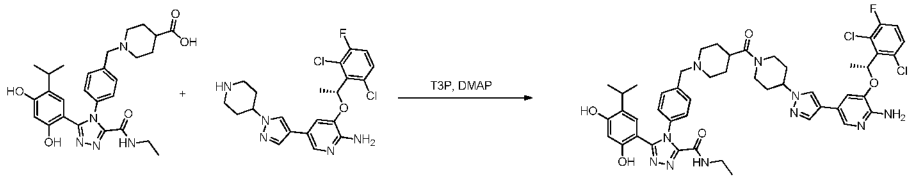
SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0039	2925
SDC-TRAP-0040	4741

SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0069	1232
SDC-TRAP-0211	289

[00695] Example 23: SDC-TRAPs comprising crizotinib

[00696] SDC-TRAP-0134 preparation:

(R)-4-(4-((4-(4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carbonyl)piperidin-1-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide

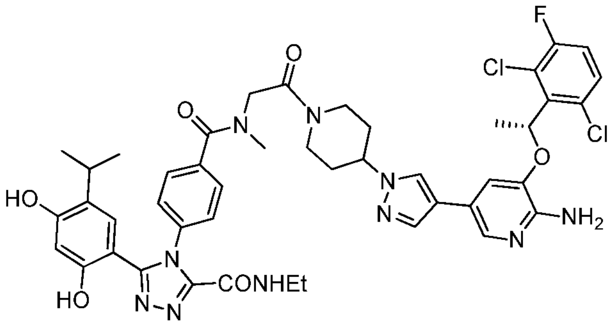


[00697] A mixture of 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carboxylic acid (a, 25 mg, 0.05 mmol), crizotinib (23mg, 0.05 mmol), DMAP (0.1 mmol) and T3P (0.10 mmol) in 5mL THF was heated in a microwave reactor at 80°C for 1h. The mixture was diluted with 100 mL each of 1M $NaHCO_3$ solution and EtOAc. The organic layer was separated, dried, concentrated and purified by column chromatography to give (R)-4-(4-((4-(4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carbonyl)piperidin-1-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide (SDC-TRAP-0134, 20 mg) as white solid.

[00698] ^{1}H-NMR ($CDCl_3$) δδ 7.7 (d, 1H, J=4), 7.5 (m, 4H), 7.4 (m, 1H), 7.3 (m, 3H), 7.0 (t, 1H, J=8), 6.9 (d, 1H, J=$), 6.54 (s, 1H), 6.50 (s, 1H), 6.1 (q, 1H, t=8), 4.95 (s, 2H), 4.8 (m, 1H), 4.4 (m, 1H), 4.1 (m, 1H), 3.57 (s, 1H), 3.4(m, 1H), 2.8 (m, 1H), 2.6 (m, 1H), 1.8-2.2 (m, 12H), 1.9 (d, 3H, J=8), 1.7 (m, 1H), 1.2 (m, 6H), 0.7 (d, 6H, J=8) ppm; ESMS calculated for $C_{48}H_{53}Cl_2FN_{10}O_5$: 938.4; found: 939.4 (M + H^+).

[00699] SDC-TRAP-0139:

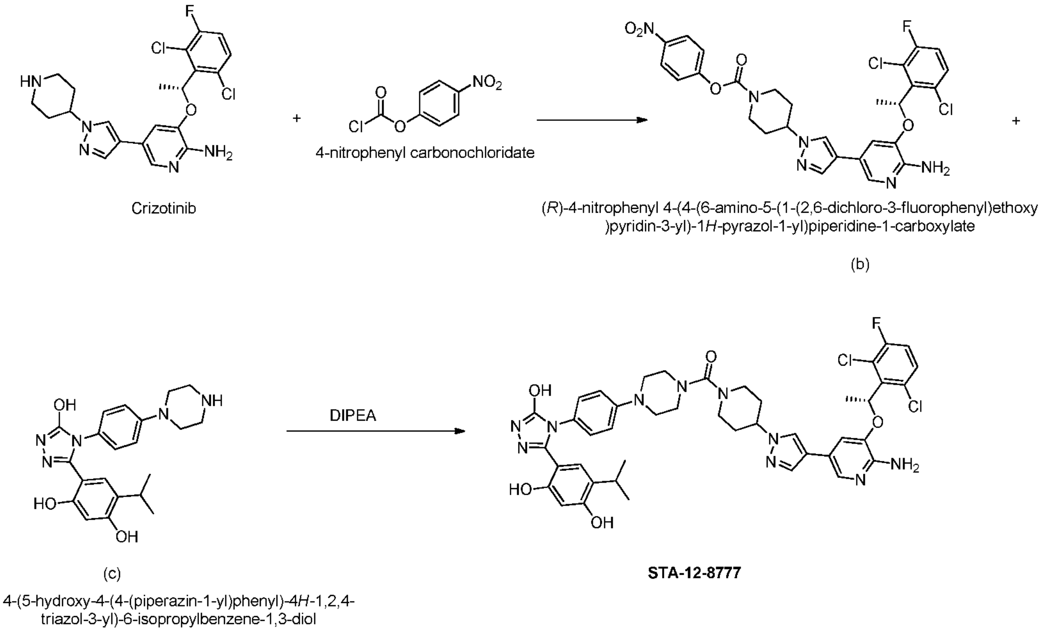
[00700] (R)-4-(4-((2-(4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-y)piperidin-1-yl)-2-oxoethyl)(methyl)carbamoyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide



[00701] ^{1}H-NMR ($CDCl_3$) δ 7.7 (m, 3H), 7.57 (s, 1H), 7.53 (s, 1H), 7.4 (m, 3H), 7.3 (m, 1H), 7.0 (t, 1H, J=8), 6.89 (s, 1H), 6.51 (s, 1H), 6.45 (s, 1H),m 6.1 (t, 1H, J=8), 4.89 (s, 2H), 4.7 (m, 1H), 4.4 (m, 2H), 4.1 (m, 1H), 3.4 (m, 2H), 3.2 (m, 2H), 2.9 (m, 2H), 2.2-2.4 (m, 2H), 2.1 (m, 2H), 1.9 (d, 3H, J=8), 1.2 (m, 6H), 0.7 (d, 6H, J=8) ppm; ESMS calculated for $C_{45}H_{47}Cl_2FN_{10}O_6$: 912.3; found: 913.3 (M + H^+).

[00702] SDC-TRAP-0138:

[00703] (R)-(4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidin-1-yl)(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)methanone



[00704] To a mixture of crizotinib (22 mg, 0.05 mmol) and 4-nitrophenyl carbonochloridate (10mg, 0.05 mmol) was added 2 mL $CHCl_3$ whereafter the mixture was stirred for 1h. Solvent was removed to yield crude (R)-4-nitrophenyl 4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (b, 0.05 mmol).

[00705] To the above crude solids was added a solution of 4-(5-hydroxy-4-(4-(piperazin-1-yl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (c, 20 mg, 0.05 mmol) in DMF (2mL), and the mixture was heated to 110°C for 10 h. The mixture was diluted in 100 mL each of water and EtOAc. The organic layer was separated, dried, concentrated and purified by column chromatography to give (R)-(4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidin-1-yl)(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)methanone (SDC-TRAP-0138, 4mg) as a white solid.

[00706] ^1H-NMR (CD_3OD) δ 7.7 (m, 1H), 7.6 (m, 2H), 7.4 (m, 3H), 7.2 (m, 2H), 7.1 (m, 3H), 6.9 (m, 1H), 6.53 (s, 1H), 6.48 (s, 1H), 6.1 (m, 1H), 4.3 (m, 1H), 3.9 (m, 1H), 3.2-3.8 (m, 7H), 3.0 (m, 2H), 1.8-2.3 (m, 8H), 1.3 (3H, d, J=8), 0.8 (d, 6H, J=8) ppm; ESMS calculated for $C_{43}H_{45}Cl_2FN_{10}O_5$: 870.3; found: 871.3 ($M + H^+$).

[00707] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

No	SDC-TRAP-#	HER2 IC_{50} (nM)
1	SDC-TRAP-0134	77
2	SDC-TRAP-0138	707
3	SDC-TRAP-0139	1000-2000

[00708] Hsp90□□binding activity data:

No	SDC-TRAP-#	Binding EC_{50} (nM)
1	SDC-TRAP-0134	95.42nM

[00709] Hsp90□□binding data:

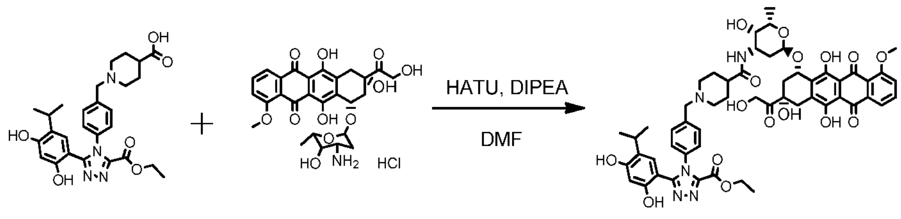
SDC-TRAP-#	EC_{50} (nM)
SDC-TRAP-0134	95.42nM

[00710] Mouse plasma stability data:

SDC-TRAP-#	% Remaining (1h)
SDC-TRAP-0143	89.9%
SDC-TRAP-0144	96.2%

[00711] Example 24: SDC-TRAPs comprising doxorubicin

[00712] Exemplary synthesis:



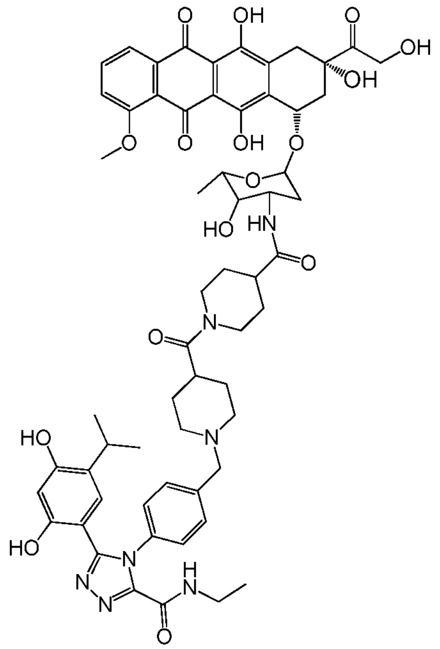
[00713] To a solution of Hsp90 inhibitor fragment 1 (102mg, 0.2mmol) in anhydrous DMF (6 mL) was added HATU (78mg, 0.2mmol) under nitrogen at 0°C, followed by diisopropylamine (78mg, 0.6mmol). The reaction mixture was stirred at 0°C for 15 min, followed by the addition of doxorubicin hydrochloride 2 (135mg, 0.25mmol), and stirring was continued for 18h at room temperature. The reaction mixture was diluted with methylene chloride and washed with water and brine. The organic phase was dried with sodium sulfate, filtered and concentrated, leaving a dark red residue. The product was isolated using column chromatography (95:5 dichloromethane /methanol) to give SDC-TRAP-0142 (ethyl-5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-((4-(((2S,3S,4S,6R)-3-hydroxy-2-methyl-6-(((1S,3S)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy) tetrahydro-2H-pyran-4-yl)carbamoyl)piperidin-1-yl)methyl)phenyl)-4H-1,2,4-triazole-3-carboxylate, 115mg, 55%) as a red solid.

[00714] ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.02 (s, 1H), 13.27 (s, 1H), 10.62 (s, 1H), 9.76 (s, 1H), 8.93 (t, J = 5.9 Hz, 1H), 7.90 (d, J = 4.8 Hz, 2H), 7.64 (p, J = 3.8 Hz, 1H), 7.44 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 6.55 (s, 1H), 6.33 (s, 1H), 5.44 (s, 1H), 5.22 (d, J = 3.4 Hz, 1H), 4.94 (t, J = 4.4 Hz, 1H), 4.85 (t, J = 5.9 Hz, 1H), 4.72 (d, J = 5.8 Hz, 1H), 4.57 (d, J = 5.9 Hz, 2H), 4.16 (q, J = 6.7 Hz, 1H), 4.08 – 3.93 (m, 3H), 3.41 (d, J = 17.4 Hz, 3H), 3.15 (p, J = 7.0 Hz, 2H), 3.05 – 2.77 (m, 5H), 2.24 – 2.06 (m, 3H), 1.95 – 1.79

(m, 3H), 1.60 – 1.36 (m, 5H), 1.15 (dd, *J* = 23.9, 6.7 Hz, 2H), 1.02 (t, *J* = 7.1 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 6H). ESMS calculated for $C_{54}H_{59}N_5O_{16}$: 1033.40; Found: 1033.8 $(M+H)^+$.

[00715] The following compounds were made in the same general manner as above:

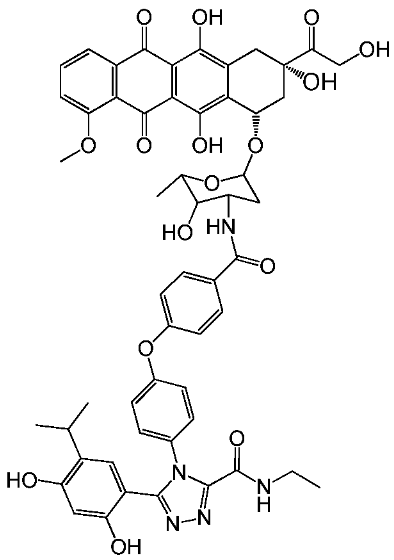
[00716] SDC-TRAP-0198



[00717] 1-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)-N-((2S,3S,4S,6R)-3-hydroxy-2-methyl-6-(((1S,3S)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2H-pyran-4-yl)piperidine-4-carboxamide

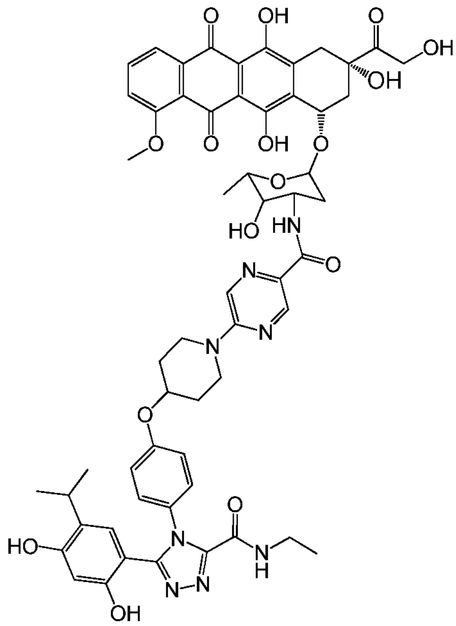
[00718] ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.04 (s, 1H), 13.28 (s, 1H), 10.61 (s, 1H), 9.79 (s, 1H), 8.96 (t, *J* = 5.8 Hz, 1H), 7.91 (d, *J* = 4.8 Hz, 2H), 7.69 – 7.61 (m, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 6.57 (s, 1H), 6.34 (s, 1H), 5.47 (s, 1H), 5.22 (d, *J* = 3.4 Hz, 1H), 4.96 – 4.83 (m, 2H), 4.77 (t, *J* = 6.0 Hz, 1H), 4.57 (d, *J* = 5.9 Hz, 2H), 4.33 - 4.16 (m, 2H), 3.98 (s, 3H), 3.46 (s, 2H), 3.21 – 3.09 (m, 2H), 3.05 – 2.84 (m, 4H), 2.82 - 2.39 (m, 2H), 2.24 – 2.08 (m, 2H), 1.85 (t, *J* = 12.1 Hz, 1H), 1.61 (s, 3H), 1.54 (s, 4H), 1.41 -1.26 (m, 3H), 1.16 – 0.98 (m, 8H), 0.79 (d, *J* = 6.8 Hz, 6H); ESMS calculated for $C_{60}H_{69}N_7O_{16}$: 1143.48; Found: 1144.2 $(M+H)^+$.

[00719] SDC-TRAP-0199



[00720] 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(4-(((2S,3S,4S,6R)-3-hydroxy-2-methyl-6-(((1S,3S)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2H-pyran-4-yl)carbamoyl)phenoxy)phenyl)-4H-1,2,4-triazole-3-carboxamide; ESMS calculated for $C_{54}H_{53}N_5O_{16}$: 1027.35; Found: 1028.2 $(M+H)^+$.

[00721] SDC-TRAP-0199

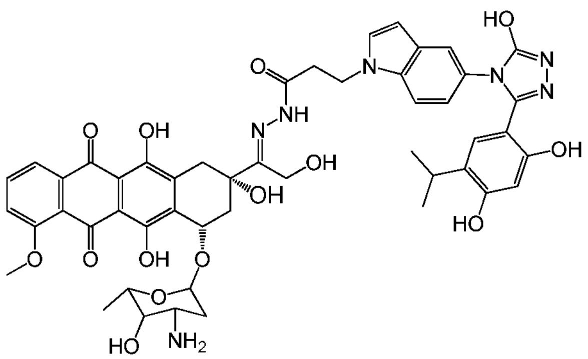


[00722] 5-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazo l-4-yl)phenoxy)piperidin-1-yl)-N-((2S,3S,4S,6R)-3-hydroxy-2-methyl-6-(((1S,3S)-3,5,12-tri hydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2H-pyran-4-yl)pyrazine-2-carboxamide; ESMS calculated for $C_{57}H_{60}N_8O_{16}$: 1112.41; Found: 1113.2 $(M+H)^+$.

[00723] SDC-TRAP-0219

[00724] (E)-N'-(1-((2S,4S)-4-(((2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl)-2-hydroxyethylidene)-3-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)propanehydrazide;

[00725] ESMS calculated for $C_{49}H_{51}N_7O_{14}$: 961.35; Found: 962.2 $(M+H)^+$.



[00726] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

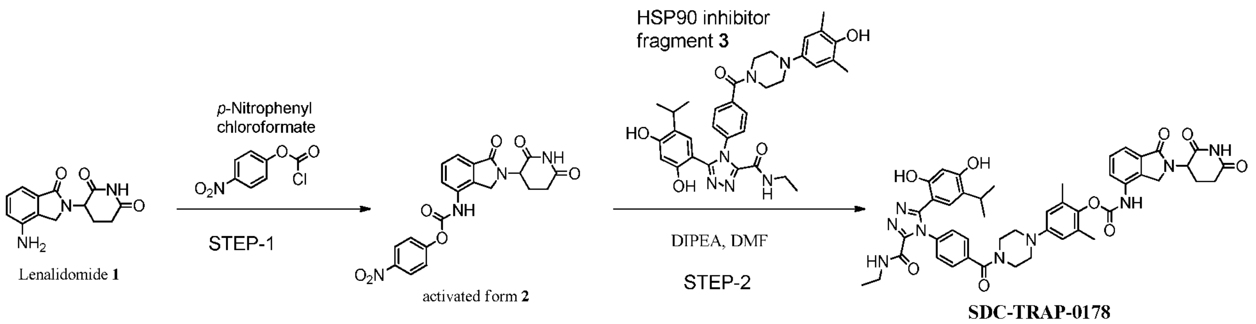
SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0142	>10,000
SDC-TRAP-0198	>10,000
SDC-TRAP-0199	>10,000
SDC-TRAP-0200	>10,000

Hsp90$^{\alpha}$ binding assay data

SDC-TRAP-#	EC_{50} (nM)
SDC-TRAP-0198	93.32
SDC-TRAP-0199	136.3
SDC-TRAP-0200	252.6

[00727] **Example 25: SDC-TRAPs comprising lenalidomide**

[00728] Exemplary synthesis:



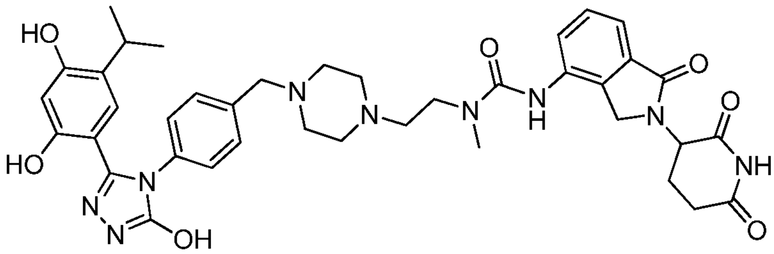
[00729] STEP-1: To a stirred suspension of lenalidomide **1** (520mg, 2mmol) in dry THF (70 mL) was added 4-nitrophenylchloroformate (605mg, 3mmol). The reaction mixture was refluxed for 2h, concentrated to approximately 40mL and triturated with ethyl acetate to yield a white precipitate. The solid was collected by filtration and washed with ethyl acetate to give activated lenalidomide **2** (650mg, 77%).

[00730] STEP-2: Diisopropylethylamine (33mg, 0.25mmol) was added to a stirred solution of Hsp90 inhibitor fragment **3** (120mg, 0.2mmol) and the activated lenalidomide **2** (86mg, 0.2mmol) in anhydrous DMF (5 mL). The reaction mixture was stirred at room temperature for 18h. The reaction mixture was diluted with water (5 mL) and extracted with ethyl acetate (100mL). Organic phase was dried (sodium sulfate) filtered and evaporation, followed by flash chromatography (hexane-ethyl acetate 1:1 and ethyl acetate-methanol 98:2) gave SDC-TRAP-0178 (95mg, 53%) as a white solid.

[00731] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.22 (s, 1H), 10.17 (s, 1H), 9.74 (s, 1H), 9.02 (t, J = 5.9 Hz, 1H), 7.86 – 7.77 (m, 1H), 7.58 – 7.46 (m, 4H), 7.45 – 7.37 (m, 2H), 6.73 (d, J = 11.9 Hz, 3H), 6.33 (s, 1H), 5.13 (dd, J = 13.2, 5.1 Hz, 1H), 4.50 (d, J = 17.6 Hz, 1H), 4.41 (d, J = 17.6 Hz, 1H), 3.76 (s, 2H), 3.48 (s, 2H), 3.25 – 3.13 (m, 4H), 3.02 – 2.85 (m, 2H), 2.66 – 2.57 (m, 1H), 2.45 – 2.31 (m, 1H), 2.14 (s, 6H), 2.04-2.02(m, 1H), 1.06 (t, J = 7.2 Hz, 3H), 0.91 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{47}H_{49}N_9O_9$: 883.37; Found: 884.1 $(M+H)^+$.

[00732] SDC-TRAP-0105

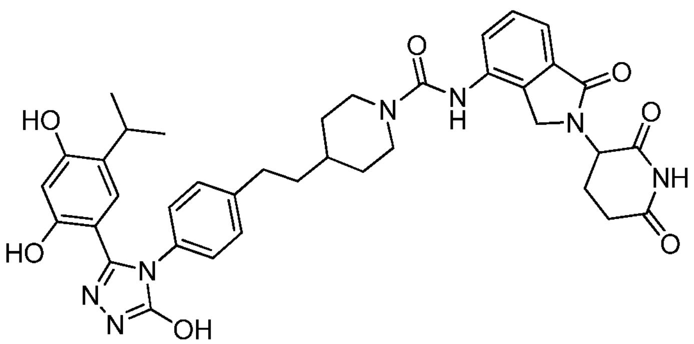
[00733] 1-(2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) benzyl)piperazin-1-yl)ethyl)-3-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-1-methylurea



[00734] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (dd, *J* = 8.9, 6.4 Hz, 1H), 7.49 (dp, *J* = 6.6, 3.6 Hz, 3H), 7.42 – 7.22 (m, 4H), 6.43 (dd, *J* = 40.6, 2.5 Hz, 1H), 5.17 (dd, *J* = 13.7, 5.6 Hz, 1H), 4.41 (d, *J* = 19.5 Hz, 2H), 4.13 (tt, *J* = 8.7, 4.3 Hz, 1H), 3.35 (d, *J* = 17.6 Hz, 2H), 3.00 (p, *J* = 4.9, 4.0 Hz, 4H), 2.93 – 2.31 (m, 11H), 2.21 (d, *J* = 13.0 Hz, 1H), 2.12 – 1.99 (m, 2H), 1.28 (qd, *J* = 7.5, 2.9 Hz, 3H), 0.92 (td, *J* = 10.3, 9.7, 4.7 Hz, 1H), 0.75 (td, *J* = 7.2, 2.7 Hz, 6H). ppm; ESMS calculated for $C_{39}H_{45}N_9O_7$: 751.3; found: 752.3 (M + H^+).

[00735] SDC-TRAP-0108

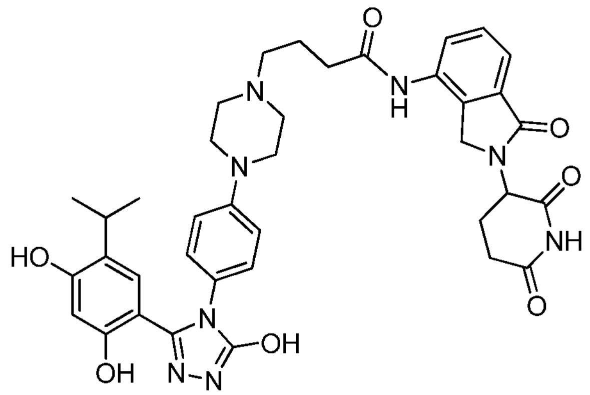
[00736] 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenethyl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) piperidine-1-carboxamide



[00737] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 – 7.97 (m, 1H), 7.63 (ddd, *J* = 12.2, 7.1, 3.1 Hz, 1H), 7.53 – 7.39 (m, 1H), 7.37 – 7.30 (m, 1H), 7.27 – 7.19 (m, 2H), 6.43 (d, *J* = 29.7 Hz, 1H), 5.14 (td, *J* = 12.9, 5.2 Hz, 1H), 4.58 – 4.29 (m, 2H), 4.22 – 4.01 (m, 2H), 3.59 (s, 2H), 3.37 (dt, *J* = 3.4, 1.7 Hz, 1H), 3.10 – 2.65 (m, 6H), 2.53 – 2.11 (m, 2H), 1.85 (d, *J* = 14.3 Hz, 2H), 1.62 (tdd, J = 18.4, 9.2, 5.3 Hz, 3H), 1.37 – 1.14 (m, 3H), 0.75 (d, J = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{38}H_{41}N_7O_7$: 707.3; found: 708.2 (M + H^+).

[00738] SDC-TRAP-0126

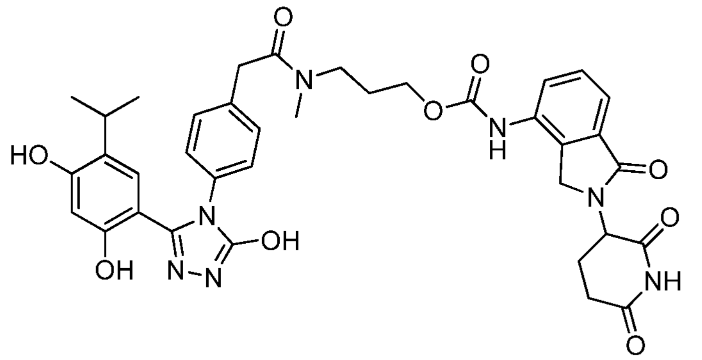
[00739] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) butanamide



[00740] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.76 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.48 (s, 3H), 7.28 – 7.18 (m, 2H), 7.09 – 7.02 (m, 2H), 6.55 (s, 1H), 6.37 (s, 1H), 5.16 (dd, J = 13.3, 5.1 Hz, 1H), 4.50 (s, 2H), 3.39 (s, 2H), 3.36 (p, J = 1.6 Hz, 4H), 2.99 (p, J = 6.8 Hz, 2H), 2.93 – 2.82 (m, 2H), 2.64 (t, J = 6.9 Hz, 2H), 2.55 – 2.33 (m, 1H), 2.22 (dp, J = 12.9, 4.4 Hz, 1H), 2.09 (dt, J = 13.7, 6.7 Hz, 3H), 0.80 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{38}H_{42}N_8O_7$: 722.3; found: 723.3 (M + H^+).

[00741] SDC-TRAP-0132

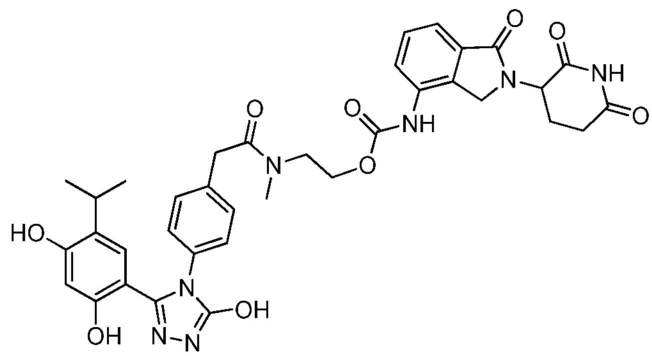
[00742] 3-(2-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)-N-methylacetamido)propyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00743] ESMS calculated for $C_{37}H_{39}N_7O_9$: 725.3; found: 726.2 (M + H^+).

[00744] SDC-TRAP-0127

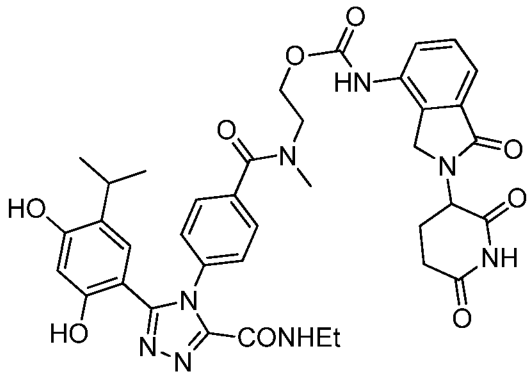
[00745] 2-(2-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)-N-methylacetamido)ethyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00746] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 11.00 (s, 1H), 9.75 – 9.28 (m, 3H), 7.70 (d, J = 20.2 Hz, 1H), 7.57 – 7.38 (m, 3H), 7.21 (d, J = 8.1 Hz, 2H), 7.15 – 7.05 (m, 2H), 6.82 (d, J = 2.2 Hz, 1H), 6.25 (s, 1H), 5.12 (dd, J = 13.3, 5.2 Hz, 1H), 4.55 – 4.11 (m, 4H), 3.89 – 3.48 (m, 4H), 3.07 (s, 1H), 3.03 – 2.79 (m, 1H), 2.74 – 2.55 (m, 1H), 2.50 (s, 3H), 0.98 (dd, J = 7.0, 5.2 Hz, 6H). ppm; ESMS calculated for $C_{36}H_{37}N_7O_9$: 711.3; found: 712.1 (M + H^+).

[00747] SDC-TRAP-0133

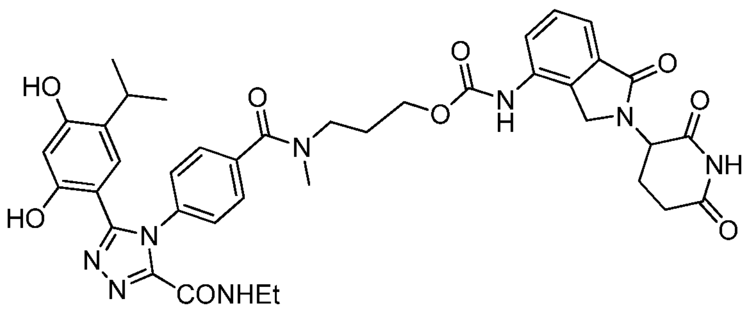
[00748] 2-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)-N-methylbenzamido)ethyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00749] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.21 (d, J = 17.5 Hz, 1H), 9.72 (s, 1H), 9.60 (s, 1H), 9.01 (t, J = 5.9 Hz, 1H), 7.70 (d, J = 36.6 Hz, 1H), 7.57 – 7.28 (m, 6H), 6.71 (s, 1H), 6.32 (s, 1H), 5.12 (dd, J = 13.2, 5.1 Hz, 1H), 4.52 – 4.16 (m, 4H), 3.77 (s, 1H), 3.52 (s, 1H), 3.18 (qd, J = 7.3, 4.7 Hz, 2H), 3.10 – 2.79 (m, 5H), 2.75 – 2.55 (m, 1H), 2.45 – 2.23 (m, 1H), 2.12 – 1.91 (m, 1H), 1.05 (t, J = 7.2 Hz, 3H), 0.88 (d, J = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{38}H_{40}N_8O_9$: 752.3; found: 753.3 (M + H$^+$).

[00750] SDC-TRAP-0135

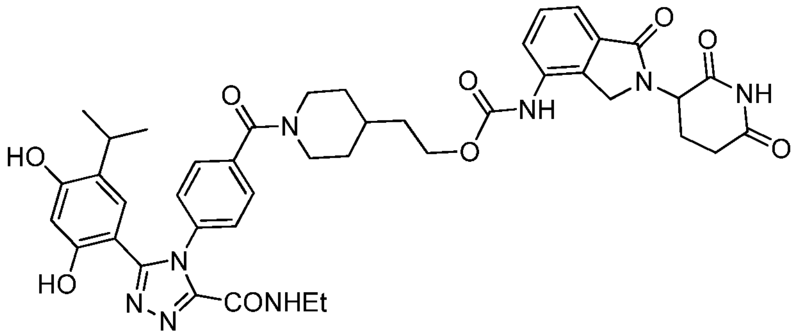
[00751] 3-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)-N-methylbenzamido)propyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00752] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.18 (s, 1H), 9.71 (s, 1H), 9.57 (s, 1H), 9.00 (t, J = 5.9 Hz, 1H), 7.77 (s, 1H), 7.51 – 7.43 (m, 5H), 7.41 – 7.34 (m, 2H), 6.73 (s, 1H), 6.32 (s, 1H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.41 (q, J = 17.1, 16.2 Hz, 2H), 4.19 (s, 2H), 3.58 (s, 2H), 3.31 (s, 2H), 3.18 (s, 3H), 3.02 – 2.84 (m, 3H), 2.60 (dt, J = 15.7, 3.3 Hz, 1H), 2.34 (d, J = 13.0 Hz, 2H), 1.05 (t, J = 7.4 Hz, 3H), 0.90 (d, J = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{39}H_{42}N_8O_9$: 766.3; found: 767.3 (M + H$^+$).

[00753] SDC-TRAP-0140

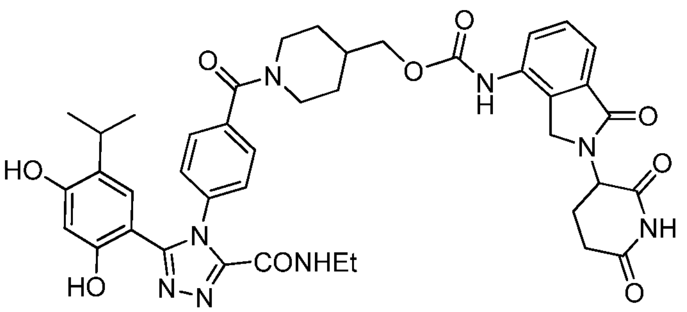
[00754] 2-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperidin-4-yl)ethyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00755] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.30 (s, 1H), 9.75 (s, 1H), 9.54 (s, 1H), 9.01 (t, J = 5.9 Hz, 1H), 7.77 (dt, J = 7.7, 3.8 Hz, 1H), 7.54 – 7.36 (m, 6H), 6.68 (s, 1H), 6.33 (s, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.40 (q, J = 17.6 Hz, 3H), 4.17 (t, J = 6.5 Hz, 2H), 3.56 (s, 1H), 3.24 – 3.13 (m, 2H), 3.07 (s, 1H), 2.92 (ddd, J = 17.1, 13.5, 5.8 Hz, 2H), 2.78 (s, 1H), 2.67 – 2.57 (m, 1H), 2.35 (qd, J = 13.2, 4.4 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.71 (m, 4H), 1.62 (q, J = 6.6 Hz, 2H), 1.22 (d, J = 13.2 Hz, 2H), 1.06 (t, J = 7.2 Hz, 3H), 0.88 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{42}H_{46}N_8O_9$: 806.3; found: 807.3 (M + H^+).

[00756] SDC-TRAP-0136

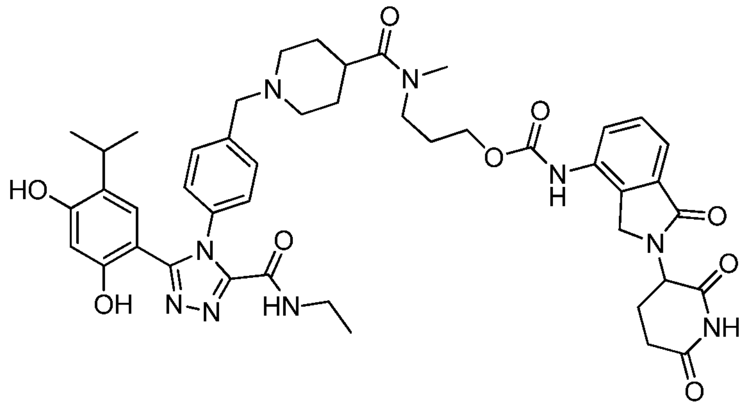
[00757] (1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperidin-4-yl)methyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00758] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.88 (s, 1H), 10.16 (s, 1H), 9.60 (s, 1H), 9.40 (s, 1H), 8.87 (t, J = 5.8 Hz, 1H), 7.63 (dd, J = 6.7, 2.4 Hz, 1H), 7.39 – 7.22 (m, 6H), 6.53 (s, 1H), 6.19 (s, 1H), 4.99 (dd, J = 13.2, 5.1 Hz, 1H), 4.35 – 4.17 (m, 2H), 3.94 – 3.81 (m, 3H), 3.10 – 2.98 (m, 2H), 2.85 – 2.70 (m, 2H), 2.67 (s, 1H), 2.51 – 2.42 (m, 1H), 1.93 – 1.81 (m, 4H), 1.52 (s, 2H), 1.03 (t, J = 7.1 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.73 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{41}H_{44}N_8O_9$: 792.3; found: 793.2 (M + H^+).

[00759] SDC-TRAP-0231

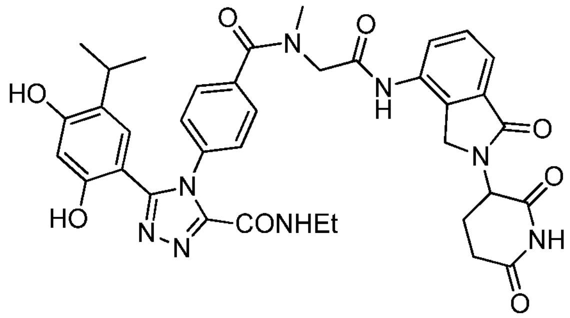
[00760] 3-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)-N-methylpiperidine-4-carboxamido)propyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00761] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.88 (d, J = 8.1 Hz, 1H), 7.61 (t, J = 6.8 Hz, 2H), 7.57 – 7.49 (m, 2H), 7.51 – 7.41 (m, 2H), 7.32 (d, J = 8.3 Hz, 2H), 6.57 – 6.40 (m, 2H), 5.19 (dd, J = 13.2, 5.1 Hz, 1H), 4.55 – 4.31 (m, 2H), 4.13 (td, J = 6.2, 3.0 Hz, 2H), 3.71 – 3.46 (m, 5H), 3.46 – 3.30 (m, 3H), 3.08 (s, 3H), 3.01 – 2.72 (m, 4H), 2.29 – 2.14 (m, 1H), 2.06 (dd, J = 11.8, 6.7 Hz, 2H), 1.87 (dp, J = 13.0, 7.6, 6.9 Hz, 4H), 1.70 (d, J = 13.3 Hz, 2H), 1.41 – 1.12 (m, 6H), 0.71 (dd, J = 13.5, 6.9 Hz, 6H). ppm; ESMS calculated for $C_{45}H_{53}N_9O_9$: 863.4; found: 864.3 (M + H^+).

[00762] SDC-TRAP-0147

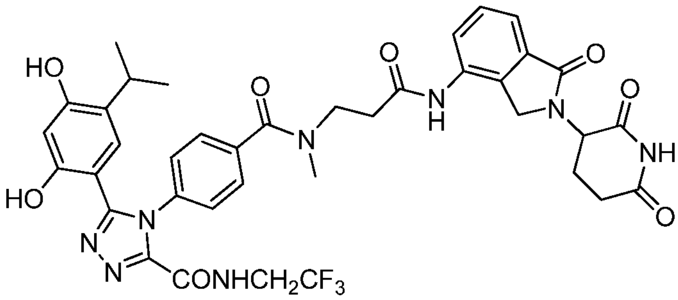
[00763] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-((2-((2-(2,6-dioxopiperidin-3-yl)-1-oxo isoindolin-4-yl)amino)-2-oxoethyl)(methyl)carbamoyl) phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide



[00764] ESMS calculated for $C_{37}H_{38}N_8O_8$: 722.3; found: 723.2 (M + H^+).

[00765] SDC-TRAP-0165

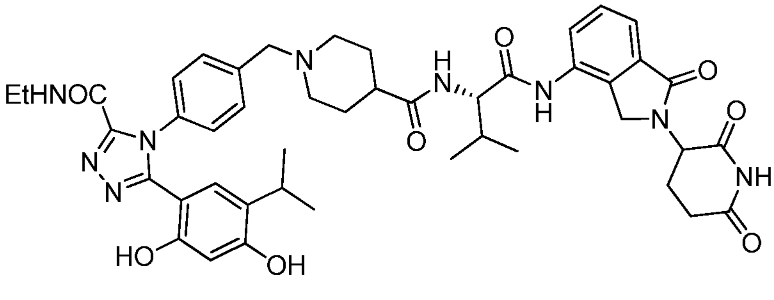
[00766] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-((3-((2-(2,6-dioxopiperidin-3-yl)-1-oxo isoindolin-4-yl)amino)-3-oxopropyl)(methyl)carbamoyl) phenyl)-N-(2,2,2-trifluoroethyl)-4H-1,2,4-triazole-3-carboxamide



[00767] ESMS calculated for $C_{38}H_{37}F_3N_8O_8$: 790.3; found: 791.1 (M + H^+).

[00768] SDC-TRAP-0163

[00769] 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)-N-((2S)-1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-3-methyl-1-oxobutan-2-yl)piperidine-4-carboxamide

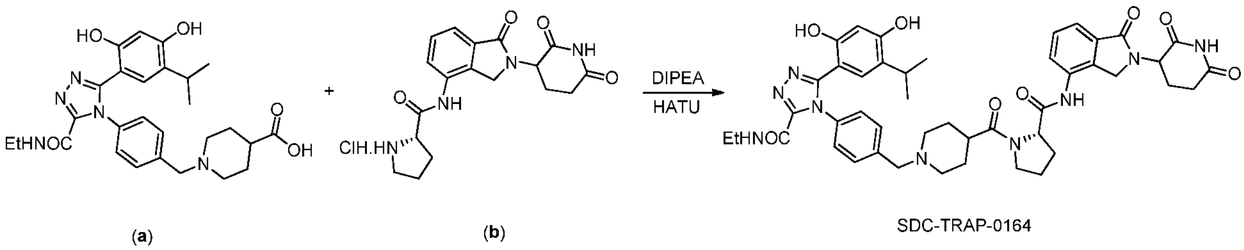


[00770] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.80 (ddd, J = 26.0, 8.0, 1.0 Hz, 1H), 7.70 (ddd, J = 7.6, 4.3, 1.0 Hz, 1H), 7.59 – 7.43 (m, 3H), 7.41 (s, 1H), 7.38 – 7.31 (m, 2H), 6.50 (s,

1H), 6.43 (s, 1H), 5.15 (ddd, J = 13.3, 5.1, 3.6 Hz, 1H), 4.60 – 4.22 (m, 3H), 3.63 (s, 2H), 3.43 – 3.28 (m, 3H), 3.09 – 2.77 (m, 5H), 2.52 – 2.01 (m, 6H), 1.94 – 1.70 (m, 4H), 1.32 – 1.13 (m, 4H), 1.03 (dd, J = 12.4, 6.7 Hz, 6H), 0.98 – 0.83 (m, 1H), 0.75 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{45}H_{53}N_9O_8$: 847.4; found: 848.3 ($M + H^+$).

[00771] SDC-TRAP-0164

[00772] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-((4-((2S)-2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)pyrrolidine-1-carbonyl)piperidin-1-yl)methyl)phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide

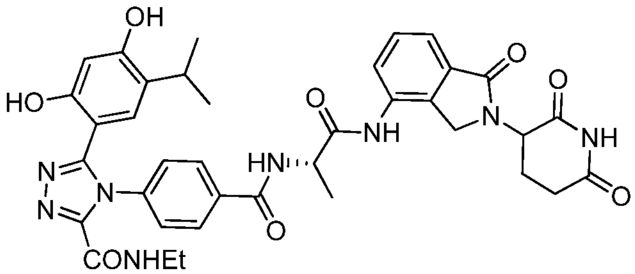


[00773] To a mixture of 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carboxylic acid (a, 0.90 mmol), (2S)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) pyrrolidine-2-carboxamide hydrochloride (b, 0.80 mmol) and HATU (1.0 mmol) in DMF (10 mL) at room temperature was added DIPEA (3.0 mmol) and the mixture was stirred at room temperature for 16 h. The mixture was added to a solution of $NaHCO_3$ (200 mL, 0.1M) and stirred for 30 min before filtering. The yellow filter cake was purified by column to yield SDC-TRAP-0164 as a white solid (0.25 g, 0.29 mmol).

[00774] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.06 (d, J = 6.8 Hz, 1H), 10.69 – 10.60 (m, 1H), 9.90 (s, 1H), 9.77 (s, 1H), 8.97 (t, J = 5.9 Hz, 1H), 7.81 – 7.72 (m, 1H), 7.60 – 7.46 (m, 2H), 7.42 – 7.27 (m, 4H), 6.57 (d, J = 9.4 Hz, 1H), 6.34 (s, 1H), 5.19 – 5.11 (m, 1H), 4.47 (d, J = 8.3 Hz, 1H), 4.33 (t, J = 12.4 Hz, 2H), 3.68 (s, 1H), 3.61 (s, 1H), 3.49 (s, 2H), 3.21 – 3.13 (m, 2H), 2.90 (d, J = 18.7 Hz, 5H), 2.63 (s, 1H), 2.00 (s, 7H), 1.67 (s, 2H), 1.58 (s, 3H), 1.03 (td, J = 7.2, 3.1 Hz, 4H), 0.79 (ddd, J = 17.0, 6.9, 2.3 Hz, 6H). ppm; ESMS calculated for $C_{45}H_{51}N_9O_8$: 845.4; found: 846.2 ($M + H^+$).

[00775] SDC-TRAP-0166

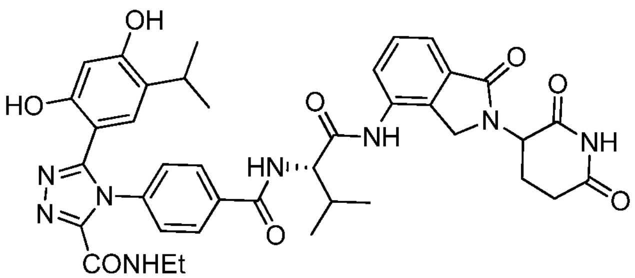
[00776] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(((2S)-1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-1-oxopropan-2-yl)carbamoyl)phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide:



[00777] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.09 – 7.98 (m, 2H), 7.92 – 7.76 (m, 1H), 7.71 (dd, J = 7.6, 2.4 Hz, 1H), 7.56 – 7.39 (m, 3H), 6.40 (dd, J = 5.6, 1.5 Hz, 2H), 5.17 (ddd, J = 13.5, 5.2, 1.7 Hz, 1H), 4.93 – 4.75 (m, 1H), 4.58 – 4.28 (m, 2H), 3.49 – 3.30 (m, 3H), 3.30-3.10 (m, 5H), 2.88 (dddd, J = 26.5, 12.7, 6.1, 2.9 Hz, 3H), 2.53 – 2.33 (m, 1H), 2.32 – 2.08 (m, 1H), 1.70 – 1.53 (m, 3H), 1.34 – 1.11 (m, 4H), 0.72 (dd, J = 6.9, 3.6 Hz, 6H). ppm; ESMS calculated for $C_{37}H_{38}N_8O_8$: 722.3; found: 723.1 (M + H$^+$).

[00778] SDC-TRAP-0188

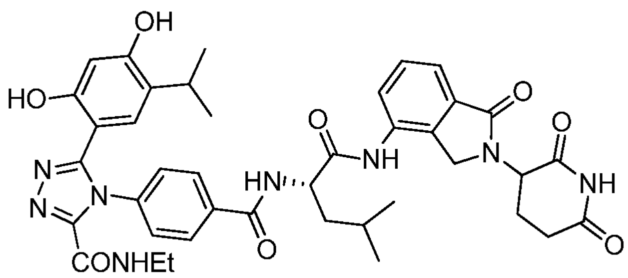
[00779] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(((2S)-1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamoyl) phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide



[00780] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.07 (ddd, J = 8.9, 4.5, 2.1 Hz, 2H), 7.90 – 7.64 (m, 2H), 7.58 – 7.41 (m, 3H), 6.46 – 6.28 (m, 2H), 5.17 (dd, J = 13.3, 5.1 Hz, 1H), 4.67 – 4.35 (m, 3H), 3.45 – 3.26 (m, 4H), 3.04 – 2.67 (m, 3H), 2.52 – 2.14 (m, 3H), 1.58 (dq, J = 19.9, 7.5 Hz, 1H), 1.30 – 1.17 (m, 5H), 1.18 – 1.03 (m, 5H), 1.04 – 0.90 (m, 1H), 0.72 (dt, J = 7.1, 1.4 Hz, 6H). ppm; ESMS calculated for $C_{39}H_{42}N_8O_8$: 750.3; found: 751.1 (M + H$^+$).

[00781] SDC-TRAP-0189

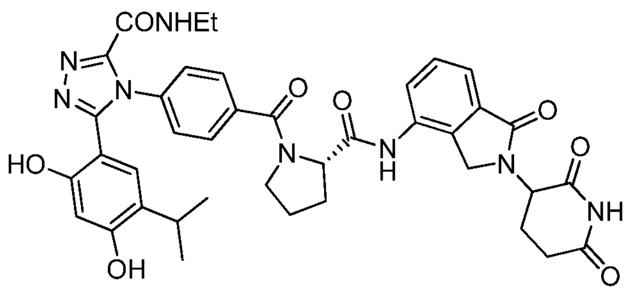
[00782] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(((2S)-1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-methyl-1-oxopentan-2-yl) carbamoyl)phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide



[00783] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.13 – 8.01 (m, 2H), 7.95 – 7.77 (m, 1H), 7.74 – 7.63 (m, 1H), 7.56 – 7.39 (m, 3H), 6.41 (d, *J* = 2.0 Hz, 1H), 6.35 (d, *J* = 5.0 Hz, 1H), 5.17 (ddd, *J* = 13.3, 5.1, 2.2 Hz, 1H), 5.01 – 4.78 (m, 1H), 4.59 – 4.26 (m, 2H), 3.47 – 3.25 (m, 4H), 2.98 – 2.79 (m, 3H), 2.53 – 2.11 (m, 2H), 1.91 – 1.67 (m, 3H), 1.24 (dt, *J* = 17.9, 7.2 Hz, 4H), 1.08 – 0.95 (m, 6H), 0.70 (ddd, *J* = 7.0, 4.2, 1.3 Hz, 6H). ppm; ESMS calculated for $C_{40}H_{44}N_8O_8$: 764.3; found: 765.1 (M + H^+).

[00784] SDC-TRAP-0190

[00785] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-((2S)-2-((2-(2,6-dioxopiperidin-3-yl)-1 -oxoisoindolin-4-yl)carbamoyl)pyrrolidine-1-carbonyl)phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide

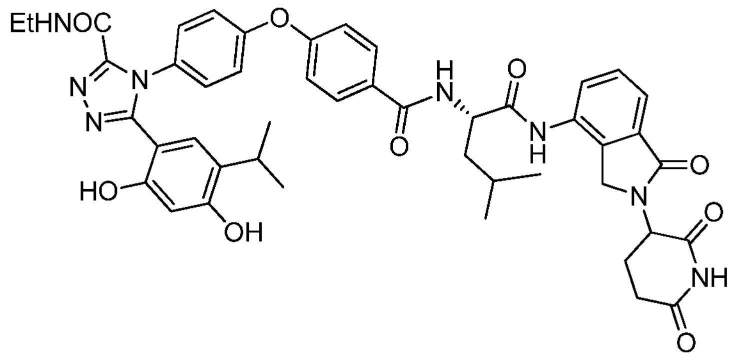


[00786] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.20 (d, *J* = 3.7 Hz, 1H), 10.03 (d, *J* = 3.1 Hz, 1H), 9.72 (s, 1H), 9.03 (t, *J* = 5.9 Hz, 1H), 7.80 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.69 – 7.58 (m, 2H), 7.60 – 7.47 (m, 2H), 7.41 (d, *J* = 8.0 Hz, 3H), 6.72 (s, 1H), 6.31 (d, *J* = 1.3 Hz, 1H), 5.15 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.66 (t, *J* = 6.5 Hz, 1H), 4.50 – 4.29 (m, 2H), 3.56 (ddd, *J* = 22.5, 9.7, 5.7 Hz, 2H), 3.19 (p, *J* = 6.8 Hz, 2H), 2.92 (qt, *J* = 14.8, 7.4 Hz, 3H), 2.61 (d, *J* = 17.0

Hz, 1H), 2.35 (t, J = 11.7 Hz, 3H), 2.15 – 1.80 (m, 4H), 1.06 (t, J = 7.2 Hz, 3H), 0.90 (dd, J = 7.3, 2.1 Hz, 6H). ppm; ESMS calculated for $C_{39}H_{40}N_8O_8$: 748.3; found: 749.1 (M + H^+).

[00787] SDC-TRAP-0191

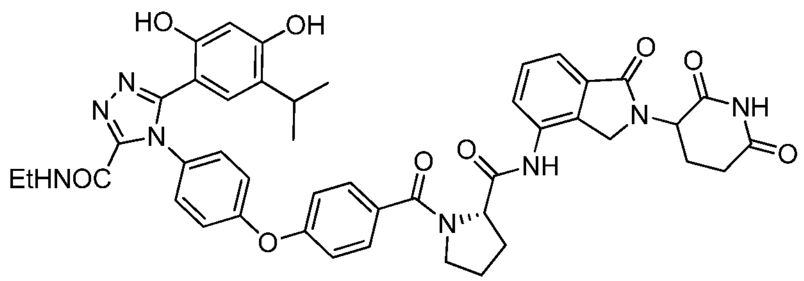
[00788] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(4-(((2S)-1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-methyl-1-oxopentan-2-yl)carbamoyl)phenoxy)phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide



[00789] [1]H NMR (400 MHz, Methanol-d_4) δ 7.98 – 7.80 (m, 4H), 7.68 (ddd, J = 7.7, 5.3, 1.0 Hz, 1H), 7.48 (td, J = 7.8, 3.4 Hz, 1H), 7.36 (d, J = 6.9 Hz, 1H), 7.24 – 7.13 (m, 4H), 6.55 (s, 1H), 6.45 (s, 1H), 5.16 (ddd, J = 13.3, 5.1, 1.8 Hz, 1H), 4.86 (ddp, J = 8.7, 5.2, 2.5 Hz, 1H), 4.64 – 4.23 (m, 2H), 3.49 – 3.27 (m, 3H), 3.04 (p, J = 6.9 Hz, 1H), 2.85 (ddt, J = 9.4, 5.1, 2.3 Hz, 2H), 2.51 – 2.29 (m, 1H), 2.20 (ddd, J = 13.5, 6.9, 3.7 Hz, 1H), 1.89 – 1.74 (m, 3H), 1.25 (dt, J = 13.4, 7.2 Hz, 5H), 1.12 – 1.00 (m, 6H), 1.00 – 0.91 (m, 1H), 0.87 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{46}H_{48}N_8O_9$: 856.4; found: 857.1 (M + H^+).

[00790] SDC-TRAP-0192

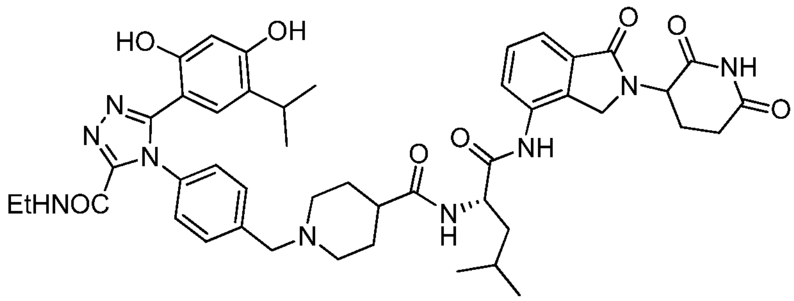
[00791] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(4-((2S)-2-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)pyrrolidine-1-carbonyl)phenoxy)phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide



[00792] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.94 (ddd, J = 25.0, 8.1, 1.0 Hz, 1H), 7.81 (dt, J = 8.3, 4.1 Hz, 1H), 7.72 – 7.58 (m, 3H), 7.48 (td, J = 7.8, 6.2 Hz, 1H), 7.42 – 7.30 (m, 1H), 7.23 – 7.11 (m, 4H), 6.54 (d, J = 1.7 Hz, 1H), 6.44 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.87 (dt, J = 8.1, 5.3 Hz, 1H), 4.56 – 4.33 (m, 2H), 3.75-3.65 (m, 3H), 3.52 – 3.29 (m, 4H), 3.03 (p, J = 6.8 Hz, 1H), 2.83 (ddd, J = 10.6, 5.5, 2.8 Hz, 2H), 2.53 – 2.09 (m, 7H), 1.97 (dtd, J = 15.5, 8.2, 7.2, 4.7 Hz, 1H), 1.25 (dt, J = 13.5, 7.2 Hz, 4H), 0.87 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{45}H_{44}N_8O_9$: 840.3; found: 841.1 (M + H$^+$).

[00793] SDC-TRAP-0193

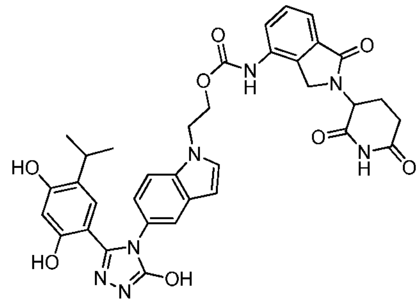
[00794] 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)-N-((2S)-1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-methyl-1-oxopentan-2-yl)piperidine-4-carboxamide



[00795] ^{1}H NMR (400 MHz, Chloroform-d) δ 7.93 – 7.83 (m, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.62 – 7.41 (m, 4H), 7.32 (dd, J = 8.2, 2.7 Hz, 2H), 6.51 – 6.45 (m, 1H), 6.43 (d, J = 1.8 Hz, 1H), 5.16 (ddd, J = 13.9, 9.4, 5.1 Hz, 1H), 4.67 – 4.52 (m, 1H), 4.53 – 4.20 (m, 2H), 3.68 – 3.49 (m, 2H), 3.46 – 3.28 (m, 3H), 3.07 – 2.72 (m, 6H), 2.35-2.25 (m, 4H), 2.05 (d, J = 6.5 Hz, 1H), 1.91 – 1.53 (m, 6H), 1.34 – 1.14 (m, 6H), 1.05 – 0.92 (m, 6H), 0.71 (dt, J = 6.9, 2.9 Hz, 6H). ppm; ESMS calculated for $C_{46}H_{55}N_9O_8$: 861.4; found: 862.2 (M + H$^+$).

[00796] SDC-TRAP-0122

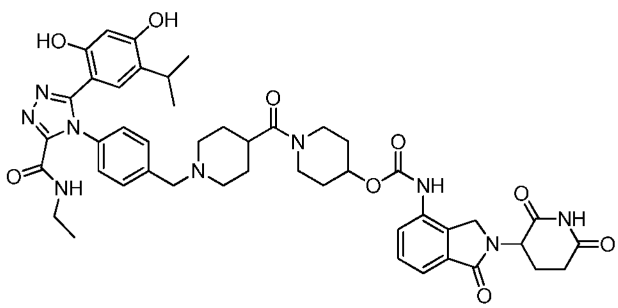
[00797] 2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00798] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 11.02 (s, 1H), 9.56 (d, J = 14.1 Hz, 2H), 9.46 (s, 1H), 7.65 (s, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.52 – 7.39 (m, 4H), 6.95 (dd, J = 8.7, 2.0 Hz, 1H), 6.74 (d, J = 1.7 Hz, 1H), 6.46 (d, J = 3.1 Hz, 1H), 6.21 (s, 1H), 5.11 (dd, J = 13.4, 5.0 Hz, 1H), 4.49 (t, J = 5.2 Hz, 2H), 4.44 – 4.25 (m, 4H), 2.84-2.85 (m, 2H), 2.65 – 2.56 (m, 1H), 2.33 (td, J = 13.4, 8.7 Hz, 1H), 2.03 – 1.95 (m, 1H), 0.83 (dd, J = 7.1, 1.7 Hz, 6H); ESMS calculated ($C_{35}H_{33}N_7O_8$): 679.2; found: 680.2 (M+H).

[00799] SDC-TRAP-0123

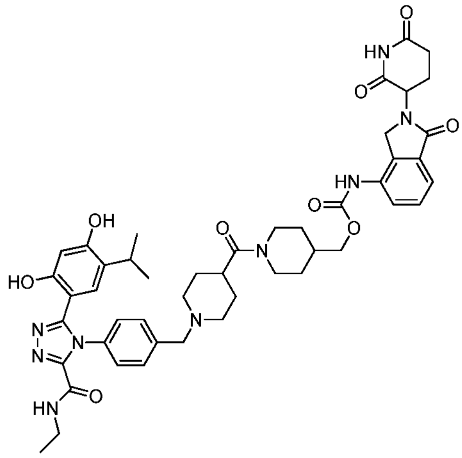
[00800] 1-(1-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4*H*-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)piperidin-4-yl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00801] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 10.62 (s, 1H), 9.76 (s, 1H), 9.55 (s, 1H), 8.96 (t, J = 5.9 Hz, 1H), 7.77 (dd, J = 6.6, 2.6 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.42 – 7.35 (m, 2H), 7.34 – 7.26 (m, 2H), 6.58 (s, 1H), 6.35 (s, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.93 – 4.86 (m, 1H), 4.40 (q, J = 17.6 Hz, 2H), 4.10 (q, J = 5.3 Hz, 1H), 3.92 (s, 1H), 3.77 (s, 1H), 3.49 (s, 2H), 3.30 (s, 2H), 3.20-3.13 (m, 5H), 2.96-2.83 (m, 4H), 2.67-2.60 (m, 2H), 2.39-2.29 (m, 1H), 2.06-1.89 (m, 5H), 1.90 (s, 1H), 1.53-1.47 (m, 1H), 1.04 (t, J = 7.2 Hz, 3H), 0.81 (d, J = 6.9 Hz, 6H); ESMS calculated ($C_{46}H_{53}N_9O_9$): 875.4; found: 876.4 (M+H).

[00802] SDC-TRAP-0124

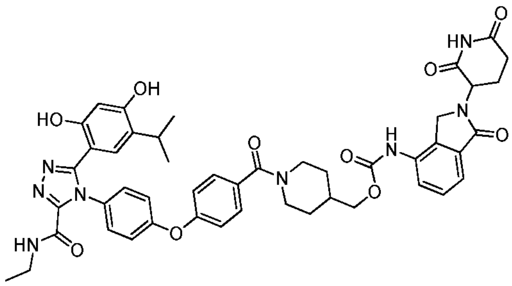
[00803] (1-(1-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4*H*-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)piperidin-4-yl)methyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00804] ESMS calculated ($C_{47}H_{55}N_9O_9$): 889.4; found: 890.3 (M+H).

[00805] SDC-TRAP-0125

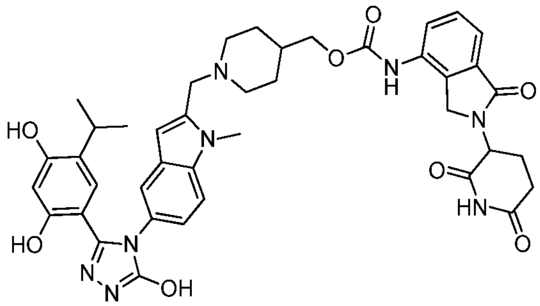
[00806] (1-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)benzoyl)piperidin-4-yl)methyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00807] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.41 (s, 1H), 9.77 (s, 1H), 9.55 (s, 1H), 8.99 (t, *J* = 5.9 Hz, 1H), 7.77 (d, *J* = 6.8 Hz, 1H), 7.54 – 7.42 (m, 4H), 7.41 – 7.34 (m, 2H), 7.14 – 7.04 (m, 4H), 6.68 (s, 1H), 6.35 (s, 1H), 5.13 (dd, *J* = 13.3, 5.1 Hz, 1H), 4.39 (q, *J* = 17.6 Hz, 2H), 4.03 (q, *J* = 7.1 Hz, 2H), 3.19 (p, *J* = 6.9 Hz, 2H), 3.03 – 2.85 (m, 2H), 2.60 (d, *J* = 16.8 Hz, 1H), 2.36-2.29 (m, 1H), 1.99 (s, 3H), 1.75 (s, 2H), 1.29 – 1.13 (m, 5H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 6H); ESMS calculated ($C_{47}H_{48}N_8O_{10}$): 884.3; found: 885.3 (M+H).

[00808] SDC-TRAP-0155

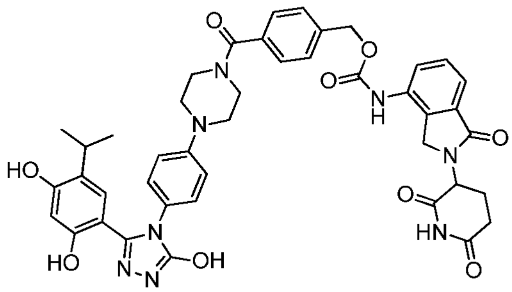
[00809] (1-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1-methyl-1H-indol-2-yl)methyl)piperidin-4-yl)methyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00810] ESMS calculated ($C_{41}H_{44}N_8O_8$): 776.3; found: 777.3 (M+H).

[00811] SDC-TRAP-0156

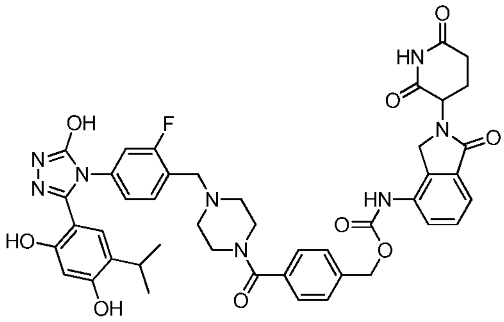
[00812] 4-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazine-1-carbonyl)benzyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00813] ESMS calculated ($C_{43}H_{42}N_8O_9$): 814.3; found: 815.0 (M+H).

[00814] SDC-TRAP-0157

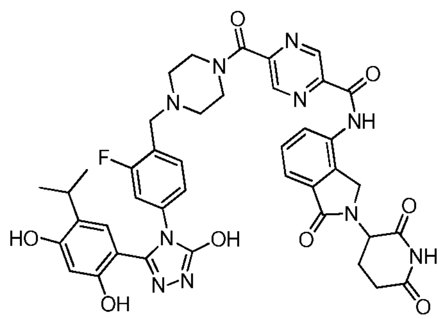
[00815] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carbonyl)benzyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00816] ESMS calculated ($C_{44}H_{43}N_8O_9$): 846.3; found: 847.2 (M+H).

[00817] SDC-TRAP-0160

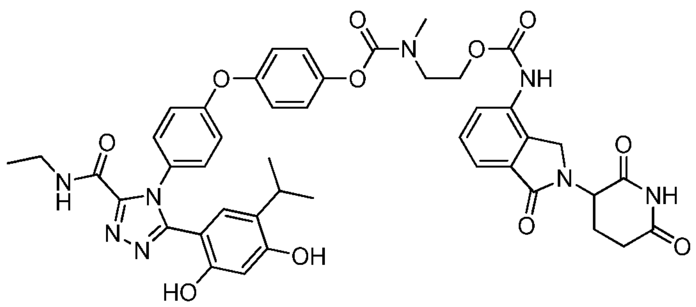
[00818] 5-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carbonyl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pyrazine-2-carboxamide



[00819] ESMS calculated ($C_{41}H_{39}FN_{10}O_8$): 818.3; found: 819.2 (M+H).

[00820] SDC-TRAP-0167

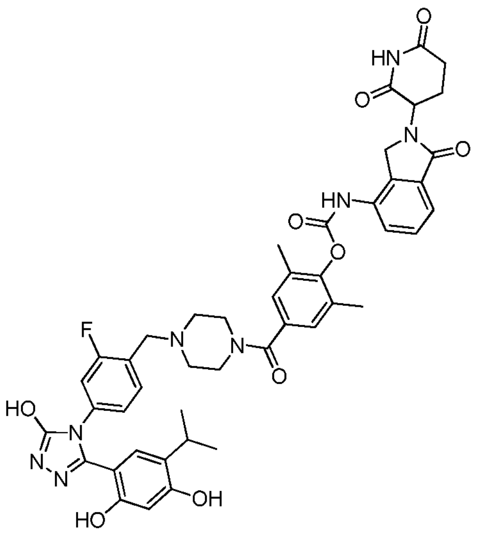
[00821] 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)phenyl(2-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)oxy)ethyl)(methyl)carbamate



[00822] ESMS calculated ($C_{44}H_{44}N_8O_{11}$): 860.3; found: 861.1 (M+H).

[00823] SDC-TRAP-0168

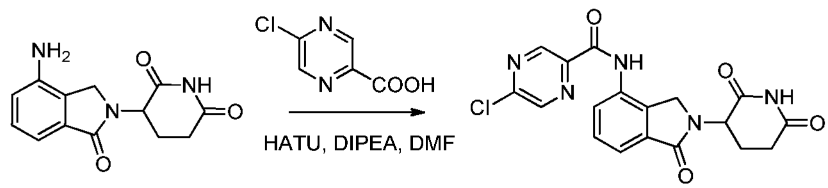
[00824] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carbonyl)-2,6-dimethylphenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



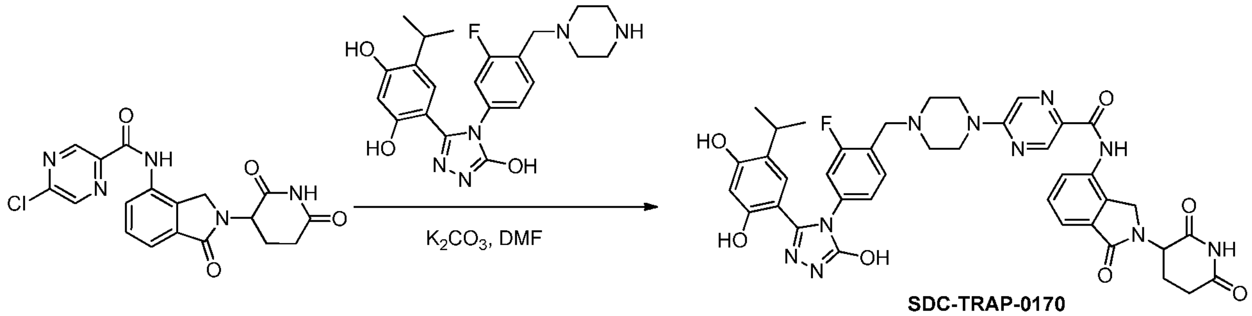
[00825] ESMS calculated ($C_{45}H_{45}FN_8O_9$): 860.3; found: 861.2 (M+H).

[00826] SDC-TRAP-0170

[00827] 5-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pyrazine-2-carboxamide



[00828] To a solution of lenalidomide (0.2g, 0.77 mmol) in DMF (4 mL) was added 5-chloropyrazine-2-carboxylic acid (0.15g, 0.95 mmol), HATU, (0.29g, 0.77 mmol), and DIPEA (0.27mL, 1.54 mmol). The reaction was stirred at room temperature for 1 hr before it was quenched with saturated NH_4Cl (5 mL). The mixture was extracted with EtOAc (10 mL×3), and the combined organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave 5-chloro-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)pyrazine-2-carboxamide (0.1 g, 33%).

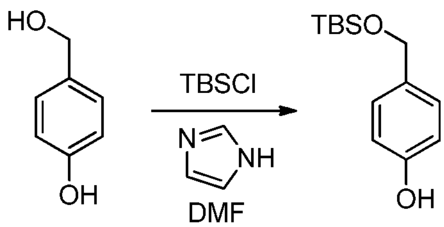


[00829] The solution of 5-chloro-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) pyrazine-2-carboxamide (0.05 g, 0.13 mmol), 4-(4-(3-fluoro-4-(piperazin-1-ylmethyl)phenyl)-5-hydroxy-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (0.06 g, 0.13 mmol), and K_2CO_3 (0.07 g, 0.51 mmol) in DMF (3 mL) was heated in a microwave at 50 °C for 1 hr. The solution was diluted with saturated NH_4Cl (5 mL), extracted with EtOAc (10 mL×3) and the combined organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave SDC-TRAP-0170 (0.86 g, 87%).

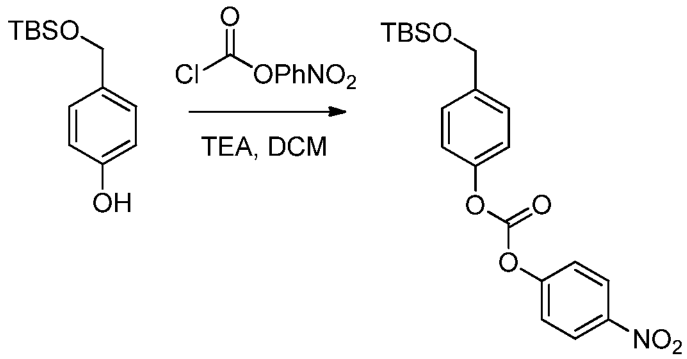
[00830] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.00 (s, 1H), 11.00 (s, 1H), 10.29 (s, 1H), 9.64 (s, 1H), 9.41 (s, 1H), 8.73 (d, J = 1.2 Hz, 1H), 8.34 (d, J = 1.4 Hz, 1H), 7.85 (dd, J = 7.6, 1.4 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.44 (t, J = 8.2 Hz, 1H), 7.09 (dd, J = 10.8, 2.0 Hz, 1H), 6.99 (dd, J = 8.2, 2.0 Hz, 1H), 6.87 (s, 1H), 6.27 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.55 – 4.38 (m, 2H), 3.74 (t, J = 4.8 Hz, 4H), 3.59 (s, 2H), 3.33 (s, 2H), 3.17 (d, J = 5.3 Hz, 1H), 3.06 – 2.83 (m, 2H), 2.63 – 2.53 (m, 2H), 2.48 – 2.32 (m, 1H), 2.03 – 1.95 (m, 1H), 1.00 (d, J = 6.9 Hz, 6H); ESMS calculated ($C_{40}H_{39}FN_{10}O_7$): 790.3; found: 791.2 (M+H).

[00831] SDC-TRAP-0171

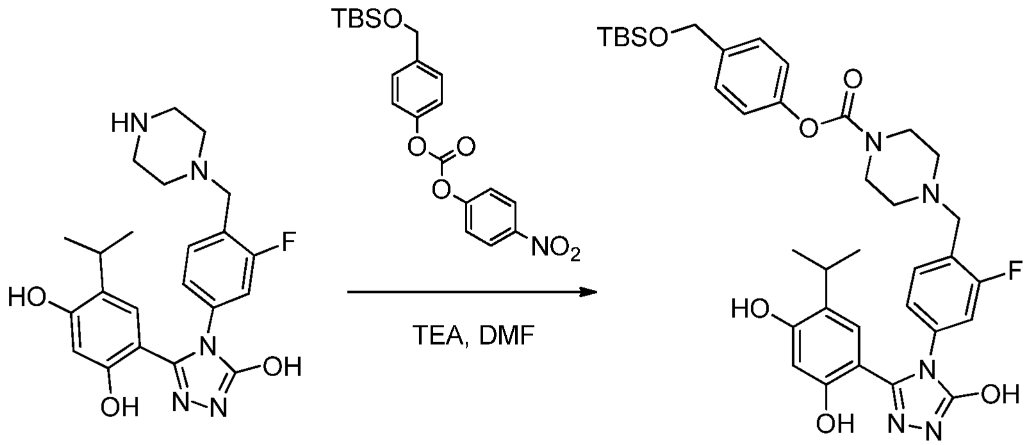
[00832] 4-((((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)oxy) methyl)phenyl-4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carboxylate



[00833] To a solution of 4-(hydroxymethyl)phenol (2 g, 16.1 mmol) in DMF (20 mL) was added TBSCl (2.7 g, 17.9 mmol) and imidazole (2.2 g, 32.3 mmol). The reaction was stirred at room temperature for 2 hr. The reaction was diluted with EtOAc (100 mL) and washed with 0.1 N HCl (50 mL×3). The organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave 4-(((tert-butyldimethylsilyl)oxy)methyl)phenol (2.6 g, 68%).

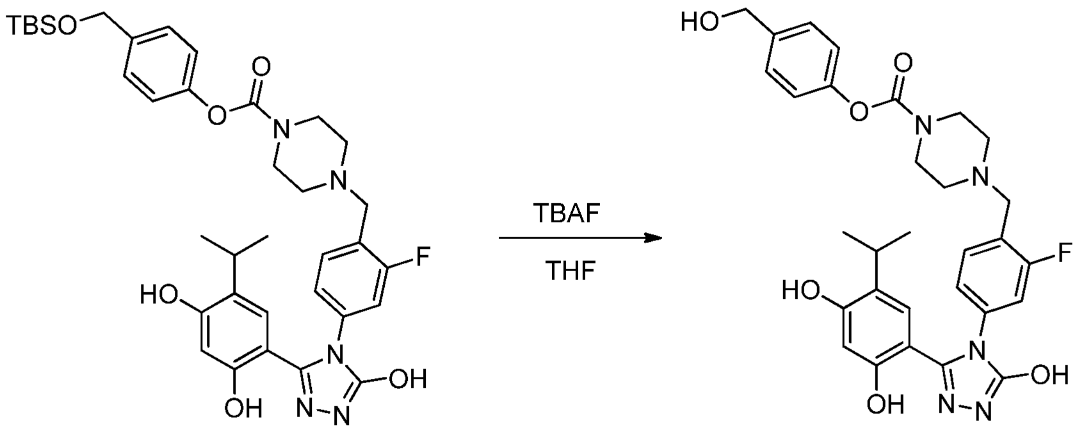


[00834] To the solution of 4-(((tert-butyldimethylsilyl)oxy)methyl)phenol (1.0 g, 4.2 mmol) in DCM (15 mL) was added 4-nitrophenyl chloroformate (1.0 g, 4.96 mmol) followed by TEA (1.8 mL, 12.9 mmol). The reaction was stirred at room temperature overnight. The reaction solution was concentrated and column chromatography gave 4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl (4-nitrophenyl) carbonate (1.44 g, 85%).

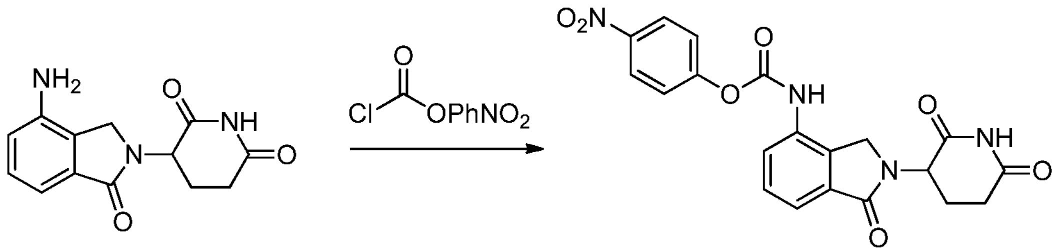


[00835] To a solution of 4-(4-(3-fluoro-4-(piperazin-1-ylmethyl)phenyl)-5-hydroxy-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (0.32 g, 0.75 mmol) in DMF (5 mL) was added 4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl (4-nitrophenyl) carbonate (0.36 g, 0.89 mmol) and TEA (0.31 mL, 2.22 mmol). The reaction was stirred at room temperature for 1 hr before it was quenched with saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (20 mL×2) and the combined organic phase was dried over Na_2SO_4 and concentrated. Column

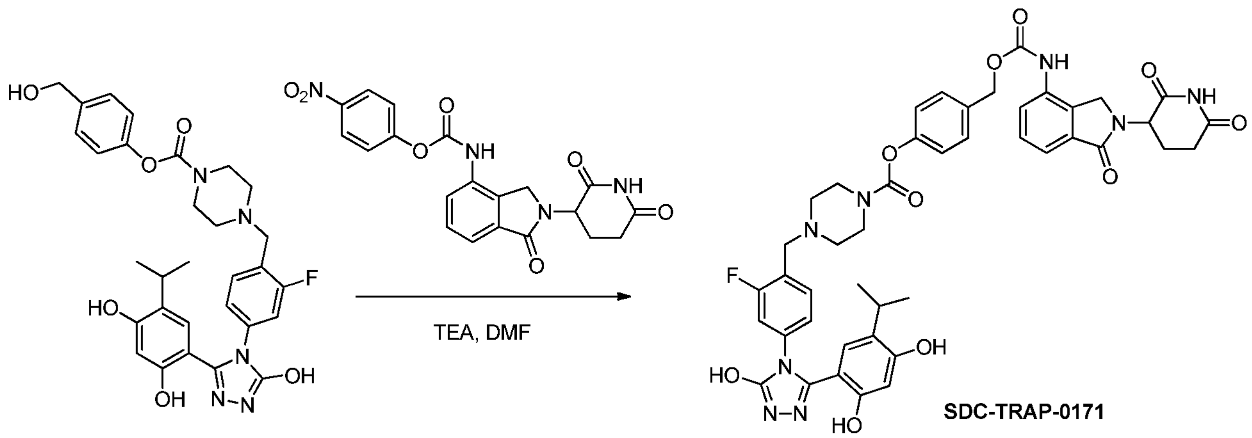
chromatography gave 4-(((tert-butyldimethylsilyl)oxy)methyl)phenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carboxylate (0.38 g, 75%).



[00836] A solution of 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carboxylate (0.38 g, 0.55 mmol) and TBAF (0.29 g, 1.10 mmol) was heated at 40 °C for 30 min. The solution was concentrated and column chromatography gave 4-(hydroxymethyl)phenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carboxylate (0.22 g, 70%).



[00837] A solution of lenalidomide (1.0 g, 3.86 mmol) and 4-nitrophenyl chloroformate (1.15 g, 5.70 mmol) was heated at 65 °C for 1 hr. The solution was allowed to cool to room temperature, then filtered. The solid was dried and used for the next step without further purification.

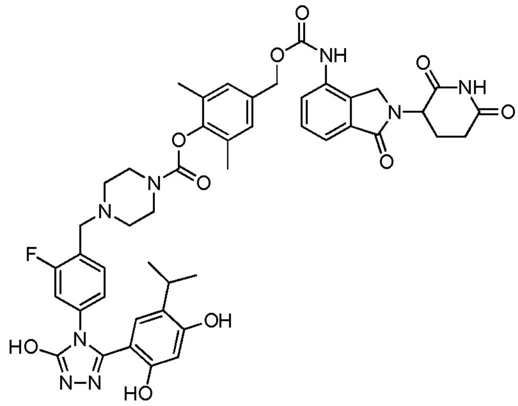


[00838] To the solution of 4-(hydroxymethyl)phenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carboxylate (0.23 g, 0.39 mmol) in DMF (4 mL) was added 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (0.27 g, 0.62 mmol) and TEA (0.17 mL, 1.17 mmol). The reaction was stirred at room temperature overnight before it was quenched with NH_4Cl (5 mL). The mixture was extracted with EtOAc (20 mL×2) and combined organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave SDC-TRAP-0171 (0.21 g, 65%) as an off-white solid.

[00839] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.96 (s, 1H), 10.98 (s, 1H), 9.65 (s, 1H), 9.59 (s, 1H), 9.37 (s, 1H), 7.79 (dd, J = 6.5, 2.5 Hz, 1H), 7.54 – 7.37 (m, 5H), 7.18 – 7.04 (m, 3H), 6.99 (dd, J = 8.1, 2.0 Hz, 1H), 6.87 (s, 1H), 6.27 (s, 1H), 5.19 – 5.06 (m, 3H), 4.38 (q, J = 17.6 Hz, 2H), 4.11 – 3.98 (m, 1H), 3.57 (s, 3H), 3.41 (d, J = 7.6 Hz, 1H), 3.28 (s, 1H), 3.17 (d, J = 5.3 Hz, 1H), 3.07 – 2.83 (m, 2H), 2.60 (d, J = 17.3 Hz, 1H), 2.45 (s, 3H), 2.39 – 2.24 (m, 1H), 2.04-1.99 (m, 1H), 1.00 (d, J = 6.9 Hz, 6H); ESMS calculated ($C_{44}H_{43}FN_8O_{10}$): 862.3; found: 863.2 (M+H).

[00840] SDC-TRAP-0182

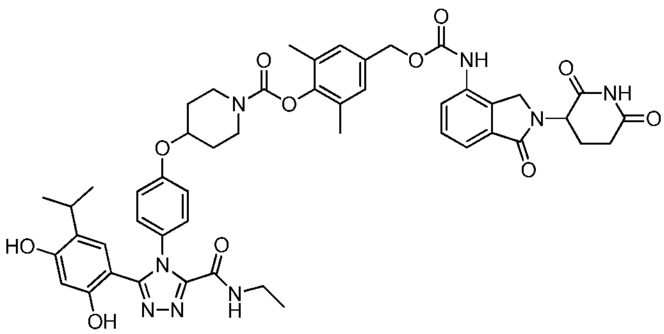
[00841] 4-((((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)oxy)methyl)-2,6-dimethylphenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carboxylate



[00842] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 11.02 (s, 1H), 9.65 (d, J = 13.1 Hz, 2H), 9.41 (s, 1H), 7.79 (dd, J = 6.8, 2.3 Hz, 1H), 7.54 – 7.38 (m, 3H), 7.16 (s, 2H), 7.08 (dd, J = 11.0, 2.0 Hz, 1H), 6.99 (dd, J = 8.2, 2.0 Hz, 1H), 6.88 (s, 1H), 6.27 (s, 1H), 5.17 – 5.06 (m, 3H), 4.47 – 4.29 (m, 2H), 3.72 – 3.61 (m, 2H), 3.56 (s, 2H), 3.44 (d, J = 6.5 Hz, 2H), 3.07 – 2.84 (m, 2H), 2.65 – 2.55 (m, 1H), 2.45 (s, 4H), 2.38 – 2.23 (m, 1H), 2.10 (s, 6H), 2.05 – 1.96 (m, 1H), 1.01 (d, J = 6.9 Hz, 6H); ESMS calculated ($C_{46}H_{47}FN_8O_{10}$): 890.3; found: 891.2 (M+H).

[00843] SDC-TRAP-0187

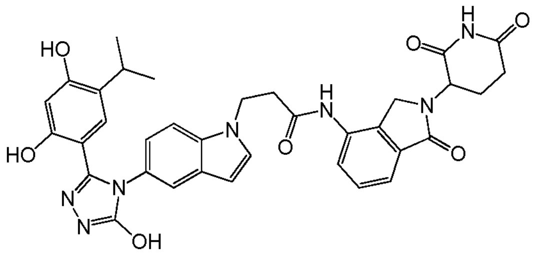
[00844] 4-((((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)oxy) methyl)-2,6-dimethylphenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidine-1-carboxylate



[00845] ESMS calculated ($C_{49}H_{52}N_8O_{11}$): 928.4; found: 929.1 (M+H).

[00846] SDC-TRAP-0017

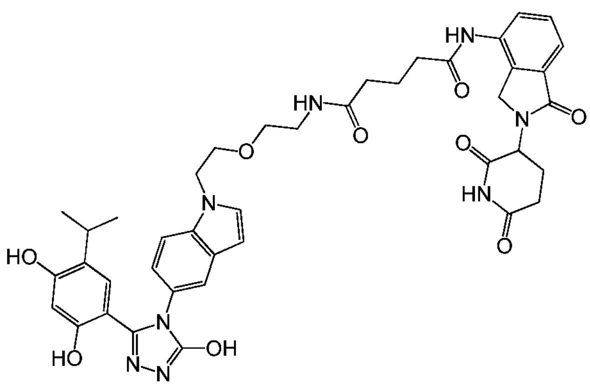
[00847] 3-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) propanamide



[00848] ESMS calculated for $C_{35}H_{33}N_7O_7$: 663.24; Found: 664.2(M+H)$^+$.

[00849] SDC-TRAP-0015

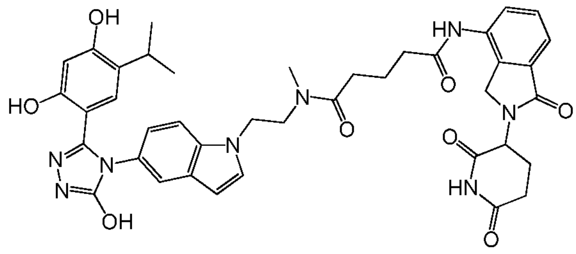
[00850] N1-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)glutaramide



[00851] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 11.02 (s, 1H), 9.90 (s, 1H), 9.52 (s, 1H), 9.47 (s, 1H), 7.97 -7.83 (m 2H), 7.55 – 7.38 (m, 4H), 6.92 (d, J = 8.7 Hz, 1H), 6.73 (s, 1H), 6.41 (s, 1H), 6.23 (s, 1H), 5.13 (d, J = 13.6 Hz, 1H), 4.37 (dd, J = 26.6, 17.5 Hz, 4H), 3.70- 3.39 (m, 6H), 2.91 (q, J = 12.5, 11.7 Hz, 3H), 2.37 (d, J = 8.9 Hz, 4H), 2.13 (t, J = 7.3 Hz, 2H), 2.06 – 1.96 (m, 2H), 1.86 – 1.77 (m, 2H), 1.22 -0.90 (m, 2H), 0.83 (d, J = 6.7 Hz, 6H). ESMS calculated for $C_{41}H_{44}N_8O_9$: 792.32; Found: 793.2 (M+H)$^+$.

[00852] SDC-TRAP-0018

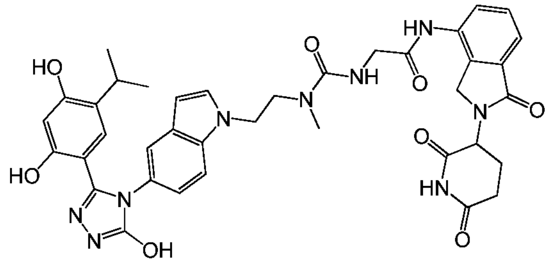
[00853] N1-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-N5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-N1-methylglutaramide



[00854] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (bs, 1H), 11.01 (s, 1H), 9.79 (s, 1H), 9.45 (d, J = 7.0 Hz, 2H), 7.79 (dd, J = 18.5, 7.1 Hz, 1H), 7.50 -7.38 (m, 5H), 6.94 (t, J = 7.6 Hz, 1H), 6.74 (d, J = 9.7 Hz, 1H), 6.44 (s, 1H), 6.23 (s, 1H), 5.14 (dd, J = 12.6, 6.1 Hz, 1H), 4.49 – 4.24 (m, 4H), 3.65 – 3.54 (m, 4H), 3.17 (d, J = 4.6 Hz, 1H), 2.89 (d, J = 12.7 Hz, 5H), 2.76 (s, 2H), 2.45 – 2.24 (m, 4H), 2.13 – 1.97 (m, 4H), 1.80 (d, J = 13.2 Hz, 2H), 1.60 – 1.52 (m, 1H), 0.82 (d, J = 7.9 Hz, 6H). ESMS calculated for $C_{40}H_{42}N_8O_8$: 762.31; Found: 763.2 $(M+H)^+$.

[00855] SDC-TRAP-0021

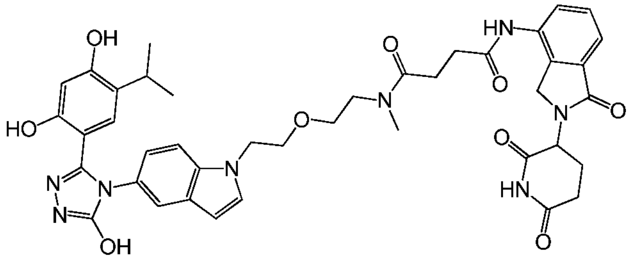
[00856] 2-(3-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-3-methylureido)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide



[00857] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 11.01 (s, 1H), 9.83 (s, 1H), 9.53 (s, 1H), 9.47 (s, 1H), 7.86 (dd, J = 6.3, 2.7 Hz, 1H), 7.58 – 7.46 (m, 3H), 7.41 (dd, J = 8.3, 2.6 Hz, 2H), 6.94 (dd, J = 8.7, 2.0 Hz, 1H), 6.82 – 6.70 (m, 2H), 6.43 (dd, J = 3.2, 0.8 Hz, 1H), 6.23 (s, 1H), 5.14 (dd, J = 13.3, 5.1 Hz, 1H), 4.46 – 4.26 (m, 4H), 3.91 – 3.84(m, 2H), 3.59 – 3.50 (m, 2H), 2.97 – 2.83 (m, 2H), 2.59 (s, 4H), 2.36 – 2.20 (m, 1H), 1.99 (s, 1H), 0.82 (d, J = 6.8 Hz, 6H). ESMS calculated for $C_{38}H_{39}N_9O_8$: 749.29; Found: 750.2 $(M+H)^+$.

[00858] SDC-TRAP-0033

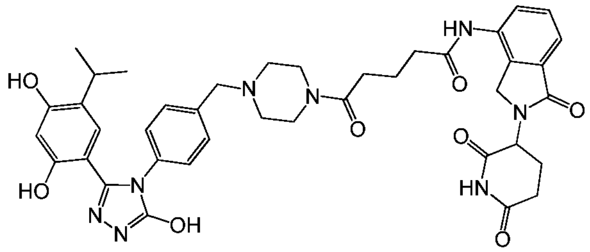
[00859] N1-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-N1-methylsuccinamide



[00860] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (m, 1H), 11.03 (s, 1H), 9.86 (s, 1H), 9.58 (s, 1H), 9.50 (s, 1H), 7.94 – 7.81 (m, 2H), 7.74 – 7.30 (m, 7H), 6.93 (d, J = 8.7 Hz, 1H), 6.74 (s, 1H), 6.42 (d, J = 7.5 Hz, 1H), 6.24 (s, 1H), 5.15 (d, J = 12.7 Hz, 1H), 4.51- 4.37 (m, 4H), 3.86 - 3.42 (m, 5H), 3.19 (m, 1H), 2.90 - 2.51 (m, 9H), 2.31 -2.04 (m, 4H), 0.84 (d, J = 5.9 Hz, 6H). ESMS calculated for $C_{41}H_{44}N_8O_9$: 792.32; Found: 793.3 $(M+H)^+$.

[00861] SDC-TRAP-0041

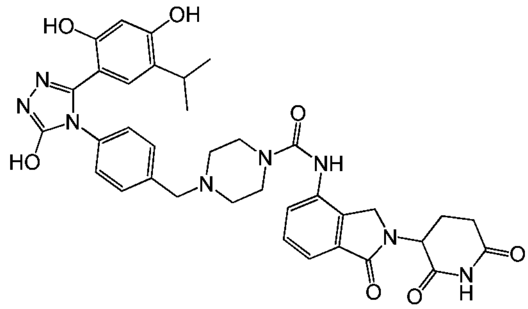
[00862] 5-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-5-oxopentanamide



[00863] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 11.03 (s, 1H), 9.80 (s, 1H), 9.62 (s, 1H), 9.42 (s, 1H), 7.83 (dd, J = 6.9, 2.1 Hz, 1H), 7.50 (d, J = 7.1 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 6.78 (s, 1H), 6.27 (s, 1H), 5.15 (dd, J = 13.2, 5.1 Hz, 1H), 4.45 – 4.29 (m, 2H), 3.62 – 3.54 (m, 1H), 3.44 (dd, J = 14.8, 8.9 Hz, 8H), 3.03 – 2.85 (m, 2H), 2.60 (dd, J = 22.9, 8.3 Hz, 2H), 2.49 – 2.25 (m, 10H), 2.08 – 1.97 (m, 1H), 1.82 (p, J = 7.4 Hz, 2H), 0.95 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{40}H_{44}N_8O_8$: 764.33; Found: 765.3 $(M+H)^+$.

[00864] SDC-TRAP-0109

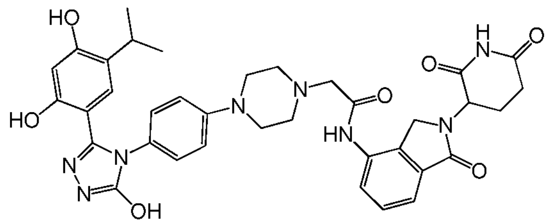
[00865] 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) piperazine-1-carboxamide



[00866] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 10.99 (s, 1H), 9.61 (s, 1H), 9.42 (s, 1H), 8.57 (s, 1H), 7.53 – 7.39 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.77 (s, 1H), 6.27 (s, 1H), 5.12 (dd, J = 13.2, 5.2 Hz, 1H), 4.36 – 4.30 (m, 2H), 3.53 – 3.41 (m, 6H), 3.38 (s, 1H), 2.92 (ddd, J = 31.5, 15.9, 6.1 Hz, 2H), 2.64 – 2.54 (m, 1H), 2.47 – 2.35 (m, 5H), 0.94 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{36}H_{38}N_8O_7$: 694.29; Found: 695.2 $(M+H)^+$.

[00867] SDC-TRAP-0110

[00868] 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) acetamide

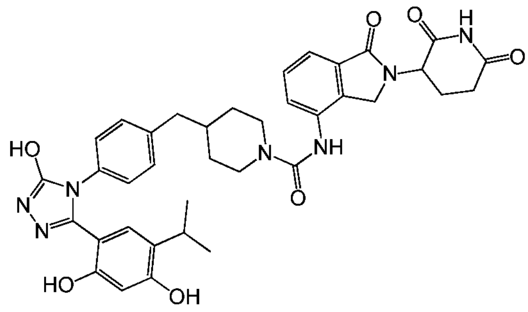


[00869] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 11.00 (s, 1H), 9.77 (s, 1H), 9.57 (s, 1H), 9.44 (s, 1H), 7.80 (dd, J = 7.5, 1.5 Hz, 1H), 7.58 – 7.47 (m, 2H), 7.06 – 6.98 (m, 2H), 6.97 – 6.89 (m, 2H), 6.78 (s, 1H), 6.27 (s, 1H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.47 – 4.32 (m, 2H), 3.23 (d, J = 5.8 Hz, 6H), 3.03 – 2.83 (m, 3H), 2.76 – 2.55 (m, 6H), 2.47 – 2.32 (m, 1H), 2.02 (td, J = 7.5, 3.9 Hz, 1H), 0.96 (d, J = 6.9 Hz, 6H).

[00870] ESMS calculated for $C_{36}H_{38}N_8O_7$: 694.29; Found: 695.2 $(M+H)^+$.

[00871] SDC-TRAP-0114

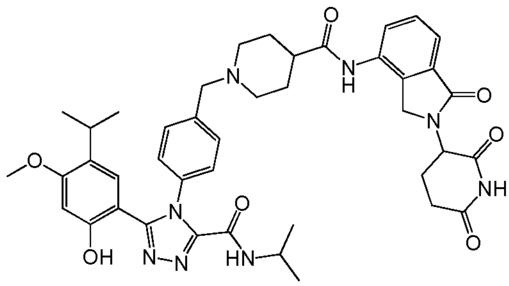
[00872] 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benz yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)piperidine-1- carboxamide



[00873] ESMS calculated for $C_{37}H_{39}N_7O_7$: 693.29; Found: 694.2 $(M+H)^+$.

[00874] SDC-TRAP-0115

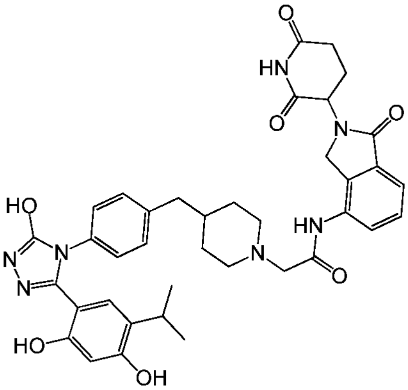
[00875] N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-1-(4-(3-(2-hydroxy-5-isopropyl-4-methoxyphenyl)-5-(isopropylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carboxamide



[00876] ESMS calculated for $C_{42}H_{48}N_8O_7$: 776.36; Found: 777.3 $(M+H)^+$.

[00877] SDC-TRAP-0116

[00878] 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) acetamide

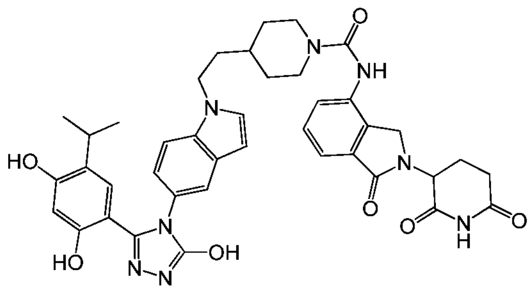


[00879] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 11.01 (s, 1H), 9.69 (s, 1H), 9.58 (s, 1H), 9.42 (s, 1H), 7.77 (dd, J = 7.5, 1.5 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.18 (d, J = 8.4 Hz, 2H), 7.14 – 7.06 (m, 2H), 6.74 (s, 1H), 6.27 (s, 1H), 5.13 (dd, J = 13.2, 5.1 Hz, 1H), 4.45 – 4.30 (m, 2H), 3.20 – 3.09 (m, 3H), 3.03 – 2.83 (m, 4H), 2.60 (ddd, J = 17.4, 4.3, 2.4 Hz, 1H), 2.37 (qd, J = 12.5, 11.8, 5.9 Hz, 1H), 2.14 – 1.96 (m, 3H), 1.60 – 1.44 (m, 3H), 1.38 – 1.24 (m, 2H), 0.92 (d, J = 6.9 Hz, 6H).

[00880] ESMS calculated for $C_{38}H_{41}N_7O_7$: 707.31; Found: 708.2 $(M+H)^+$.

[00881] SDC-TRAP-0119

[00882] 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) piperidine-1-carboxamide

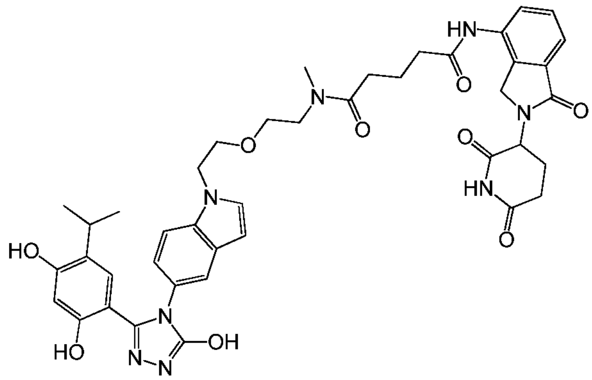


[00883] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 10.99 (s, 1H), 9.54 (d, J = 17.1 Hz, 2H), 8.50 (s, 1H), 7.53 – 7.41 (m, 6H), 6.95 (d, J = 8.7 Hz, 1H), 6.69 (s, 1H), 6.47 – 6.41 (m, 1H), 6.25 (s, 1H), 5.12 (dd, J = 13.1, 5.2 Hz, 1H), 4.33 (s, 2H), 4.24 (t, J = 6.9 Hz, 2H), 4.11 – 3.99 (m, 2H), 2.90 (td, J = 13.9, 6.3 Hz, 2H), 2.75 (t, J = 12.8 Hz, 2H), 2.60-2.55(m, 1H), (2.45 – 2.34 (m, 1H), 2.00 (d, J = 8.5 Hz, 1H), 1.74 (d, J = 13.1 Hz, 4H), 1.43 (s, 1H), 1.21 – 1.07 (m, 2H), 0.80 (d, J = 6.8 Hz, 6H).

[00884] ESMS calculated for $C_{40}H_{42}N_8O_7$: 746.32; Found: 747.3 $(M+H)^+$.

[00885] SDC-TRAP-0120

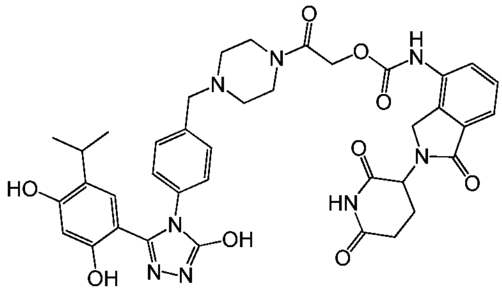
[00886] N1-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N5-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-N1-methylglutaramide



[00887] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 11.02 (s, 1H), 9.80 (d, J = 4.4 Hz, 1H), 9.54 (s, 1H), 9.47 (s, 1H), 7.82 (dt, J = 7.4, 2.1 Hz, 1H), 7.54 – 7.31 (m, 5H), 6.91 (dd, J = 8.7, 2.0 Hz, 1H), 6.73 (d, J = 2.1 Hz, 1H), 6.40 (dd, J = 7.0, 3.1 Hz, 1H), 6.22 (s, 1H), 5.19 – 5.09 (m, 1H), 4.45 – 4.26 (m, 4H), 3.70 – 3.63 (m, 2H), 3.49 – 3.33 (m, 4H), 2.98 – 2.80 (m, 4H), 2.75 (s, 1H), 2.60 (ddd, J = 17.1, 4.3, 2.3 Hz, 1H), 2.35 (ddd, J = 31.6, 15.2, 7.4 Hz, 5H), 1.80 (p, J = 7.4 Hz, 2H), 0.83 (dd, J = 6.9, 2.1 Hz, 6H). ESMS calculated for $C_{42}H_{46}N_8O_9$: 806.34; Found: 807.3 $(M+H)^+$.

[00888] SDC-TRAP-0121

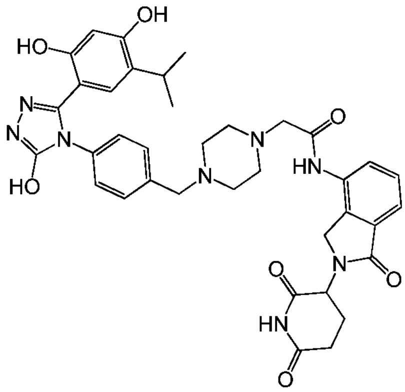
[00889] 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-2-oxoethyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00890] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 11.01 (s, 1H), 9.77 (s, 1H), 9.60 (s, 1H), 9.40 (s, 1H), 7.77 (dt, J = 7.0, 3.6 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 6.78 (s, 1H), 6.27 (s, 1H), 5.12 (dd, J = 13.3, 5.1 Hz, 1H), 4.85 (s, 2H), 4.45-4.35 (m, 2H), 3.49 (s, 2H), 3.44 (s, 3H), 3.03 – 2.84 (m, 2H), 2.61 (d, J = 17.6 Hz, 1H), 2.42 – 2.26 (m, 6H), 2.07 – 1.99 (m, 1H), 0.95 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{38}H_{40}N_8O_9$: 752.29; Found: 753.3 $(M+H)^+$.

[00891] SDC-TRAP-0128

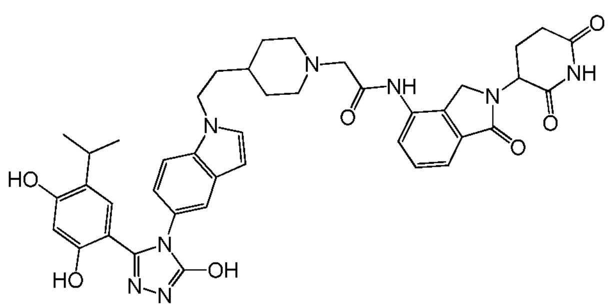
[00892] 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide



[00893] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 11.01 (s, 1H), 9.71 (s, 1H), 9.59 (s, 1H), 9.40 (s, 1H), 7.79 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.58 – 7.46 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.77 (s, 1H), 6.26 (s, 1H), 5.12 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.45 – 4.29 (m, 2H), 3.46 (s, 2H), 3.16 (s, 2H), 3.02 – 2.84 (m, 2H), 2.65 – 2.50 (m, 5H), 2.47 – 2.32 (m, 5H), 1.99 (m, 1H), 0.94 (d, *J* = 6.9 Hz, 6H). ESMS calculated for $C_{37}H_{40}N_8O_7$: 708.30; Found: 709.3 $(M+H)^+$.

[00894] SDC-TRAP-0129

[00895] 2-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)acetamide

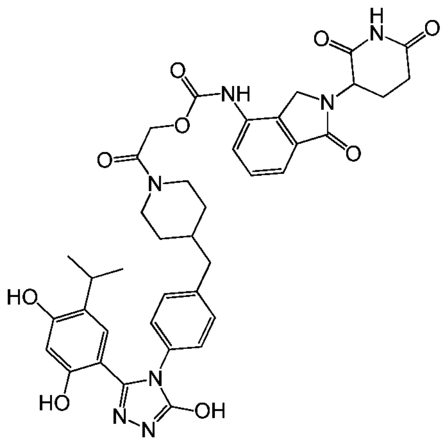


[00896] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 11.00 (s, 1H), 9.70 (s, 1H), 9.54 (d, *J* = 14.6 Hz, 2H), 7.77 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.58 – 7.40 (m, 5H), 6.94 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.67 (s, 1H), 6.43 (d, *J* = 3.1 Hz, 1H), 6.24 (s, 1H), 5.12 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.45 –

4.29 (m, 2H), 4.22 (t, J = 7.2 Hz, 2H), 3.12 (s, 2H), 2.87 (q, J = 6.9 Hz, 4H), 2.59 (d, J = 17.3 Hz, 1H), 2.46 – 2.33 (m, 1H), 2.09-2.04 (m, 5H), 1.69 (d, J = 6.9 Hz, 4H), 1.36 – 1.25 (m, 2H), 0.78 (d, J = 6.8 Hz, 6H). ESMS calculated for $C_{41}H_{44}N_8O_7$: 760.33; Found: 761.2 $(M+H)^+$.

[00897] SDC-TRAP-0131

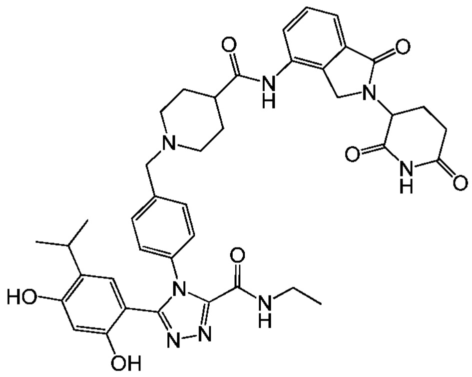
[00898] 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-2-oxoethyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00899] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 11.01 (s, 1H), 9.75 (s, 1H), 9.60 (s, 1H), 9.42 (s, 1H), 7.81 – 7.74 (m, 1H), 7.54 – 7.46 (m, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 6.75 (s, 1H), 6.27 (s, 1H), 5.12 (dd, J = 13.2, 5.2 Hz, 1H), 4.90 – 4.75 (m, 2H), 4.45 (d, J = 17.6 Hz, 1H), 4.40 – 4.24 (m, 2H), 3.69 (d, J = 13.1 Hz, 1H), 3.02 – 2.84 (m, 3H), 2.61 (d, J = 17.6 Hz, 2H), 2.34 (td, J = 14.4, 9.8 Hz, 1H), 2.08 – 1.96 (m, 2H), 1.75 (s, 1H), 1.59 (t, J = 12.0 Hz, 2H), 1.26 – 1.08 (m, 2H), 1.01 (s, 1H), 0.94 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{39}H_{41}N_7O_9$: 751.30; Found: 752.2 $(M+H)^+$.

[00900] SDC-TRAP-0149

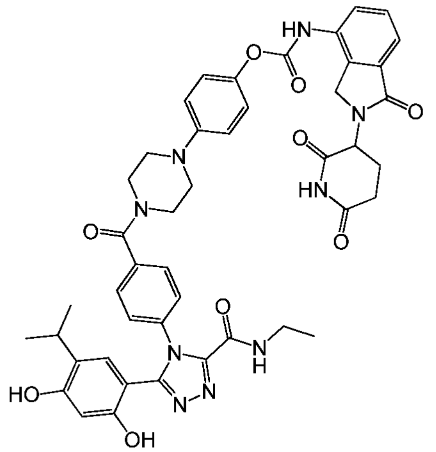
[00901] 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl) piperidine-4-carboxamide



[00902] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.61 (s, 1H), 9.76 (d, J = 9.5 Hz, 2H), 8.97 (t, J = 5.9 Hz, 1H), 7.82 (dd, J = 7.2, 1.9 Hz, 1H), 7.55 – 7.44 (m, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.35 – 7.27 (m, 2H), 6.59 (s, 1H), 6.35 (s, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.44 – 4.28 (m, 2H), 3.51 (s, 2H), 3.31 (s, 1H), 3.23 – 3.11 (m, 2H), 2.92 (dq, J = 13.4, 7.5, 6.4 Hz, 4H), 2.61 (d, J = 17.6 Hz, 1H), 2.39 (dtt, J = 26.4, 13.3, 6.3 Hz, 2H), 2.01 (dd, J = 12.9, 8.7 Hz, 3H), 1.81 (d, J = 12.2 Hz, 2H), 1.70 (q, J = 11.4 Hz, 2H), 1.04 (t, J = 7.1 Hz, 3H), 0.82 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{40}H_{44}N_8O_7$: 748.33; Found: 749.3 $(M+H)^+$.

[00903] SDC-TRAP-0152

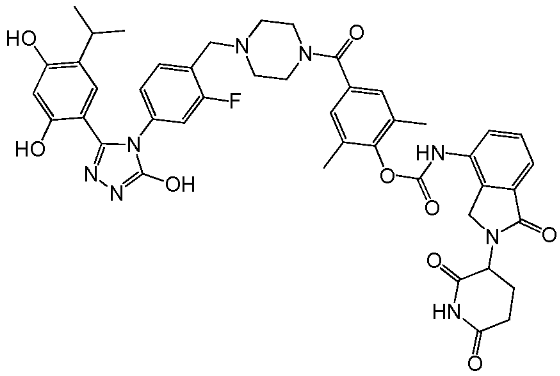
[00904] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperazin-1-yl)phenyl(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00905] ESMS calculated for $C_{45}H_{45}N_9O_9$: 855.33; Found: 856.2 $(M+H)^+$.

[00906] SDC-TRAP-0168

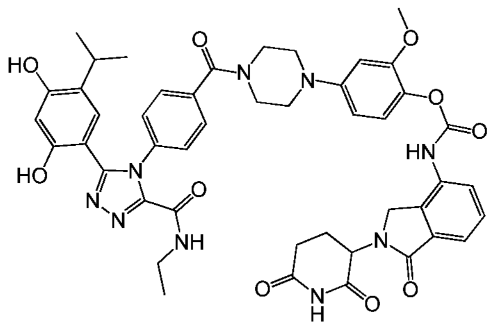
[00907] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carbonyl)-2,6-dimethylphenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00908] ESMS calculated for $C_{45}H_{45}FN_8O_9$: 860.33; Found: 861.2 $(M+H)^+$.

[00909] SDC-TRAP-0173

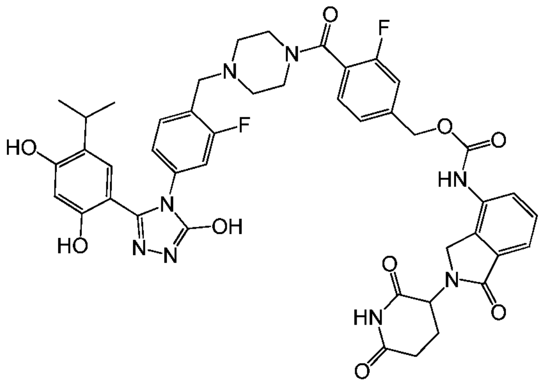
[00910] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperazin-1-yl)-2-methoxyphenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00911] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.04 (s, 1H), 10.22 (s, 1H), 10.08 (s, 1H), 9.75 (s, 1H), 9.03 (t, J = 6.2 Hz, 1H), 7.80 (s, 1H), 7.50-7.41 (m, 6H), 7.04 (d, J = 8.5 Hz, 1H), 6.73 (d, J = 11.0 Hz, 2H), 6.56 – 6.49 (m, 1H), 6.33 (s, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.44 – 4.28 (m, 2H), 3.79 (s, 3H), 3.29 – 3.13 (m, 8H), 2.95-2.55 (m ,2H), 2.36 (d, J = 14.6 Hz, 1H), 2.11-2.02(m,1H), 1.06 (t, J = 7.4 Hz, 3H), 0.91 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{46}H_{47}N_9O_{10}$: 885.34; Found: 886.3 $(M+H)^+$.

[00912] SDC-TRAP-0174

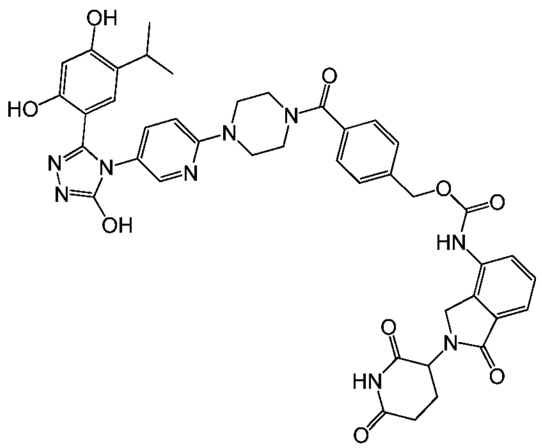
[00913] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carbonyl)-3-fluorobenzyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00914] ESMS calculated for $C_{44}H_{42}FN_8O_9$: 864.30; Found: 865.2 $(M+H)^+$.

[00915] SDC-TRAP-0175

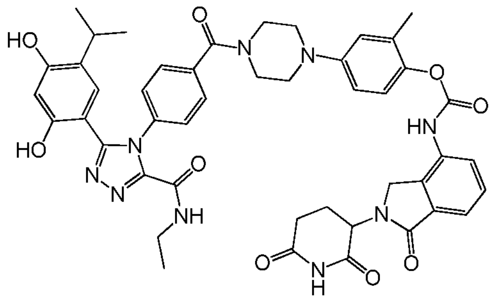
[00916] 4-(4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)pyridin-2-yl)piperazine-1-carbonyl)benzyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00917] ESMS calculated for $C_{42}H_{41}N_9O_9$: 815.30; Found: 816.1 $(M+H)^+$.

[00918] SDC-TRAP-0176

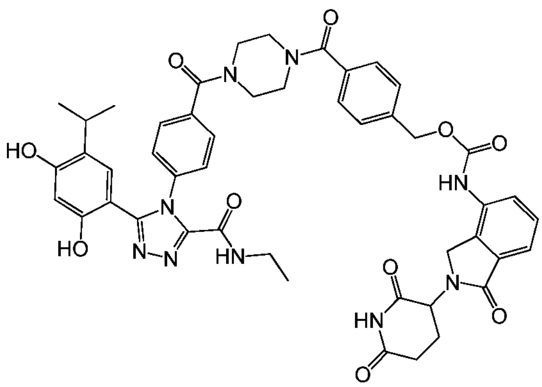
[00919] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperazin-1-yl)-2-methylphenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00920] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.25 (s, 1H), 10.11 (s, 1H), 9.75 (s, 1H), 9.02 (t, J = 6.1 Hz, 1H), 7.81 (p, J = 3.5 Hz, 1H), 7.58 – 7.46 (m, 4H), 7.42 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 2.7 Hz, 1H), 6.84 (dd, J = 8.8, 2.9 Hz, 1H), 6.72 (s, 1H), 6.34 (s, 1H), 5.14 (dd, J = 13.2, 5.1 Hz, 1H), 4.51 (d, J = 17.7 Hz, 1H), 4.42 (d, J = 17.7 Hz, 1H), 3.78 (s, 2H), 3.50 (s, 2H), 3.18 (dt, J = 20.9, 11.0 Hz, 6H), 2.94 (dp, J = 18.6, 6.2, 4.7 Hz, 2H), 2.53 – 2.47 (m, 2H), 2.46 – 2.30 (m, 1H), 2.18 (s, 3H), 2.04 (dd, J = 11.6, 5.9 Hz, 1H), 1.07 (t, J = 7.2 Hz, 3H), 0.91 (d, J = 6.8 Hz, 6H). ESMS calculated for $C_{46}H_{47}N_9O_9$: 869.35; Found: 870.1 $(M+H)^+$.

[00921] SDC-TRAP-0177

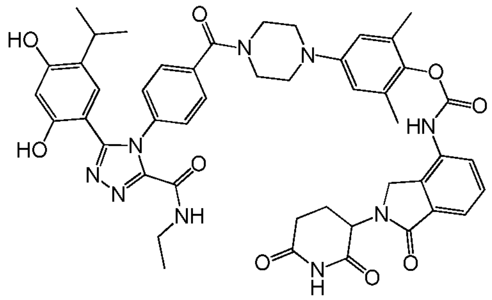
[00922] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperazine-1-carbonyl)benzyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00923] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.19 (s, 1H), 9.73 (s, 2H), 9.02 (t, J = 6.0 Hz, 1H), 7.84 – 7.77 (m, 1H), 7.50 (dq, J = 11.4, 6.5 Hz, 8H), 7.40 (d, J = 6.8 Hz, 2H), 6.70 (s, 1H), 6.33 – 6.28 (m, 1H), 5.23 (s, 2H), 5.13 (dd, J = 13.2, 5.1 Hz, 1H), 4.40 (d, J = 17.8 Hz, 2H), 3.68 (d, J = 24.7 Hz, 4H), 3.22 – 3.12 (m, 2H), 2.93 (d, J = 12.6 Hz, 2H), 2.65-2.55 (m, 1H), 2..30-2.25(m, 1H), 2.02 (dd, J = 15.0, 7.1 Hz, 1H), 1.05 (t, J = 7.1 Hz, 3H), 0.88 (d, J = 7.5 Hz, 6H). ESMS calculated for $C_{47}H_{47}N_9O_{10}$: 897.34; Found: 898.1 $(M+H)^+$.

[00924] SDC-TRAP-0178

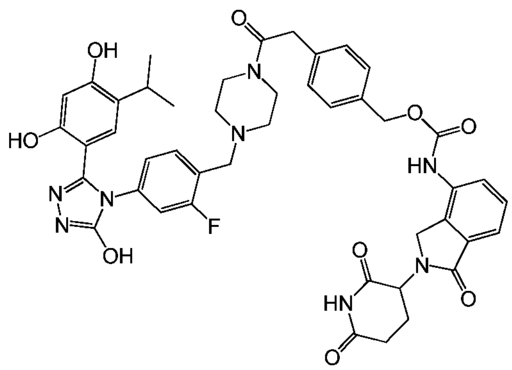
[00925] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperazin-1-yl)-2,6-dimethylphenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00926] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.22 (s, 1H), 10.17 (s, 1H), 9.74 (s, 1H), 9.02 (t, *J* = 5.9 Hz, 1H), 7.86 – 7.77 (m, 1H), 7.58 – 7.46 (m, 4H), 7.45 – 7.37 (m, 2H), 6.73 (d, *J* = 11.9 Hz, 3H), 6.33 (s, 1H), 5.13 (dd, *J* = 13.2, 5.1 Hz, 1H), 4.50 (d, *J* = 17.6 Hz, 1H), 4.41 (d, *J* = 17.6 Hz, 1H), 3.76 (s, 2H), 3.48 (s, 2H), 3.25 – 3.13 (m, 4H), 3.02 – 2.85 (m, 2H), 2.66 – 2.57 (m, 1H), 2.45 – 2.31 (m, 1H), 2.14 (s, 6H), 2.04-2.02(m, 1H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 6H). ESMS calculated for $C_{47}H_{49}N_9O_9$: 883.37; Found: 884.1 $(M+H)^+$.

[00927] SDC-TRAP-0194

[00928] 4-(2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazin-1-yl)-2-oxoethyl)benzyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate

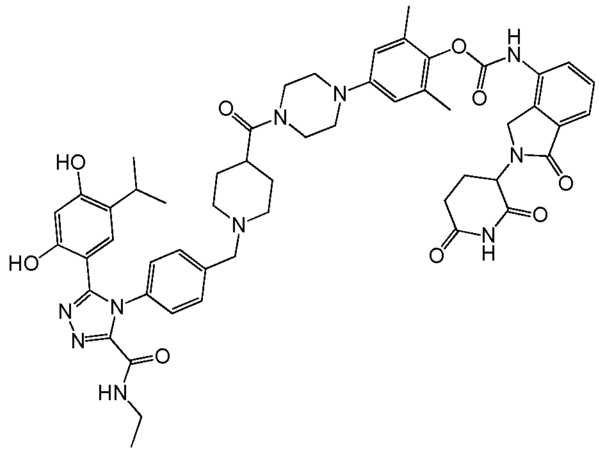


[00929] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 11.06 (s, 1H), 9.70 (d, *J* = 7.6 Hz, 2H), 9.45 (s, 1H), 7.88 – 7.81 (m, 1H), 7.59 – 7.49 (m, 2H), 7.42 (d, *J* = 8.2 Hz, 3H), 7.31 – 7.24 (m, 2H), 7.12 (dd, *J* = 10.5, 2.1 Hz, 1H), 7.02 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.92 (s, 1H), 6.33

(s, 1H), 5.22 – 5.12 (m, 3H), 4.56 – 4.35 (m, 2H), 3.73 (d, *J* = 15.5 Hz, 2H), 3.57 – 3.46 (m, 6H), 3.13 – 2.89 (m, 2H), 2.71 – 2.61 (m, 1H), 2.37 (h, *J* = 6.4, 5.4 Hz, 5H), 2.12 – 1.99 (m, 1H), 1.05 (d, *J* = 6.9 Hz, 6H). ESMS calculated for $C_{45}H_{45}FN_8O_9$: 860.33; Found: 861.2 $(M+H)^+$.

[00930] SDC-TRAP-0195

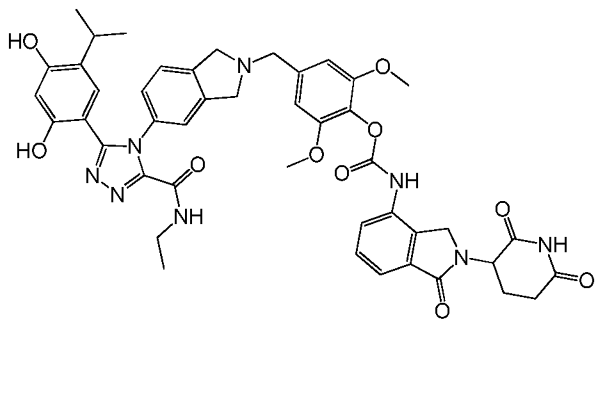
[00931] 4-(4-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)piperazin-1-yl)-2,6-dimethylphenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00932] ESMS calculated for $C_{53}H_{60}N_{10}O_9$: 980.45; Found: 981.3 $(M+H)^+$.

[00933] SDC-TRAP-0196

[00934] 4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)isoindolin-2-yl)methyl)-2,6-dimethoxyphenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[00935] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.56 (s, 1H), 10.15 (s, 1H), 9.77 (s, 1H), 8.99 (t, J = 5.9 Hz, 1H), 7.82 (dd, J = 5.7, 3.2 Hz, 1H), 7.52 (q, J = 4.1, 3.4 Hz, 2H), 7.36 – 7.24 (m, 2H), 7.17 (dd, J = 7.9, 2.1 Hz, 1H), 6.79 (s, 2H), 6.57 (s, 1H), 6.33 (s, 1H), 5.14 (dd, J = 13.2, 5.2 Hz, 1H), 4.49 (d, J = 17.7 Hz, 1H), 4.40 (d, J = 17.6 Hz, 1H), 3.90 (d, J = 16.3 Hz, 5H), 3.79 (s, 6H), 3.17 (p, J = 7.0 Hz, 2H), 2.92 (tt, J = 12.5, 6.2 Hz, 2H), 2.62 (d, J = 16.8 Hz, 1H), 2.42 – 2.31 (m, 1H), 2.10 – 2.01 (m, 1H), 1.05 (t, J = 7.1 Hz, 3H), 0.85 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{45}H_{46}N_8O_{10}$: 858.33; Found: 859.2 $(M+H)^+$.

[00936] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

SDC-TRAP-#	HER2 Degradation IC_{50} (nM)
SDC-TRAP-0015	2347
SDC-TRAP-0017	>10,000
SDC-TRAP-0018	8205
SDC-TRAP-0021	>5000
SDC-TRAP-0033	>5000
SDC-TRAP-0041	>10000
SDC-TRAP-0109	>10000
SDC-TRAP-0110	>10000
SDC-TRAP-0114	4,311
SDC-TRAP-0115	1890
SDC-TRAP-0116	967
SDC-TRAP-0105	>10000
SDC-TRAP-0119	>10,000
SDC-TRAP-0108	>10,000
SDC-TRAP-0122	>10000
SDC-TRAP-0121	3,000
SDC-TRAP-0128	6,909
SDC-TRAP-0129	4,519
SDC-TRAP-0126	8,636
SDC-TRAP-0132	>5000
SDC-TRAP-0127	8,086
SDC-TRAP-0131	>5,000
SDC-TRAP-0123	657

SDC-TRAP-#	HER2 Degradation IC_{50} (nM)
SDC-TRAP-0135	9667
SDC-TRAP-0133	>10000
SDC-TRAP-0136	>5000
SDC-TRAP-0140	>5000
SDC-TRAP-0149	1692
SDC-TRAP-0231	696
SDC-TRAP-0152	254
SDC-TRAP-0124	358
SDC-TRAP-0125	312
SDC-TRAP-0156	3495
SDC-TRAP-0157	696
SDC-TRAP-0167	2861
SDC-TRAP-0168	276
SDC-TRAP-0173	323
SDC-TRAP-0174	693
SDC-TRAP-0160	239
SDC-TRAP-0170	296
SDC-TRAP-0171	199
SDC-TRAP-0162	>5,000
SDC-TRAP-0147	4329
SDC-TRAP-0175	2,629
SDC-TRAP-0178	170 91
SDC-TRAP-0176	178
SDC-TRAP-0177	4,352
SDC-TRAP-0182	359
SDC-TRAP-0194	2,121
SDC-TRAP-0166	>5,000
SDC-TRAP-0188	3,950
SDC-TRAP-0189	1,091
SDC-TRAP-0195	49
SDC-TRAP-0163	885
SDC-TRAP-0164	493
SDC-TRAP-0190	>5000
SDC-TRAP-0191	1,177
SDC-TRAP-0192	>5000
SDC-TRAP-0196	89
SDC-TRAP-0187	72

SDC-TRAP-#	HER2 Degradation IC_{50} (nM)
SDC-TRAP-0193	266
SDC-TRAP-0155	1190

Hsp90$^{\alpha}$ binding assay data

No	SDC	Binding EC_{50} (nM)
1	SDC-TRAP-0196	93.11
2	SDC-TRAP-0115	203.2
3	SDC-TRAP-0116	158.8
4	SDC-TRAP-0127	102.2

Mouse plasma stability data

Compound ID	% Remaining (1h, 10μM)
SDC-TRAP-0187	102%
SDC-TRAP-0196	66.2%
SDC-TRAP-0147	98.1%
SDC-TRAP-0167	51.2%
SDC-TRAP-0163	93.0%
SDC-TRAP-0164	98.0%
SDC-TRAP-0171	17.7%
SDC-TRAP-0178	82.0%
SDC-TRAP-0195	98.4%
SDC-TRAP-0115	85.9%
SDC-TRAP-0116	91.1%
SDC-TRAP-0121	89.1%
SDC-TRAP-0127	87.3%
SDC-TRAP-0124	112%
SDC-TRAP-0125	99.4%
SDC-TRAP-0231	98.3%
SDC-TRAP-0156	90.3%
SDC-TRAP-0157	81.4%

[00937] Tissue distribution data for SDC-TRAP-0116

Analyte	Plasma Conc. (µM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
Target	SDC-TRAP-0116		Lenalidomide	SDC-TRAP-0116		Lenalidomide	SDC-TRAP-0116		Lenalidomide
Time (h)									
0.083	693	--	0.560	17.7	--	0.0856	0.03	--	0.15
1	65.2	--	1.76	13.7	--	0.736	0.21	--	0.42
6	0.595	--	0.113	6.09	--	0.120	10.2	--	1.07
24	0.0111	--	BQL	2.78	--	BQL	251	--	--
48	0.0315	--	BQL	1.46	--	BQL	46.5	--	--

[00938] Tissue distribution data for SDC-TRAP-0171

Analyte	Plasma Conc. (µM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
Target	SDC-TRAP-0171	SDC-TRAP-0080	Lenalidomide	SDC-TRAP-0171	SDC-TRAP-0080	Lenalidomide	SDC-TRAP-0171	SDC-TRAP-0080	Lenalidomide
Time (h)									
0.083	618	0.0312	3.23	0.083	618	0.0312	0.0164	3.80	0.613
1	32.2	0.258	2.03	1	32.2	0.258	0.249	0.636	1.06
6	1.21	0.153	0.252	6	1.21	0.153	3.10	2.09	1.16
24	0.00162	0.0574	BQL	24	0.00162	0.0574	407	6.91	--
48	BQL	0.0143	BQL	48	BQL	0.0143	--	26.8	--

[00939] Tissue distribution data for SDC-TRAP-0178

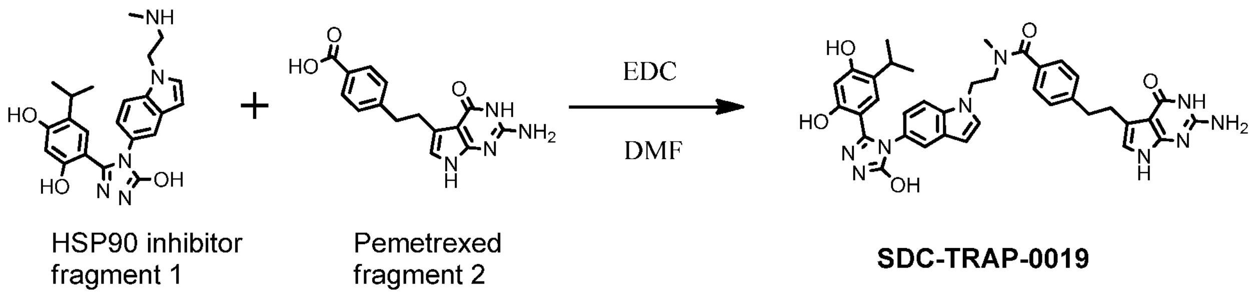
Analyte	Plasma Conc. (µM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
Target	SDC-TRAP-0178	SDC-TRAP-0183	Lenalidomide	SDC-TRAP-0178	SDC-TRAP-0183	Lenalidomide	SDC-TRAP-0178	SDC-TRAP-0183	Lenalidomide
Time (h)									
0.083	918	N/A	1.39	16.4	0.320	0.623	0.0179	--	0.449
1	217	N/A	0.963	12.8	0.316	0.629	0.0589	--	0.653
6	4.51	N/A	0.00447	7.17	0.418	0.0532	1.59	--	11.9
24	0.0280	N/A	BQL	2.81	0.556	BQL	100	--	--
48	0.241	N/A	BQL	1.01	0.508	BQL	--	--	--

[00940] Tissue distribution data for SDC-TRAP-0195

Analyte	Plasma Conc. (μM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
Target	SDC-TRAP-0195	SDC-TRAP-0197	Lenalidomide	SDC-TRAP-0195	SDC-TRAP-0197	Lenalidomide	SDC-TRAP-0195	SDC-TRAP-0197	Lenalidomide
Time (h)									
0.083	1220	N/A	0.923	17.1	0.206	0.477	0.0140	--	0.517
1	211	N/A	0.511	23.0	0.305	0.402	0.109	--	0.786
6	7.23	N/A	0.00316	17.1	0.662	0.0458	2.36	--	14.51
24	2.03	N/A	BQL	11.2	1.60	BQL	5.50	--	--
48	BQL	N/A	BQL	12.6	2.64	BQL	--	--	--

[00941] **Example 26: SDC-TRAPs comprising pemetrexed fragment**

[00942] Exemplary synthesis of SDC-TRAPs:



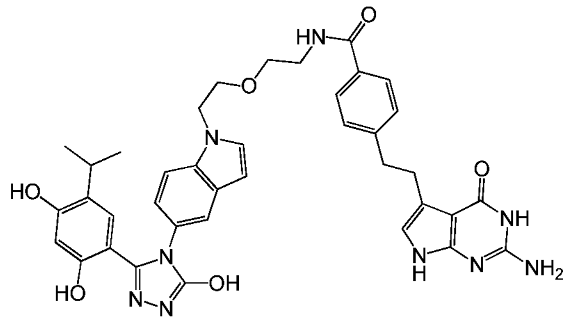
[00943] To a solution of pemetrexed-fragment **2** (60mg, 0.2mmol) and amine SDC-TRAP-0004 (82mg, 0.2mmol) in anhydrous DMF (3 mL) was added EDC (60mg, 0.3mmol). The reaction mixture was stirred at room temperature for 18h. The reaction mixture was then diluted with water (5 mL) and extracted with ethyl acetate (100mL). The organic phase was dried with sodium sulfate, filtered and evaporated, followed by flash chromatography (hexane-ethyl acetate 1:1 and ethyl acetate-methanol 98:2) to give SDC-TRAP-0019 (95mg, 70%) as a white solid.

[00944] 4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)-N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-N-methylbenzamide

[00945] ^{1}H NMR (400 MHz, DMSO-d_6) δ: 11.86 (s, 1H); 10.61(s, 1H); 10.14(s,1H); 9.51 (s, 1H); 9.47 (s, 1H); 7.59-7.45 (m, 2H); 7.28-6.96 (m, 5H); 6.72 (m, 2H); 6.47(s,1H); 6.32 (s, 1H); 6.24 (s, 1H); 6.00(bs, 2H); 4.46-4.28 (m, 2H);3.75-3.49(m,2H); 2.96 -2.80(m, 5H); 2.61(s, 3H); 0.81 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{37}H_{37}N_9O_5$: 687.29; Found: 688.2 $(M+H)^+$.

[00946] SDC-TRAP-0020

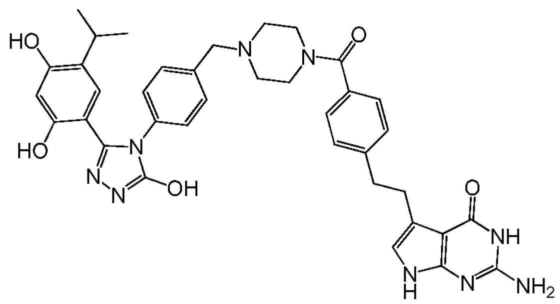
[00947] 4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)-N-(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)benzamide



[00948] ^{1}H NMR (400 MHz, DMSO-d6), δ (ppm): 11.86 (s, 1H); 10.61(s, 1H); 10.14(s,1H); 9.51 (s, 1H); 9.47 (s, 1H); 7.59-7.45 (m, 2H); 7.28-6.96 (m, 5H); 6.72 (m, 2H); 6.47(s,1H); 6.32 (s, 1H); 6.24 (s, 1H); 6.01(s, 2H); 4.33 (d, *J* = 6.5 Hz, 2H), 3.73 (d, *J* = 6.3 Hz, 2H), 3.54 – 3.46 (m, 2H); 3.00 – 2.82 (m, 7H), 0.81 (d, *J* = 6.9 Hz, 6H); ESMS calculated for $C_{38}H_{39}N_{9}O_{6}$: 717.30; Found: 718.2 $(M+H)^{+}$.

[00949] SDC-TRAP-0068

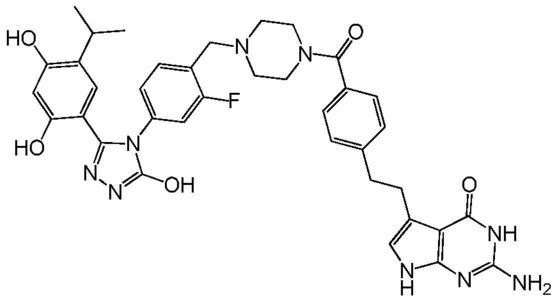
[00950] 2-amino-5-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carbonyl)phenethyl)-3H-pyrrolo[2,3-d] pyrimidin-4(7H)-one



[00951] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 10.62 (d, *J* = 2.2 Hz, 1H), 10.15 (s, 1H), 9.60 (s, 1H), 9.38 (s, 1H), 7.34 – 7.22 (m, 6H), 7.17 – 7.10 (m, 2H), 6.79 (s, 1H), 6.33 (d, *J* = 2.2 Hz, 1H), 6.26 (s, 1H), 6.00 (s, 2H), 3.48 (s, 2H), 3.33 (s, 2H), 3.03 – 2.88 (m, 3H), 2.84 (dd, *J* = 9.5, 5.7 Hz, 2H), 2.37-2.34 (m, 4H), 0.95 (d, *J* = 6.9 Hz, 6H); ESMS calculated for $C_{37}H_{39}N_{9}O_{5}$: 689.31; Found: 690.1 $(M+H)^{+}$.

[00952] SDC-TRAP-0078

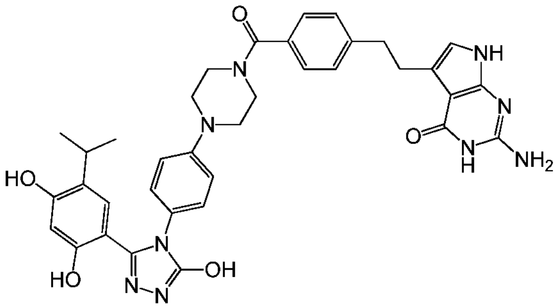
[00953] 2-amino-5-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carbonyl)phenethyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one



[00954] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 10.63 (d, J = 2.3 Hz, 1H), 10.15 (s, 1H), 9.63 (s, 1H), 9.39 (s, 1H), 7.96 (s, 1H), 7.40 (t, J = 8.1 Hz, 1H), 7.27 (s, 4H), 7.06 (dd, J = 10.9, 2.1 Hz, 1H), 6.97 (dd, J = 8.2, 2.0 Hz, 1H), 6.88 (s, 1H), 6.34 (d, J = 2.2 Hz, 1H), 6.26 (s, 1H), 6.00 (s, 2H), 3.54 (bs, 4H), 3.07 – 2.80 (m, 3H), 2.74 (s, 2H), 2.40 (bs, 4H), 1.01 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{37}H_{38}FN_9O_5$: 707.30; Found: 708.2 $(M+H)^+$.

[00955] SDC-TRAP-0082

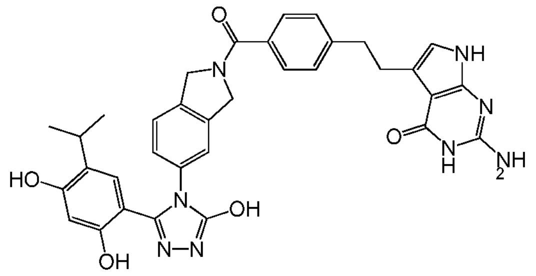
[00956] 2-amino-5-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazine-1-carbonyl)phenethyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one



[00957] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 10.63 (d, J = 2.1 Hz, 1H), 10.15 (s, 1H), 9.59 (s, 1H), 9.44 (s, 1H), 7.37 – 7.25 (m, 4H), 7.04 (d, J = 8.6 Hz, 2H), 6.97 – 6.90 (m, 2H), 6.81 (s, 1H), 6.35 (d, J = 2.2 Hz, 1H), 6.27 (s, 1H), 6.01 (s, 2H), 3.69 (s, 2H), 3.52 (s, 2H), 3.18 (s, 4H), 3.04 – 2.90 (m, 3H), 2.86 (dd, J = 9.5, 5.8 Hz, 2H), 0.98 (d, J = 6.9 Hz, 6H); ESMS calculated for $C_{36}H_{37}N_9O_5$: 675.29; Found: 676.2 $(M+H)^+$.

[00958] SDC-TRAP-0093

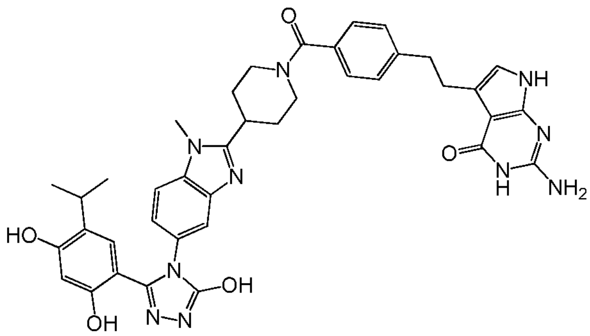
[00959] 2-amino-5-(4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)isoindoline-2-carbonyl)phenethyl)-3H-pyrrolo[2,3-d] pyrimidin-4(7H)-one



[00960] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 10.64 (s, 1H), 10.23 (s, 1H), 9.62 (s, 1H), 9.38 (s, 1H), 7.51 (dd, J = 8.2, 3.4 Hz, 2H), 7.40 – 7.17 (m, 4H), 7.07 – 6.96 (m, 1H), 6.91 (s, 1H), 6.36 (s, 1H), 6.25 (s, 1H), 6.06 (s, 2H), 4.78 (dd, J = 31.3, 14.1 Hz, 4H), 3.07 – 2.93 (m, 3H), 2.87 (dd, J = 9.5, 5.8 Hz, 2H), 1.02 (dd, J = 10.8, 6.8 Hz, 6H); ESMS calculated for $C_{34}H_{32}N_8O_5$: 632.25; Found: 633.1 $(M+H)^+$.

[00961] SDC-TRAP-0102

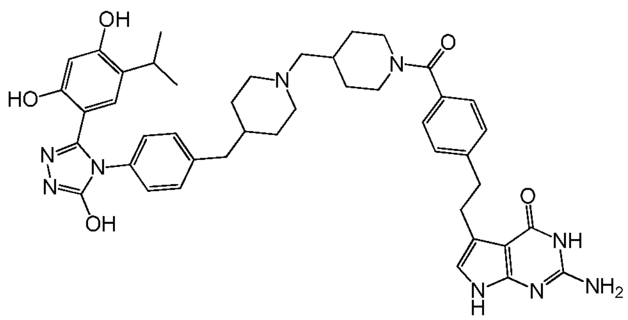
[00962] 2-amino-5-(4-(4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2-yl)piperidine-1-carbonyl)phenethyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one



[00963] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 10.66 – 10.60 (m, 1H), 10.17 (s, 1H), 9.57 (s, 1H), 9.36 (s, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.40 – 7.25 (m, 4H), 7.06 – 6.99 (m, 1H), 6.86 (s, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.20 (s, 1H), 6.02 (s, 2H), 4.53 (s, 1H), 3.79 (s, 3H), 3.02 – 2.81 (m, 5H), 1.95 (s, 2H), 1.76 (q, J = 11.9 Hz, 2H), 0.96 (d, J = 6.7 Hz, 6H); ESMS calculated for $C_{39}H_{40}N_{10}O_5$: 728.32; Found: 729.2 $(M+H)^+$.

[00964] SDC-TRAP-0103

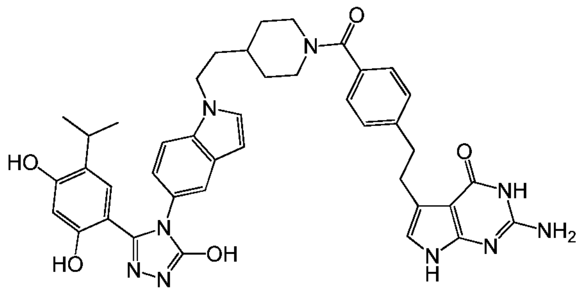
[00965] 2-amino-5-(4-(4-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)methyl)piperidine-1-carbonyl)phenethyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one



[00966] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 10.63 (s, 1H), 10.20 (s, 1H), 9.69 (s, 1H), 9.49 (s, 1H), 7.20 (d, J = 39.7 Hz, 6H), 7.08 (d, J = 8.0 Hz, 2H), 6.73 (s, 1H), 6.31 (d, J = 19.5 Hz, 2H), 6.04 (s, 2H), 4.42 (s, 1H), 3.58 (s, 1H), 2.95 (dt, J = 13.8, 7.4 Hz, 4H), 2.85 (d, J = 8.1 Hz, 2H), 2.77 (d, J = 10.7 Hz, 3H), 2.08 (d, J = 6.7 Hz, 2H), 1.76– 1.59 (m, 6H), 1.51 - 1.43 (m, 3H), 1.12 – 0.89 (m, 6H); ESMS calculated for $C_{44}H_{51}N_9O_5$: 785.40; Found: 786.3 $(M+H)^+$.

[00967] SDC-TRAP-0130

[00968] 2-amino-5-(4-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carbonyl)phenethyl)-3H-pyrrolo[2,3-d]pyrimidin-4(7H)-one



[00969] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 10.62 (s, 1H), 10.17 – 10.11 (m, 1H), 9.53 (dd, J = 20.0, 2.8 Hz, 2H), 7.52 – 7.39 (m, 3H), 7.25 (d, J = 2.8 Hz, 4H), 6.97 – 6.89 (m, 1H), 6.68 (d, J = 2.7 Hz, 1H), 6.42 (t, J = 3.1 Hz, 1H), 6.33 (d, J = 2.8 Hz, 1H), 6.23 (d, J = 2.8 Hz, 1H), 6.00 (s, 2H), 4.41 (s, 1H), 4.21 (t, J = 7.4 Hz, 2H), 2.98 – 2.80 (m, 6H), 1.76 – 1.66 (m, 4H), 1.47 (bs, 2H), 1.20 – 1.10 (m, 3H), 0.78 (dd, J = 7.1, 2.7 Hz, 6H); ESMS calculated for $C_{41}H_{43}N_9O_5$: 741.34; Found: 742.3 $(M+H)^+$.

[00970] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0020	>5000
SDC-TRAP-0019	4419
SDC-TRAP-0068	262
SDC-TRAP-0078	1005
SDC-TRAP-0082	1042
SDC-TRAP-0093	>5,000
SDC-TRAP-0102	>5,000
SDC-TRAP-0103	245
SDC-TRAP-0130	1829

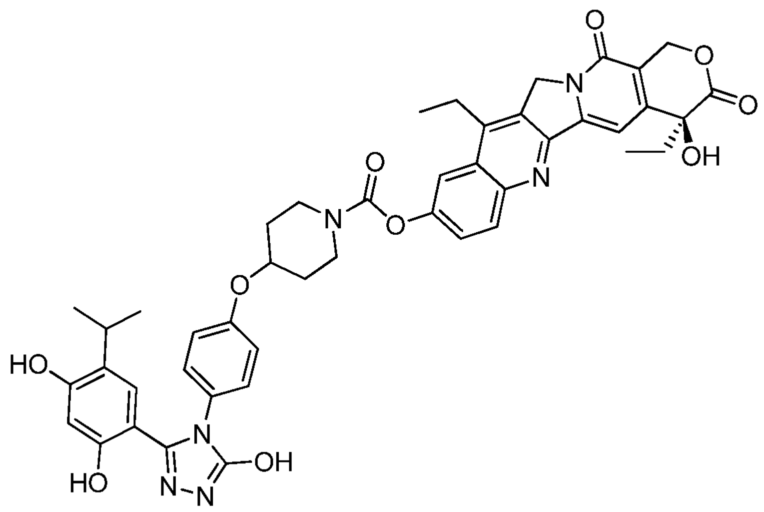
[00971] Mouse Plasma Stability

SDC-TRAP-#	% Remaining (1h)
SDC-TRAP-0068	96.5%
SDC-TRAP-0141	101%

[00972] **Example 27: SDC-TRAPs comprising SN-38**

[00973] SDC-TRAP-0011

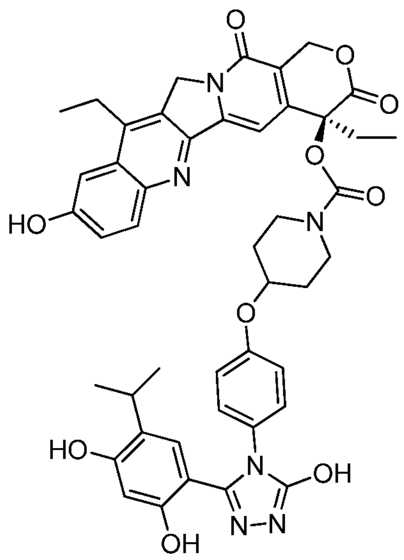
[00974] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenoxy)piperidine-1-carboxylate



[00975] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 3H), 8.17 (d, J = 9.2 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.74 – 7.62 (m, 2H), 7.18 – 7.01 (m, 4H), 6.70 (s, 1H), 6.40 (s, 1H), 6.05 (s, 1H), 5.44 (d, J = 4.7 Hz, 1H), 5.25 (s, 2H), 4.92 (dd, J = 11.8, 6.8 Hz, 1H), 4.69 (d, J = 10.6 Hz, 2H), 4.03 (q, J = 7.1 Hz, 1H), 3.79 (s, 1H), 3.59 (s, 1H), 3.17 (q, J = 7.6 Hz, 2H), 3.03 – 2.87 (m, 2H), 2.55 (s, 1H), 2.21 – 1.96 (m, 2H), 1.73 (s, 2H), 1.30 (t, J = 7.6 Hz, 3H), 1.01 – 0.81 (m, 9H) ppm; ESMS calculated for $C_{45}H_{44}N_6O_{10}$: 828.3; found: 829.1 (M + H^+).

[00976] SDC-TRAP-0012

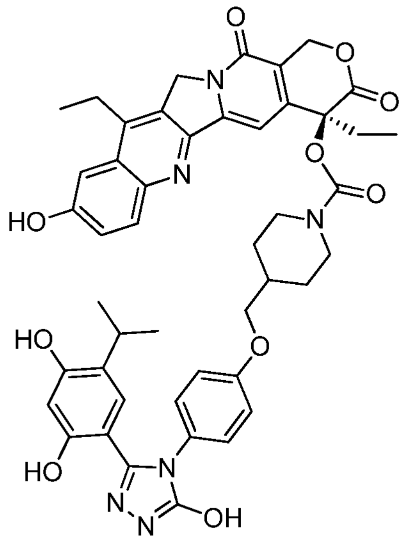
[00977] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano [3',4':6,7]indolizino[1,2-b]quinolin-4-yl-4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenoxy)piperidine-1-carboxylate hydrochloride



[00978] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 10.34 (s, 1H), 9.60 (s, 1H), 9.43 (s, 1H), 8.02 (t, J = 10.0 Hz, 1H), 7.46 – 7.38 (m, 2H), 7.15 – 7.07 (m, 2H), 6.98 (d, J = 15.2 Hz, 3H), 6.78 (s, 1H), 6.27 (s, 1H), 5.45 (d, J = 3.6 Hz, 2H), 5.30 (d, J = 2.4 Hz, 2H), 4.64 (d, J = 9.6 Hz, 1H), 4.03 (m, 1H), 3.57 (s, 1H), 3.20 (s, 1H), 3.09 (q, J = 7.6 Hz, 3H), 2.98 (q, J = 6.9 Hz, 1H), 2.55 (s, 4H), 2.14 (q, J = 11.2, 9.3 Hz, 3H), 1.46 (s, 1H), 1.29 (t, J = 7.6 Hz, 3H), 0.99 – 0.87 (m, 9H).ppm; ESMS calculated for $C_{45}H_{44}N_6O_{10}$: 828.3; found: 829.0 (M + H$^+$).

[00979] SDC-TRAP-0014

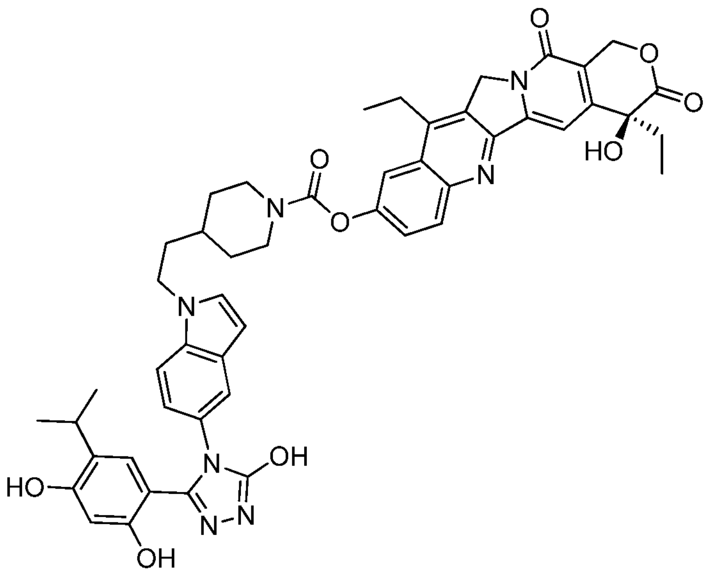
[00980] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano [3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenoxy)methyl)piperidine-1-carboxylate



[00981] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.07 (d, J = 9.1 Hz, 1H), 7.91 (d, J = 9.1 Hz, 1H), 7.52 – 7.36 (m, 4H), 7.35 – 7.16 (m, 2H), 7.04 (d, J = 8.4 Hz, 1H), 6.94 (d, J = 8.5 Hz, 1H), 6.57 – 6.49 (m, 1H), 6.37 (s, 1H), 5.67 (d, J = 16.9 Hz, 1H), 5.42 (d, J = 17.0 Hz, 1H), 4.45 (s, 2H), 4.12 – 4.00 (m, 1H), 3.88 (dd, J = 17.8, 7.5 Hz, 1H), 3.78 (d, J = 7.6 Hz, 1H), 3.39 (s, 2H), 3.14 (q, J = 10.3, 6.7 Hz, 2H), 2.99 (dt, J = 14.4, 7.1 Hz, 1H), 2.83 (d, J = 14.9 Hz, 1H), 2.37 – 1.96 (m, 5H), 1.86 (d, J = 13.2 Hz, 2H), 1.77 (d, J = 13.5 Hz, 1H), 1.62 (td, J = 27.9, 24.2, 13.8 Hz, 1H), 1.39 (t, J = 7.6 Hz, 3H), 1.04 (t, J = 7.5 Hz, 3H), 0.91 – 0.73 (m, 6H). ppm; ESMS calculated for $C_{46}H_{46}N_6O_{10}$: 842.3; found: 843.1 (M + H$^+$).

[00982] SDC-TRAP-0063

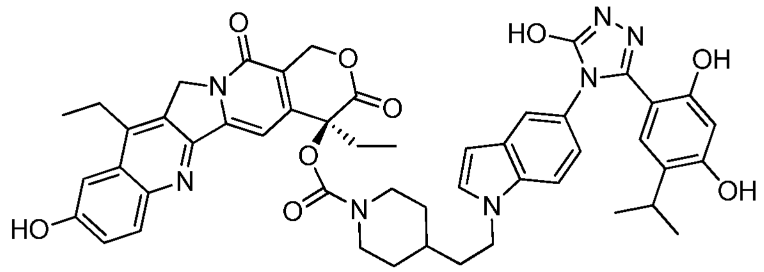
[00983] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate



[00984] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.68 (s, 1H), 7.64 – 7.56 (m, 2H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.24 – 7.12 (m, 2H), 6.55 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.37 (d, *J* = 4.2 Hz, 2H), 5.73 (d, *J* = 16.3 Hz, 1H), 5.36 – 5.24 (m, 3H), 4.41 (d, *J* = 13.5 Hz, 1H), 4.29 (q, *J* = 9.3, 7.5 Hz, 3H), 3.17 (q, *J* = 7.7 Hz, 2H), 3.06 (t, *J* = 12.7 Hz, 1H), 2.96 – 2.77 (m, 2H), 2.42 (s, 2H), 1.90 (dq, *J* = 14.2, 7.1 Hz, 6H), 1.45 – 1.33 (m, 5H), 1.31 – 1.22 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.50 (d, *J* = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{49}H_{49}N_7O_9$: 879.4; found: 880.2 (M + H$^+$).

[00985] SDC-TRAP-0064

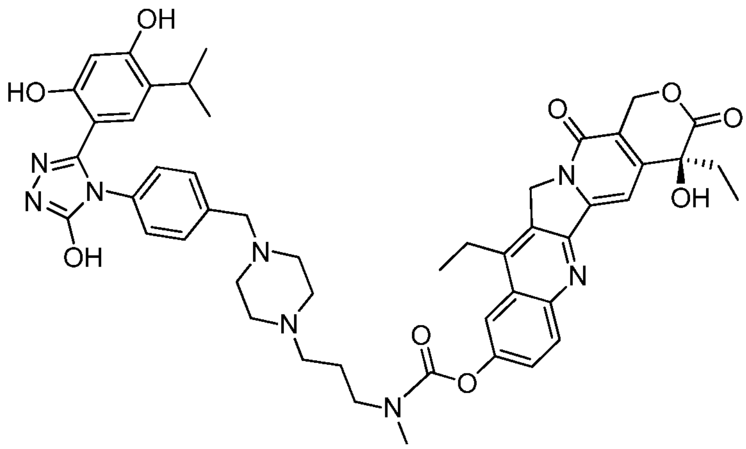
[00986] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate



[00987] ESMS calculated for $C_{49}H_{49}N_7O_9$: 879.4; found: 880.1 (M + H$^+$).

[00988] SDC-TRAP-0065

[00989] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) benzyl)piperazin-1-yl)propyl)(methyl)carbamate

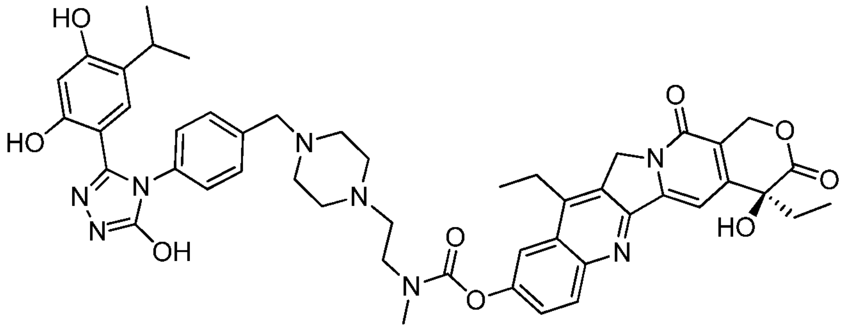


[00990] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (dd, *J* = 9.3, 2.0 Hz, 1H), 7.86 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.70 (d, *J* = 2.2 Hz, 1H), 7.66 – 7.56 (m, 1H), 7.49 (d, *J* = 7.9 Hz, 2H), 7.37 – 7.24 (m, 4H), 6.47 (d, *J* = 16.0 Hz, 1H), 6.41 – 6.35 (m, 1H), 5.72 (dd, *J* = 16.2, 2.2 Hz, 1H), 5.37 – 5.26 (m, 3H), 4.0 (m, 1H), 3.57 (d, *J* = 4.1 Hz, 3H), 3.51 – 3.35 (m, 3H), 3.19 (d, *J* = 8.4 Hz, 4H), 3.09 (d, *J* = 2.2 Hz, 1H), 2.92 (dt, *J* = 19.0, 7.0 Hz, 1H), 2.58 – 2.42 (m, 6H), 1.92 (dq, *J* = 15.4, 7.4 Hz, 5H), 1.41 (tt, *J* = 7.7, 4.1 Hz, 4H), 1.32 – 1.22 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.78 – 0.65 (m, 6H). ppm; ESMS calculated for $C_{49}H_{54}N_8O_9$: 898.4; found: 899.2 (M + H$^+$).

[00991] SDC-TRAP-0066

[00992] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl

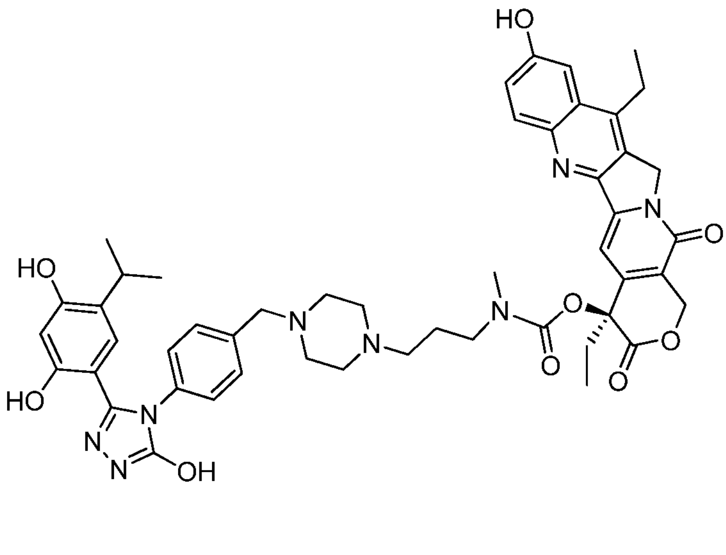
(2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) benzyl)piperazin-1-yl)ethyl)(methyl)carbamate



[00993] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.87 (t, *J* = 2.5 Hz, 1H), 7.70 (d, *J* = 1.3 Hz, 1H), 7.62 (ddd, *J* = 8.7, 5.9, 2.4 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.31 – 7.23 (m, 2H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.39 – 6.31 (m, 1H), 5.70 (d, *J* = 16.4 Hz, 1H), 5.37 – 5.26 (m, 3H), 3.61 – 3.53 (m, 3H), 3.43 – 3.33 (m, 3H), 3.25 – 3.13 (m, 3H), 3.10 (s, 1H), 2.96 – 2.84 (m, 1H), 2.77 – 2.60 (m, 5H), 2.55 (s, 4H), 1.99 – 1.85 (m, 2H), 1.41 (t, *J* = 7.7 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.77 – 0.65 (m, 6H). ppm; ESMS calculated for $C_{48}H_{52}N_8O_9$: 884.4; found: 885.1 (M + H^{+}).

[00994] SDC-TRAP-0084

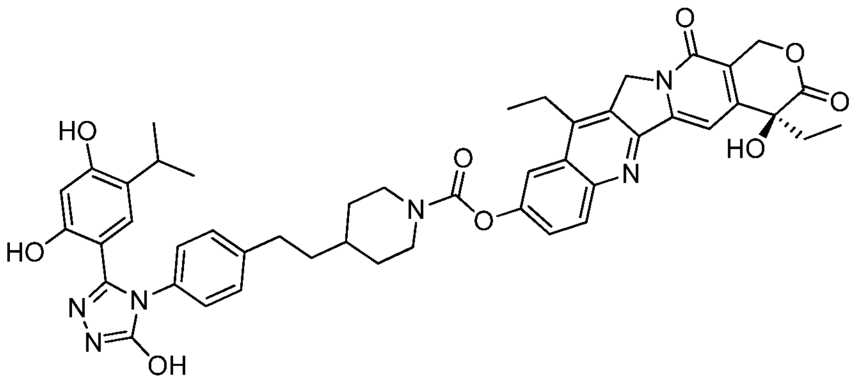
[00995] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) benzyl)piperazin-1-yl)propyl)(methyl)carbamate



[00996] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 9.74 (s, 1H), 8.02 (dd, *J* = 9.9, 6.7 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.27 – 7.17 (m, 2H), 7.01 (d, *J* = 5.8 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.26 (d, *J* = 3.2 Hz, 1H), 5.44 (d, *J* = 2.4 Hz, 2H), 5.28 (s, 2H), 4.12 (d, *J* = 16.9 Hz, 1H), 3.96 (s, 1H), 3.69 (s, 2H), 3.64 (s, 1H), 3.31 – 3.22 (m, 1H), 3.18 (m, 7H), 3.09 (d, *J* = 16.2 Hz, 3H), 2.98 (p, *J* = 6.8 Hz, 1H), 2.89 (s, 2H), 2.76 (s, 1H), 2.46 (s, 2H), 2.20 – 2.05 (m, 2H), 1.84 (t, *J* = 8.2 Hz, 1H), 1.27 (td, *J* = 7.7, 4.8 Hz, 3H), 1.02 – 0.85 (m, 9H).ppm; ESMS calculated for $C_{49}H_{54}N_8O_9$: 898.4; found: 899.3 (M + H^+).

[00997] SDC-TRAP-0086

[00998] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) phenethyl)piperidine-1-carboxylate

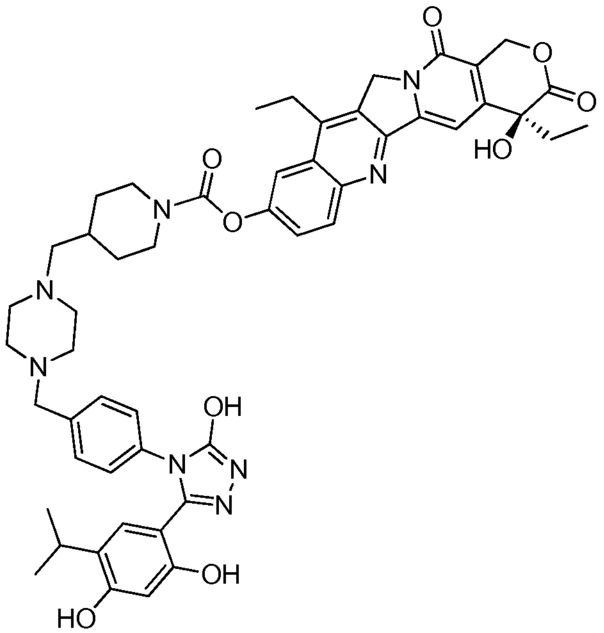


[00999] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 9.2 Hz, 1H), 7.85 (d, *J* = 2.5 Hz, 1H), 7.69 – 7.57 (m, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 6.44 (d, *J* = 1.6 Hz, 1H), 6.37 (d, *J* = 1.1 Hz, 1H), 5.74 (dt, *J* = 16.3, 1.2 Hz, 1H), 5.36 – 5.24 (m, 3H), 4.42 (d, *J* = 13.4 Hz, 1H), 4.31 (d, *J* = 13.3 Hz, 1H), 3.23 – 3.03 (m, 3H), 2.94 (dq, *J* = 14.0, 7.3 Hz, 2H), 2.76 (t, *J* = 7.7 Hz, 2H), 2.05 (d, *J* = 0.9 Hz, 1H), 1.91 (dq, *J* = 14.6, 7.4 Hz, 4H), 1.66 (d, *J* = 7.7 Hz, 2H), 1.40 (q, *J* = 9.8, 8.7 Hz, 5H), 1.08 – 0.89 (m, 3H), 0.74 (d, *J* = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{47}H_{48}N_6O_9$: 840.4; found: 841.2 (M + H^+).

[001000] SDC-TRAP-0088

[001001] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl

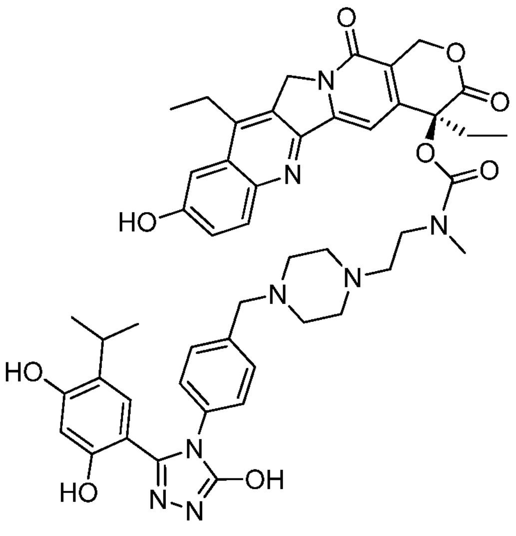
4-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) benzyl)piperazin-1-yl)methyl)piperidine-1-carboxylate



[001002] ESMS calculated for $C_{51}H_{56}N_8O_9$: 924.4; found: 925.4 ($M + H^+$).

[001003] SDC-TRAP-0087

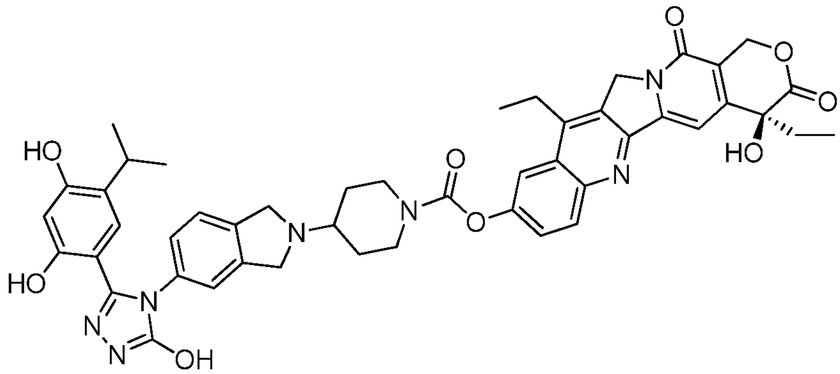
[001004] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) benzyl)piperazin-1-yl)ethyl)(methyl)carbamate



[001005] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.54 (s, 1H), 8.20 (s, 1H), 7.90-7.50 (m, 4H), 7.41 (s, 1H), 7.28 (s, 1H), 6.90-6.20 (m, 2H), 5.70-5.30 (m, 6H), 4.40-4.10 (m, 7H), 3.98 (s, 2H), 3.77 (s, 2H), 3.71 (s, 2H), 3.59 (s, 2H), 3.37 (d, *J* = 19.0 Hz, 5H), 3.05 (s, 1H), 2.94 (s, 1H), 1.44 (s, 2H), 1.05 (dd, *J* = 19.6, 6.6 Hz, 6H), 0.96 (d, *J* = 6.6 Hz, 6H). ppm; ESMS calculated for $C_{48}H_{52}N_8O_9$: 884.4; found: 885.3 (M + H^+).

[001006] SDC-TRAP-0089

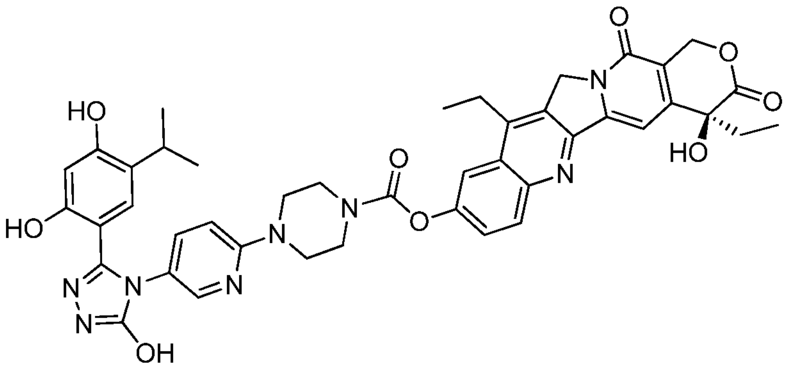
[001007] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) isoindolin-2-yl)piperidine-1-carboxylate



[001008] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (d, *J* = 9.2 Hz, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.69 (s, 1H), 7.62 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 2H), 6.49 (s, 1H), 6.36 (s, 1H), 5.71 (d, *J* = 16.4 Hz, 1H), 5.36 – 5.25 (m, 3H), 4.31 (d, *J* = 13.3 Hz, 1H), 4.18 (d, *J* = 13.3 Hz, 1H), 4.11 – 4.03 (m, 4H), 3.42 – 3.30 (m, 1H), 3.19 (q, *J* = 7.7 Hz, 1H), 3.00 (h, *J* = 7.4, 6.9 Hz, 1H), 2.81 – 2.71 (m, 1H), 2.09 – 2.00 (m, 2H), 1.98 – 1.85 (m, 5H), 1.42 (t, *J* = 7.7 Hz, 3H), 1.32 – 1.23 (m, 3H), 1.04 (t, *J* = 7.4 Hz, 3H), 0.79 (d, *J* = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{47}H_{47}N_7O_9$: 853.3; found: 854.3 (M + H^+).

[001009] SDC-TRAP-0090

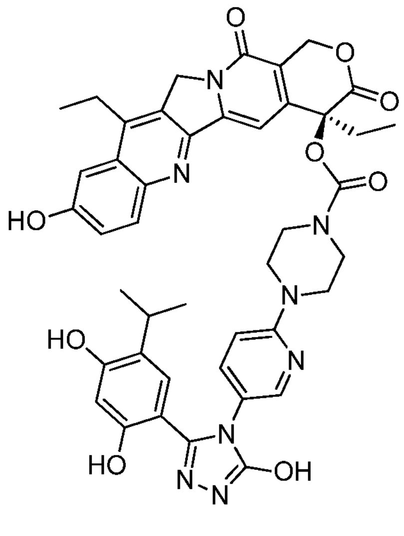
[001010] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) pyridin-2-yl)piperazine-1-carboxylate



[001011] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 9.3 Hz, 1H), 8.12 (d, *J* = 2.8 Hz, 1H), 7.91 (d, *J* = 2.7 Hz, 1H), 7.78 – 7.57 (m, 2H), 7.51 (dd, *J* = 9.1, 2.8 Hz, 1H), 6.85 (dd, *J* = 9.4, 2.8 Hz, 1H), 6.62 (d, *J* = 2.8 Hz, 1H), 6.39 (d, *J* = 2.8 Hz, 1H), 5.71 (d, *J* = 16.5 Hz, 1H), 5.39 – 5.22 (m, 4H), 4.07 (s, 1H), 3.98 – 3.68 (m, 4H), 3.21 (d, *J* = 7.8 Hz, 2H), 3.12 – 2.95 (m, 1H), 2.06 (d, *J* = 2.8 Hz, 2H), 2.01 – 1.86 (m, 2H), 1.61 (d, *J* = 7.0 Hz, 1H), 1.44 (td, *J* = 7.7, 2.8 Hz, 4H), 1.26 (d, *J* = 3.4 Hz, 2H), 1.05 (td, *J* = 7.3, 2.8 Hz, 3H), 0.94 – 0.80 (m, 6H). ppm; ESMS calculated for $C_{43}H_{42}N_8O_9$: 814.3; found: 815.2 ($M + H^+$).

[001012] SDC-TRAP-0091

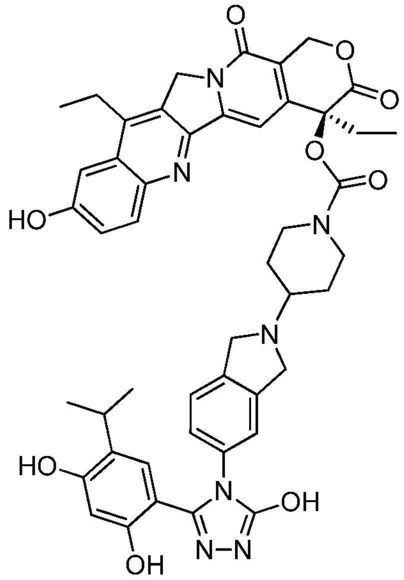
[001013] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)pyridin-2-yl)piperazine-1-carboxylate



[001014] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 9.64 (s, 1H), 9.48 (s, 1H), 7.99 – 7.87 (m, 2H), 7.49 – 7.37 (m, 3H), 7.04 (s, 1H), 6.98 – 6.91 (m, 2H), 6.28 (s, 1H), 5.53 – 5.38 (m, 2H), 5.29 (d, *J* = 1.8 Hz, 2H), 3.78 – 3.60 (m, 4H), 3.51 – 3.34 (m, 4H), 3.14 – 2.95 (m, 3H), 2.14 (dd, J = 14.3, 7.0 Hz, 2H), 1.38 – 1.21 (m, 3H), 1.04 (dd, J = 6.9, 1.9 Hz, 6H), 0.92 (t, J = 7.4 Hz, 3H). ppm; ESMS calculated for $C_{43}H_{42}N_8O_9$: 814.3; found: 815.2 (M + H^+).

[001015] SDC-TRAP-0092

[001016] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) isoindolin-2-yl)piperidine-1-carboxylate

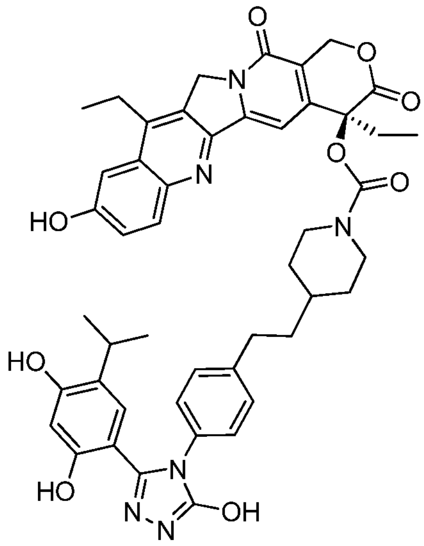


[001017] [1]H NMR (400 MHz, Chloroform-d) δ 8.02 (d, J = 9.1 Hz, 1H), 7.89 (d, J = 9.1 Hz, 1H), 7.47 – 7.37 (m, 1H), 7.30 – 7.20 (m, 2H), 7.17 (dd, J = 9.8, 2.6 Hz, 2H), 7.04 (s, 1H), 6.50 (d, J = 27.1 Hz, 1H), 6.32 (d, J = 4.2 Hz, 1H), 5.68 (d, J = 16.9 Hz, 1H), 5.40 (d, J = 16.9 Hz, 1H), 5.18 – 4.87 (m, 2H), 4.41 – 4.19 (m, 1H), 4.10 – 3.81 (m, 4H), 3.76 – 3.60 (m, 1H), 3.48 – 3.36 (m, 1H), 3.09 – 2.85 (m, 6H), 2.72 (s, 1H), 2.28 (dd, J = 13.8, 7.5 Hz, 1H), 2.22 – 2.08 (m, 1H), 1.88 (d, J = 10.1 Hz, 1H), 1.68 – 1.54 (m, 1H), 1.35 – 1.18 (m, 3H), 1.02 (dt, J = 12.6, 6.1 Hz, 3H), 0.85 – 0.69 (m, 6H). ppm; ESMS calculated for $C_{47}H_{47}N_7O_9$: 853.3; found: 854.2 (M + H^+).

[001018] SDC-TRAP-0104

[001019] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl

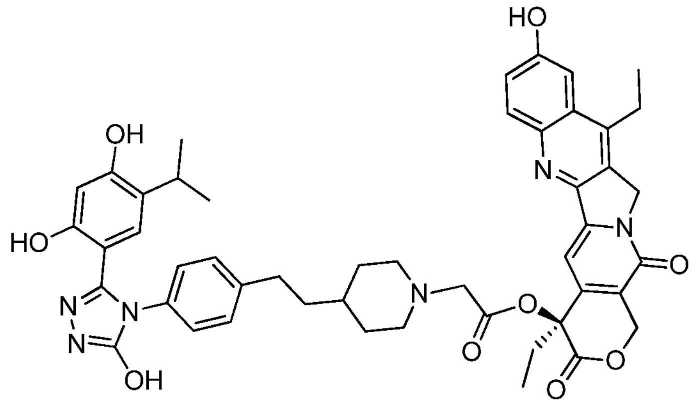
4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) phenethyl)piperidine-1-carboxylate



[001020] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.44 (d, *J* = 9.2 Hz, 1H), 8.11 – 7.96 (m, 2H), 7.72 (s, 1H), 7.53 (d, *J* = 9.2 Hz, 1H), 7.35 (s, 1H), 7.30 – 7.13 (m, 4H), 6.50 – 6.29 (m, 2H), 5.68 (d, *J* = 17.3 Hz, 1H), 5.40 (d, *J* = 17.3 Hz, 1H), 5.18 (t, *J* = 5.4 Hz, 2H), 4.42 (dd, *J* = 24.8, 13.2 Hz, 1H), 4.05 – 3.89 (m, 1H), 3.44 (s, 3H), 2.84 – 2.60 (m, 4H), 2.44 – 2.10 (m, 2H), 1.94 – 1.80 (m, 5H), 1.61 (dd, *J* = 11.7, 3.7 Hz, 3H), 1.36 (dt, *J* = 12.3, 4.9 Hz, 3H), 1.05 (dq, *J* = 13.8, 7.0 Hz, 3H), 0.78 – 0.61 (m, 6H). ppm; ESMS calculated for $C_{47}H_{48}N_6O_9$: 840.4; found: 841.2 (M + H$^+$).

[001021] SDC-TRAP-0106

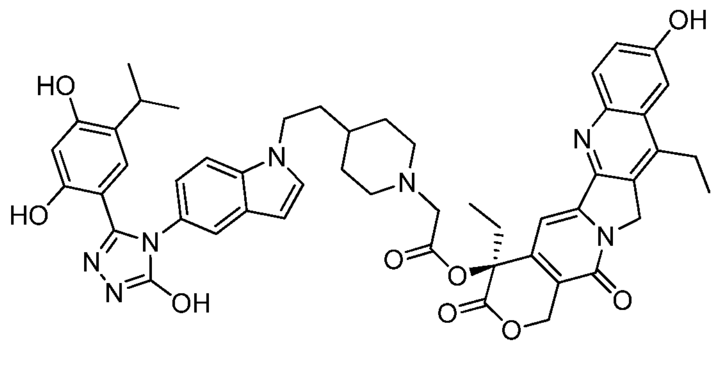
[001022] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) phenethyl)piperidin-1-yl)acetate



[001023] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (d, *J* = 9.1 Hz, 1H), 7.39 (dd, *J* = 5.2, 2.5 Hz, 1H), 7.31 (d, *J* = 2.6 Hz, 1H), 7.29 – 7.14 (m, 4H), 6.40 (d, *J* = 23.7 Hz, 2H), 5.68 (d, *J* = 17.0 Hz, 1H), 5.42 (dd, *J* = 17.0, 3.1 Hz, 1H), 5.22 (s, 2H), 3.11 (q, *J* = 7.9 Hz, 2H), 2.98 – 2.81 (m, 2H), 2.59 (dt, *J* = 10.3, 4.7 Hz, 2H), 2.45 – 2.08 (m, 6H), 1.80 – 1.44 (m, 4H), 1.44 – 1.19 (m, 6H), 0.99 (t, *J* = 7.4 Hz, 3H), 0.70 (dd, *J* = 6.8, 2.3 Hz, 6H). ppm; ESMS calculated for $C_{48}H_{50}N_6O_9$: 854.4; found: 855.3 (M + H^+).

[001024] SDC-TRAP-0107

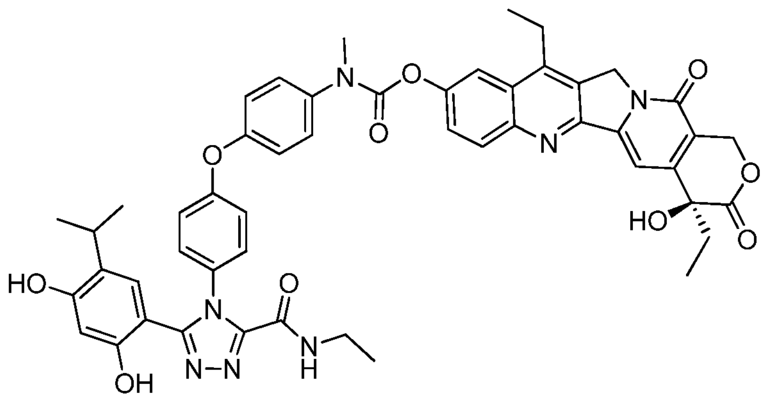
[001025] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 2-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)acetate



[001026] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.07 – 7.92 (m, 1H), 7.54 (d, *J* = 7.2 Hz, 1H), 7.36 (dq, *J* = 5.9, 3.7 Hz, 5H), 7.30 – 7.19 (m, 1H), 7.19 – 6.99 (m, 2H), 6.47 (d, *J* = 3.5 Hz, 1H), 6.41 – 6.27 (m, 2H), 5.75 – 5.59 (m, 1H), 5.41 (d, *J* = 17.1 Hz, 1H), 5.21 (s, 2H), 4.26 – 3.94 (m, 2H), 3.51 – 3.24 (m, 5H), 3.11 (q, *J* = 7.6 Hz, 2H), 2.93 (t, *J* = 13.0 Hz, 2H), 2.80 (q, *J* = 6.8 Hz, 1H), 2.23 (ddd, *J* = 36.9, 13.1, 7.3 Hz, 4H), 1.71 (td, *J* = 14.1, 13.5, 5.4 Hz, 4H), 1.48 – 1.15 (m, 5H), 1.05 – 0.89 (m, 3H), 0.52 – 0.32 (m, 6H).ppm; ESMS calculated for $C_{50}H_{51}N_7O_9$: 893.4; found: 894.3 (M + H^+).

[001027] SDC-TRAP-0145

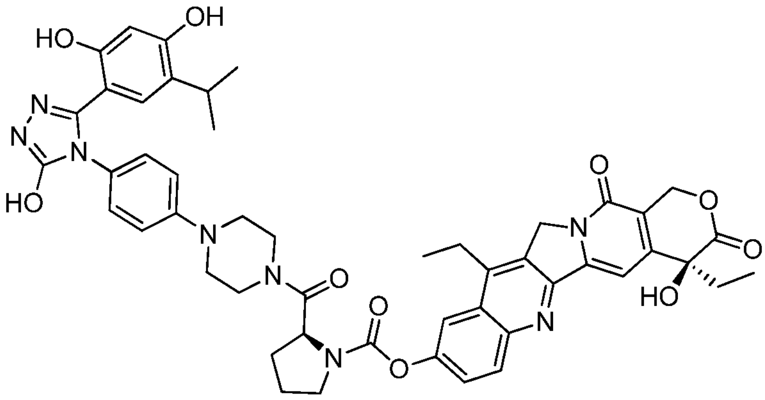
[001028] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)phenyl)(methyl)carbamate



[001029] ESMS calculated for $C_{50}H_{47}N_7O_{10}$: 905.3; found: 906.3 (M + H^+).

[001030] SDC-TRAP-0204

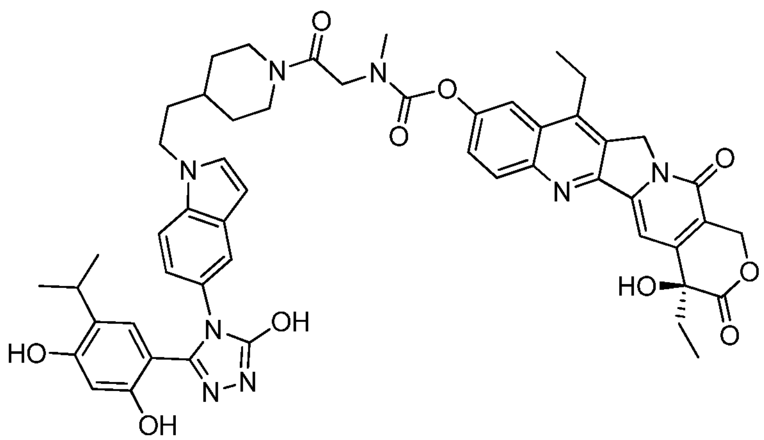
[001031] (S)-(S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) phenyl)piperazine-1-carbonyl)pyrrolidine-1-carboxylate



[001032] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 (dd, *J* = 9.2, 5.6 Hz, 1H), 7.86 (dd, *J* = 42.0, 2.5 Hz, 1H), 7.72 – 7.50 (m, 2H), 7.22 – 7.08 (m, 2H), 6.95 (dd, *J* = 35.5, 8.8 Hz, 2H), 6.49 – 6.25 (m, 2H), 5.72 (dd, *J* = 16.4, 4.4 Hz, 1H), 5.42 – 5.23 (m, 3H), 5.05 – 4.79 (m, 1H), 4.05 – 3.51 (m, 5H), 3.39 – 3.02 (m, 5H), 2.67 – 2.20 (m, 5H), 2.15-2.00 (m, 2H), 1.90 (h, *J* = 7.0 Hz, 2H), 1.50 – 1.31 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 2H), 1.03 (td, *J* = 7.4, 2.6 Hz, 3H), 0.56 (ddd, *J* = 73.4, 8.4, 6.9 Hz, 6H). ppm; ESMS calculated for $C_{49}H_{50}N_8O_{10}$: 910.4; found: 911.1 (M + H$^+$).

[001033] SDC-TRAP-0207

[001034] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-2-oxoethyl)(methyl)carbamate

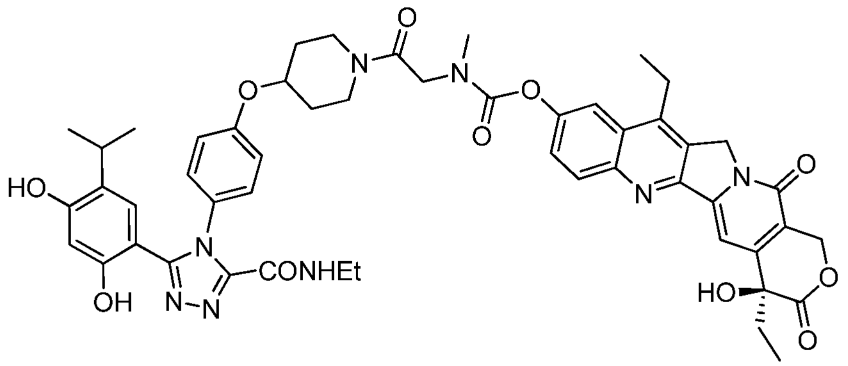


[001035] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.95 – 7.78 (m, 1H), 7.71 – 7.49 (m, 3H), 7.38 (dd, *J* = 28.1, 8.6 Hz, 1H), 7.18 – 7.05 (m, 2H), 6.50 (dd, *J* = 15.3, 3.4 Hz, 1H), 6.37 – 6.15 (m, 2H), 5.72 (d, *J* = 16.3 Hz, 1H), 5.38 – 5.09 (m, 3H), 4.49 –

4.02 (m, 5H), 3.78 (dd, J = 12.7, 5.5 Hz, 1H), 3.27 (s, 2H), 3.23 – 2.95 (m, 4H), 2.86 – 2.55 (m, 2H), 2.00 – 1.68 (m, 6H), 1.67 – 1.48 (m, 2H), 1.47 – 1.13 (m, 6H), 1.08 – 0.83 (m, 4H), 0.53 – 0.19 (m, 6H). ppm; ESMS calculated for $C_{52}H_{54}N_8O_{10}$: 950.4; found: 951.2 (M + H^+).

[001036] SDC-TRAP-0206

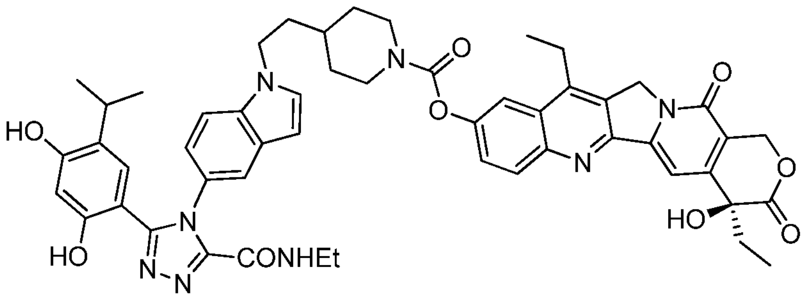
[001037] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidin-1-yl)-2-oxoethyl)(methyl)carbamate



[001038] ^{1}H NMR (400 MHz, Chloroform-d) δ 8.16 (t, J = 8.8 Hz, 1H), 7.87 (dd, J = 16.2, 2.5 Hz, 1H), 7.69 – 7.51 (m, 2H), 7.39 (t, J = 5.9 Hz, 1H), 7.30-7.25 (m, 2H), 7.05 (dd, J = 8.6, 5.3 Hz, 2H), 6.59 – 6.30 (m, 2H), 5.73 (dd, J = 16.3, 2.6 Hz, 1H), 5.41 – 5.13 (m, 3H), 4.66 (s, 1H), 4.45 – 4.16 (m, 2H), 4.00 – 3.77 (m, 1H), 3.71 (d, J = 15.5 Hz, 1H), 3.49 (d, J = 13.3 Hz, 1H), 3.45 – 3.33 (m, 2H), 3.31 (s, 3H), 3.14 (d, J = 9.0 Hz, 3H), 3.01 – 2.84 (m, 1H), 2.03 – 1.79 (m, 4H), 1.76 – 1.51 (m, 4H), 1.43 – 1.32 (m, 3H), 1.30 – 1.14 (m, 3H), 1.02 (td, J = 7.4, 3.6 Hz, 3H), 0.98 – 0.89 (m, 1H), 0.76 (dd, J = 6.8, 4.1 Hz, 6H). ppm; ESMS calculated for $C_{51}H_{54}N_8O_{11}$: 954.4; found: 955.2 (M + H^+).

[001039] SDC-TRAP-0205

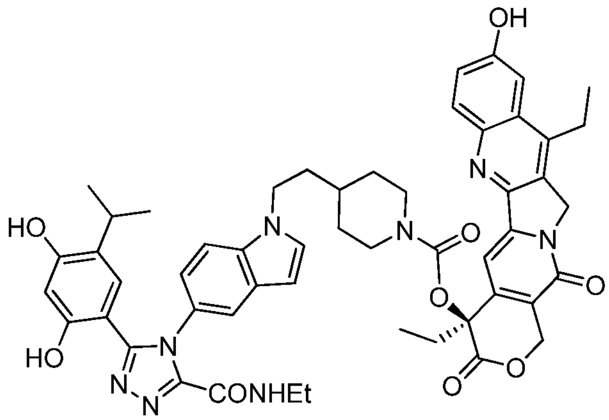
[001040] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate



[001041] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 (d, *J* = 9.2 Hz, 1H), 7.84 (d, *J* = 2.5 Hz, 1H), 7.71 – 7.45 (m, 4H), 7.38 (t, *J* = 5.9 Hz, 1H), 7.26 – 7.11 (m, 2H), 6.61 – 6.23 (m, 3H), 5.75 (d, *J* = 16.3 Hz, 1H), 5.39 – 5.17 (m, 3H), 4.55 – 4.17 (m, 4H), 3.49 – 3.28 (m, 2H), 3.24 – 2.84 (m, 4H), 2.79 (p, *J* = 6.9 Hz, 1H), 2.00 – 1.77 (m, 6H), 1.65 – 1.55 (m, 2H), 1.40 (q, *J* = 7.5 Hz, 5H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H), 0.48 (ddd, *J* = 58.3, 7.0, 4.0 Hz, 6H). ppm; ESMS calculated for $C_{52}H_{54}N_8O_9$: 934.4; found: 935.2 (M + H^+).

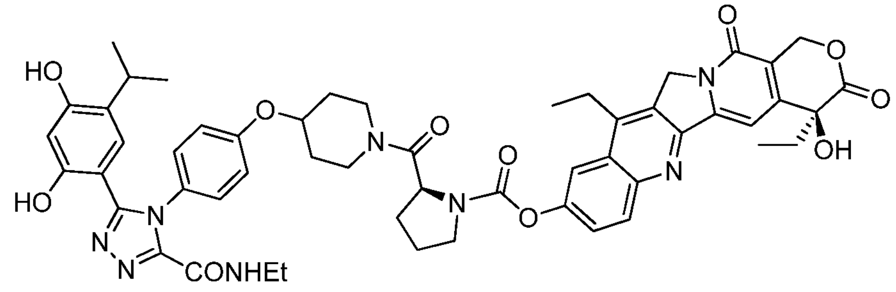
[001042] SDC-TRAP-0208

[001043] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate



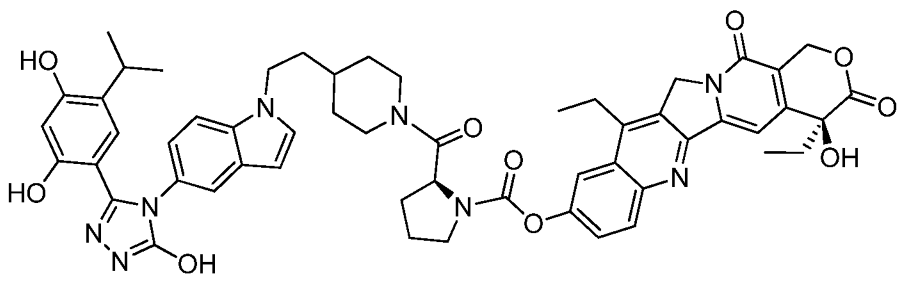
[001044] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.84 (d, *J* = 12.7 Hz, 1H), 10.08 (d, *J* = 16.6 Hz, 1H), 8.75 (s, 1H), 7.75 (dd, *J* = 51.2, 8.9 Hz, 1H), 7.44 – 7.13 (m, 4H), 7.13 – 6.64 (m, 3H), 6.40 – 6.02 (m, 3H), 5.35 – 4.86 (m, 4H), 4.09 (s, 3H), 3.56 (s, 1H), 3.05 – 2.71 (m, 5H), 2.69 – 2.39 (m, 2H), 2.00 – 1.85 (m, 2H), 1.44 (d, *J* = 84.1 Hz, 5H), 1.14 – 0.99 (m, 4H), 0.82 (td, *J* = 7.2, 4.4 Hz, 3H), 0.71 (q, *J* = 10.2, 8.4 Hz, 4H), 0.32 (dd, *J* = 19.9, 8.4 Hz, 6H). ppm; ESMS calculated for $C_{52}H_{54}N_8O_9$: 934.4; found: 935.1 (M + H^+).

[001045] SDC-TRAP-0209



[001046] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.34 (s, 1H), 8.17 – 8.05 (m, 1H), 7.85 (dt, *J* = 10.0, 2.6 Hz, 1H), 7.78 – 7.67 (m, 1H), 7.63 – 7.49 (m, 2H), 7.45 – 7.36 (m, 1H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.43 – 6.30 (m, 2H), 5.69 (tt, *J* = 14.8, 5.9 Hz, 1H), 5.35 – 5.14 (m, 3H), 4.90 (d, *J* = 7.9 Hz, 1H), 4.62 (s, 1H), 4.14 – 3.93 (m, 3H), 3.83 (dt, *J* = 9.9, 7.1 Hz, 2H), 3.77 – 3.65 (m, 2H), 3.54 (d, *J* = 12.6 Hz, 1H), 3.43 – 3.31 (m, 2H), 3.12 (q, *J* = 8.5, 7.0 Hz, 2H), 2.99 – 2.82 (m, 1H), 2.45 – 2.19 (m, 2H), 2.11 (s, 1H), 2.09 – 1.99 (m, 2H), 1.88 (p, *J* = 6.9 Hz, 2H), 1.75 (s, 2H), 1.44 – 1.15 (m, 7H), 1.06 – 0.89 (m, 4H), 0.88 – 0.60 (m, 6H).; ESMS calculated for $C_{53}H_{56}N_8O_{11}$: 980.4; found: 980.1 (M + H$^+$).

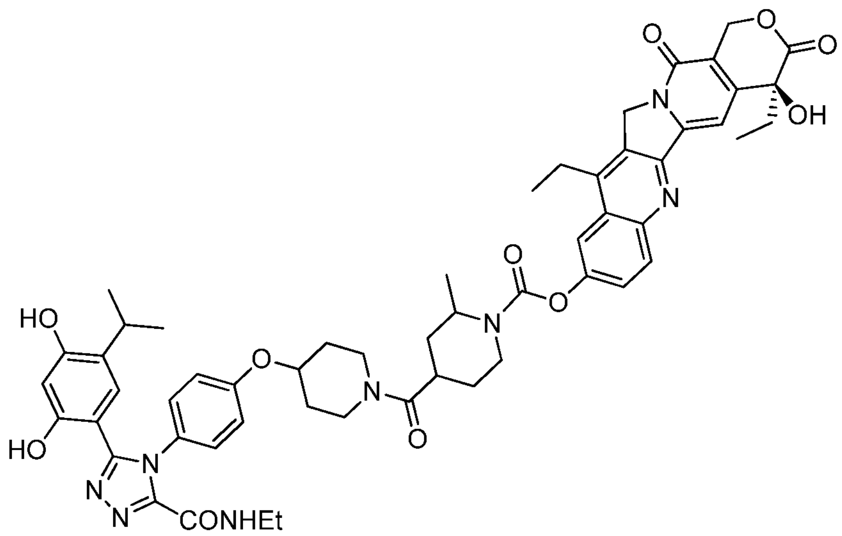
[001047] SDC-TRAP-0210



[001048] ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.91 – 11.84 (m, 1H), 9.58 – 9.46 (m, 2H), 8.22 – 8.13 (m, 1H), 7.97 (d, *J* = 2.6 Hz, 1H), 7.83 (dd, *J* = 4.4, 2.4 Hz, 1H), 7.64 (ddd, *J* = 8.2, 5.0, 2.4 Hz, 1H), 7.59 – 7.30 (m, 6H), 6.99 – 6.83 (m, 2H), 6.68 (d, *J* = 7.8 Hz, 1H), 6.52 (d, *J* = 7.3 Hz, 1H), 6.43 (dt, *J* = 6.4, 3.2 Hz, 1H), 6.27 – 6.19 (m, 1H), 5.44 (s, 2H), 5.31 (d, *J* = 15.6 Hz, 2H), 5.02 (q, *J* = 7.9, 6.0 Hz, 1H), 4.83 (d, *J* = 9.7 Hz, 1H), 4.44 – 4.28 (m, 2H), 4.22 (q, *J* = 7.6 Hz, 2H), 4.08 – 3.91 (m, 4H), 3.73 (q, *J* = 6.7 Hz, 1H), 3.52 (dq, *J* = 11.4, 5.5, 4.8 Hz, 1H), 3.10 (ddt, *J* = 49.9, 25.2, 10.0 Hz, 2H), 2.84 (ddt, *J* = 32.9, 13.9, 6.6 Hz, 2H), 2.68 – 2.52 (m, 4H), 2.36 (d, *J* = 8.3 Hz, 1H), 1.45 (s, 3H), 1.36 – 1.06 (m, 3H), 0.93 – 0.74 (m, 6H).; ESMS calculated for $C_{54}H_{56}N_8O_{10}$: 976.4; found: 977.2 (M + H$^+$).

[001049] SDC-TRAP-0213

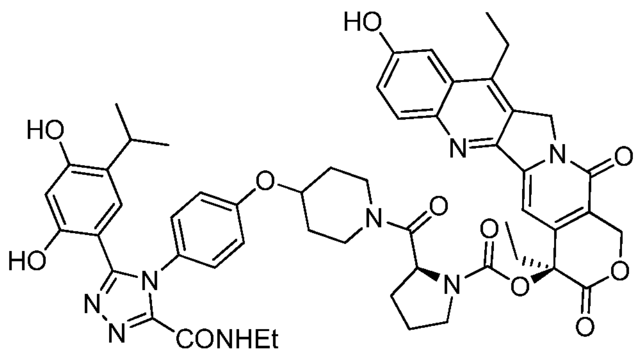
[001050] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidine-1-carbonyl)-2-methylpiperidine-1-carboxylate



[001051] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (d, *J* = 9.2 Hz, 1H), 7.87 (s, 1H), 7.65 (s, 1H), 7.50 (m, 1H), 7.4 (m, 1H), 7.3 (m, 1H), 7.1 (d, *J* = 1.2 Hz, 1H), 6.49 (s, 1H), 6.42 (s, 1H), 5.75 (d, *J* = 16.3 Hz, 1H), 5.35 – 5.24 (m, 3H), 4.72 (s, 1H), 4.30 (m, 1H), 4.17 – 4.02 (m, 2H), 3.60-3.30 (m, 4H), 3.16 (q, *J* = 7.8 Hz, 3H), 3.06 (s, 2H), 2.97 (s, 1H), 2.91 (p, *J* = 7.3, 6.9 Hz, 1H), , 1.90 (m, 5H), 1.72 (d, *J* = 12.6 Hz, 3H), 1.67 – 1.53 (m, 1H), 1.39 (dt, *J* = 13.1, 7.4 Hz, 4H), 1.30 – 1.16 (m, 6H), 1.03 (t, *J* = 7.4 Hz, 3H), 0.99 – 0.77 (m, 1H), 0.77 – 0.69 (m, 6H). ppm; ESMS calculated for $C_{55}H_{60}N_8O_{11}$: 1008.4; found: 1009.4 (M + H+).

[001052] SDC-TRAP-0214

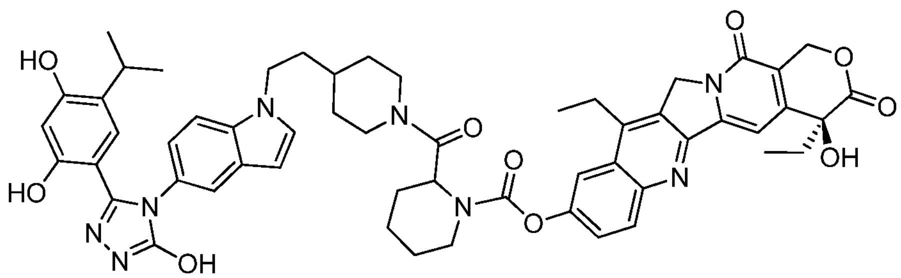
[001053] (S)-(S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidine-1-carbonyl)pyrrolidine-1-carboxylate



[001054] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.75 (s, 1H), 10.23 (s, 2H), 9.78 (s, 1H), 8.92 (dt, J = 11.8, 5.9 Hz, 1H), 7.98 – 7.90 (m, 1H), 7.41 (tq, J = 5.0, 2.6 Hz, 2H), 7.36 – 7.22 (m, 2H), 7.17 – 6.95 (m, 3H), 6.63 – 6.50 (m, 1H), 6.40 – 6.30 (m, 1H), 5.48 – 5.19 (m, 3H), 4.99 (dd, J = 8.4, 4.5 Hz, 1H), 4.87 – 4.73 (m, 1H), 4.66 – 4.57 (m, 1H), 4.02 (tt, J = 12.8, 5.5 Hz, 1H), 3.50 – 3.34 (m, 1H), 3.25 – 3.04 (m, 4H), 2.41 – 2.32 (m, 1H), 2.16 (d, J = 10.8 Hz, 2H), 2.13 – 1.76 (m, 6H), 1.73 – 1.63 (m, 2H), 1.60 – 1.46 (m, 1H), 1.40 – 1.14 (m, 3H), 1.10 – 0.99 (m, 3H), 0.95 – 0.76 (m, 6H), 0.71 (dd, J = 6.8, 2.8 Hz, 3H). ppm; ESMS calculated for $C_{53}H_{56}N_8O_{11}$: 980.4; found: 981.2 (M + H+).

[001055] SDC-TRAP-0215

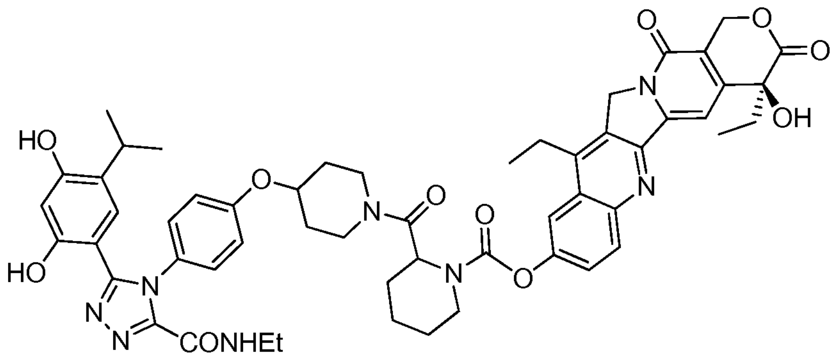
[001056] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 2-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carbonyl)piperidine-1-carboxylate



[001057] ^{1}H NMR (400 MHz, Chloroform-d) δ 8.21 (d, J = 9.5 Hz, 1H), 7.87 (s, 1H), 7.70 (s, 1H), 7.66 – 7.48 (m, 3H), 7.36 (s, 1H), 7.12 (d, J = 31.7 Hz, 2H), 6.42 (d, J = 60.7 Hz, 2H), 5.71 (d, J = 16.5 Hz, 1H), 5.42 – 5.03 (m, 3H), 4.25 (m, 4H), 3.77 (d, J = 14.9 Hz, 3H), 3.38 (dt, J = 3.3, 1.7 Hz, 3H), 3.18 (s, 3H), 2.80-2.50 (m, 2H), 2.28 (t, J = 7.7 Hz, 1H), 1.85 (d, J = 64.6 Hz, 11H), 1.61 (s, 4H), 1.39 (d, J = 7.9 Hz, 3H), 1.04 (t, J = 7.4 Hz, 3H), 0.45 (d, J = 21.7 Hz, 6H). ppm; ESMS calculated for $C_{55}H_{58}N_8O_{10}$: 990.4; found: 991.3 (M + H+).

[001058] SDC-TRAP-0216

[001059] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidine-1-carbonyl)piperidine-1-carboxylate

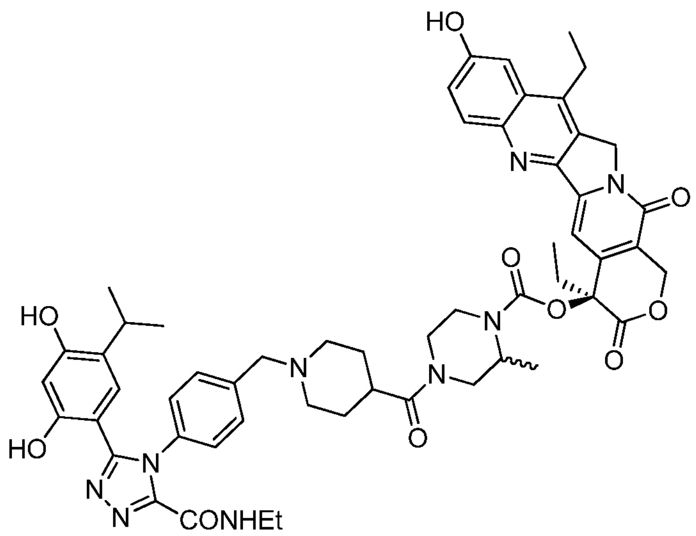


[001060] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 (t, *J* = 9.0 Hz, 1H), 7.84 (d, *J* = 2.6 Hz, 1H), 7.73 – 7.45 (m, 2H), 7.34 (t, *J* = 5.9 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 6.43 (s, 1H), 6.33 (s, 1H), 5.74 (d, *J* = 16.8 Hz, 1H), 5.44 – 5.06 (m, 5H), 4.62 (s, 1H), 4.29 (d, *J* = 12.8 Hz, 1H), 3.75 (d, *J* = 98.1 Hz, 4H), 3.38 (p, *J* = 7.0 Hz, 2H), 3.15 (q, *J* = 7.3 Hz, 2H), 2.90 (s, 1H), 2.03 – 1.49 (m, 11H), 1.46 – 1.33 (m, 4H), 1.25 – 1.14 (m, 6H), 1.01 (q, *J* = 7.3 Hz, 3H), 0.97 – 0.80 (m, 1H), 0.74 (d, *J* = 6.5 Hz, 6H). ppm; ESMS calculated for $C_{54}H_{58}N_8O_{11}$: 994.4; found: 995.4 (M + H+).

[001061] SDC-TRAP-0217

[001062] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)-2-methylpiperazine-1-

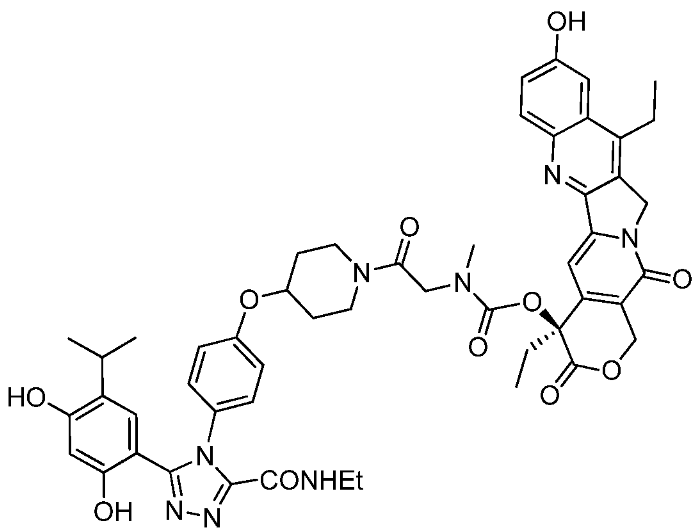
[001063] carboxylate



[001064] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (s, 1H), 7.54 (s, 2H), 7.32 (s, 3H), 7.19 (s, 3H), 6.45 (dd, *J* = 18.5, 11.0 Hz, 2H), 5.67 (s, 1H), 5.41 (s, 1H), 5.14 (s, 1H), 4.07 (tt, *J* = 6.3, 2.8 Hz, 3H), 3.57 (s, 3H), 3.41 (d, *J* = 16.0 Hz, 4H), 2.97 (d, *J* = 56.0 Hz, 4H), 2.40 – 2.19 (m, 2H), 1.82 – 1.50 (m, 5H), 1.50 – 1.13 (m, 12H), 1.09 – 0.79 (m, 8H), 0.72 (s, 6H). ppm; ESMS calculated for $C_{55}H_{61}N_9O_{10}$: 1007.5; found: 1008.5 (M + H+).

[001065] SDC-TRAP-0218

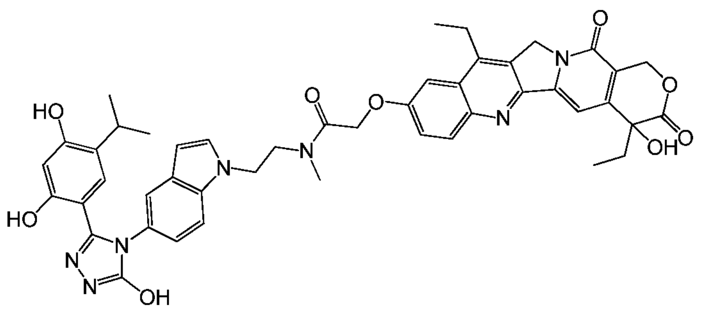
[001066] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidin-1-yl)-2-oxoethyl)(methyl)carbamate



[001067] [1]H NMR (400 MHz, Chloroform-*d*) δ 8.94 (s, 2H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.68 (dd, *J* = 22.4, 7.6 Hz, 4H), 7.32 (t, *J* = 2.5 Hz, 1H), 7.18 (s, 1H), 7.08 (s, 1H), 6.79 – 6.68 (m, 1H), 6.47 (d, *J* = 8.8 Hz, 1H), 6.39 (d, *J* = 15.8 Hz, 1H), 5.74 (dd, *J* = 16.8, 3.4 Hz, 2H), 5.35 (dd, *J* = 16.7, 2.7 Hz, 2H), 5.22 (d, *J* = 3.0 Hz, 2H), 4.93 – 4.75 (m, 2H), 4.45 (s, 1H), 4.02 (s, 1H), 3.64 – 3.45 (m, 4H), 3.22 (d, *J* = 11.8 Hz, 3H), 3.11 – 3.02 (m, 3H), 2.95 – 2.83 (m, 2H), 2.24 – 2.09 (m, 4H), 1.34 (td, *J* = 7.1, 2.3 Hz, 6H), 1.12 (td, *J* = 7.4, 4.3 Hz, 3H), 0.90 – 0.78 (m, 3H), 0.73 (d, *J* = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{51}H_{54}N_8O_{11}$: 954.4; found: 955.4 (M + H+).

[001068] SDC-TRAP-0027

[001069] 2-((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)-N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-N-methylacetamide



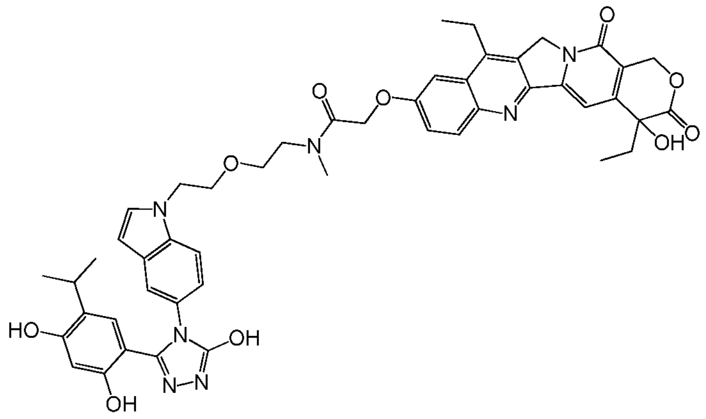
[001070] [1]H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 9.52 (s, 1H), 9.45 (d, *J* = 11.1 Hz, 1H), 8.09 (dd, *J* = 13.5, 9.1 Hz, 1H), 7.63 – 7.41 (m, 5H), 7.33 (dd, *J* = 32.2, 3.0 Hz, 1H), 6.94 (ddd, *J* = 8.7, 3.3, 2.0 Hz, 1H), 6.74 (d, *J* = 13.7 Hz, 1H), 6.50 (s, 1H), 6.43 (dd, *J* = 3.1, 0.8 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 5.44 (s, 2H), 5.33 – 5.28 (m, 2H), 5.05 (s, 1H), 4.65 (s, 1H), 4.51 (d, *J* = 6.3 Hz, 1H), 4.32 (t, *J* = 6.5 Hz, 1H), 3.80 (t, *J* = 6.2 Hz, 1H), 3.65 (t, *J* = 6.5 Hz, 1H), 3.15 (dd, *J* = 17.6, 8.3 Hz, 2H), 2.95 – 2.80 (m, 4H), 1.88 (hept, *J* = 7.2 Hz, 2H), 1.28 (q, *J* = 7.5 Hz, 3H), 0.93 – 0.78 (m, 9H).

[001071] ESMS calculated for $C_{46}H_{45}N_7O_9$: 839.33; Found: 840.1 $(M+H)^+$.

[001072] SDC-TRAP-0028

[001073] 2-((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl)oxy)-N-

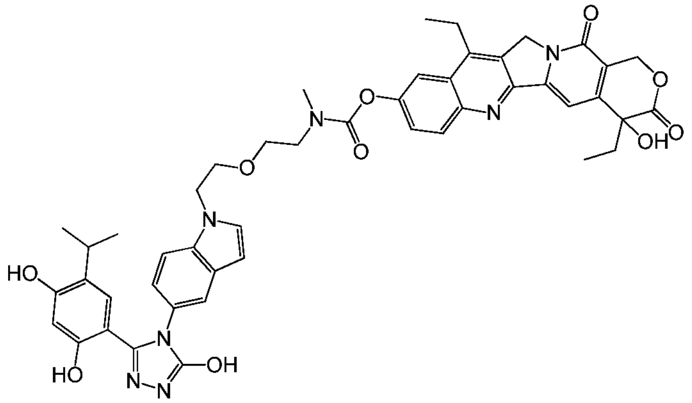
(2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)-N-methylacetamide



[001074] ESMS calculated for $C_{48}H_{49}N_7O_{10}$: 883.35; Found: 884.3 $(M+H)^+$.

[001075] SDC-TRAP-0029

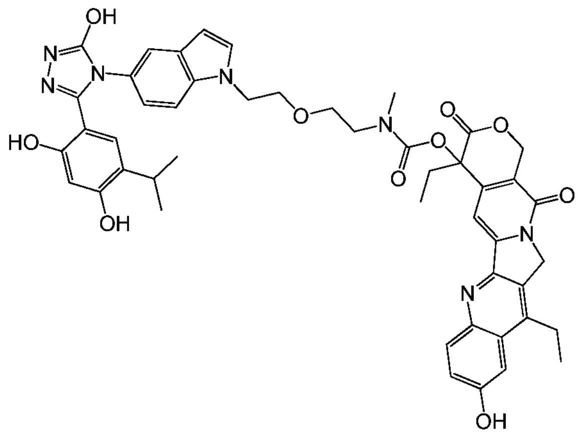
[001076] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)(methyl)carbamate



[001077] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 9.50 (d, J = 19.6 Hz, 2H), 8.21 – 8.14 (m, 1H), 7.96 (d, J = 9.5 Hz, 1H), 7.64 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.43 (d, J = 7.0 Hz, 2H), 7.33 (s, 1H), 6.91 (dd, J = 15.2, 8.5 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 6.52 (s, 1H), 6.43 (d, J = 13.7 Hz, 1H), 6.23 (s, 1H), 5.44 (s, 2H), 5.33 (s, 2H), 4.42 – 4.36 (m, 2H), 3.77 (d, J = 11.5 Hz, 2H), 3.69 - 3.44 (m, 4H), 3.17 (t, J = 7.3 Hz, 2H), 3.03 (s, 1H), 2.89 (d, J = 13.3 Hz, 2H), 1.89 (dq, J = 17.0, 9.1, 8.1 Hz, 2H), 1.27 (d, J = 10.5 Hz, 3H), 0.85 - 0.74 (m, 9H). ESMS calculated for $C_{47}H_{47}N_7O_{10}$: 869.34; Found: 870.2 $(M+H)^+$.

[001078] SDC-TRAP-0037

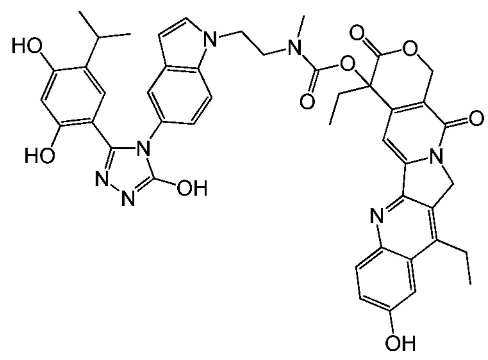
[001079] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (2-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)ethyl)(methyl)carbamate



[001080] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 10.30 (s, 1H), 9.54 (s, 1H), 9.48 (s, 1H), 7.97 (t, J = 9.4 Hz, 1H), 7.45 – 7.25 (m, 4H), 7.00 (d, J = 23.6 Hz, 1H), 6.92 – 6.81 (m, 1H), 6.70 (d, J = 2.3 Hz, 1H), 6.39 (d, J = 3.0 Hz, 1H), 6.23 (d, J = 3.2 Hz, 1H), 5.45 (s, 2H), 5.28 (s, 1H), 5.21 (d, J = 6.9 Hz, 1H), 4.53 – 4.47 (m, 1H), 3.90 (d, J = 6.3 Hz, 1H), 3.18– 2.97 (m, 6H), 2.88 (dt, J = 13.9, 7.0 Hz, 2H), 2.70 (s, 3H), 2.18 – 2.05 (m, 2H), 1.27 (dt, J = 14.6, 7.3 Hz, 3H), 1.10 - 0.76 (m, 9H). ESMS calculated for $C_{47}H_{47}N_7O_{10}$: 869.34; Found: 870.3 $(M+H)^+$.

[001081] SDC-TRAP-0038

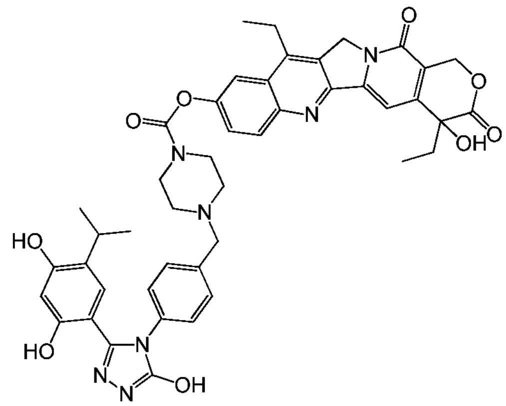
[001082] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)(methyl)carbamate



[001083] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 10.33 (s, 1H), 9.52 (s, 1H), 9.44 (s, 1H), 8.01 (t, J = 9.5 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 3.0 Hz, 1H), 7.41 -7.25(m, 4H), 7.13 – 7.08 (m, 1H), 7.04 – 6.94 (m, 2H), 6.73 (dd, J = 7.0, 4.4 Hz, 1H), 6.22 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.56 (s, 1H), 3.91 – 3.84 (m, 2H), 3.59 – 3.50 (m, 2H), 2.97 – 2.83 (m, 2H), 2.59 (s, 3H), , 2.31 (s, 1H), 2.14 (q, J = 7.3 Hz, 2H), 1.30 (t, J = 7.5 Hz, 3H), 1.01 – 0.86 (m, 9H). ESMS calculated for $C_{45}H_{43}N_7O_9$: 825.31; Found: 826.4 $(M+H)^+$.

[001084] SDC-TRAP-0046

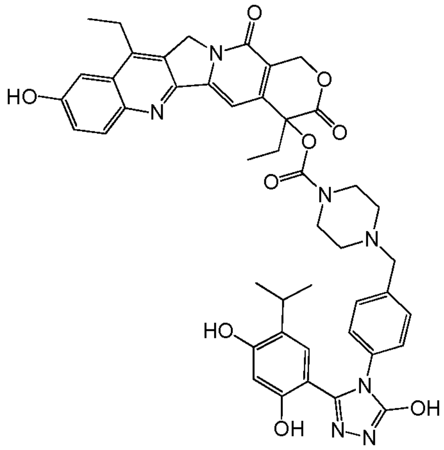
[001085] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate



[001086] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 9.62 (s, 1H), 9.43 (s, 1H), 8.18 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.67 (dd, J = 9.1, 2.5 Hz, 1H), 7.40 – 7.31 (m, 3H), 7.18 (d, J = 7.9 Hz, 2H), 6.80 (s, 1H), 6.53 (s, 1H), 6.28 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 3.69 - 3.46 (m, 4H), 3.19 (q, J = 7.7 Hz, 2H), 2.99 (p, J = 7.0 Hz, 1H), 1.88 (hept, J = 7.1 Hz, 2H), 1.30 (t, $J = 7.5$ Hz, 3H), 0.97 (d, $J = 6.9$ Hz, 6H), 0.89 (t, $J = 7.3$ Hz, 3H). ESMS calculated for $C_{45}H_{45}N_7O_9$: 827.33; Found: 828.2 $(M+H)^+$.

[001087] SDC-TRAP-0047

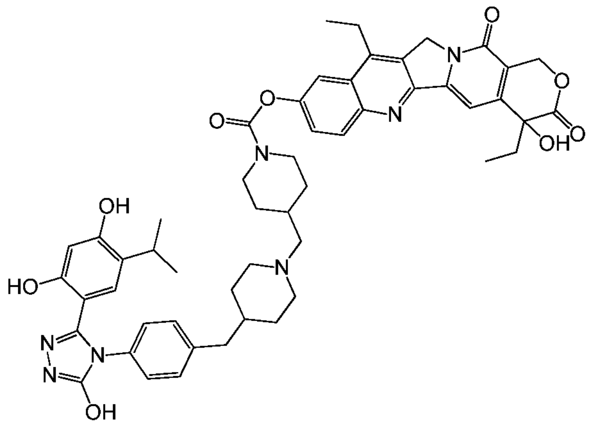
[001088] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate



[001089] [1]H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 10.34 (s, 1H), 9.60 (s, 1H), 9.41 (s, 1H), 8.08 – 8.00 (m, 1H), 7.47 – 7.39 (m, 2H), 7.32 (d, $J = 8.0$ Hz, 3H), 7.15 (d, $J = 8.1$ Hz, 2H), 6.96 (s, 1H), 6.78 (s, 1H), 6.27 (s, 1H), 5.44 (d, $J = 2.6$ Hz, 2H), 5.32 – 5.27 (m, 2H), 3.71 (s, 1H), 3.62 (s, 1H), 3.56 – 3.47 (m, 2H), 3.39 (s, 5H), 3.37 – 3.23 (m, 6H), 3.09 (q, $J = 7.5$ Hz, 2H), 2.97 (p, $J = 6.9$ Hz, 1H), 2.31 (s, 1H), 2.22 (s, 1H), 2.14 (q, $J = 7.3$ Hz, 2H), 1.30 (t, $J = 7.5$ Hz, 3H), 1.01 – 0.86 (m, 9H). ESMS calculated for $C_{45}H_{45}N_7O_9$: 827.33; Found: 828.3 $(M+H)^+$.

[001090] SDC-TRAP-0067

[001091] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)methyl)piperidine-1-carboxylate

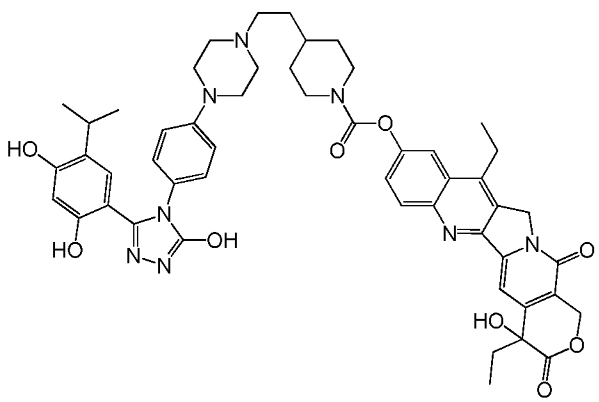


[001092] ESMS calculated for $C_{52}H_{57}N_7O_9$: 923.42; Found: 924.3 $(M+H)^+$.

[001093] SDC-TRAP-0070

[001094] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)ethyl)piperidine-1-

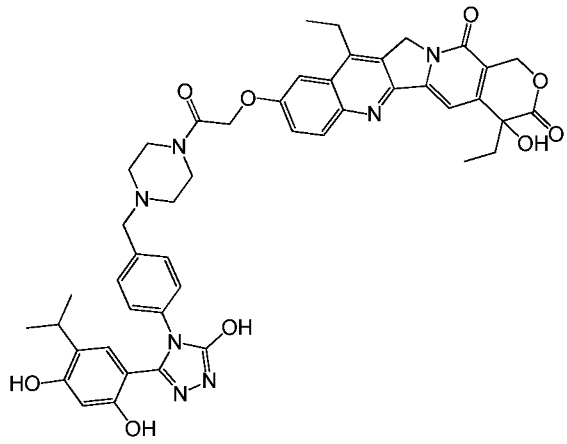
[001095] carboxylate



[001096] ESMS calculated for $C_{51}H_{56}N_8O_9$: 924.42; Found: 925.3 $(M+H)^+$.

[001097] SDC-TRAP-0077

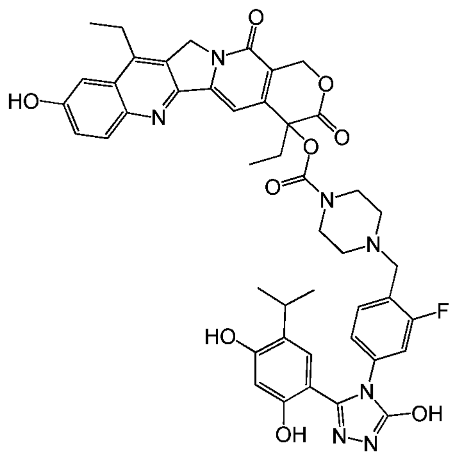
[001098] 9-(2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-2-oxoethoxy)-4,11-diethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione



[001099] [1]H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 9.61 (s, 1H), 9.41 (s, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 7.53 (dd, *J* = 9.2, 2.7 Hz, 1H), 7.44 (d, *J* = 2.8 Hz, 1H), 7.37 – 7.25 (m, 3H), 7.15 (d, *J* = 8.3 Hz, 2H), 6.78 (s, 1H), 6.51 (s, 1H), 6.27 (s, 1H), 5.43 (s, 2H), 5.30 (s, 2H), 5.10 (s, 2H), 3.55 (s, 2H), 3.49 (d, *J* = 9.1 Hz, 4H), 3.16 (q, *J* = 7.6 Hz, 2H), 2.97 (p, *J* = 6.9 Hz, 1H), 2.46 (d, *J* = 5.8 Hz, 2H), 2.33 (s, 2H), 1.87 (hept, *J* = 7.0 Hz, 2H), 1.29 (t, *J* = 7.5 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 6H), 0.89 (t, *J* = 7.3 Hz, 3H). ESMS calculated for $C_{46}H_{47}N_7O_9$: 841.34; Found: 842.1 $(M+H)^+$.

[001100] SDC-TRAP-0079

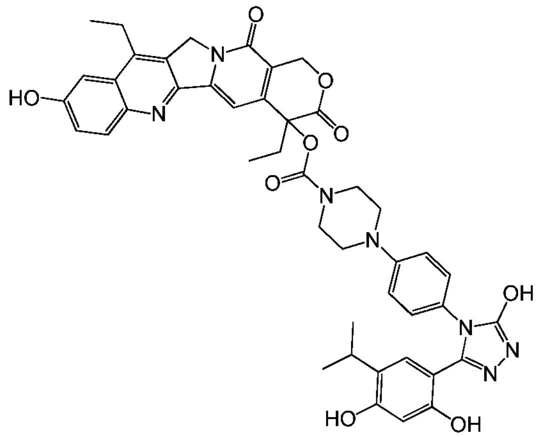
[001101] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazine-1-carboxylate



[001102] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 10.35 (s, 1H), 9.64 (s, 1H), 9.40 (s, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.41 (d, J = 6.9 Hz, 3H), 7.07 (d, J = 10.8 Hz, 1H), 6.97 (d, J = 9.8 Hz, 2H), 6.87 (s, 1H), 6.27 (s, 1H), 5.44 (s, 2H), 5.29 (s, 2H), 3.73 (d, J = 13.4 Hz, 1H), 3.56 (d, J = 16.6 Hz, 3H), 3.32 – 3.23 (m, 4H), 3.09 (d, J = 8.0 Hz, 2H), 3.05 – 2.96 (m, 1H), 2.55 (s, 2H), 2.39 – 2.32 (m, 1H), 2.24 (s, 2H), 2.13 (d, J = 7.7 Hz, 2H), 1.28 (q, J = 13.0, 10.1 Hz, 3H), 0.96 (d, J = 6.9 Hz, 6H), 0.89 (t, J = 7.3 Hz, 3H). ESMS calculated for $C_{45}H_{44}FN_7O_9$: 845.32; Found: 846.2 $(M+H)^+$.

[001103] SDC-TRAP-0081

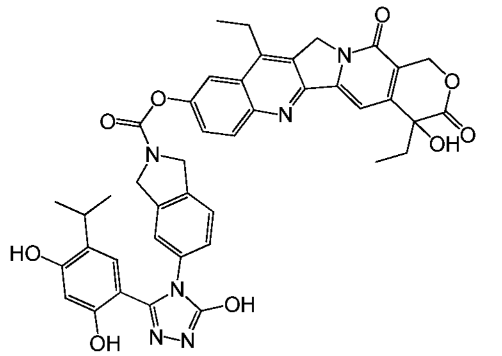
[001104] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl-4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazine-1-carboxylate



[001105] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 10.38 (s, 1H), 9.66 (s, 1H), 9.51 (s, 1H), 7.99 (d, J = 9.4 Hz, 1H), 7.46 (d, J = 5.6 Hz, 2H), 7.21 (s, 1H), 7.12 (d, J = 8.5 Hz, 2H), 7.04 (d, J = 9.9 Hz, 3H), 6.84 (s, 1H), 6.33 (s, 1H), 5.52 (s, 2H), 5.35 (s, 2H), 3.91 - 3.83 (m, 4H), 3.20 – 3.09 (m, 6H), 3.02 (p, J = 7.0 Hz, 1H), 2.23 (q, J = 7.3 Hz, 2H), 1.35 (t, J = 7.3 Hz, 3H), 1.07 – 0.91 (m, 9H). ESMS calculated for $C_{44}H_{43}N_7O_9$: 813.31; Found: 814.2 $(M+H)^+$.

[001106] SDC-TRAP-0083

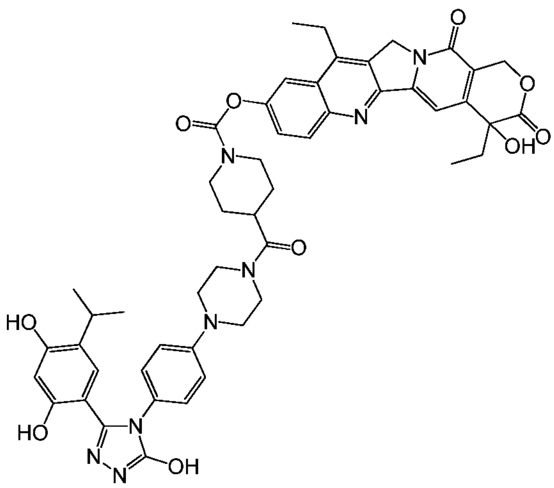
[001107] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)isoindoline-2-carboxylate



[001108] ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 9.66 (s, 1H), 9.45 (s, 1H), 8.27 (d, J = 9.2 Hz, 1H), 8.15 (s, 1H), 7.85 – 7.77 (m, 1H), 7.48 – 7.35 (m, 3H), 7.15 (d, J = 8.0 Hz, 1H), 6.99 (s, 1H), 6.60 (s, 1H), 6.32 (s, 1H), 5.50 (s, 2H), 5.41 (s, 2H), 5.03 (d, J = 13.8 Hz, 2H), 4.80 (d, J = 13.5 Hz, 2H), 3.29 – 3.20 (m, 2H), 3.09 (p, J = 7.1 Hz, 1H), 1.94 (hept, J = 7.2 Hz, 2H), 1.37 (t, J = 7.4 Hz, 3H), 1.11 (d, J = 6.9 Hz, 6H), 0.95 (t, J = 7.3 Hz, 3H). ESMS calculated for $C_{42}H_{38}N_6O_9$: 770.27; Found: 771.2 $(M+H)^+$.

[001109] SDC-TRAP-0094

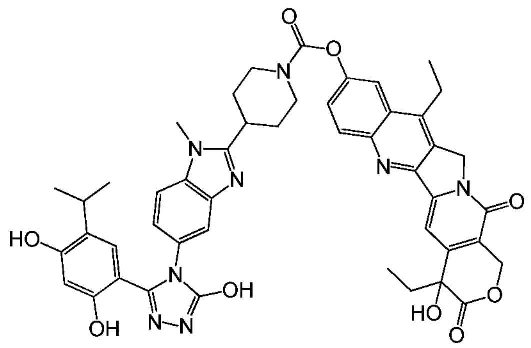
[001110] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazine-1-carbonyl)piperidine-1-carboxylate



[001111] ESMS calculated for $C_{50}H_{52}N_8O_{10}$: 924.38; Found: 925.1 $(M+H)^+$.

[001112] SDC-TRAP-0095

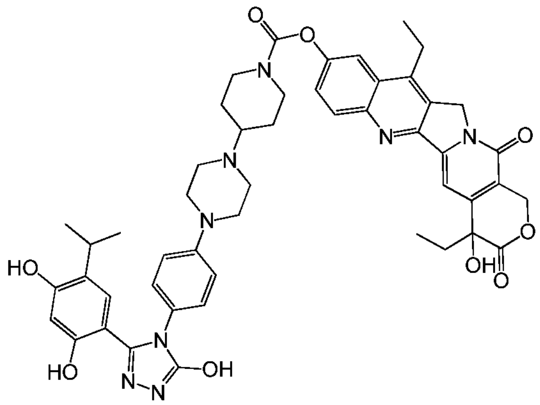
[001113] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2-yl)piperidine-1-carboxylate



[001114] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 9.53 (s, 1H), 9.34 (s, 1H), 8.19 (d, J = 9.1 Hz, 1H), 8.04 (d, J = 2.6 Hz, 1H), 7.71 (dd, J = 9.2, 2.5 Hz, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 1.9 Hz, 1H), 7.34 (s, 1H), 7.05 (dd, J = 8.6, 2.0 Hz, 1H), 6.87 (s, 1H), 6.54 (s, 1H), 6.21 (s, 1H), 5.45 (s, 2H), 5.35 (s, 2H), 4.37 (s, 1H), 4.18 (d, J = 12.6 Hz, 1H), 3.83 (s, 3H), 3.43 – 3.28 (m, 4H), 3.27 – 3.15 (m, 4H), 2.97 (p, J = 6.9 Hz, 1H), 1.88 (hept, J = 7.2 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H), 0.97 (d, J = 6.9 Hz, 6H), 0.89 (t, J = 7.3 Hz, 3H). ESMS calculated for $C_{47}H_{46}N_8O_9$: 866.34; Found: 867.2 $(M+H)^+$.

[001115] SDC-TRAP-0101

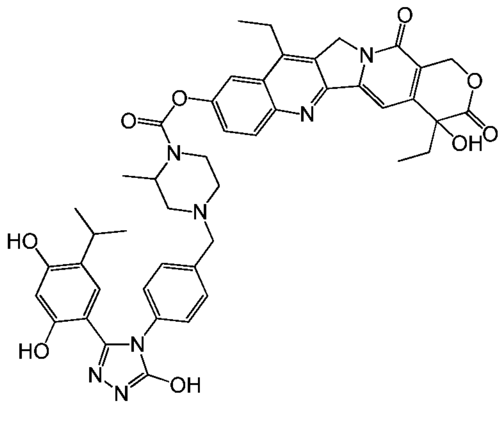
[001116] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)piperidine-1-carboxylate



[001117] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.74 (s, 1H), 9.50 (s, 1H), 9.37 (s, 1H), 8.05 (d, *J* = 9.2 Hz, 1H), 7.87 (d, *J* = 2.5 Hz, 1H), 7.55 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.20 (s, 1H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.65 (s, 1H), 6.42 (s, 1H), 6.16 (s, 1H), 5.32 (s, 2H), 5.21 (s, 2H), 4.15 (s, 1H), 4.00 – 3.85 (m, 1H), 3.12 – 3.00 (m, 7H), 2.84 (dq, *J* = 12.6, 6.4, 5.9 Hz, 2H), 2.38 (p, *J* = 1.8 Hz, 12H), 1.87 (s, 1H), 1.75 (hept, *J* = 7.0, 6.5 Hz, 4H), 1.42 (s, 1H), 1.36 (s, 1H), 1.11 (dt, *J* = 47.7, 7.3 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 6H), 0.76 (t, *J* = 7.2 Hz, 3H). ESMS calculated for $C_{49}H_{52}N_8O_9$: 896.39; Found: 897.3 $(M+H)^+$.

[001118] SDC-TRAP-0220

[001119] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)-2-methylpiperazine-1-carboxylate

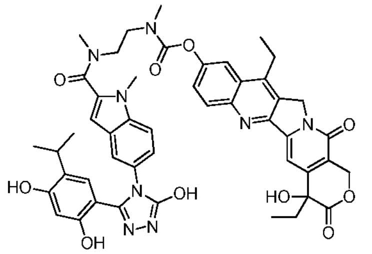


[001120] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H), 9.44 (s, 1H), 9.25 (s, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.83 (d, *J* = 2.5 Hz, 1H), 7.50 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.24 – 7.14 (m, 3H), 7.01 (d, *J* = 7.9 Hz, 2H), 6.63 (s, 1H), 6.36 (s, 1H), 6.11 (s, 1H), 5.27 (s, 2H), 5.17 (s, 2H), 4.18 (s, 1H), 3.41 (d, *J* = 13.7 Hz, 1H), 3.32 (d, *J* = 13.6 Hz, 1H), 3.14 (d, *J* = 11.5 Hz, 3H), 3.03 (q,

J = 7.8 Hz, 2H), 2.82 (p, J = 6.9 Hz, 1H), 2.69 (d, J = 10.9 Hz, 1H), 2.07 (s, 1H), 1.93 (s, 1H), 1.71 (hept, J = 7.2 Hz, 2H), 1.24 – 1.08 (m, 6H), 0.80 (d, J = 6.9 Hz, 6H), 0.72 (t, J = 7.3 Hz, 3H). ESMS calculated for $C_{46}H_{47}N_7O_9$: 841.34; Found: 842.4 $(M+H)^+$.

[001121] SDC-TRAP-0010

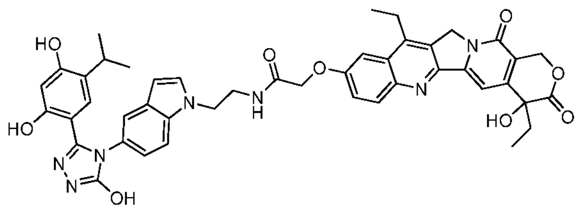
[001122] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)-*N*,1-dimethyl-1*H*-indole-2- carboxamido)ethyl)(methyl)carbamate



[001123] ESMS calculated ($C_{48}H_{48}N_8O_{10}$): 896.4; found: 897.2 (M+H).

[001124] SDC-TRAP-0023

[001125] 2-((4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-9-yl)oxy)-*N*-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)-1*H*-indol-1-yl)ethyl)acetamide

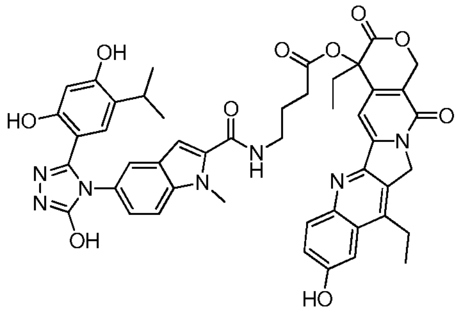


[001126] ESMS calculated ($C_{45}H_{43}N_7O_9$): 825.3; found: 826.2 (M+H).

[001127] SDC-TRAP-0024

[001128] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl-4-

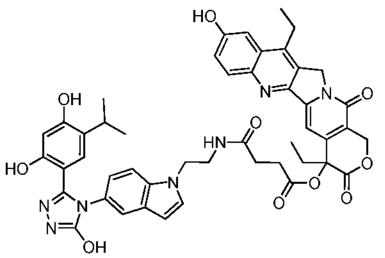
(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)-1-methyl-1*H*-indole-2-carboxamido)butanoate



[001129] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.88 (d, *J* = 9.1 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.38 – 7.24 (m, 4H), 7.15 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.74 (s, 1H), 6.67 (s, 1H), 6.26 (s, 1H), 5.62 (d, *J* = 16.6 Hz, 1H), 5.44 (d, *J* = 16.7 Hz, 1H), 5.05 (d, *J* = 18.7 Hz, 1H), 4.81 (d, *J* = 18.7 Hz, 1H), 3.58 (s, 3H), 3.49-3.42 (m, 1H), 3.40 – 3.32 (m, 1H), 3.10 – 2.96 (m, 1H), 2.96 – 2.83 (m, 2H), 2.73 (td, *J* = 6.8, 2.5 Hz, 2H), 2.19 (ddt, *J* = 18.2, 14.3, 7.2 Hz, 2H), 2.09 – 1.90 (m, 2H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.74 (dd, *J* = 10.2, 6.8 Hz, 6H); ESMS calculated ($C_{47}H_{45}N_7O_{10}$): 867.3; found: 868.3 (M+H).

[001130] SDC-TRAP-0026

[001131] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl-4-((2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)-1*H*-indol-1-yl)ethyl)amino)-4-oxobutanoate

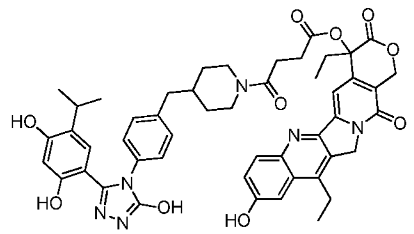


[001132] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.00 – 7.88 (m, 2H), 7.42 (d, *J* = 2.0 Hz, 1H), 7.37 – 7.23 (m, 3H), 7.02 (d, *J* = 3.2 Hz, 1H), 6.87 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.45 (s, 1H), 6.33 (d, *J* = 3.1 Hz, 1H), 6.23 (s, 1H), 5.61 (d, *J* = 16.7 Hz, 1H), 5.44 (d, *J* = 16.6 Hz, 1H), 5.06 (d, *J* = 18.6 Hz, 1H), 4.89 (d, *J* = 18.6 Hz, 1H), 4.58 (s, 1H), 4.08 – 3.97 (m, 1H), 3.45-3.40 (m, 1H), 3.35-3.29 (m, 1H), 2.99-2.74 (m, 5H), 2.51 – 2.40 (m, 2H), 2.27 – 2.12 (m, 2H), 1.36 –

1.18 (m, 3H), 1.02 (t, *J* = 7.4 Hz, 3H), 0.58 (dd, *J* = 6.9, 5.1 Hz, 6H); ESMS calculated ($C_{47}H_{45}N_7O_{10}$): 867.3; found: 868.3 (M+H).

[001133] SDC-TRAP-0042

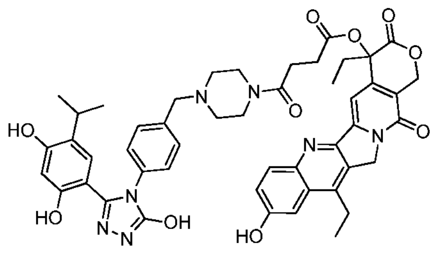
[001134] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)-4-oxobutanoate



[001135] [1]H NMR (400 MHz, Methanol-d_4) δ 7.99 (d, *J* = 9.5 Hz, 1H), 7.45 – 7.33 (m, 3H), 7.27 – 7.05 (m, 4H), 6.64 (d, *J* = 8.7 Hz, 1H), 6.26 (s, 1H), 5.60 (dd, *J* = 16.7, 3.0 Hz, 1H), 5.51 – 5.40 (m, 1H), 5.24 (d, *J* = 1.5 Hz, 2H), 4.48 (d, *J* = 12.9 Hz, 1H), 3.88 (d, *J* = 13.7 Hz, 1H), 3.34 (s, 2H), 3.13 (q, *J* = 7.4 Hz, 2H), 3.02 – 2.83 (m, 3H), 2.83 – 2.63 (m, 3H), 2.55 (d, *J* = 7.0 Hz, 1H), 2.46 (d, *J* = 13.3 Hz, 2H), 2.21 (dp, *J* = 21.6, 7.1 Hz, 2H), 1.70 – 1.56 (m, 2H), 1.36 (td, *J* = 7.7, 3.6 Hz, 3H), 1.03 (td, *J* = 7.5, 1.4 Hz, 3H), 0.88 – 0.79 (m, 6H); ESMS calculated ($C_{49}H_{50}N_6O_{10}$): 882.4; found: 883.3 (M+H).

[001136] SDC-TRAP-0043

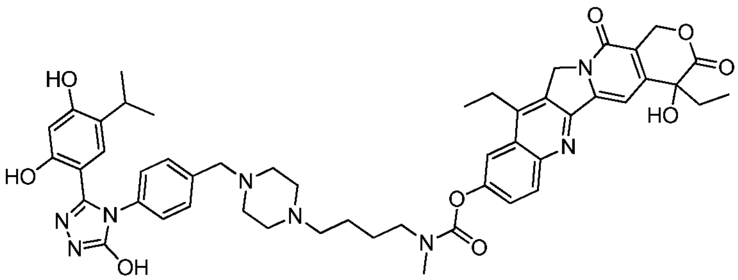
[001137] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-4-oxobutanoate



[001138] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.99 (d, J = 8.9 Hz, 1H), 7.43 – 7.28 (m, 5H), 7.26 – 7.17 (m, 2H), 6.68 (s, 1H), 6.24 (s, 1H), 5.59 (d, J = 16.6 Hz, 1H), 5.45 (d, J = 16.6 Hz, 1H), 5.24 (s, 2H), 3.59 (s, 2H), 3.54 – 3.31 (m, 4H), 3.13 (q, J = 7.7 Hz, 2H), 3.02 – 2.83 (m, 2H), 2.81 – 2.62 (m, 3H), 2.45 (s, 1H), 2.35 (s, 1H), 2.30 – 2.10 (m, 4H), 1.40 (m, 3H), 1.03 (t, J = 7.4 Hz, 3H), 0.84 (t, J = 6.7 Hz, 6H); ESMS calculated ($C_{48}H_{49}N_7O_{10}$): 883.3; found: 884.3 (M+H).

[001139] SDC-TRAP-0044

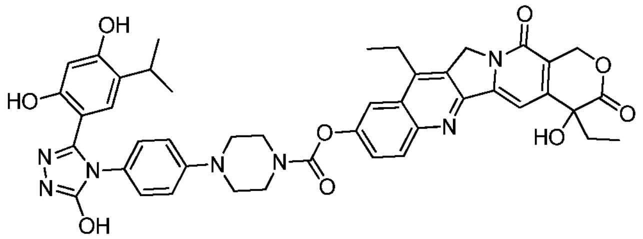
[001140] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)butyl)(methyl)carbamate



[001141] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.13 (dd, J = 9.9, 7.8 Hz, 1H), 7.93 (d, J = 2.7 Hz, 1H), 7.66-7.59 (m, 2H), 7.45-7.40 (m, 2H), 7.26-7.20 (m, 2H), 6.66 (d, J = 16.5 Hz, 1H), 6.27 – 6.19 (m, 1H), 5.58 (d, J = 16.2 Hz, 1H), 5.38 (dd, J = 16.2, 1.8 Hz, 1H), 5.27 (s, 2H), 4.85 (s, 1H), 3.64 – 3.52 (m, 3H), 3.48 – 3.40 (m, 1H), 3.17 (s, 3H), 3.05 (s, 1H), 3.01 – 2.87 (m, 2H), 2.70-2.49 (m, 9H), 1.99-1.91 (m, 2H), 1.80-1.64 (m, 5H), 1.37 (td, J = 7.3, 2.1 Hz, 3H), 1.00 (td, J = 7.3, 4.3 Hz, 3H), 0.95 – 0.77 (m, 6H); ESMS calculated ($C_{50}H_{56}N_8O_9$): 912.4; found: 913.3 (M+H).

[001142] SDC-TRAP-0045

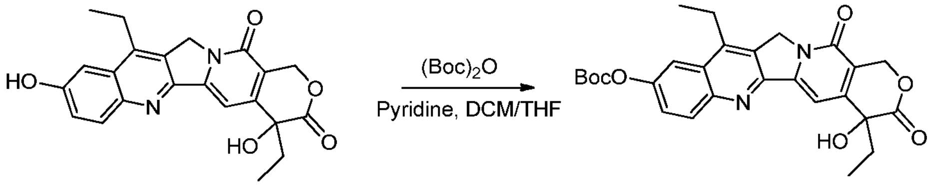
[001143] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)phenyl)piperazine-1-carboxylate



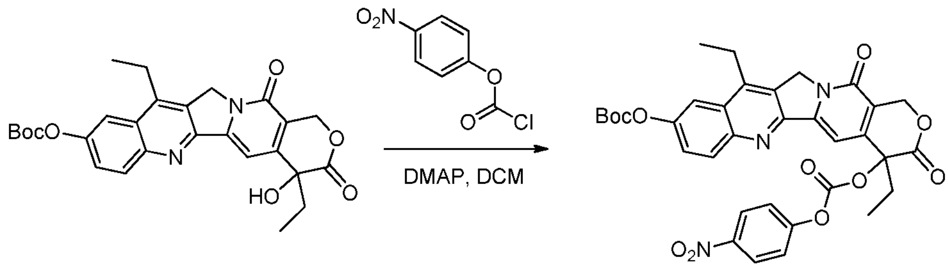
[001144] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 9.62 (s, 1H), 9.46 (s, 1H), 8.19 (d, *J* = 9.1 Hz, 1H), 8.04 (d, *J* = 2.6 Hz, 1H), 7.71 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.33 (s, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 9.1 Hz, 2H), 6.82 (s, 1H), 6.56 (s, 1H), 6.27 (s, 1H), 5.44 (s, 2H), 5.35 (s, 2H), 3.81 (s, 2H), 3.72 – 3.52 (m, 4H), 3.48-3.19 (m, 4H), 2.99 (p, *J* = 6.8 Hz, 1H), 1.87 (dt, *J* = 14.9, 7.0 Hz, 2H), 1.30 (t, *J* = 7.6 Hz, 3H), 0.99 (d, *J* = 6.9 Hz, 6H), 0.88 (t, *J* = 7.3 Hz, 3H); ESMS calculated ($C_{44}H_{43}N_7O_9$): 813.3; found: 814.3 (M+H).

[001145] SDC-TRAP-0055

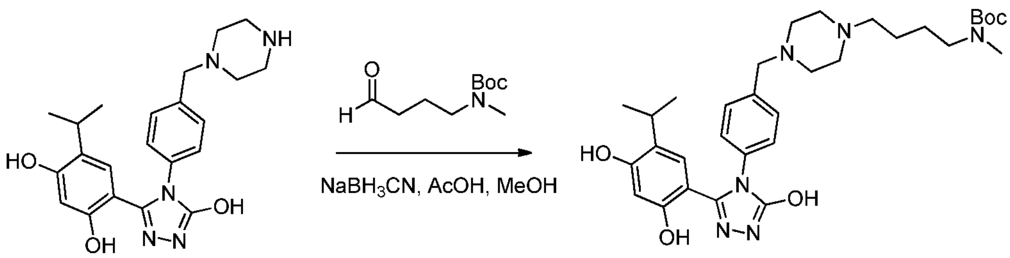
[001146] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)butyl)(methyl)carbamate



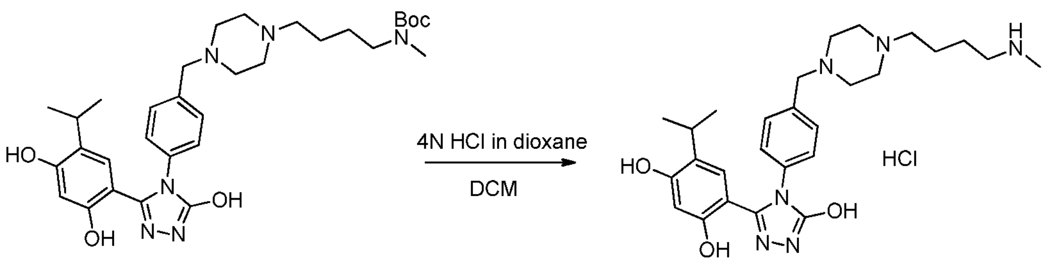
[001147] To a solution of SN-38 (3g, 7.65 mmol) in DCM/THF (150 mL/150mL) was added $(Boc)_2O$ (2g, 9.16 mmol) and pyridine (20 mL). The suspension was stirred at room temperature until the solution turned clear. The solution was diluted with DCM (100 mL) and washed with 2N HCl (100 mL×3). The organic phase was collected, dried over Na_2SO_4 and concentrated. The resulting crude product was used directly for the next step without purification.



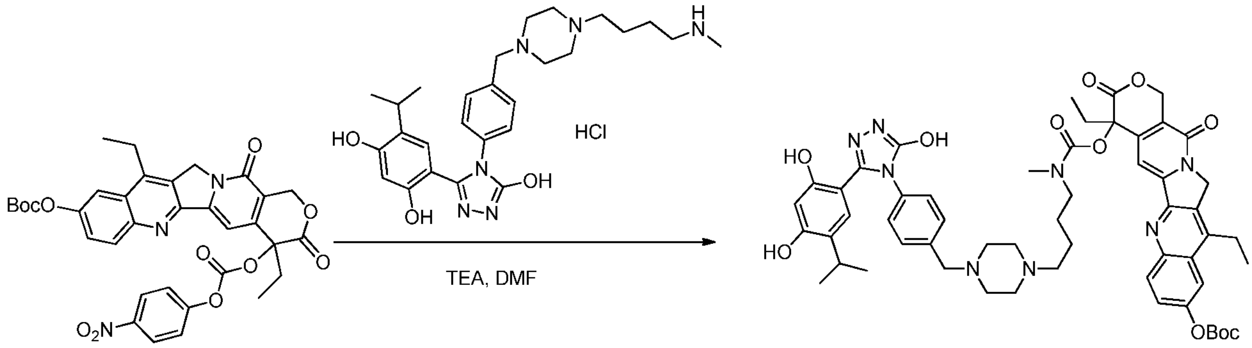
[001148] To the solution of SN-38-[10]OBoc (1g, 2.03 mmol) in DCM (50 mL) was added 4-nitrophenyl chloroformate (0.49 g, 2.44 mmol) followed by DMAP (0.74 g, 6.05 mmol). The reaction was stirred at room temperature for 1 hr before it was diluted with 100 mL of DCM. The reaction solution was washed with 0.1 N HCl (50 mL×3), dried over Na_2SO_4 and concentrated. The resulting solid was washed with Et_2O to remove excess 4-nitrophenyl chloroformate. The resulting crude product is used directly for the next step without purification.



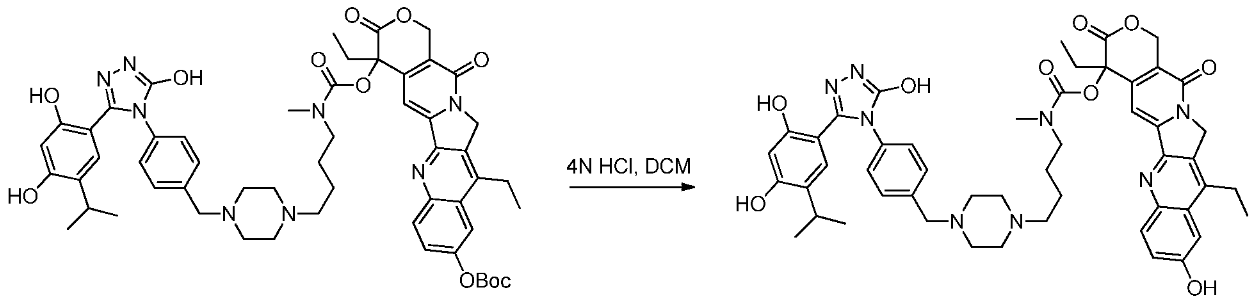
[001149] To the solution of 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4*H*-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (0.46 g, 1.12 mmol) in MeOH (10 mL) was added *t*-butyl methyl(4-oxobutyl)carbamate (0.45 g, 2.23 mmol) and acetic acid (3 drops) at room temperature. $NaBH_3CN$ (0.28 g, 4.44 mmol) was added as two portions in 10 min. The resulting solution was stirred at room temperature for 30 min before it was concentrated. Column chromatography gave *t*-butyl-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl) piperazin-1-yl)butyl)(methyl)carbamate (0.48 g, 72%).



[001150] To the solution of *t*-butyl-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl) piperazin-1-yl)butyl)(methyl)carbamate (0.48 g, 0.81 mmol) in DCM (15 mL) was added 4N HCl in dioxane (5 mL). The reaction was stirred at room temperature for 3 hr before it was concentrated. The resulting crude product was used directly for the next step without purification.



[001151] To the solution of 4-(5-hydroxy-4-(4-((4-(4-(methylamino)butyl) piperazin-1-yl)methyl)phenyl)-4*H*-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (HCl salt, 0.1 g, 0.19 mmol) in DMF (4 mL) was added *t*-butyl (4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b] quinoline-4,9-diyl) (4-nitrophenyl) dicarbonate (0.16 g, 0.24 mmol) and TEA (0.09 mL, 0.65 mmol). The reaction was stirred at room temperature for 2 hr before it was diluted with H_2O (20 mL) and EtOAc (20 mL). The organic phase was collected, dried over Na_2SO_4 and concentrated. Column chromatography gave 9-((*t*-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin -1-yl)butyl)(methyl)carbamate (0.15 g, 75%).



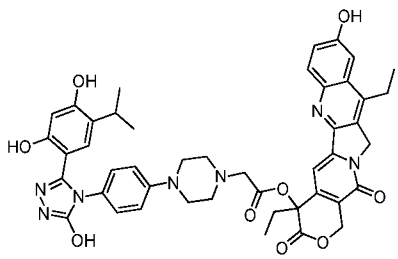
SDC-TRAP-0055

[001152] To the solution of 9-((*t*-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl) benzyl)piperazin-1-yl)butyl)(methyl)carbamate (0.15 g, 0.15 mmol) in DCM (5 mL) was added 4N HCl in dioxane (5 mL). The reaction was stirred at room temperature for 3 hr before it was concentrated. Column chromatography gave SDC-TRAP-0055 (0.09 g, 66%) as yellow solid.

[001153] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.93 (dd, J = 9.5, 2.8 Hz, 1H), 7.40 – 7.28 (m, 4H), 7.26 – 7.13 (m, 3H), 6.63 (d, J = 6.4 Hz, 1H), 6.17 (s, 1H), 5.48 (dd, J = 16.7, 11.7 Hz, 1H), 5.41 – 5.27 (m, 1H), 5.17 (d, J = 2.4 Hz, 2H), 3.57 (s, 1H), 3.45 (s, 1H), 3.25 (m, 5H), 3.15 – 3.00 (m, 8H), 2.92 (p, J = 6.9 Hz, 3H), 2.75 (s, 1H), 2.10 (dp, J = 21.9, 7.3 Hz, 2H), 1.82-1.46 (m, 5H), 1.28 (td, J = 7.6, 1.9 Hz, 3H), 0.95 (dt, J = 13.8, 7.4 Hz, 3H), 0.81 (dd, J = 7.0, 2.0 Hz, 6H); ESMS calculated ($C_{50}H_{56}N_8O_9$): 912.4; found: 913.1 (M+H).

[001154] SDC-TRAP-0056

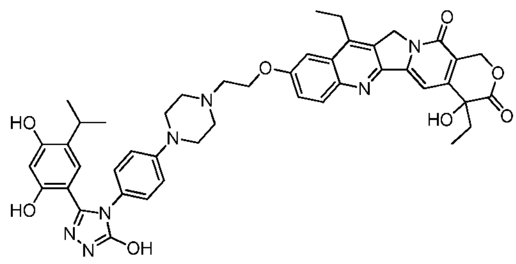
[001155] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)acetate



[001156] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 10.32 (s, 1H), 9.57 (s, 1H), 9.44 (s, 1H), 8.00 – 7.92 (m, 1H), 7.40-7.37 (m, 2H), 6.99-6.97 (m, 3H), 6.90 – 6.83 (m, 2H), 6.76 (s, 1H), 6.25 (s, 1H), 5.50 (s, 2H), 5.30 (d, J = 3.5 Hz, 2H), 3.58 (d, J = 16.5 Hz, 1H), 3.42 (d, J = 16.4 Hz, 1H), 3.18-3.07 (m, 6H), 2.95 (p, J = 6.8 Hz, 1H), 2.65 (t, J = 5.2 Hz, 4H), 2.15 (dt, J = 9.4, 6.5 Hz, 2H), 1.29 (t, J = 7.5 Hz, 3H), 0.93 (dd, J = 6.8, 1.8 Hz, 9H); ESMS calculated ($C_{45}H_{45}N_7O_9$): 827.3; found: 828.0 (M+H).

[001157] SDC-TRAP-0057

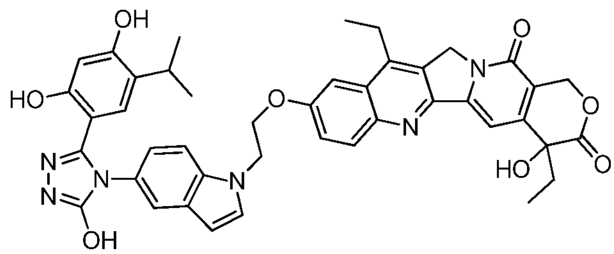
[001158] 9-(2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)ethoxy)-4,11-diethyl-4-hydroxy-1*H*-pyrano[3',4':6,7] indolizino[1,2-b]quinoline-3,14(4*H*,12*H*)-dione



[001159] ESMS calculated ($C_{45}H_{47}N_7O_8$): 813.3; found: 814.1 (M+H).

[001160] SDC-TRAP-0058

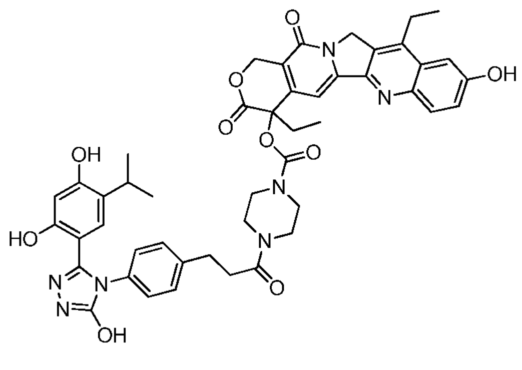
[001161] 9-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethoxy)-4,11-diethyl-4-hydroxy-1H-pyrano[3',4':6,7] indolizino[1,2-b]quinoline-3,14(4H,12H)-dione



[001162] ESMS calculated ($C_{43}H_{40}N_6O_8$): 768.3; found: 769.1 (M+H).

[001163] SDC-TRAP-0060

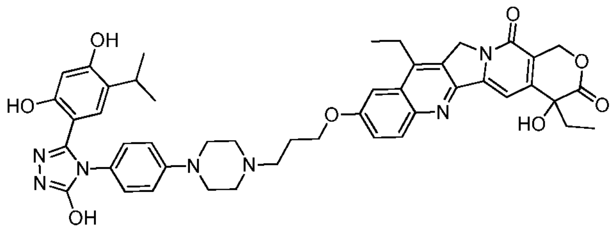
[001164] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(3-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)phenyl)propanoyl)piperazine-1-carboxylate



[001165] ESMS calculated ($C_{47}H_{47}N_7O_{10}$): 869.3; found: 870.0 (M+H).

[001166] SDC-TRAP-0061

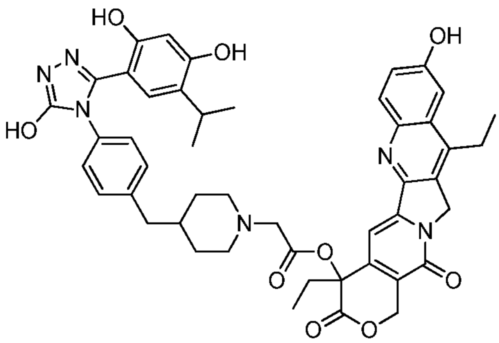
[001167] 9-(3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)propoxy)-4,11-diethyl-4-hydroxy-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione



[001168] ESMS calculated ($C_{46}H_{49}N_7O_8$): 827.3; found: 828.1 (M+H).

[001169] SDC-TRAP-0071

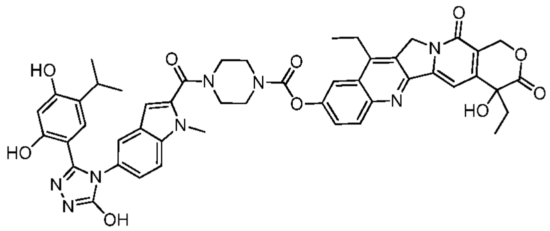
[001170] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)benzyl)piperidin-1-yl)acetate



[001171] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.86 (d, J = 9.1 Hz, 1H), 7.32 – 7.21 (m, 2H), 7.18 (s, 1H), 7.15 – 7.06 (m, 2H), 7.06 – 6.98 (m, 2H), 6.49 (s, 1H), 6.16 (s, 1H), 5.52 (d, J = 16.7 Hz, 1H), 5.35 (d, J = 16.7 Hz, 1H), 5.08 (s, 2H), 3.49 – 3.31 (m, 2H), 2.99 (q, J = 7.6 Hz, 2H), 2.87 – 2.66 (m, 3H), 2.42 (d, J = 6.9 Hz, 2H), 2.21 – 2.00 (m, 4H), 1.54 – 1.33 (m, 3H), 1.28 – 1.15 (m, 5H), 0.93 (t, J = 7.4 Hz, 3H), 0.66 (t, J = 7.1 Hz, 6H); ESMS calculated ($C_{47}H_{48}N_6O_9$): 840.3; found: 841.2 (M+H).

[001172] SDC-TRAP-0072

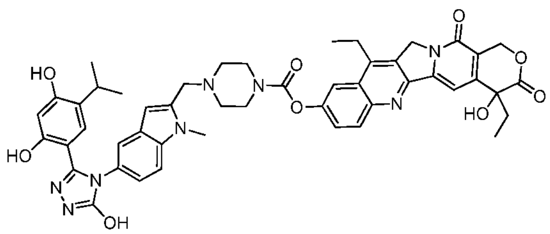
[001173] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1-methyl-1H-indole-2-carbonyl)piperazine-1-carboxylate



[001174] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 9.55 (s, 1H), 9.38 (s, 1H), 8.20 (d, J = 9.1 Hz, 1H), 8.03 (d, J = 2.6 Hz, 1H), 7.70 (dd, J = 9.2, 2.5 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.33 (s, 1H), 7.03 (dd, J = 8.7, 2.1 Hz, 1H), 6.84 (s, 1H), 6.76 (s, 1H), 6.54 (s, 1H), 6.21 (s, 1H), 5.44 (s, 2H), 5.35 (s, 2H), 3.79 (brs, 7H), 3.60 (s, 2H), 3.25 – 3.14 (m, 3H), 2.95 (p, J = 7.0 Hz, 1H), 1.95 – 1.79 (m, 3H), 1.30 (t, J = 8.0 Hz, 3H), 0.94-0.85 (m, 9H); ESMS calculated ($C_{48}H_{46}N_8O_{10}$): 894.3; found: 895.0 (M+H).

[001175] SDC-TRAP-0073

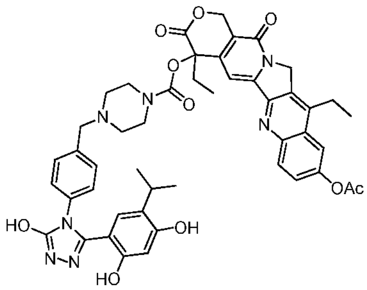
[001176] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)-1-methyl-1*H*-indol-2-yl)methyl)piperazine-1-carboxylate



[001177] ESMS calculated ($C_{48}H_{48}N_8O_9$): 880.4; found: 881.1 (M+H).

[001178] SDC-TRAP-0074

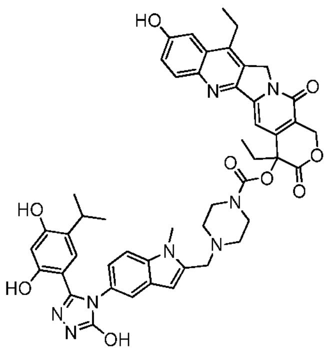
[001179] 9-acetoxy-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)benzyl) piperazine-1-carboxylate



[001180] ^{1}H NMR (400 MHz, DMSO- d_6) δ 11.94 (s, 1H), 9.61 (s, 1H), 9.42 (s, 1H), 8.21 (d, J = 9.2 Hz, 1H), 8.03 (s, 1H), 7.68 (d, J = 9.1 Hz, 1H), 7.32 (d, J = 7.9 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 7.05 (s, 1H), 6.78 (s, 1H), 6.26 (s, 1H), 5.46 (d, J = 4.8 Hz, 2H), 5.35 (s, 2H), 3.73 (s, 1H), 3.62 (s, 1H), 3.52 – 3.44 (m, 3H), 3.28 – 3.13 (m, 4H), 2.97 (p, J = 7.1 Hz, 1H), 2.38 (s, 3H), 2.30 (s, 1H), 2.24 – 2.10 (m, 4H), 1.28 (t, J = 7.3 Hz, 3H), 0.92 (dd, J = 19.9, 7.5 Hz, 9H); ESMS calculated ($C_{47}H_{47}N_7O_{10}$): 880.4; found: 881.1 (M+H).

[001181] SDC-TRAP-0075

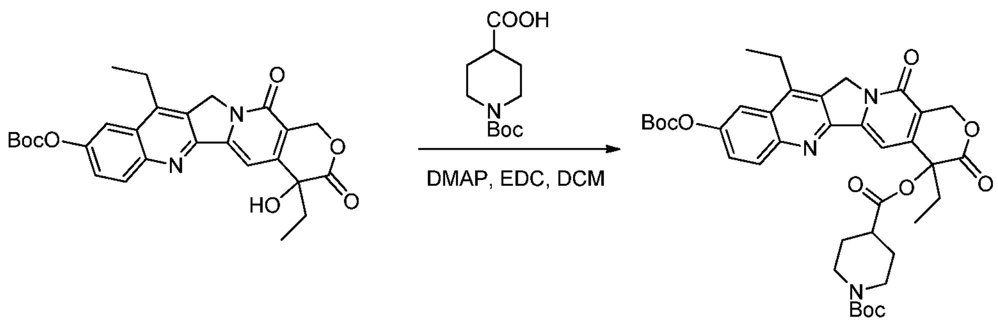
[001182] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)-1-methyl-1H-indol-2-yl)methyl)piperazine-1-carboxylate



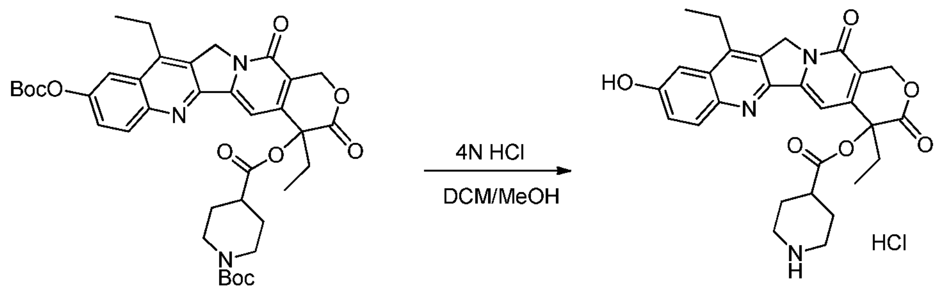
[001183] ESMS calculated ($C_{48}H_{48}N_8O_9$): 880.4; found: 881.2 (M+H).

[001184] SDC-TRAP-0076

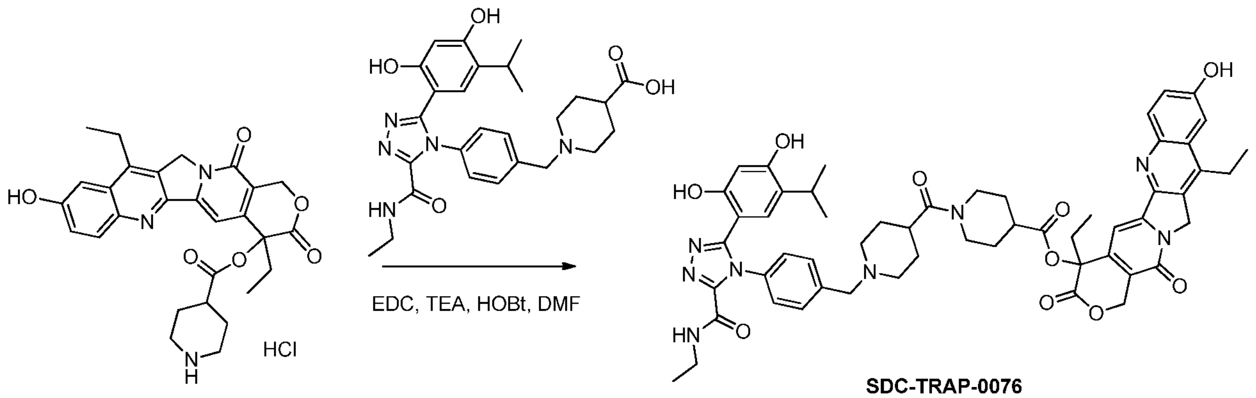
[001185] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 1-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4*H*-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)piperidine-4-carboxylate



[001186] To the solution of SN-38-[10]OBoc (0.85g, 1.73 mmol) in DCM (50 mL) was added 1-(*t*-butoxycarbonyl)piperidine-4-carboxylic acid (0.48 g, 2.09 mmol) followed by DMAP (0.42 g, 3.44 mmol) and EDC (1 g, 5.2 mmol). The reaction was stirred at room temperature for 1 hr before it was diluted with DCM (100 mL). The organic phase was washed with 2N HCl (50 mL×2), dried over Na_2SO_4 and concentrated. Column chromatography gave 4-(9-((*t*-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7] indolizino[1,2-b]quinolin-4-yl) 1-*t*-butyl piperidine-1,4-dicarboxylate (1.03g, 85%).



[001187] To the solution of 4-(9-((*t*-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7] indolizino[1,2-b]quinolin-4-yl) 1-*t*-butyl piperidine-1,4-dicarboxylate (1.03 g, 1.46 mmol) in DCM (15 mL) was added 4N HCl in dioxane (10 mL). The reaction was heated at 45 °C for 30 min before it was concentrated. The resulting crude product is used directly for the next step without purification.

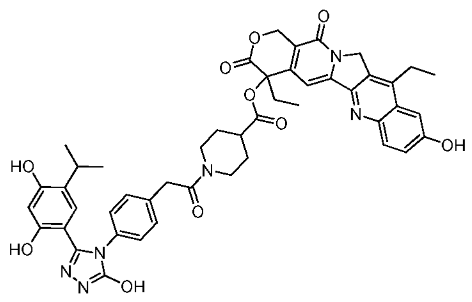


[001188] The suspension of 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl piperidine-4-carboxylate (HCl salt, 0.35 g, 0.65 mmol) in DMF and TEA (20 mL/3 mL) was heated until it turned clear. To the resulting solution was added 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carboxylic acid (0.3 g, 0.6 mmol), EDC (0.35 g, 1.82 mmol), and HOBt (Cat.). The reaction was stirred at room temperature overnight before it was diluted with EtOAc (30 mL) and NH_4Cl (20 mL). The organic phase was collected, dried over Na_2SO_4 and concentrated. Column chromatography gave SDC-TRAP-0076 as a light yellow solid (0.28 g, 47%).

[001189] ^1H NMR (400 MHz, DMSO-d_6) δ 10.63 (s, 1H), 10.32 (s, 1H), 9.75 (s, 1H), 8.94 (t, J = 5.9 Hz, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.45 – 7.34 (m, 4H), 7.33 – 7.26 (m, 2H), 6.93 (s, 1H), 6.56 (s, 1H), 6.34 (s, 1H), 5.49 (s, 2H), 5.29 (d, J = 2.2 Hz, 2H), 4.14 (s, 1H), 3.87 (s, 1H), 3.47 (s, 2H), 3.25 – 3.05 (m, 4H), 2.92 – 2.82 (m, 5H), 2.59 (s, 1H), 2.22 – 2.11 (m, 2H), 2.04-1.88 (m, 4H), 1.56 (s, 5H), 1.27 (dd, J = 16.8, 9.1 Hz, 5H), 1.03 (t, J = 7.2 Hz, 3H), 0.97 – 0.83 (m, 3H), 0.79 (d, J = 6.6 Hz, 6H); ESMS calculated ($C_{55}H_{60}N_8O_{10}$): 992.4; found: 993.5 (M+H).

[001190] SDC-TRAP-0097

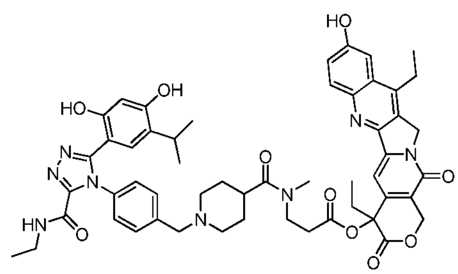
[001191] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 1-(2-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)acetyl)piperidine-4-carboxylate



[001192] ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.91 (d, J = 9.5 Hz, 1H), 7.31 (d, J = 7.7 Hz, 2H), 7.23 (t, J = 5.6 Hz, 2H), 7.15 (d, J = 4.2 Hz, 1H), 7.04 (dd, J = 27.7, 8.1 Hz, 2H), 6.12 (d, J = 6.1 Hz, 1H), 5.51 (d, J = 16.4 Hz, 1H), 5.42 – 5.31 (m, 1H), 5.15 (d, J = 15.5 Hz, 2H), 4.50 (s, 3H), 4.04 (s, 1H), 3.76 (s, 2H), 3.69 (d, J = 16.0 Hz, 2H), 3.25 (s, 6H), 3.06 (d, J = 13.2 Hz, 5H), 2.81 (d, J = 13.5 Hz, 2H), 2.17 – 2.07 (m, 2H), 1.80 (s, 1H), 1.60 (s, 2H), 1.27 (q, J = 7.8 Hz, 3H), 1.19 (s, 2H), 0.92 (q, J = 6.8 Hz, 3H), 0.85 – 0.68 (m, 7H); ESMS calculated ($C_{47}H_{46}N_6O_{10}$): 854.3; found: 855.2 (M+H).

[001193] SDC-TRAP-0100

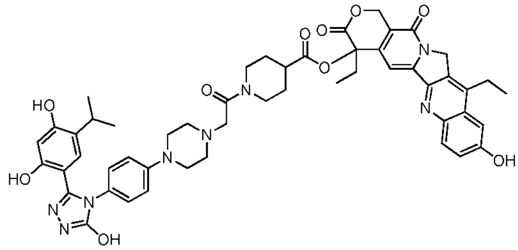
[001194] 4,11-Diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 3-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)-N-methylpiperidine-4-carboxamido)propanoate



[001195] ESMS calculated ($C_{53}H_{58}N_8O_{10}$): 966.4; found: 967.4 (M+H).

[001196] SDC-TRAP-0111

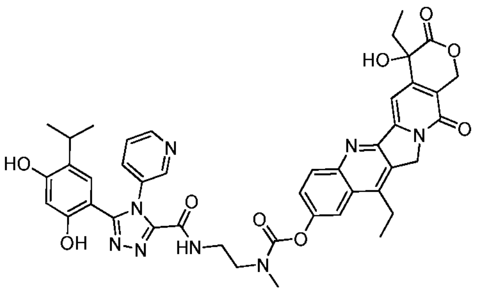
[001197] 4,11-Diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 1-(2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)acetyl)piperidine-4-carboxylate



[001198] ESMS calculated ($C_{51}H_{54}N_8O_{10}$): 938.4; found: 939.4 (M+H).

[001199] SDC-TRAP-0112

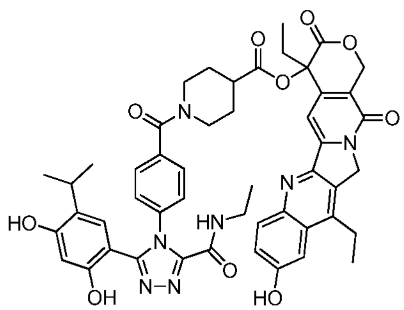
[001200] 4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(5-(2,4-dihydroxy-5-isopropylphenyl)-4-(pyridin-3-yl)-4*H*-1,2,4-triazole-3-carboxamido)ethyl)(methyl)carbamate



[001201] ESMS calculated ($C_{43}H_{42}N_8O_9$): 814.3; found: 815.2 (M+H).

[001202] SDC-TRAP-0113

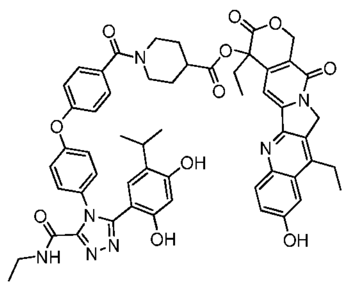
[001203] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4*H*-1,2,4-triazol-4-yl)benzoyl)piperidine-4-carboxylate



[001204] ^1H NMR (400 MHz, DMSO- d_6) δ 10.33 (s, 2H), 9.73 (s, 1H), 8.98 (t, J = 6.0 Hz, 1H), 7.99 (s, 1H), 7.48 – 7.35 (m, 6H), 6.95 (s, 1H), 6.66 (s, 1H), 6.32 (s, 1H), 5.49 (s, 2H), 5.29 (d, J = 2.6 Hz, 2H), 4.25 (s, 1H), 3.54 (s, 1H), 3.42 - 2.90 (m, 10H), 2.15 (t, J = 7.7 Hz, 2H), 1.61 (s, 2H), 1.29 (t, J = 7.6 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H), 0.85 (d, J = 6.8 Hz, 6H); ESMS calculated ($C_{49}H_{49}N_7O_{10}$): 895.4; found: 896.3 (M+H).

[001205] SDC-TRAP-0154

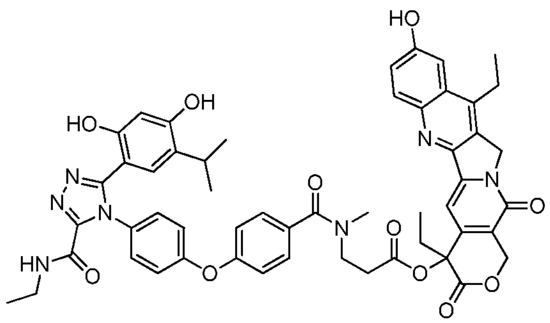
[001206] 4,11-Diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)benzoyl)piperidine-4-carboxylate



[001207] ^1H NMR (400 MHz, DMSO-d_6) δ 10.41 (s, 1H), 10.34 (s, 1H), 9.76 (s, 1H), 8.98 (t, J = 6.0 Hz, 1H), 8.00 (d, J = 9.0 Hz, 1H), 7.49 – 7.33 (m, 6H), 7.14 – 7.01 (m, 4H), 6.95 (s, 1H), 6.68 (s, 1H), 6.34 (s, 1H), 5.49 (s, 2H), 5.30 (s, 2H), 3.18 (p, J = 6.9 Hz, 4H), 3.08 (d, J = 7.3 Hz, 3H), 2.95 (dd, J = 15.7, 8.7 Hz, 3H), 2.16 (q, J = 7.4 Hz, 2H), 1.96 (s, 2H), 1.60 (s, 2H), 1.28 (t, J = 7.5 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H), 0.92 (dd, J = 11.6, 7.0 Hz, 9H); ESMS calculated ($C_{55}H_{53}N_7O_{11}$): 987.4; found: 988.4 (M+H).

[001208] SDC-TRAP-0169

[001209] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)-N-methylbenzamido)propanoate

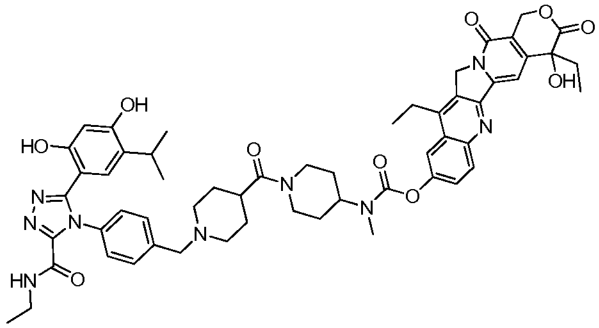


[001210] ESMS calculated ($C_{53}H_{51}N_7O_{11}$): 961.4; found: 962.3 (M+H).

[001211] SDC-TRAP-0172

[001212] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (1-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)piperidin-4-yl)(methyl)

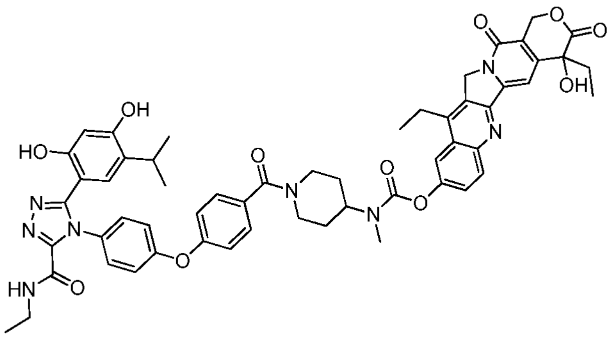
[001213] carbamate



[001214] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 9.77 (s, 1H), 8.97 (t, J = 5.9 Hz, 1H), 8.18 (d, J = 9.2 Hz, 1H), 8.01 (s, 1H), 7.68 (dd, J = 9.2, 2.4 Hz, 1H), 7.39 (d, J = 8.2 Hz, 2H), 7.35 – 7.27 (m, 3H), 6.56 (d, J = 17.5 Hz, 2H), 6.35 (s, 1H), 5.44 (s, 2H), 5.35 (s, 2H), 4.56 (s, 1H), 4.07 (s, 1H), 3.50 (s, 2H), 3.31 (s, 4H), 3.20-3.13 (m, 4H), 3.00 (s, 2H), 2.95 – 2.83 (m, 4H), 2.68-2.60 (m, 2H), 2.04 (s, 2H), 1.87 (dt, J = 14.8, 7.1 Hz, 3H), 1.61 (s, 5H), 1.30 (t, J = 8.0 Hz, 3H), 1.04 (t, J = 7.2 Hz, 3H), 0.88 (t, J = 8.0 Hz, 3H), 0.81 (d, J = 8.0 Hz, 6H); ESMS calculated ($C_{56}H_{63}N_9O_{10}$): 1021.5; found: 1022.5 (M+H).

[001215] SDC-TRAP-0180

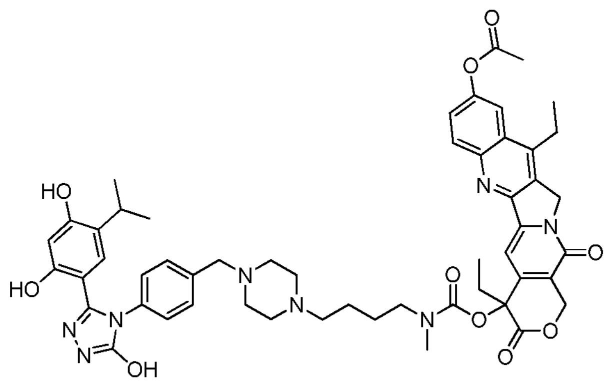
[001216] 4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)benzoyl)piperidin-4-yl)(methyl)carbamate



[001217] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H), 9.77 (s, 1H), 8.98 (t, J = 5.9 Hz, 1H), 8.18 (d, J = 9.1 Hz, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.68 (dd, J = 9.1, 2.4 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.44 – 7.35 (m, 2H), 7.33 (s, 1H), 7.16 – 7.06 (m, 4H), 6.69 (s, 1H), 6.53 (s, 1H), 6.35 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.62-4.22 (m, 2H), 3.77 (s, 1H), 3.26 – 3.14 (m, 5H), 3.05 (s, 2H), 2.98 (p, J = 6.9 Hz, 1H), 2.90 (s, 2H), 1.91-1.80 (m, 6H), 1.34 – 1.21 (m, 3H), 1.07 (t, J = 7.2 Hz, 3H), 0.93 (d, J = 15.2, 8.0 Hz, 6H), 0.88 (t, J = 8.0 Hz, 3H); ESMS calculated ($C_{56}H_{56}N_8O_{11}$): 1016.4; found: 1017.5 (M+H).

[001218] SDC-TRAP-0181

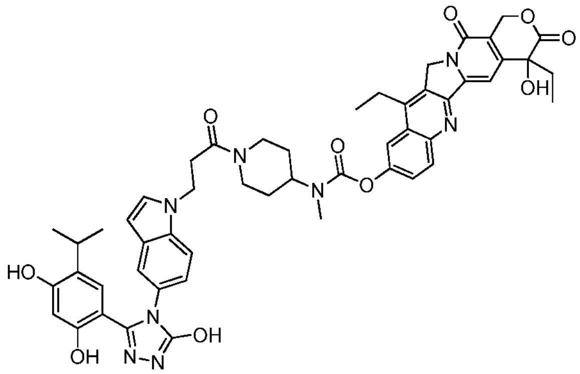
[001219] 4-(((4-(4-(4-(3-(2,4-Dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)butyl)(methyl)carbamoyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b] quinolin-9-yl acetate



[001220] ESMS calculated ($C_{52}H_{58}N_8O_{10}$): 954.4; found: 955.3 (M+H).

[001221] SDC-TRAP-0184

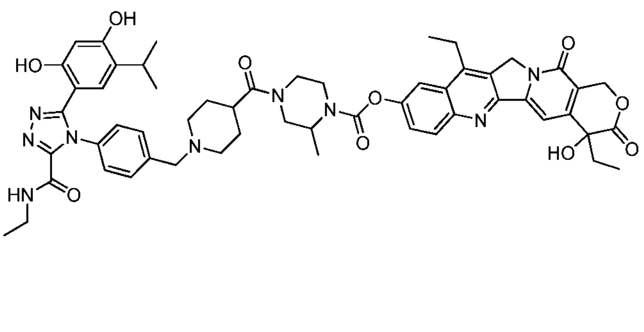
[001222] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (1-(3-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)propanoyl)piperidin-4-yl)(methyl)carbamate



[001223] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.83 (s, 1H), 9.51 (s, 1H), 9.45 (s, 1H), 8.17 (d, J = 9.1 Hz, 1H), 7.99 (s, 1H), 7.70 – 7.62 (m, 1H), 7.54 – 7.38 (m, 3H), 7.32 (s, 1H), 6.95 (dd, J = 8.7, 2.0 Hz, 1H), 6.74 (s, 1H), 6.50 (s, 1H), 6.42 (d, J = 3.1 Hz, 1H), 6.23 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.53 (s, 1H), 4.43 (t, J = 6.8 Hz, 2H), 3.83 (s, 1H), 3.29 (s, 3H), 3.22 – 3.14 (m, 3H), 2.93-2.66 (s, 7H), 1.87 (p, J = 7.1 Hz, 2H), 1.49 (s, 2H), 1.29 (t, J = 8.0 Hz, 3H), 0.92 – 0.82 (m, 9H); ESMS calculated ($C_{51}H_{52}N_8O_{10}$): 936.4; found: 937.0 (M+H).

[001224] SDC-TRAP-0185

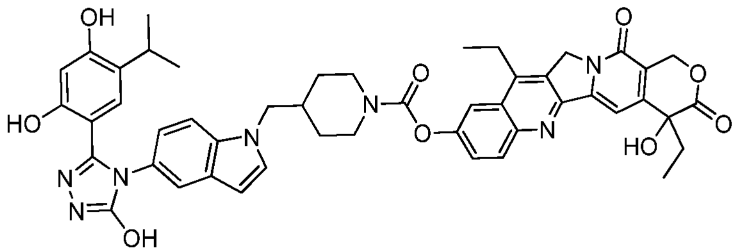
[001225] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)-2-methylpiperazine-1-carboxylate



[001226] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.64 (d, J = 1.8 Hz, 1H), 9.77 (s, 1H), 8.96 (t, J = 5.9 Hz, 1H), 8.20 (d, J = 9.2 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H), 7.70 (dd, J = 9.2, 2.5 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.37 – 7.24 (m, 3H), 6.59 (s, 1H), 6.52 (s, 1H), 6.36 (s, 1H), 5.45 (s, 2H), 5.35 (s, 2H), 4.29 (d, J = 17.9 Hz, 2H), 4.15 – 3.81 (m, 2H), 3.51 (s, 2H), 3.27 – 3.12 (m, 5H), 2.95-2.88 (m, 5H), 2.07 (s, 2H), 1.96 – 1.79 (m, 2H), 1.71-1.63 (m, 5H), 1.37 – 1.13 (m, 6H), 1.05 (t, J = 7.2 Hz, 3H), 0.89 (t, J = 7.3 Hz, 3H), 0.82 (d, J = 6.9 Hz, 6H). ESMS calculated ($C_{55}H_{61}N_9O_{10}$): 1007.5; found: 1008.3 (M+H).

[001227] SDC-TRAP-0186

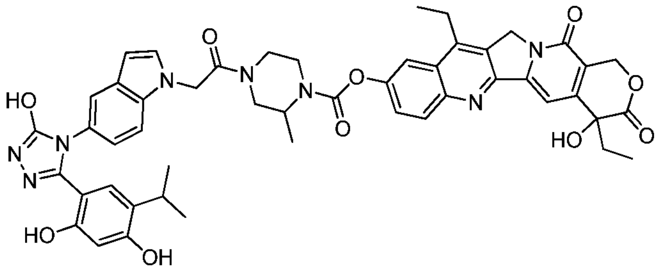
[001228] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)methyl)piperidine-1-carboxylate



[001229] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 9.57 (d, J = 4.4 Hz, 2H), 8.17 (d, J = 9.1 Hz, 1H), 7.97 (d, J = 2.5 Hz, 1H), 7.69 – 7.56 (m, 2H), 7.46 (dd, J = 4.9, 2.6 Hz, 2H), 7.32 (s, 1H), 6.98 (dd, J = 8.7, 2.0 Hz, 1H), 6.67 (s, 1H), 6.53 (s, 1H), 6.47 (d, J = 3.1 Hz, 1H), 6.25 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.25-4.07 (m, 4H), 3.22 – 3.14 (m, 2H), 3.01 (s, 1H), 2.88-2.85 (m, 2H), 2.09 (s, 1H), 1.87 (dt, J = 14.7, 7.0 Hz, 2H), 1.58 (d, J = 12.2 Hz, 2H), 1.33 – 1.21 (m, 5H), 0.88 (t, J = 7.3 Hz, 3H), 0.77 (d, J = 6.9 Hz, 6H); ESMS calculated ($C_{48}H_{47}N_7O_9$): 865.3; found: 866.0 (M+H).

[001230] SDC-TRAP-0201

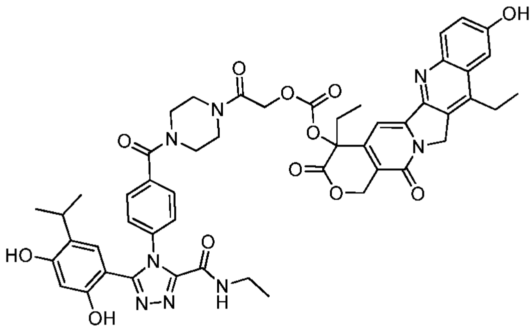
[001231] 4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)acetyl)-2-methylpiperazine-1-carboxylate



[001232] ESMS calculated ($C_{49}H_{48}N_8O_{10}$): 908.3; found: 909.0 (M+H).

[001233] SDC-TRAP-0202

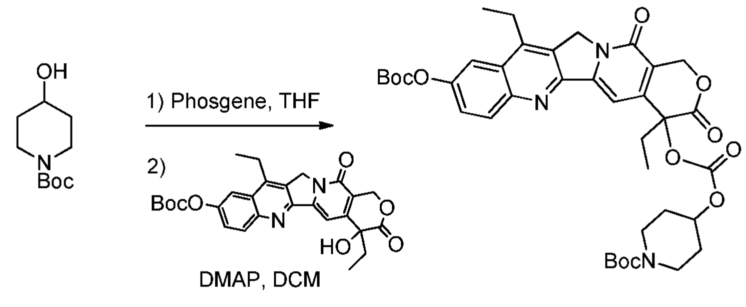
[001234] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (2-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperazin-1-yl)-2-oxoethyl) carbonate



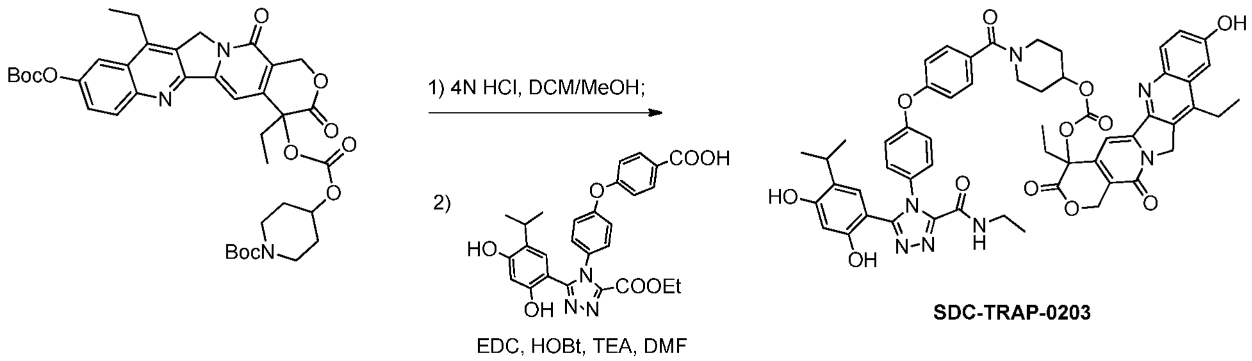
[001235] ESMS calculated ($C_{50}H_{50}N_8O_{12}$): 954.4; found: 955.1 (M+H).

[001236] SDC-TRAP-0203

[001237] 4,11-Diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)benzoyl)piperidin-4-yl) carbonate



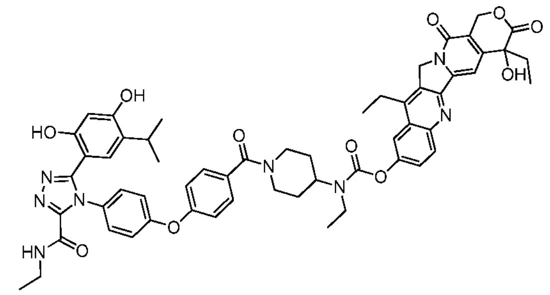
[001238] To a solution of tert-butyl 4-hydroxypiperidine-1-carboxylate (0.2g, 1.0 mmol) in THF (4 mL) was added phosgene (15%wt in toluene, 0.66 mL). The reaction was stirred at room temperature for 1 hr. SN-38-^{10}OBoc (0.2 g, 0.4 mmol) was added to the reaction solution, followed by DMAP (0.15 g, 1.2 mmol). The reaction was stirred at room temperature for 5 hr. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (15 mL×3). The organic phases were combined, dried over Na_2SO_4 and concentrated. Column chromatography gave tert-butyl 4-((((9-((tert-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl)oxy)carbonyl)oxy)piperidine-1-carboxylate (0.21 g, 73%).



[001239] To the solution of 4-((((9-((tert-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl)oxy)carbonyl)oxy)piperidine-1-carboxylate (0.2 g, 0.28 mmol) in DCM/MeOH (5mL/4mL) was added 4N HCl in dioxane (5 mL). The reaction was stirred at room temperature for 2 hr before it was concentrated. The resulting solid was dissolved in DMF (4 mL), and 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethoxycarbonyl)-4H-1,2,4-triazol-4-yl)phenoxy)benzoic acid (0.14 g, 0.28 mmol), EDC (0.16 g, 0.83 mmol), TEA (1 mL), and HOBt (Cat.) were added. The reaction was stirred at room temperature overnight. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with EtOAc (15 mL×3). The combined organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave SDC-TRAP-0203 (0.15g, 54%). ESMS calculated ($C_{55}H_{53}N_7O_{12}$): 1003.4; found: 1004.5 (M+H).

[001240] SDC-TRAP-0221

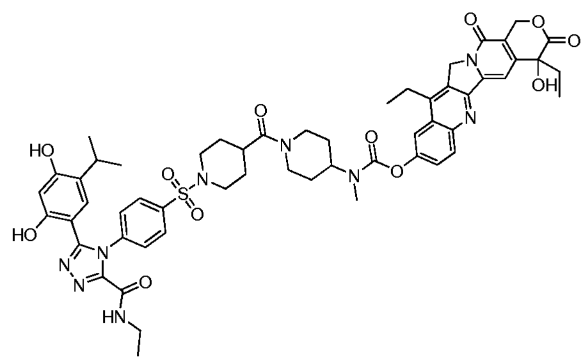
[001241] 4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)benzoyl)piperidin-4-yl)(ethyl)carbamate



[001242] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.43 (s, 1H), 9.80 (s, 1H), 8.97 (t, J = 5.8 Hz, 1H), 8.19 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 2.5 Hz, 1H), 7.67 (dd, J = 9.2, 2.4 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.43 – 7.31 (m, 3H), 7.16 – 7.05 (m, 4H), 6.68 (s, 1H), 6.54 (s, 1H), 6.35 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.59 (s, 1H), 4.13 (s, 1H), 3.52 – 3.35 (m, 4H), 3.20 (dt, J = 13.1, 6.8 Hz, 4H), 2.98 (p, J = 6.9 Hz, 1H), 1.93-1.80 (m, 6H), 1.30 (t, J = 7.5 Hz, 6H), 1.22 – 1.13 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H), 0.96 – 0.84 (m, 9H); ESMS calculated ($C_{57}H_{58}N_8O_{11}$): 1030.4; found: 1031.5 (M+H).

[001243] SDC-TRAP-0222

[001244] 4,11-Diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (1-(1-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperidine-4-carbonyl)piperidin-4-yl)(methyl) carbamate



[001245] [1]H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 1H), 9.69 (s, 1H), 9.05 (t, *J* = 6.0 Hz, 1H), 8.18 (d, *J* = 9.2 Hz, 1H), 8.00 (d, *J* = 2.7 Hz, 1H), 7.81 – 7.73 (m, 2H), 7.67 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.32 (s, 1H), 6.74 (s, 1H), 6.51 (s, 1H), 6.28 (s, 1H), 5.75 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.53 (s, 1H), 4.06 (s, 2H), 3.70 (s, 2H), 3.25 – 3.14 (m, 6H), 3.02 – 2.93 (m, 3H), 2.84 (s, 1H), 2.67-2.32 (m, 3H), 1.87 (p, *J* = 7.0 Hz, 2H), 1.74-1.55 (m, 7H), 1.29 (t, *J* = 8.0 Hz, 3H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.95 (d, *J* = 8.0 Hz, 6H), 0.88 (t, *J* = 8.0 Hz, 3H); ESMS calculated ($C_{55}H_{61}N_9O_{12}S$): 1071.4; found: 1072.6 (M+H).

[001246] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0016	>5000
SDC-TRAP-0027	>5000
SDC-TRAP-0028	>5000
SDC-TRAP-0030	>5000
SDC-TRAP-0031	1270
SDC-TRAP-0022	>5000
SDC-TRAP-0023	4300
SDC-TRAP-0010	>5000
SDC-TRAP-0038	>5000
SDC-TRAP-0037	2112
SDC-TRAP-0026	1780
SDC-TRAP-0029	1373
SDC-TRAP-0046	246
SDC-TRAP-0042	1057
SDC-TRAP-0043	2135
SDC-TRAP-0047	875
SDC-TRAP-0044	602
SDC-TRAP-0045	464
SDC-TRAP-0054	1469
SDC-TRAP-0059	184
SDC-TRAP-0014	>5000
SDC-TRAP-0012	>5000
SDC-TRAP-0011	>5000
SDC-TRAP-0055	402

SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0056	1271
SDC-TRAP-0057	449
SDC-TRAP-0058	2929
SDC-TRAP-0060	>5000
SDC-TRAP-0063	793
SDC-TRAP-0067	196
SDC-TRAP-0070	263
SDC-TRAP-0064	1129
SDC-TRAP-0065	661
SDC-TRAP-0071	307
SDC-TRAP-0072	>5000
SDC-TRAP-0073	478
SDC-TRAP-0077	2791
SDC-TRAP-0079	1430
SDC-TRAP-0081	622
SDC-TRAP-0083	1438
SDC-TRAP-0094	<78 953
SDC-TRAP-0086	>5,000
SDC-TRAP-0084	1132
SDC-TRAP-0095	>5000
SDC-TRAP-0101	280
SDC-TRAP-0087	535
SDC-TRAP-0090	4599
SDC-TRAP-0089	1466
SDC-TRAP-0088	221
SDC-TRAP-0074	4120
SDC-TRAP-0075	953
SDC-TRAP-0076	<78 227
SDC-TRAP-0097	>5,000
SDC-TRAP-0091	>5000
SDC-TRAP-0104	350
SDC-TRAP-0092	4706
SDC-TRAP-0100	80
SDC-TRAP-0111	>5000
SDC-TRAP-0112	>5000
SDC-TRAP-0154	191
SDC-TRAP-0145	183

SDC-TRAP-#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0146	1295
SDC-TRAP-0169	611
SDC-TRAP-0161	3694
SDC-TRAP-0172	<78 56
SDC-TRAP-0180	325
SDC-TRAP-0181	164
SDC-TRAP-0185	38
SDC-TRAP-0186	1,619
SDC-TRAP-0184	4,002
SDC-TRAP-0205	564
SDC-TRAP-0206	321
SDC-TRAP-0207	>5,000
SDC-TRAP-0204	>10,000
SDC-TRAP-0208	480
SDC-TRAP-0209	1,130
SDC-TRAP-0210	>10,000
SDC-TRAP-0213	248
SDC-TRAP-0212	2,294
SDC-TRAP-0201	4,670
SDC-TRAP-0202	>5,000
SDC-TRAP-0214	>5,000
SDC-TRAP-0215	2,746
SDC-TRAP-0220	474 445
SDC-TRAP-0203	446

Hsp90$^{\alpha}$ binding assay

No	SDC-TRAP-#	Binding EC_{50} (nM)
1	SDC-TRAP-0045	96.6
2	SDC-TRAP-0046	101.8
3	SDC-TRAP-0063	157.5
4	SDC-TRAP-0064	122.2
5	SDC-TRAP-0184	86.62
6	SDC-TRAP-0204	82.59
7	SDC-TRAP-0209	54.59
8	SDC-TRAP-0210	91.03

Mouse plasma stability data

SDC-TRAP-#	% Remaining (1h, 37 °C)
SDC-TRAP-0022	21%
SDC-TRAP-0028	41%
SDC-TRAP-0029	47%
SDC-TRAP-0037	95%
SDC-TRAP-0044	61%
SDC-TRAP-0045	45%
SDC-TRAP-0046	52%
SDC-TRAP-0054	41.0%
SDC-TRAP-0071	102%
SDC-TRAP-0076	96%
SDC-TRAP-0104	95.5%
SDC-TRAP-0063	11.1%
SDC-TRAP-0064	91.5%
SDC-TRAP-0172	74.7%
SDC-TRAP-0180	72.4%
SDC-TRAP-0184	18.0%
SDC-TRAP-0185	68.1%
SDC-TRAP-0186	57.9%
SDC-TRAP-0042	74%
SDC-TRAP-0047	89%
SDC-TRAP-0055	103%
SDC-TRAP-0056	78%
SDC-TRAP-0059	51%
SDC-TRAP-0145	14.1%
SDC-TRAP-0203	71.2%
SDC-TRAP-0215	77.2%
SDC-TRAP-0216	67.7%
SDC-TRAP-0220	78.3%
SDC-TRAP-0202	21.2%
SDC-TRAP-0205	58.4%
SDC-TRAP-0206	68.6%
SDC-TRAP-0208	86.1%

SDC-TRAP-#	% Remaining (1h, 37 °C)
SDC-TRAP-0209	67.1%
SDC-TRAP-0213	74.7%

Tissue distribution data for SDC-TRAP-0045

Analyte	Plasma Conc. (μM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
Target	SDC-TRAP-0045	SDC-TRAP-0053	SN-38	SDC-TRAP-0045	SDC-TRAP-0053	SN-38	SDC-TRAP-0045	SDC-TRAP-0053	SN-38
Time (h)									
0.083	689	2.70	0.0716	4.30	0.0461	0.344	0.00624	0.0171	4.80
6	1.88	0.289	0.00471	2.55	0.590	0.473	1.35	2.04	101
12	0.141	0.0953	BQL	1.13	0.780	0.229	8.02	8.18	--
24	0.0113	0.0464	BQL	BQL	0.0622	0.0596	---	1.34	---
48	BQL	0.00618	BQL	BQL	0.764	BQL	--	124	--

Tissue distribution data for SDC-TRAP-0046

Analyte Target	Plasma Conc. (μM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
	SDC-TRAP-0046	SDC-TRAP-0052	SN-38	SDC-TRAP-0046	SDC-TRAP-0052	SN-38	SDC-TRAP-0046	SDC-TRAP-0052	SN-38
Time (h)									
0.083	360	0.0782	2.29	6.94	BQL	0.298	0.0193	--	0.130
6	5.88	0.0917	0.0773	4.97	0.241	0.448	0.844	2.63	5.80
12	2.37	0.0612	0.0389	5.21	0.407	0.344	2.20	6.65	8.83
24	0.0542	0.0364	0.00955	2.19	1.71	1.01	40.3	46.9	105
48	BQL	0.0107	BQL	0.188	1.01	BQL	--	94.4	--

Tissue distribution data for SDC-TRAP-0056

Analyte Target	Plasma Conc. (µM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
	SDC-TRAP-0056	SDC-TRAP-0096	SN-38	SDC-TRAP-0056	SDC-TRAP-0096	SN-38	SDC-TRAP-0056	SDC-TRAP-0096	SN-38
Time (h)									
0.083	1220	274	134	6.40	1.654	1.18	0.00525	0.00604	0.00881
6	2.06	0.510	0.483	2.65	0.726	0.490	1.28	1.42	1.02
12	0.382	0.151	0.176	0.746	0.252	0.152	1.95	1.67	0.86
24	0.0343	0.0130	0.0235	BQL	BQL	0.105	--	---	4.48
48	BQL	BQL	BQL	BQL	0.0581	0.0259	--	--	--

Tissue distribution data for SDC-TRAP-0063

Analyte Target	Plasma Conc. (µM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
	SDC-TRAP-0063	DP-1	SN-38	SDC-TRAP-0063	DP-1	SN-38	SDC-TRAP-0063	DP-1	SN-38
Time (h)									
0.083	526	0.0662	20.4	6.43	0.00758	1.47	0.0122	0.114	0.0721
6	1.69	0.0397	0.0509	1.61	0.111	0.730	0.958	2.79	14.3
24	0.00675	0.0175	0.0240	0.203	0.404	0.618	30.1	23.1	25.8
48	BQL	0.00793	0.00524	0.0188	1.06	0.296	--	134	56.4

Tissue distribution data for SDC-TRAP-0076

Analyte	Plasma Conc. (μM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
Target	SDC-TRAP-0076		SN-38	SDC-TRAP-0076		SN-38	SDC-TRAP-0076		SN-38
Time (h)									
0.083	671	--	73.4	8.66	--	0.503	0.01	--	0.01
1	52.9	--	8.60	9.12	--	0.642	0.17	--	0.07
6	4.00	--	1.18	8.98	--	0.670	2.25	--	0.57
24	0.359	--	0.0755	7.32	--	0.572	20.4	--	7.58
48	1.11	--	0.160	7.60	--	0.489	6.85	--	3.06

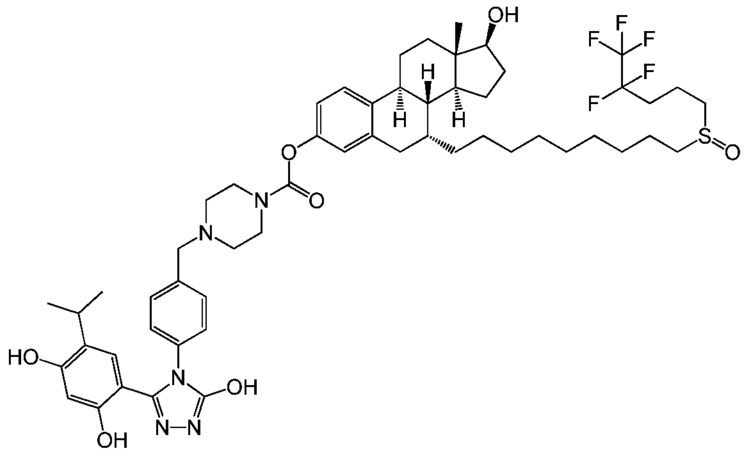
Tissue distribution data for SDC-TRAP-0154

Analyte	Plasma Conc. (μM)			Tumor Conc. (nmol/g of tissue)			Tumor/Plasma Ratio		
Target	SDC-TRAP-0154	SDC-TRAP-0179	SN-38	SDC-TRAP-0154	SDC-TRAP-0179	SN-38	SDC-TRAP-0154	SDC-TRAP-0179	SN-38
Time (h)									
0.083	928	84.3	34.5	11.8	0.350	0.241	0.01	0.004	0.007
1	251	14.6	4.34	14.1	0.732	0.463	0.06	0.05	0.11
6	5.08	1.50	1.12	9.46	0.656	0.293	1.86	0.44	0.26
24	0.198	0.0428	0.0198	2.35	0.115	0.0562	11.9	2.68	2.84
48	0.0218	0.00344	BQL	1.88	0.0921	0.0465	86.0	26.8	--

[001247] Example 28: SDC-TRAP comprising fulvestrant

[001248] SDC-TRAP-0148

[001249] (7R,8R,9S,13S,14S,17S)-17-hydroxy-13-methyl-7-(9-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate

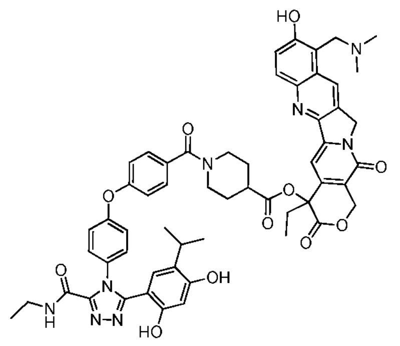


[001250] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 9.61 (s, 1H), 9.42 (s, 1H), 7.30 (dd, *J* = 25.2, 8.6 Hz, 3H), 7.18 – 7.11 (m, 2H), 6.88 – 6.75 (m, 3H), 6.26 (s, 1H), 4.51 (dd, *J* = 4.6, 2.5 Hz, 1H), 3.53 (d, *J* = 16.6 Hz, 5H), 2.97 (p, *J* = 6.9 Hz, 1H), 2.91 – 2.58 (m, 8H), 2.43 – 2.22 (m, 6H), 2.04 – 1.77 (m, 7H), 1.66 – 1.44 (m, 4H), 1.42 – 1.13 (m, 18H), 0.92 (dd, *J* = 22.4, 7.1 Hz, 6H), 0.67 (s, 3H); ESMS calculated for $C_{55}H_{72}F_5N_5O_7S$: 1041.51; Found: 1042.9 $(M+H)^+$.

[001251] Example 29: SDC-TRAP comprising topotecan

[001252] SDC-TRAP-0159

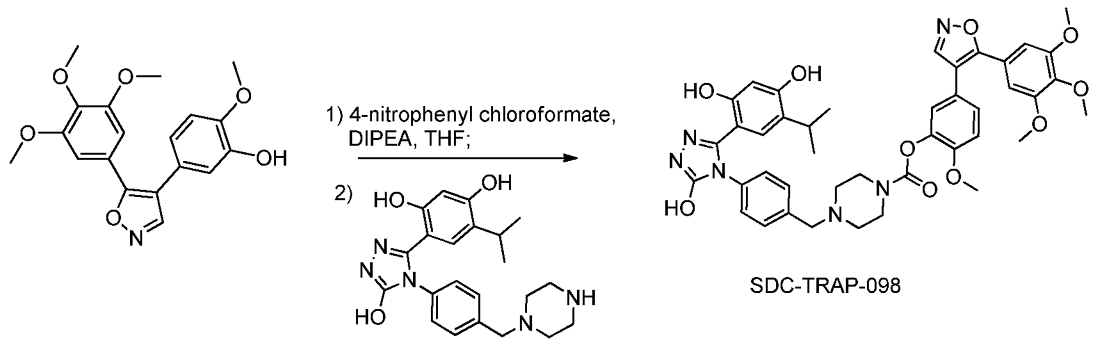
[001253] 10-((dimethylamino)methyl)-4-ethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl-1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)benzoyl)piperidine-4-carboxylate



[001254] ESMS calculated ($C_{56}H_{56}N_8O_{11}$): 1016.4; found: 1017.6 (M+H).

[001255] Example 30: SDC-TRAPs comprising VDAs (Vascular Disrupting Agents)

[001256] 2-Methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl-4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)benzyl) piperazine-1-carboxylate



SDC-TRAP-098

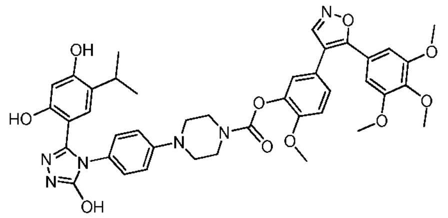
[001257] To a solution of 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl) phenol (0.1 g, 0.28 mmol) in THF (4 mL) was added 4-nitrophenyl chloroformate (0.07 g, 0.35 mmol) and DIPEA (0.1 mL, 0.57 mmol). The reaction was stirred at room temperature for 30 min before adding a solution of 4-(5-hydroxy-4-(4-(piperazin-1-yl methyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (0.13 g, 0.31 mmol) and DIPEA (0.1 mL, 0.57 mmol) in DMF (2 mL). After stirring at room temperature for 30 min, the reaction was diluted with H_2O (10 mL), extracted with EtOAc (10 mL×3), and the combined organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave SDC-TRAP-0098 (0.13 g, 59%).

[001258] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.52 (s, 1H), 7.52 – 7.44 (m, 2H), 7.29 (td, J = 8.3, 2.0 Hz, 3H), 7.19 – 7.09 (m, 2H), 6.92 (s, 2H), 6.74 (s, 1H), 6.29 (s, 1H), 3.85 (s, 3H), 3.80 (s, 3H), 3.73 (s, 6H) 3.68 (s, 2H), 3.62 (s, 2H), 3.53 (s, 2H), 3.03 (p, J = 6.9 Hz, 1H), 2.52 (t, J

= 4.7 Hz, 4H), 0.92 (d, *J* = 6.9 Hz, 6H); ESMS calculated ($C_{42}H_{44}N_6O_{10}$): 792.3; found: 793.2 (M+H).

[001259] SDC-TRAP-0099

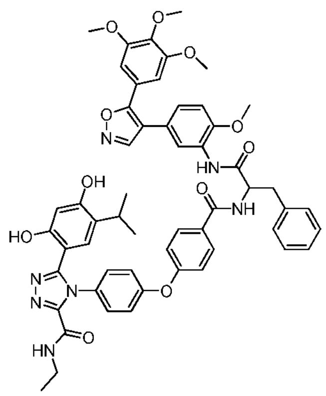
[001260] 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl-4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)phenyl) piperazine-1-carboxylate



[001261] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 9.60 (s, 1H), 9.45 (s, 1H), 8.87 (s, 1H), 7.33 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.27 (d, *J* = 2.2 Hz, 1H), 7.20 (d, *J* = 8.6 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.88 (s, 2H), 6.79 (s, 1H), 6.26 (s, 1H), 3.79 (s, 3H), 3.70 (d, *J* = 1.1 Hz, 10H), 3.53 (s, 2H), 3.23 – 3.14 (m, 5H), 2.98 (p, *J* = 6.8 Hz, 1H), 0.97 (d, *J* = 6.8 Hz, 6H); ESMS calculated ($C_{41}H_{42}N_6O_{10}$): 778.3; found: 779.2 (M+H).

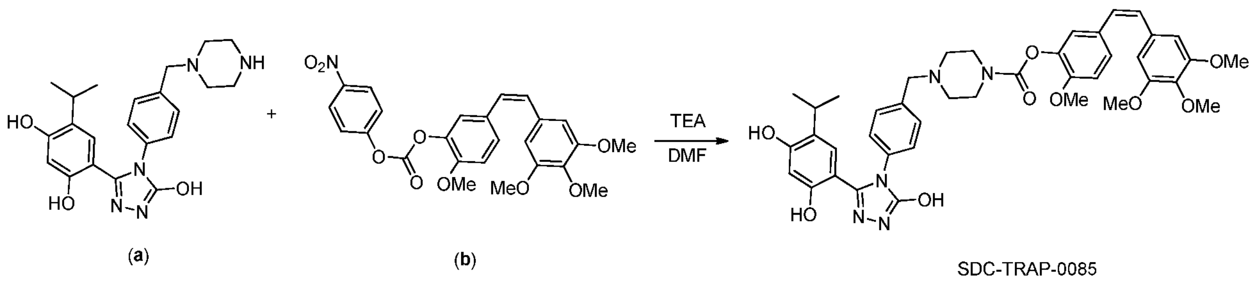
[001262] SDC-TRAP-0158

[001263] 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(4-((1-((2-methoxy-5-(5-(3,4,5 -trimethoxyphenyl)isoxazol-4-yl)phenyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamoyl)phen oxy)phenyl)-4H-1,2,4-triazole-3-carboxamide ESMS calculated ($C_{55}H_{53}N_7O_{11}$): 987.4; found: 988.3 (M+H).



[001264] SDC-TRAP-0085

[001265] (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl) piperazine-1-carboxylate

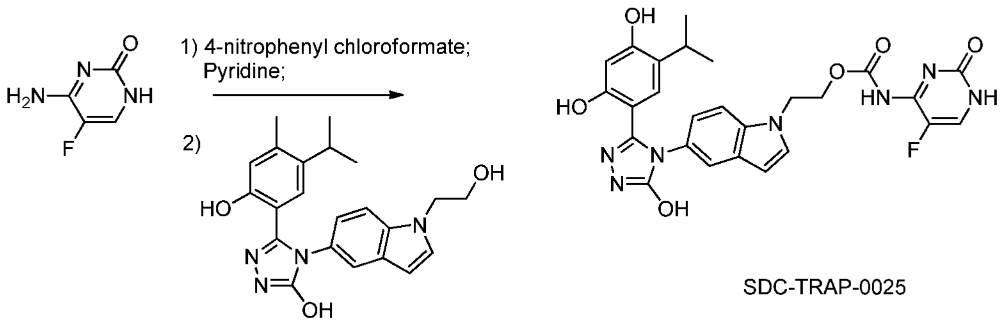


[001266] A mixture of 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (a, 0.1 mmol), (Z)-2-methoxy-5-(3,4,5-trimethoxystyryl)phenyl (4-nitrophenyl) carbonate (b, 0.1 mmol) and TEA (0.2 mmol) in DMF (2 mL) was stirred at room temperature for 2 days. The mixture was diluted with water (50 mL) and extracted with EtOAc. The organic layers were combined, concentrated and purified by column to give SDC-TRAP-0085 as a white solid (13 mg, 0.02 mmol).

[001267] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.78 (s, 1H), 9.76 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.15 – 7.04 (m, 2H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.56 – 6.38 (m, 6H), 6.35 (s, 1H), 3.82 (d, *J* = 10.9 Hz, 6H), 3.71 (s, 9H), 3.57 (d, *J* = 16.1 Hz, 4H), 2.53 (s, 4H), 0.70 (d, *J* = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{41}H_{45}N_5O_9$: 751.3; found: 752.2 (M + H^+).

[001268] SDC-TRAP-0025

[001269] 1-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4*H*-1,2,4-triazol-4-yl)-1*H*-indol-1-yl)ethyl)-3-(5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl)urea



[001270] To a solution of 5-fluorocytosine (0.14 g, 1.1 mmol) in pyridine (4 mL) was added 4-nitrophenyl chloroformate (0.22 g, 1.1 mmol). The reaction was heated in a microwave at 90 °C for 30 min. To the resulting solution was added 4-(5-hydroxy-4-(1-(2-hydroxyethyl)-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (0.15 g, 0.38 mmol). The reaction was heated in microwave at 100 °C for 1 hr. The solution was concentrated and column chromatography gave SDC-TRAP-0025 (0.07 g, 34%).

[001271] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 9.52 (s, 1H), 9.46 (d, J = 4.8 Hz, 1H), 8.10 – 7.82 (m, 2H), 7.59 – 7.39 (m, 3H), 6.95 (t, J = 7.7 Hz, 1H), 6.73 (d, J = 9.6 Hz, 1H), 6.44 (dd, J = 16.8, 3.3 Hz, 1H), 6.22 (s, 1H), 4.31 (dt, J = 12.6, 6.4 Hz, 2H), 3.57 – 3.48 (m, 2H), 2.90 (h, J = 7.1 Hz, 1H), 0.84 (t, J = 7.8 Hz, 6H); ESMS calculated ($C_{26}H_{25}FN_8O_5$): 548.2; found: 549.1 (M+H).

[001272] *in vitro* activity was determined for these compounds using the HER2 degradation assay set forth herein:

SDC#	HER2 degradation IC_{50} (nM)
SDC-TRAP-0148	3037
SDC-TRAP-0159	>1000
SDC-TRAP-0098	232
SDC-TRAP-0099	677
SDC-TRAP-0158	>5000
SDC-TRAP-0085	889
SDC-TRAP-0025	403

Mouse plasma stability data

Compound ID	% Remaining (1h)
SDC-TRAP-0098	96.0%
SDC-TRAP-0099	95.2%
SDC-TRAP-0158	92.7%

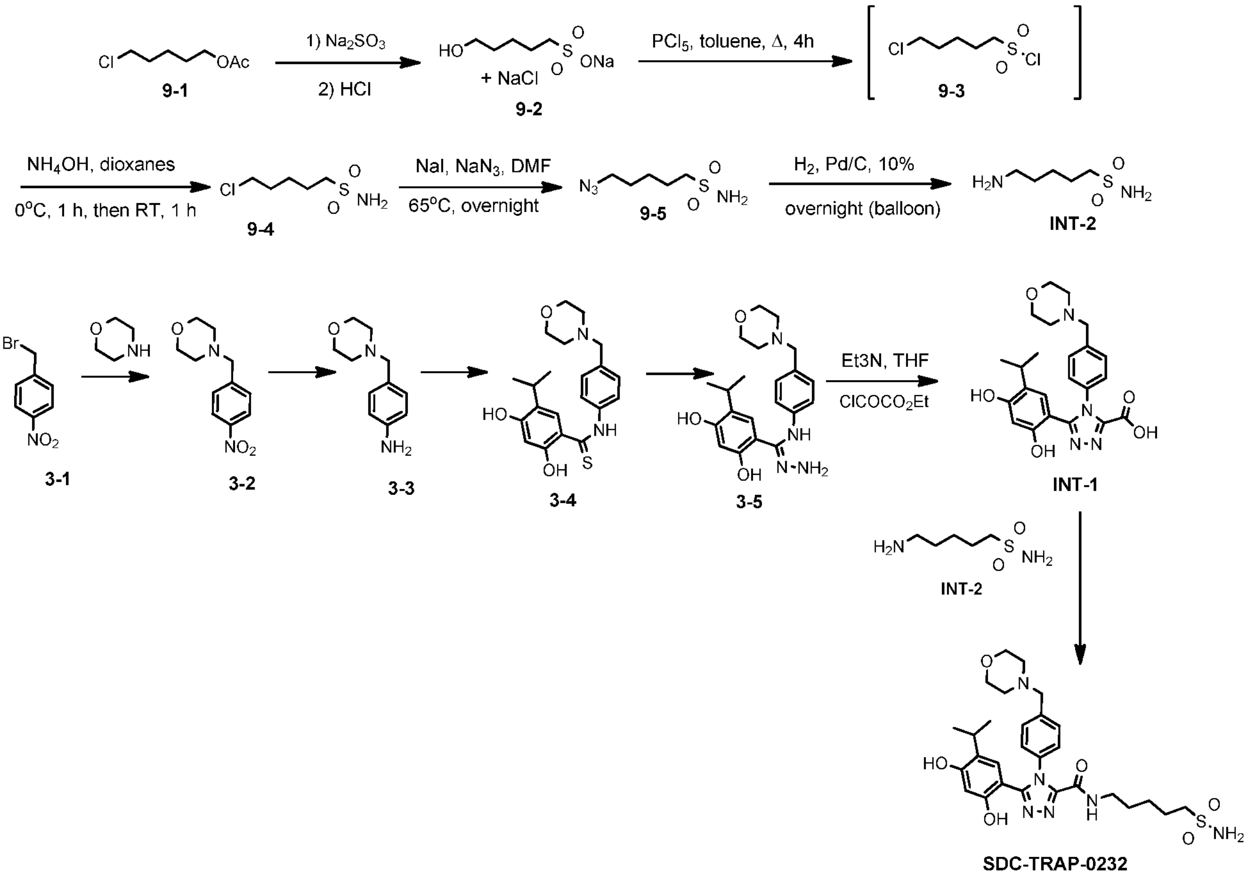
Tissue distribution data for SDC-TRAP-0098

Analyte Target	Plasma Conc. (µM)				Tumor Conc. (nmol/g of tissue)			Tumor/ Plasma Ratio	
	.8	SDC-TRAP-0052	SDC-TRAP-0001	SDC-TRAP-0098	SDC-TRAP-0052	SDC-TRAP-0001	SDC-TRAP-0098	SDC-TRAP-0052	SDC-TRAP-0001
Time (h)									
0.083	481	0.0833	0.700	5.02	0.0175	0.0360	0.01	0.21	0.05
1	7.48	0.437	0.250	4.62	0.111	0.161	0.62	0.25	0.65
6	0.387	0.131	0.0122	3.18	0.292	0.117	8.22	2.23	9.64
24	0.00306	0.0375	BQL	0.920	0.611	0.0614	300	16.3	--
48	BQL	0.0125	BQL	0.182	0.770	0.0211	--	61.8	--

[001273] Example 31: SDC-TRAP-0232

[001274] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(morpholinomethyl)phenyl)-N-(5-sulfamoylpentyl)-4H-1,2,4-triazole-3-carboxamide

[001275] The synthesis of SDC-TRAP-0232 is outlined in the following scheme. The final amide coupling was performed using boric acid as the catalyst in reflux dioxane. The synthesis of INT-2 is described elsewhere in literature.



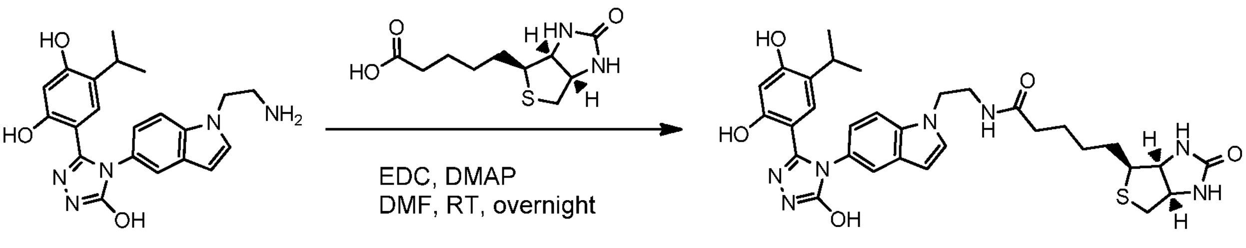
[001276] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (t, J = 6Hz, 1H), 7.39 (d, J = 8Hz, 2H), 7.30 (d, J = 8Hz, 2H), 6.71 (bs, 1H), 6.53 (s, 1H), 6.28 (s, 1H), 3.59 (bs, 4H), 3.50 (s, 2H), 3.31 (bs, 1H), 3.23-3.11 (m, 2H), 2.94-2.87 (m, 2H), 2.38 (bs, 4H), 1.67-1.61 (m, 2H), 1.47-1.36 (m, 2H), 1.36-1.30 (m, 2H), 0.78 (d, J = 7.2Hz, 6H). ESMS calculated ($C_{28}H_{38}N_6O_6S$): 586.26; found: 587.2 (M+H).

[001277] **Example 32: SDC-TRAP-233**

[001278] SDC-TRAP-0233

[001279] N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1 H-indol-1-yl)ethyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamide

[001280] SDC-TRAP-0233 was synthesized from the corresponding HSP90 inhibitor using standard amide coupling conditions.



[001281] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 9.54 (s, 1H), 9.46 (d, J = 4.8 Hz, 1H), 7.94-7.93 (m, 1H), 7.47-7.36 (m, 3H), 6.95-6.92 (m, 1H), 6.77 (s, 1H), 6.44-6.37 (m, 3H), 6.22 (s, 1H), 4.32-4.10 (m, 4H), 3.37-3.35 (m, 2H), 3.10-3.06 (m, 1H), 2.95-2.88 (m, 1H), 2.84-2.79 (m, 1H), 2.58 (d, J = 12.0 Hz, 1H), 2.02 (t, J = 8.0 Hz, 2H), 1.60-1.26 (m, 6H), 0.86 (t, J = 7.8 Hz, 6H).

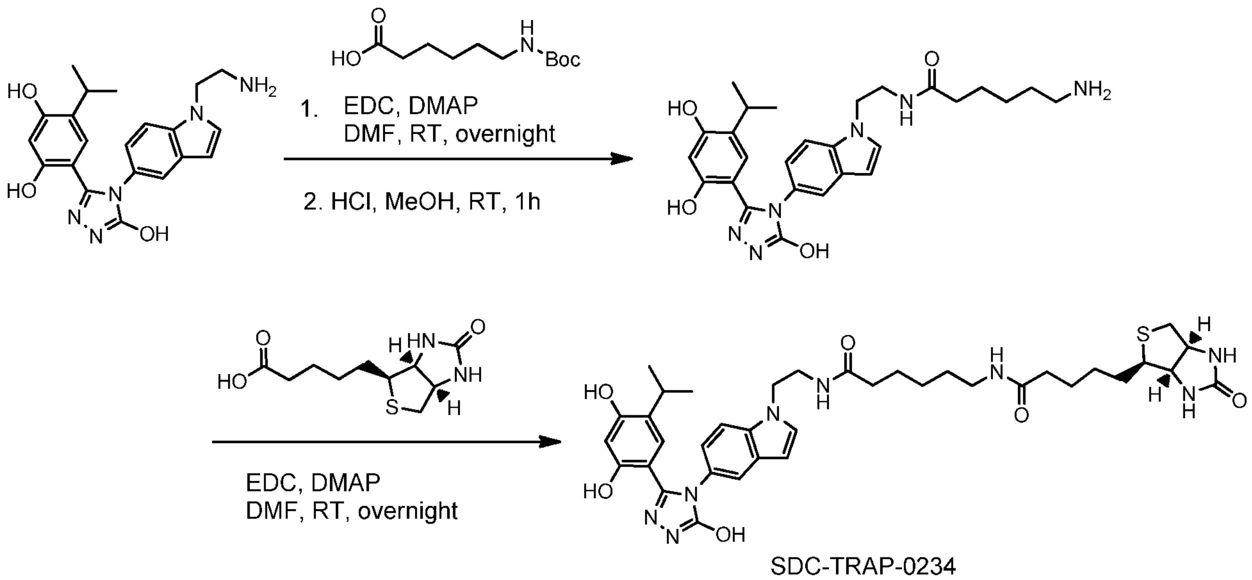
[001282] ESMS calculated (C31H37N7O5S): 619.2; found: 620.2 (M+H).

[001283] **Example 33: SDC-TRAP-234**

[001284] SDC-TRAP-0234

[001285] N-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-6-(5-((3aR,4R,6aS)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)hexanamide

[001286] SDC-TRAP-0234 was synthesized starting from the corresponding HSP90 inhibitor with the coupling of a Boc protected aminohexanoic acid. Subsequent deprotection followed by coupling of biotin using standard coupling conditions afforded the desired product.



SDC-TRAP-0234

[001287] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.86 (s, 1H), 9.55 (s, 1H), 9.46 (s, 1H), 7.93 (t, J = 6.0 Hz, 1H), 7.74 (t, J = 6.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 4.0 Hz, 1H), 7.35 (d, J = 4.0 Hz, 1H), 6.94 (dd, J = 8.0, 4.0 Hz, 1H), 6.76 (s, 1H), 6.43-6.41 (m, 2H), 6.36 (s, 1H), 6.22 (s, 1H), 4.31-4.10 (m, 4H), 3.09-2.79 (m, 8H), 2.05-2.01 (m, 4H), 1.61-1.12 (m, 12H), 0.86 (t, J = 7.8 Hz, 6H). ESMS calculated (C37H48N8O6S): 732.34; found: 733.3 (M+H).

[001288] **Example 34: Identification and Use of SDC-TRAP for Prevention and Treatment of Chronic Bronchitis and Asthma**

[001289] Chronic bronchitis is a chronic inflammation of the bronchi in the lungs. It is generally considered one of the two forms of chronic obstructive pulmonary disease (COPD), the other being emphysema. It is defined clinically as a persistent cough that produces sputum (phlegm) and mucus, for at least three months per year in two consecutive years.

[001290] Asthma is an inflammatory disorder that causes the airways of the lungs to swell and narrow, leading to wheezing, shortness of breath, chest tightness, and coughing. Asthma can be chronic or be triggered by environmental triggers including, but not limited to, animal hair or dander, dust, changes in weather, exercise, mold, and pollen.

[001291] Drugs used for the treatment of chronic bronchitis, COPD, and asthma include, but are not limited to, smooth muscarinic acetylcholine receptor inhibitors such as ipratropium bromide; anticholinergic bronchodilators such as tiotropium; long-acting β2-adrenergic receptor agonists such as salmeterol, formoterol, and albuterol; anti-inflammatory agents such

as inhaled steroids, montelukast, a leukotriene receptor antagonist (LTRA), and roflumilast, a selective, long-acting inhibitor of the enzyme phosphodiesterase-4 (PDE-4); xanthines such as theophylline; and mucolytic agents such as bromhexine and acetylcysteine. In cases where chronic bronchitis is caused or exacerbated by bacterial infection, antibiotics can be used for treatment.

[001292] Many of the agents used for the treatment of chronic bronchitis, COPD, and asthma work through receptors that are present throughout the body, thereby potentially causing undesirable side effects. Although many of the drugs are available for administration by inhalation, which can increase delivery to the target site and reduce side effects, decreased lung function in the disease population may result in improper dosing and reduced compliance.

[001293] Roflumilast (3-(cyclopropylmethoxy)-N-(3,5-dichloropyridin-4-yl)-4-(difluoromethoxy)benzamide), a selective, long-acting inhibitor of the enzyme phosphodiesterase-4 (PDE-4), is formulated as a tablet for oral administration and is approved for use in the treatment of chronic bronchitis and COPD. Roflumilast can be used as a binding moiety in combination with one or more drugs to make an SDC-TRAP that can be used for the treatment of chronic bronchitis, COPD, or asthma, such as those listed above and throughout the application, to target other agents to the site of interest, *i.e.*, the lungs, while permitting oral delivery.

[001294] A roflumilast–effector molecule SDC-TRAP can be formed, for example, using any known linker, such as those provided herein, with the desired effector molecule. The specific linker and conjugation method used will depend, for example, on the chemical nature of the effector molecule.

[001295] Assays to determine the cytotoxicity of the roflumilast SDC-TRAP molecule conjugate are performed using methods similar to those provided in Example 4. Cell viability assays are performed on non-transformed cells, preferably lung cells, to identify SDC-TRAPs with acceptable toxicities, preferably compounds with toxicity that is not greater than either of the parent compounds.

[001296] Roflumilast SDC-TRAP molecules are also tested to confirm that their efficacy is not inhibited by the formation of the complex. Assays to test PDE-4 activity are well known in the art and are commercially available (*e.g.*, PerkinElmer LANCE® Ultra cAMP kit). The activity of the effector molecule is tested using appropriate methods.

[001297] Methods to assess pharmacokinetic and pharmacodynamic properties of an agent are well known in the art. Tissue distribution studies are performed to assess distribution of the conjugate as compared to distribution of each roflumilast and the effector molecule. An increase accumulation of the roflumilast SDC-TRAP molecules in the lung as compared to the unconjugated effector molecule is observed. Such assays are performed using orally delivered SDC-TRAPs of active agents that may typically be administered by inhalation. Roflumilast SDC-TRAP molecules are also identified for having longer serum stability.

[001298] Having identified roflumilast SDC-TRAP molecules with the desired activity, cytotoxicity, pharmacokinetic properties, and improved pulmonary delivery, the SDC-TRAPs are tested for their efficacy of an appropriate animal model of chronic bronchitis, COPD, and/or asthma. Animal models of chronic bronchitis, COPD, and asthma are well known in the art. The activity of the conjugate is compared to the activity of each roflumilast and the effector molecule alone. Roflumilast SDC-TRAP molecules having one or more improved properties as compared to either of the parent molecules are further characterized in other animal systems and humans.

[001299] The SDC-TRAPs are found to have one or more improved properties in the treatment of humans including, but not limited to, decreased toxicity, improved dosing schedule, or improved efficacy.

[001300] Example 35: Identification and Use of SDC-TRAP for Prevention and Treatment of Skin Cancers and Actinic Keratosis

[001301] Skin cancers (neoplasms) are named after the type of skin cell from which they arise. Skin cancers include basal cell carcinoma, squamous cell carcinoma, malignant melanomas, and Bowen's disease. Actinic keratosis can be, but is not always, a precursor to squamous cell carcinoma.

[001302] Drugs used for the treatment of skin cancer are selected based on the type and severity of the skin cancer. Superficial, non-melanoma skin cancers can be treated with topical agents, either alone or in combination with surgery or other therapeutic interventions. Such agents include, but are not limited to, retinoids, 5-fluorouracil, diclofenac, ingenol mebutate, and imiquimod. Topical delivery permits administration of the chemotherapeutic agent directly to the site of the tumor or skin lesion. However, the delivery of active agents into the skin can be challenging. Moreover, many topical therapeutic agents can be irritating to the skin, resulting in scar formation, further inhibiting the delivery of the active agent to the site.

[001303] Imiquimod 3-(2-methylpropyl)-3,5,8-triazatricyclo[7.4.0.02,6]trideca-1(9),2(6),4,7,10,12-hexaen-7-amine) is a patient-applied cream used to treat certain diseases of the skin, including skin cancers (basal cell carcinoma, Bowen's disease, superficial squamous cell carcinoma, some superficial malignant melanomas, and actinic keratosis) as well as genital warts (condylomata acuminata). Imiquimod and its analogs activate the immune system by activating immune cells through the toll-like receptor 7 (TLR7), commonly involved in pathogen recognition. Imiquimod can be used in combination with one or more drugs used for the treatment of skin diseases to make an SDC-TRAP molecule.

[001304] An imiquimod SDC-TRAP molecule can be formed, for example, using any known linker, such as those provided herein, with the desired effector molecule. The specific linker and conjugation method used will depend, for example, on the chemical nature of the effector molecule.

[001305] Assays to determine the cytotoxicity of the imiquimod SDC-TRAP molecules are performed using methods similar to those provided in Example 4. Cell viability assays are performed on non-transformed cells, preferably skin cells, to identify SDC-TRAPs with acceptable toxicities, preferably compounds with toxicity that is not greater than either of the parent compounds. Cytotoxicity and skin irritation assays are also performed, for example, on pig skin, which is frequently used as a model for human skin in toxicity/ irritation assays, using routine methods.

[001306] Imiquimod SDC-TRAP molecules are also tested to confirm that their efficacy is not inhibited by the formation of the conjugate. A number of skin cancer cell lines are well known in the art. Dose response curves are generated to demonstrate the efficacy of imiquimod SDC-TRAP molecules in killing cancer cells. Preferably, the imiquimod SDC-TRAP molecules are more effective at killing skin cancer cells than imiquimod or the effector molecule alone.

[001307] Methods to assess pharmacokinetic and pharmacodynamic properties of an agent are well known in the art. As noted above, pig skin is frequently used as a model for human skin, both in toxicity/ irritation assays, but also in assaying uptake and delivery of agents into skin layers and cells. Topical formulations of imiquimod, the effector molecule, and imiquimod SDC-TRAP molecules are assayed for uptake, transport through the skin, and persistence in the skin using routine methods.

[001308] Having identified a imiquimod SDC-TRAP molecule with the desired activity, cytotoxicity, pharmacokinetic properties, and improved tissue delivery, the SDC-TRAPs are tested for their efficacy in an appropriate animal model of skin cancer. A animal models of skin cancer are well known in the art. For example, xenograph tumor models using squamous cell carcinoma, basal cell carcinoma, or melanoma cell lines are used with subcutaneously implanted tumors. Topical formulations of imiquimod, the effector molecule, and imiquimod SDC-TRAP molecules are applied. The activity of the conjugate is compared to the activity of each imiquimod and the effector molecule alone. Imiquimod SDC-TRAP molecules having one or more improved properties as compared to either of the parent molecules are further characterized in other animal systems and humans.

[001309] The SDC-TRAPs are found to have one or more improved properties in the treatment of humans including, but not limited to, decreased toxicity, improved dosing schedule, or alternate route of administration.

[001310] Example 36: Determining the Permeability of SDC-TRAP Molecules

[001311] In order to test the ability SDC-TRAP molecules of the invention to enter cells, an artificial membrane permeability assay ("PAMPA") was used. PAMPAs are useful tool for predicting *in vivo* drug permeability for drugs that enter cells by passive transport mechanisms. LC/MS was used in conjunction with PAMPA assays to determine the ability of the SDC-TRAP molecules of the invention to permeate cells.

[001312] Pre-coated PAMPA plates were warmed to room temperature for at least 30 minutes prior to adding assay components.

[001313] Stock solutions were prepared with the SDC-TRAP molecules to be tested. In order to make a working solution, either 50 μL of 100 μM Stock in DMSO + 950 μL of PBS or 50 μL of 200 μM stock was added to 96 deep well plate, resulting in a 5 μM final concentration or a 10 μM final concentration, respectively. 300μL of the working solution containing each compound to be tested was added to the appropriate well of a donor PAMPA plate. 200 μL of PBS was added into the corresponding wells of an acceptor PAMPA plates.

[001314] The acceptor plate was lowered onto the donor plate and allowed to incubate for five hours. After five hours, a 50 μL aliquot was removed from each well of each plate and added into a new 96 deep-well plate.

[001315] 100 μL of methanol containing an internal standard was added to each aliquot and analyzed by LC/MS. The internal standard was 150ng/ml SDC-TRAP-0002.

[001316] In order to calculate the permeability for each SDC-TRAP molecule and the control molecules, the following formula was used:

Permeability (in unit of cm/s):

$$P_e = \frac{-\ln[1 - C_A(t) / C_{equilibrium}]}{A * (1/V_D + 1/V_A) * t}$$

$$C_{equilibrium} = \frac{C_D(t) * V_D + C_A(t) * V_A}{V_D + V_A}$$

Mass Retention:

$$R = \frac{1 - [C_D(t) * V_D + C_A(t) * V_A]}{C_0 * V_D}$$

C_0 = initial compound concentration in donor well (mM)
C_D (t) = compound concentration in donor well at time t. (mM)
C_A (t) = compound concentration in acceptor well at time t. (mM)
V_D = donor well volume = 0.3 mL
V_A = acceptor well volume = 0.2 mL
A = filter area = 0.3 cm^2
t = incubation time = 18000 s (5 h)

[001317] For the data presented in the table below, peak area was used in place of concentration in the formula above.

SDC-TRAP-#	Permeability (cm/s)	Permeability (10^{-6} cm/s)	Mass Retention (%)
SDC-TRAP-0018	2.68E-08	0.0268	14.7
SDC-TRAP-0048	2.83E-08	0.0283	10.8
SDC-TRAP-0049	1.24E-08	0.0124	14.1
SDC-TRAP-0052	7.69E-09	0.00769	7.02
SDC-TRAP-0062	2.50E-08	0.025	18.0

SDC-TRAP-#	Permeability (cm/s)	Permeability (10^{-6} cm/s)	Mass Retention (%)
SDC-TRAP-0193	8.59E-09	0.00859	10.2
SDC-TRAP-0195	0.00E+00	0	27.1
SDC-TRAP-0196	0.00E+00	0	22.3
SDC-TRAP-0210	0.00E+00	0	34.8
SDC-TRAP-0232	6.89E-09	0.00689	21.0
SDC-TRAP-0233	2.10E-08	0.021	10.9
SDC-TRAP-0234	1.23E-08	0.0123	9.56
Doxorubicin	3.30E-09	0.0033	21.0
Docetaxel	5.00E-08	0.05	17.6
SN-38	6.43E-07	0.643	38.2
Lenalidomide	6.20E-08	0.062	26.0
Furosemide	1.47E-08	0.0147	7.53
Caffeine	1.17E-05	11.7	20.8

[001318] The same protocol was used to test the permeability of the SDC-TRAP molecules identified in the table below.

SDC-TRAP-#	Permeability (cm/s)	Permeability (10^{-6} cm/s)	Mass Retention (%)
SDC-TRAP-0029	6.46E-09	0.00646	84.0
SDC-TRAP-0046	1.22E-08	0.0122	88.1
SDC-TRAP-0063	0E+00	0	18.7
SDC-TRAP-0064	0E+00	0	48.4
SDC-TRAP-0154	0E+00	0	10.3
SDC-TRAP-0200	0E+00	0	10.6
SDC-TRAP-0205	0E+00	0	10.9
SDC-TRAP-0208	0E+00	0	25.0
SDC-TRAP-0210	8.99E-09	0.00899	72.2
SN-38	1.87E-06	1.87	46.6
Furosemide	2.50E-08	0.025	2.63
Caffeine	1.43E-05	14.3	-0.11

[001319] Example 37: Physical Properties and Further Characterization of SDC-TRAP-0063.

[001320] SDC-TRAP-0063 is a light yellow solid having the following chemical properties:

MW	380.46
Formula	C49H49N7O9
cLogP	4.15
LogP	4.69
pKa	9.27; 10.1
Melting Point	239°C
Solubility (mg/mL)	
In water (pH = 9.7)	0.033
In water (pH = 11.8*)	0.926 (not stable)
In EtOH:	1.56
In PEG300:	5.64

[001321] SDC-TRAP-0063 is an Hsp90 inhibitor based, for example, upon 1. co-crystallization of SDC-TRAP-0063 with Hsp90a N-terminal at Shanghai Medicilon; 2. Kd/Ki of SDC-TRAP-0063 in binding with Hsp90; and 3. client protein degradation (her2 in BT-474). SDC-TRAP-0063 can kill cells thru topoisomerase inhibition based, for example, upon 1. cytotoxicity of SDC-TRAP-0063 in multiple cell lines; 2. Topoisomerase I inhibition; 3. detection of SN-38 *in vivo*; and 4. PD (γH2AX) in mouse xenograft. As discussed in further detail in the following examples, SDC-TRAP-0063 demonstrates superior efficacy in mouse xenografts including HCT116 (Colon Cancer), MCF-7 (Breast Cancer), SKOV-3 (Ovarian Cancer), and SCLC1 (Small Cell Lung Cancer).

[001322] Determination of equilibrium solubility of SDC-TRAP-0063

[001323] Preparation of samples: A known (excess) amount of SDC-TRAP-0063 (lot 6 and lot 8) was added to the ganetespib placebo formulation (35% v/v tween 80, 40% v/v PEG-300, 25% v/v dehydrated alcohol), mixed well and kept at ambient.

[001324] HPLC analysis: Concentration of dissolved drug was determined by HPLC assay method at 1 hr, 1 day, 3 days and 7 days.

[001325] Observations: The solubility of SDC-TRAP-0063 (both lots) appear to decrease over time, although no any degradation was observed. Solubility determination at further time-points (> 7 days) would be required to find the equilibrium solubility of SDC-TRAP-0063 lots.

[001326] Kinetic solubilities of SDC-TRAP-0063 lot 6 and lot 8 in ganetespib placebo formulation (35% v/v tween 80, 40% v/v PEG-300, 25% v/v dehydrated alcohol).

SDC-TRAP-0063	Solubility (mg/mL)			
	1 hr	1 day	3 days	7 days
Lot6	11.3	10.2	9.68	7.32
Lot8	36.2	35.3	30.0	19.71

[001327] Figure 16 illustrates the kinetic solubility of SDC-TRAP-0063 lot 6 and lot 8 in ganetespib placebo formulation (35% v/v tween 80, 40% v/v PEG-300, 25% v/v dehydrated alcohol).

[001328] **Effect of type of diluent on the physical appearance of the infusion solutions**

[001329] Preparation of formulations: First, a stock solution of SDC-TRAP-0063 was prepared in DMSO at 22 mg/mL, then the required amount of tween 80 was added and mixed well. Both solutions were clear and homogenous.

[001330] Dilution of the formulations: The above formulation containing SDC-TRAP-0063 was diluted using either D5W, D5W (pH 10.5,adjusted with 4.55 mM NaOH) or carbonate buffer, pH 10) (final drug concentration.: 1 mg/mL SDC-TRAP-0063, 1.8% v/v Tween 80, 5% v/v DMSO). The physical observations on these solutions were noted before and filtration through 0.22µ PES filter and were further observed for 3 hr. Refer to the table below for summary of observations. Note: Carbonate buffer, pH 10 was prepared by mixing 0.1M sodium carbonate (27.5 mL) and 0.1M sodium bicarbonate (22.5 mL) and qs 200 mL with DIW. The total Na content of carbonate buffer was 39 mM.

[001331] Figure 17 shows the physical appearance of SDC-TRAP-0063 stock solution prepared in DMSO and after addition of Tween 80.

[001332] Figure 18 shows the physical observations of infusion solution prepared using different diluents.

[001333] **Effect of formulation composition on the physical appearance of infusion solutions prepared using carbonate buffer, pH 10**

[001334] Objective: To evaluate effect of different formulations on physical appearance of the solution prepared by dilution with carbonate buffer, pH 10.

[001335] Procedure: A stock solution of SDC-TRAP-0063 was prepared in either DMSO or PEG-300. To prepare formulations containing DMSO and tween 80, required amount of tween 80 added to the stock of DMSO (containing SDC-TRAP-0063). The formulations were then was diluted with carbonate buffer, pH 10 (composition: add and mix 0.1M sodium carbonate (27.5 mL) and 0.1M sodium bicarbonate (22.5 mL) and qs 200 mL with DIW). The samples (prepared in glass vial) were mixed well and observed for physical appearance while stirring on a magnetic stirring plate at ambient. (Note- appropriate amounts of SDC-TRAP-0063, tween 80, DMSO and PEG-300, as applicable were used to prepare the solutions at the desired concentrations and drug concentrations at 1 mg/mL through 5 mg/mL as shown).

[001336] Observations: It appears that addition of tween 80 at 1.8% v/v concn. to 5% v/v DMSO helps clear the solution, all samples were clear at 2 hr of stirring while samples prepared by diluting the DMSO-alone solution (to same dilution concn. – 5% v/v) stayed cloudy for more than 24 h at drug concn. (2 mg/mL through 5 mg/mL) with exception of 1 mg/mL.

[001337] The PEG-300 formulations diluted with carbonate buffer, pH 10 at 1 mg/mL and 2 mg/mL drug concentration appeared clear at 30 min and 1 hr of stirring respectively. The samples prepared at drug concn. 3 mg/mL, 4 mg/mL and 5 mg/mL took longer and were clear next day.

[001338] Physical appearance DMSO formulations (containing SDC-TRAP-0063) diluted with carbonate buffer, pH 10 (39 mM sodium content).

Final conc. after dilution	SDC-TRAP-0063 (mg/mL)	Observations				
		Initial	30 min	1 h	6 h	Overnight
5% v/v DMSO	1 mg/mL	Cloudy	Cloudy	Cloudy	Cloudy	Clear yellow solution
	2 mg/mL	Cloudy	Cloudy	Cloudy	Cloudy	Opaque (less cloudy than at 6 h)
	3 mg/mL	Cloudy	Cloudy	Cloudy	Cloudy	Cloudy
	4 mg/mL	Cloudy	Cloudy	Cloudy	Cloudy	Cloudy
	5 mg/mL	Cloudy	Cloudy	Cloudy	Cloudy	Cloudy

[001339] Physical appearance of DMSO and Tween 80 formulations (containing SDC-TRAP-0063) diluted with carbonate buffer, pH 10 (39 mM sodium content).

Final conc. after dilution	SDC-TRAP-0063 (mg/mL)	Observations				
		Initial	30 min	1 h	2 h	Overnight
5% v/v DMSO, 1.8 % v/v Tween 80	1 mg/mL	Clear yellow solution	Clear yellow solution	Clear yellow solution	Clear yellow solution	Clear yellow solution
	2 mg/mL	Clear yellow solution	Clear yellow solution	Clear yellow solution	Clear yellow solution	Clear yellow solution
	3 mg/mL	Cloudy	Cloudy	Clear yellow solution	Clear yellow solution	Clear yellow solution
	4 mg/mL	Cloudy	Cloudy	Cloudy	Clear yellow solution	Clear yellow solution
	5 mg/mL	Cloudy	Cloudy	Cloudy	Clear yellow solution	Clear yellow solution

[001340] Physical appearance of PEG-300 (containing SDC-TRAP-0063) diluted with carbonate buffer, pH 10 (39 mM sodium content).

Final conc. after dilution	SDC-TRAP-0063 (mg/mL)	Observations				
		Initial	30 min	1 h	2 h	Overnight
12.5% v/v PEG-300	1 mg/mL	slightly cloudy	clear, yellowish solution	clear, yellow solution	clear, yellow solution	clear, yellow solution
	2 mg/mL	cloudy	Translucent	clear, yellow solution	clear, yellow solution	clear, yellow solution
	3 mg/mL	cloudy	cloudy	cloudy	cloudy	clear, yellow solution
	4 mg/mL	cloudy	cloudy	cloudy	cloudy	clear, yellow solution
	5 mg/mL	cloudy	cloudy	cloudy	cloudy	clear, yellow solution

[001341] Effect of pH and ionic strength of carbonate buffer on physical appearance of samples prepared by dilution of DMSO and tween 80 formulations with different carbonate buffers at 5 mg/mL drug concn.

[001342] Objective: To evaluate the effect of pH and ionic strength of carbonate buffer on rate of conversion of lactone form of SDC-TRAP-0063 in to the carboxylate using the same formulation (DMSO, 5% v/v + tween 80, 1.8% v/v).

[001343] Procedure: Carbonate buffers of different pH (pH 9-10) and ionic strengths (with higher (> 2) Na contents that SDC-TRAP-0063 on molar basis) were prepared and used for diluting the DMSO/tween 80 formulation loaded with SDC-TRAP-0063 (as described in earlier section 3). The final concentrations of DMSO and tween 80 in the diluted carbonate buffer were 5% v/v and 1.8% v/v respectively. The drug concentration was kept constant (5 mg/mL) for all diluted samples.

[001344] Observations: It appears that higher pH (*e.g.*, pH 10) and higher ionic strength help the lactone conversion into carboxylate form of SDC-TRAP-0063 thereby reducing the time required to form a clear yellow solution. The time required to form a clear solution at high ionic strength at pH 10 and pH 9.5 against at low ionic strength at same pHs. Lower pH (*e.g.*, pH 9.3and pH 9.5) samples remain cloudy even after stirring overnight. The high ionic strength carbonate buffer at pH 9.5 was clear within 3 hours.

[001345] Comparison of physical appearance of samples prepared by dilution of DMSO and tween 80 formulations with different carbonate buffers at 5 mg/mL drug concn.

Final conc. after dilution	Diluent	Observations (final SDC-TRAP-0063 concn 5 mg/mL)				
		Initial	1 h	2 h	3 h	Overnight
5% v/v DMSO, 1.8 % v/v Tween 80	Carbonate buffer, pH 10 (39 mM Na)	Cloudy	Cloudy	Clear yellow solution	Clear yellow solution	Clear yellow solution
	Carbonate buffer, pH 10 (155 mM Na)	Cloudy	Clear yellow solution	Clear yellow solution	Clear yellow solution	Clear yellow solution
	Carbonate buffer, pH 9.2 (25 mM Na)	Cloudy	Cloudy	Cloudy	Cloudy	Cloudy
	Carbonate buffer, pH 9.5 (26.5 mM Na)	Cloudy	Cloudy	Cloudy	Cloudy	Cloudy
	Carbonate buffer, pH 9.5 (106 mM Na)	Cloudy	Cloudy	Cloudy	Clear	Clear

[001346] Note that (1) sodium content of Normal saline for injection is 154 mM and (2) all above solutions have 5.6 mM SDC-TRAP-0063 (i.e. lowest ionic strength carbonate buffer (pH 9.2 or pH 10) has higher Na content (25 mM) than that of drug on molar-basis).

[001347] **Overall Summary**

[001348] It appears that solubility of SDC-TRAP-0063 could be function of pH and ionic strength of the aqueous diluent / buffer used. Without wishing to be bound by any particular theory, the cloudiness seen in the infusion solutions prepared in D5W alone or pH 10, D5W (4.55 mM NaOH) could be due to the presence of insoluble drug.

[001349] The time required for conversion of lactone form (water insoluble) of SDC-TRAP-0063 to carboxylate (water soluble) in carbonate buffer, pH 10 appears to be dependent on formulation composition. Addition of 1.8 % v/v tween 80 appears to fasten the conversion along with DMSO at 5% v/v compared to using DMSO alone at the same concn (5% v/v).

[001350] The infusion solution at low drug concentration (1 mg/mL or 2 mg/mL) can be prepared by diluting PEG-300 formulations with carbonate buffer, pH 10 while higher drug concentrations take longer time. A high PEG-300 concentration (12.5% v/v) would be needed to prepare high drug concentration (5 mg/mL) in infusion solution (equilibrium solubility of SDC-TRAP-0063 Lot 8 in PEG-300 was estimated to be about 44 mg/ml).

[001351] Higher ionic strength carbonate buffer, pH 10 (at comparable sodium content to that of normal saline for injection) appears to fasten the lactone conversion into carboxylate form. This indicates that the pH about 10 and high ionic strength provide favorable conditions for preparing SDC-TRAP-0063 solutions (drug concentration can be achieved at least 5 mg/mL) in carbonate buffer with 1.8% v/v tween 80 and 5% v/v DMSO.

[001352] **Example 38: SDC-TRAP-0063 has superior antitumor activity compared with irinotecan in a SCLC model.**

[001353] The activity of the Hsp90 inhibitor/irinotecan conjugate SDC-TRAP-0063 (100 and 150 mg/kg) was compared to irinotecan and irinotecan + ganetespib in SCLC xenografts treated once weekly for three weeks, followed by a drug-free period. As shown in Figure 19, high dose SDC-TRAP-0063 displayed remarkable and durable antitumor activity compared with irinotecan or ganetespib plus irinotecan. Importantly, SDC-TRAP-0063 was very well tolerated.

[001354] Conclusions: The Hsp90 inhibitor/topoisomerase inhibitor conjugate SDC-TRAP-0063 showed superior, durable antitumor activity compared to ganetespib or irinotecan monotherapy or their combination in a xenograft model of SCLC, similar to results in breast and lung xenografts. These data provide strong supporting evidence that Hsp90 inhibitors can be used as tumor-specific delivery vehicles for cancer therapeutics in a safe and effective manner.

[001355] Example 39: Pharmacodynamics of SDC-TRAP-0063 in CRC xenograft tumors

[001356] SDC-TRAP-0063 displays potent and durable antitumor activity suggesting that the drug is slowly cleaved over its residence time in the tumor to provide long term activity. To determine whether these effects are through Hsp90 inhibition, topoisomerase inhibition or both, we analyzed the stability of Hsp90 client proteins as well as the phosphorylation of H2AX (gamma-H2AX) as a readout for DNA double-strand breaks elicited by the topoisomerase inhibitor SN38. Irinotecan shows a time dependent increase in H2AX phosphorylation, maximally induced at 4 hr and stable at 24 hr. From the literature we were anticipating that irinotecan-induced H2AX phosphorylation would decline by 24 hr, but clearly more time is required to return to baseline. Kinetics for H2AX phosphorylation by SDC-TRAP-0063 are slower than irinotecan, beginning at 8 hr and leveling off at 24 hr.

[001357] Hsp90 client protein expression was examined to determine whether the conjugate modulates client protein stability. Ganetespib (24 hr exposure) induces HSP70 expression and reduces the level of EGFR and MET compared to vehicle. Irinotecan has negligible effects on HSP70 or client protein expression. SDC-TRAP-0063 induces HSP70 comparable to irinotecan but much less than ganetespib suggesting that SDC-TRAP-0063 does not fully inhibit HSP90. This was further validated by the lack of effects on EGFR and MET stability. Similar to the PD study, both irinotecan and SDC-TRAP-0063 treatment stimulate H2AX phosphorylation at 24 hr. Ganetespib treatment also induces H2AX phosphorylation likely as a result of M-phase arrest which we showed previously. These results suggest that SDC-TRAP-0063 is a weak Hsp90 inhibitor, and the antitumor activity is derived from its persistent topoisomerase inhibition.

[001358] Figure 20 shows (A) expression of indicated analytes from HCT-116 xenografts treated as indicated and (B) expression of indicated analytes from HCT-116 tumor bearing animals 24 hr post drug exposure.

[001359] Conclusions: Preliminary data from pharmacodynamic studies in colon cancer xenograft tumors shows that the Hsp90 inhibitor/topoisomerase inhibitor conjugate SDC-TRAP-0063 is a weak Hsp90 inhibitor, and its primary mode of antitumor activity may be through durable topoisomerase-I inhibition.

[001360] Example 40: Pharmacodynamics of SDC-TRAP-0063 in SCLC xenograft tumors

[001361] In multiple xenograft models the Hsp90 inhibitor/topoisomerase inhibitor conjugate SDC-TRAP-0063 causes durable suppression of tumor growth with superior activity compared to ganetespib or irinotecan as monotherapy or combination. Prolonged activity may result from slow cleavage of SDC-TRAP-0063 resulting in steady release of topoisomerase inhibitor in the tumor. To further study the mechanism for this activity Hsp90 client proteins and induction of DNA damage response in SCLC xenograft tumors 24 hrs after drug exposure were analyzed (See Figure 21). Hsp90 clients EGFR, MET and CDC2 are diminished by ganetespib and Hsp70 expression is strongly induced. Irinotecan causes a modest increase in Hsp70 but has no effect on Hsp90 clients. The activity of SDC-TRAP-0063 closely resembles that for irinotecan; slight increase in Hsp70 with no impact on EGFR, MET or CDC2. Similarly, irinotecan and SDC-TRAP-0063 cause a dramatic increase in markers for DNA damage including acetylation of histone H3, increased phospho- and total p53 and phosphorylation of H2AX. Ganetespib increases p-H2AX but has negligible effects on p53 and histone H3. Taken together, these data demonstrate SDC-TRAP-0063 does not effectively inhibit Hsp90 and suggest that its antitumor activity results from the DNA damaging effects of topoisomerase inhibition.

[001362] Figure 21 shows expression of the indicated analytes in SCLC xenograft tumors 24 hrs after drug exposure.

[001363] Next, the PD analysis was extended out to 96 hrs to compare the kinetics of DNA damage response for irinotecan and SDC-TRAP-0063 (Figure 22). Irinotecan leads to maximal induction of acetyl-histone H3 by 24 hr and, surprisingly, the effect is stable out to 96 hr. SDC-TRAP-0063 causes a gradual increase in H3ac levels, peaking at 96 hr, consistent with slow intra-tumor cleavage of SDC-TRAP-0063. Phosphorylation of p53 was also induced by both agents, though more so with SDC-TRAP-0063. Additional PD studies with later timepoints are underway to determine if the superior antitumor activity of SDC-TRAP-0063 is due to prolonged drug effects.

[001364] Figure 22 shows expression of the indicated analytes in SCLC xenograft tumors 24, 72, and 96 hrs after drug exposure.

[001365] Conclusions: In multiple xenograft models the Hsp90 inhibitor/topoisomerase inhibitor conjugate SDC-TRAP-0063 causes durable suppression of tumor growth with superior activity compared to ganetespib or irinotecan alone or in combination. PD studies in SCLC xenograft tumors show that irinotecan leads to maximal induction of DNA damage markers by 24 hr which persist through 96 hrs while the effects of SDC-TRAP-0063 gradually increase over a period of 96 hr. These results are consistent with slow intra-tumor cleavage of SDC-TRAP-0063, providing the tumor with durable expression of the topoisomerase inhibitor.

[001366] Example 41: ADME/PK Data Summary for *In vitro* and *In vivo* Studies.

[001367] *In vitro* Studies

[001368] Mouse Plasma Stability: % Remaining of parent after 1 h incubation in mouse plasma at 37 °C (10 μM).

Compound ID	% Remaining (1h)	Compound ID	% Remaining (1h)	Compound ID	% Remaining (1h)
Irinotecan	32.5%	SDC-TRAP-0124	112%	SDC-TRAP-0170	94.1%
SN-38	63.5%	SDC-TRAP-0125	99.4%	SDC-TRAP-0182	91.9%
SDC-TRAP-0414	106%	SDC-TRAP-0127	87.3%	SDC-TRAP-0191	77.4%
SDC-TRAP-0022	21.0%	SDC-TRAP-0134	108%	SDC-TRAP-0206	68.6%
SDC-TRAP-0028	40.9%	SDC-TRAP-0141	101%	SDC-TRAP-0208	86.1%
SDC-TRAP-0029	47.0%	SDC-TRAP-0415	98.3%	SDC-TRAP-0209	67.1%
SDC-TRAP-0037	95.3%	SDC-TRAP-0143	89.9%	SDC-TRAP-0213	74.7%
SDC-TRAP-0042	73.9%	SDC-TRAP-0144	96.2%	SDC-TRAP-0416	2.4%
SDC-TRAP-0044	60.6%	SDC-TRAP-0145	14.1%	SDC-TRAP-0383	47.6%
SDC-TRAP-0045	45.0%	SDC-TRAP-0147	98.1%	SDC-TRAP-0384	108%
SDC-TRAP-0046	51.6%	SDC-TRAP-0150	103%	SDC-TRAP-0337	77.3%
SDC-TRAP-0047	88.9%	SDC-TRAP-0156	90.3%	SDC-TRAP-0417	33.3%
SDC-TRAP-0052	95.9%	SDC-TRAP-0157	81.4%	SDC-TRAP-0418	104%
SDC-TRAP-0055	103%	SDC-TRAP-0158	92.7%	SDC-TRAP-0419	75.4%
SDC-TRAP-0056	78.4%	SDC-TRAP-0159	121%	SDC-TRAP-0389	77.7%
SDC-TRAP-0059	50.8%	SDC-TRAP-0163	93.0%	SDC-TRAP-0420	70.7%
SDC-TRAP-0063	**11.1%**	SDC-TRAP-0164	98.0%	SDC-TRAP-0390	92.5%
SDC-TRAP-0064	91.5%	SDC-TRAP-0167	51.2%	SDC-TRAP-0391	15.2%
SDC-TRAP-0068	96.5%	SDC-TRAP-0171	17.7%	SDC-TRAP-0336	31.7%
SDC-TRAP-0071	102%	SDC-TRAP-0172	74.7%	SDC-TRAP-0392	44.7%
SDC-TRAP-0076	96.0%	SDC-TRAP-0178	82.0%	SDC-TRAP-0393	47.8%
SDC-TRAP-0098	96.0%	SDC-TRAP-0180	72.4%	SDC-TRAP-0356	70.9%
SDC-TRAP-0099	95.2%	SDC-TRAP-0184	18.0%	SDC-TRAP-0358	41.0%
SDC-TRAP-0104	95.5%	SDC-TRAP-0185	68.1%	SDC-TRAP-0236	60.8%
SDC-TRAP-0106	114%	SDC-TRAP-0186	57.9%	SDC-TRAP-0361	25.6%
SDC-TRAP-0107	111%	SDC-TRAP-0187	102%	SDC-TRAP-0345	63.8%
SDC-TRAP-0115	85.9%	SDC-TRAP-0195	98.4%	SDC-TRAP-0396	71.6%
SDC-TRAP-0116	91.1%	SDC-TRAP-0196	66.2%	SDC-TRAP-0267	63.2%
SDC-TRAP-0117	3.97%	SDC-TRAP-0202	21.2%	SDC-TRAP-0398	1.40%

Compound ID	% Remaining (1h)	Compound ID	% Remaining (1h)	Compound ID	% Remaining (1h)
SDC-TRAP-0121	89.1%	SDC-TRAP-0353	22.5%	SDC-TRAP-0400	70.4%
SDC-TRAP-0123	95.6%	SDC-TRAP-0205	58.4%		

[001369] Metabolite Profiling and Identification: Metabolite profiling/identification for SDC-TRAP-0063 (M+1: 880.3)

Metabolite	Mass gain/loss (amu)	M+1	Hepatocytes					Mouse *in vivo*	
			Mouse	Rat	Dog	Monkey	Human	Plasma 6 h	Tumor 24 h
Hydrolysis (SN-38)	-487	393.3	--	--	√	√	--	√	√
Hydrolysis (SDC-TRAP-0062)	-418	462.3	--	--	--	--	--	√	√
Hydrolysis (SN-38) + glucuronidation	-311	569.3	--	√	--	√	√	√	√
Hydrolysis (SN-38) + H_2O (carboxylate form)	-469	411.3	--	--	--		--	√	√
Hydrolysis (SN-38) + hydroxylation + glucuronidation	-295	585.3	--	--	--	√	--	--	--
Hydrolysis (SDC-TRAP-0062) + glucuronidation	-242	638.3	--	--	--	--	--	√	√
Hydrolysis (SDC-TRAP-0062) + H_2O (ring opened) + glucuronide	-210	670.3	--	--	--	--	--	√	--
Hydrolysis (SDC-TRAP-0062) + oxidation + glucuronide	-228	652.3	--	--	--	--	--	√	--
Hydrolysis (SDC-TRAP-0062) + di-oxidation + glucuronide	-212	668.3	--	--	--	--	--	√	--
Hydrolysis (SDC-TRAP-0062) + *N*-dealkylation + glucuronide	-353	527.3	--	--	--	--	--	√	--
Carboxylate form	+18	898.3	--	--	√	--	--	√	√
Hydroxylation	+16	896.3	--	--	√	--	--	--	--
Di-hydroxylation	+32	912.4	--	--	√	--	--	--	--
Glucuronidation	+176	1056.4	√	√ (2)	√	√ (2)	√	√	√

--: Not detected

[001370] Metabolite profiling/identification for SDC-TRAP-0062 (M+1: 462.3)

Metabolite	Mass gain/loss (amu)	M+1	Hepatocytes				
			Mouse	Rat	Dog	Monkey	Human
Glucuronidation	+176	638.3	√ (3)	√ (2)	√ (3)	√ (3)	√ (2)
Sulfation	+80	542.3	--	√	√ (2)	√ (2)	√ (2)
N-dealkylation + glucuronidation	+65	527.3	√	--	√	--	√

--: Not detected

[001371] Metabolite profiling/identification for SDC-TRAP-0397 (M+1: 960.3)

Metabolite	Mass gain/loss (amu)	M+1	Hepatocytes				
			Mouse	Rat	Dog	Monkey	Human
Hydrolysis (SDC-TRAP-0062) + glucuronidation	-322	638.3	--	--	--	√	--
Hydrolysis (SN-38) + glucuronidation	-391	569.3	--	--	--	√	--
Hydrolysis (SN-38)	-567	393.3	√	--	√	--	√
Hydrolysis (SDC-TRAP-0062)	-498	462.3	√	√	√	--	√
Hydrolysis (SDC-TRAP-0063)	-80.3	880.3	--	--	--	--	√
Hydrolysis (SDC-TRAP-0063) + glucuronidation	96.2	1056.4	√	√	--	√	√
Glucuronidation	176	1136.4	√	--	--	√	--

--: Not detected

[001372] Metabolite profiling/identification for SN-38 (M+1: 393.3)

Metabolite	Mass gain/loss (amu)	M+1	Hepatocytes				
			Mouse	Rat	Dog	Monkey	Human
Glucuronidation	+176	569.3	√	√	√	√	√
Hydroxylation + glucuronidation	+192	585.3	--	--	--	√	√

--: not detected

[001373] ***In vivo* Studies**

[001374] Distribution to Tumor in Mouse

[001375] Concentrations in Plasma and Tumor

[001376] Various SDC-TRAP molecules and appropriate controls were administered to mice and after various time points the plasma and tumor concentration of these molecules was determined. Specifically, SDC-TRAP-0046, SDC-TRAP-0075, SDC-TRAP-0056,

SDC-TRAP-0063, SDC-TRAP-0076, SDC-TRAP-0098, SDC-TRAP-0116, SDC-TRAP-0154, SDC-TRAP-0171, SDC-TRAP-0195, SDC-TRAP-0064, SDC-TRAP-0180, SDC-TRAP-0178,SDC-TRAP-0185, SDC-TRAP-0172, SDC-TRAP-0186, SDC-TRAP-0029, SDC-TRAP-0047, SDC-TRAP-0205, SDC-TRAP-0208, SDC-TRAP-0206, SDC-TRAP-0107, SN-38, Irinotecan, and Lenalidomide were administered at various concentration to mice and plasma and tumor samples were analyzed for the amount of SDC-TRAP molecules present at 5 minutes, 6 hours, 12, hours, 24 hours, and 48 hours. Samples were also analyze for the amount of active agent (SN-38, Irinotecan, or Lenalidomide).

[001377] Overall, SDC-TRAP molecules showed greater targeting to tumors than active agents alone.

[001378] Pharmacokinetics in Rodent

[001379] SDC-TRAP-0063 PK in Male CD-1 Mice (IV Bolus)

Dosed SDC-TRAP-	Monitored SDC-TRAP-	Dose (mpk)	$t_{1/2}$ (h)	Tmax (h)	Cmax (μM)	AUCt (μM·h)	AUC_{inf} (μM·h)	Vz (L/kg)	Vss (L/kg)	CL (L/h/kg)
0063	0063	50	1.9	0.083	414	235	237	0.659	0.122	0.240
		100	2.5	0.083	799	549	549	0.747	0.241	0.207
		200	2.7	0.083	1620	2882	2884	0.307	0.173	0.079
	0191	50	38.2	0.083	0.106	0.464	NR	--	--	--
		100	12.2	0.083	0.250	0.821	NR	--	--	--
		200	5.1	0.083	0.765	4.07	4.24	--	--	--
	SN-38	50	19.2	0.083	1.60	1.55	NR	--	--	--
		100	NR	0.083	1.46	2.19	NR	--	--	--
		200	5.4	0.083	1.84	9.50	9.86	--	--	--

[001380] NR: Not reportable (insufficient terminal phase characterization and/or AUCt/AUC_{inf} < 80%)

[001381] SDC-TRAP-0063 PK in Male SD Rats (Slow IV Bolus)

Dosed SDC-TRAP-	Monitored SDC-TRAP-	Dose (mpk)	$t_{1/2}$ (h)	Tmax (h)	Cmax (μM)	AUCt (μM·h)	AUC_{inf} (μM·h)	Vz (L/kg)	Vss (L/kg)	CL (L/h/kg)
0063	0063	10	1.0	0.083	102	38.8	38.8	0.441	0.0590	0.294
		50	0.8	0.083	659	687	687	0.0924	0.0640	0.0830
		100	1.6	0.083	1207	1785	1786	0.153	0.0654	0.0648
		150	1.8	0.50	1897	5302	5302	0.0855	0.0663	0.0328
	0191	10	24.5	0.83	0.0298	0.418	NR	--	--	--
		50	70.7	0.083	0.147	0.517	NR	--	--	--
		100	21.8	0.083	0.395	0.770	NR	--	--	--
		150	12.8	0.083	0.738	1.24	1.41	--	--	--
	SN-38	10	3.2	0.083	1.29	0.633	0.680	--	--	--
		50	0.083	1.74	0.035	1.60	NR	--	--	--
		100	0.083	2.46	0.0246	2.43	NR	--	--	--
		150	NR	0.083	3.28	3.74	NR	--	--	--

[001382] NR: Not reportable (insufficient terminal phase characterization and/or $AUCt/AUC_{inf} < 80\%$)

[001383] Example 42: SDC-TRAP-0063 has superior antitumor activity compared with irinotecan in an HCT-116 model.

[001384] The activity of the Hsp90 inhibitor/irinotecan conjugate SDC-TRAP-0063 (200 and 100 mg/kg) was compared to irinotecan and irinotecan + ganetespib (SYN-01) in HCT-116 xenografts treated once weekly for three weeks, followed by a drug-free period. Shown in Figure 23, high dose SDC-TRAP-0063 displayed remarkable and durable antitumor activity compared with irinotecan or ganetespib plus irinotecan. Importantly, SDC-TRAP-0063 was very well tolerated and 20-30% animal death observed in Irinotecan and Irinotecan + Ganetespib group during the treatment.

[001385] In conclusion, in the present study, either single Irinotecan (67mg/kg, IV, Q7D x 3) or Irinotecan in combination with SYN-01 (67mg/kg-100mg/kg-combination, IV, Q7D x 3) administration significantly inhibited the growth of HCT-116 human colorectal xenografts implanted S.C in female Balb/c Nude mice. Moreover, both SDC-TRAP-0063(200mg/kg or 100mg/kg, IV, Q7D x 3) and SDC-TRAP-0046(94mg/kg, IV, Q7D x 3) displayed better activity in inhibiting the growth of HCT-116 cells *in vivo* than either positive control group in the experiment. Meanwhile, SDC-TRAP-0063 demonstrated significant dose-dependent activity in inhibiting the growth of HTC-116 cells *in vivo*.

[001386] Example 43: SDC-TRAP-0063 has superior antitumor activity compared with irinotecan in an MCF-7 xenograft model.

[001387] The activity of the Hsp90 inhibitor/irinotecan conjugate SDC-TRAP-0063 (150 and 100 mg/kg) was compared to irinotecan and irinotecan + ganetespib (SYN-01) in MCF-7 xenografts treated once weekly for three weeks, followed by a drug-free period. As shown in Figure 24, both doses of SDC-TRAP-0063 displayed remarkable regression of the tumor and compared with irinotecan or ganetespib plus irinotecan where only moderate tumor growth inhibition is seen.

[001388] In conclusion, SDC-TRAP-0063 exhibited superior efficacy in MCF-7 model with good safety profile. In comparison, irinotecan and irinotecan + ganetespib combination group only exhibited moderate antitumor activity.

[001389] Example 44: SDC-TRAP-0063 exhibits superior delayed antitumor activity in SKOV-3 ovarian cancer xenografts.

[001390] This model is sensitive to HSP90 inhibition. As shown in Figure 25, two groups SDC-TRAP-0063 were compared with Irinotecan alone and in combination with ganetespib. In the early weeks, the combination of irinotecan + ganetespib exhibited comparable antitumor activity as that of 200mg/kg of SDC-TRAP-0063 due to strong HSP90 inhibition from ganetespib. However, once the dose is stopped the activity from irinotecan + ganetespib wears out leading to tumor growth. However, 200mg/kg of SDC-TRAP-0063 dose group maintains the tumor growth inhibition for several weeks.

[001391] In conclusion, in this study, SDC-TRAP-0063 or Irinotecan alone or irinotecan + ganetespib had statistically significant inhibitory impact on the growth of SK-OV-3 xenografts in female Balb/c nude mice, in the early weeks. However, once the dosing is discontinued all but 200mg/kg of SDC-TRAP-0063 dose group maintained tumor growth inhibition for a prolonged period of time.

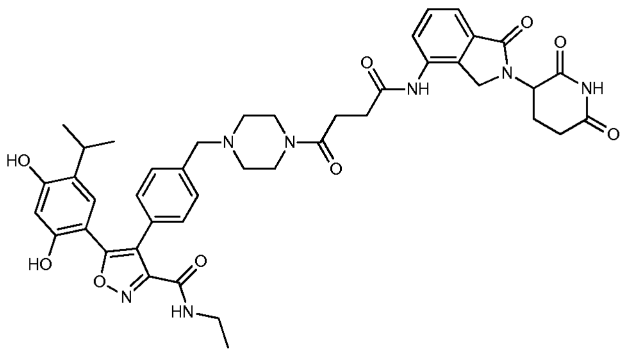
[001392] Example 45

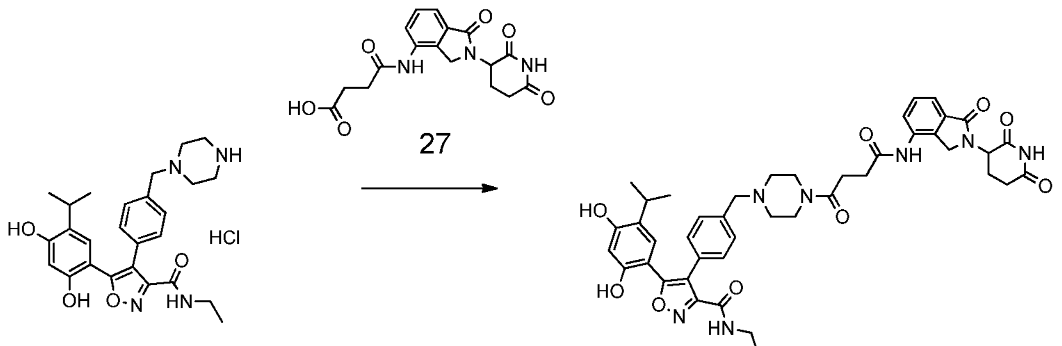
[001393] SDC-TRAPs comprising AUY-922 (available from Novartis International AG)

[001394] Unless otherwise indicated, compounds in this example were produced in a similar manner as described for SDC-TRAP-0237.

[001395] SDC-TRAP-0237

[001396] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-((4-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-oxobutanoyl)piperazin-1-yl)methyl)phenyl)-N-ethylisoxazole-3-carboxamide





26 28

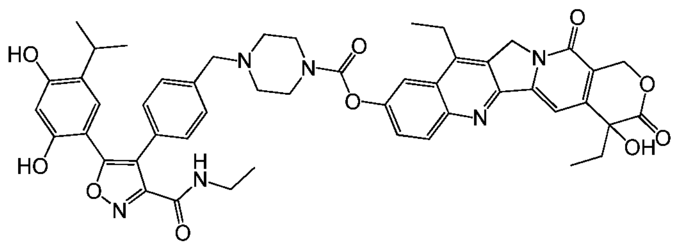
[001397] 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-(piperazin-1-ylmethyl)phenyl) isoxazole-3-carboxamide hydrochloride ((50 mgs, 0.1 mmol) 26 and 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-oxobutanoic acid 27 (38 mgs, 0.105 mmol) were combined in 2 ml of anhydrous N,N-dimethylformamide. The 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate coupling reagent (42 mgs, 0.11 mmoles) was added followed by the N,N-diisopropylethyl amine. The reaction was stirred at room temperature for 1.5 hours. The reaction was diluted with 4 mls of water and the aqueous suspension was extracted twice with 15 mls of ethyl acetate. The solvent was dried over sodium sulfate and evaporated *in vacuo*.

The crude product was purified on a medium pressure silica column eluting with 0-20% methanol/ dichloromethane. The white solid obtained was triturated with ethyl ether and filtered to give 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-((4-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-oxobutanoyl)piperazin-1-yl)methyl)phenyl)-N-ethylisoxazole-3-carboxamide (18.6 mgs, 23%).

[001398] ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 11.04 (s, 1H), 9.85 (s, 1H), 9.67 (s, 1H), 8.84 (t, J = 5.7 Hz, 1H), 7.83 (dd, J = 6.3, 2.7 Hz, 1H), 7.49 (q, J = 4.4, 3.8 Hz, 2H), 7.28 – 7.16 (m, 4H), 6.73 (s, 1H), 6.44 (s, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.44 – 4.27 (m, 2H), 3.45 (s, 6H), 3.28 – 3.17 (m, 2H), 3.03 – 2.85 (m, 2H), 2.62 (dd, J = 10.0, 5.3 Hz, 4H), 2.39 – 2.25 (m, 5H), 2.03 (d, J = 6.6 Hz, 1H), 1.08 (q, J = 7.1 Hz, 3H), 0.91 (d, J = 6.9 Hz, 6H) .
ESMS calculated for $C_{43}H_{47}N_7O_9$: 805.3; found: 806.7 (M+H+).

[001399] SDC-TRAP-0236

[001400] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazine-1-carboxylate

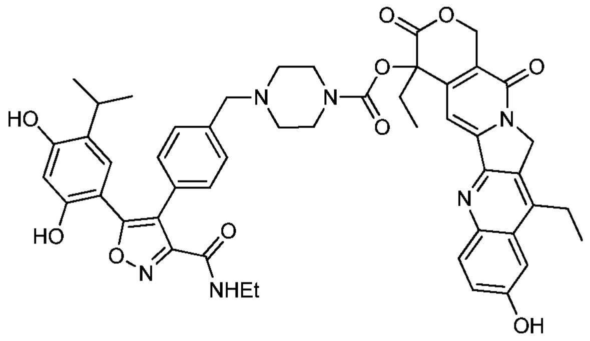


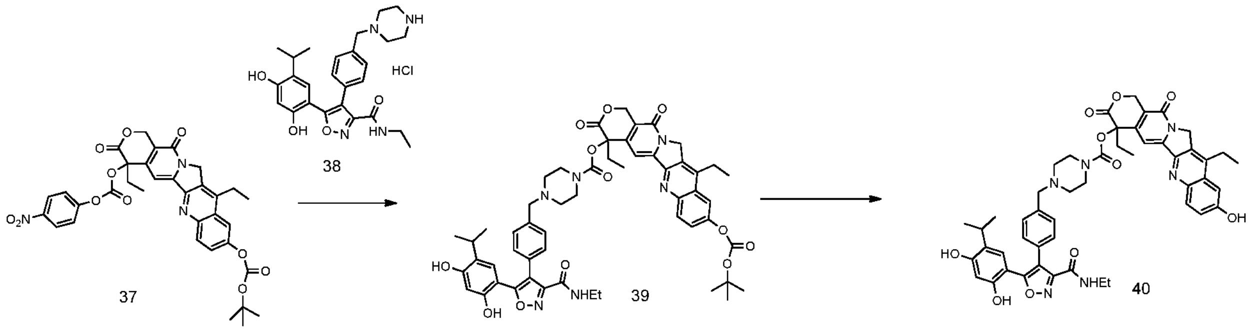
[001401] ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 9.84 (s, 1H), 9.74 (s, 1H), 8.92 (t, *J* = 5.7 Hz, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 8.05 (d, *J* = 2.6 Hz, 1H), 7.72 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.41 – 7.25 (m, 5H), 6.81 (s, 1H), 6.60 (s, 1H), 6.51 (s, 1H), 5.50 (s, 2H), 5.39 (s, 2H), 3.74 (s, 2H), 3.54– 3.49 (m, 3H), 3.30-3.24(m, 4H), 3.05 (h, *J* = 6.9 Hz, 1H), 2.52 (s, 2H), 2.03 – 1.85 (m, 2H), 1.36 (q, *J* = 7.9 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.07 – 0.90 (m, 9H). ESMS calculated for $C_{49}H_{50}N_6O_{10}$: 882.36; Found 883.2 $(M+H)^+$.

[001402] SDC-TRAP-0238

[001403] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl

4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazine-1-carboxylate

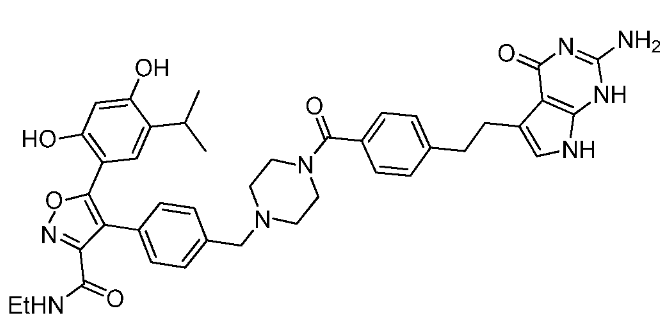


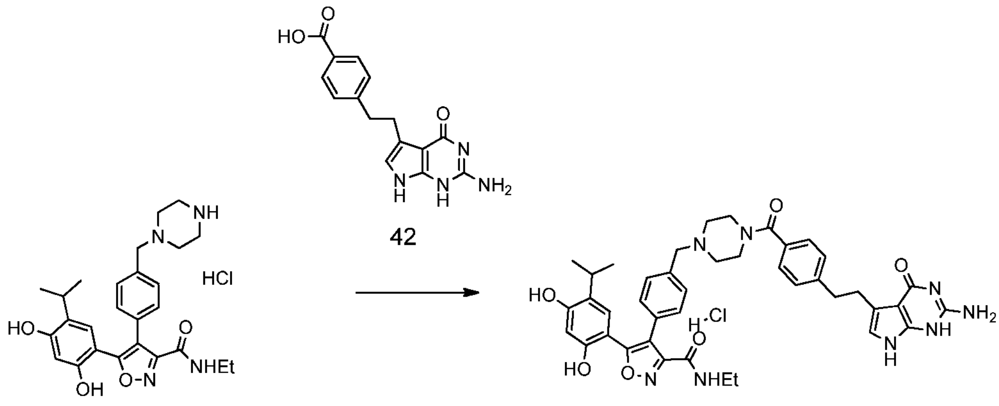


[001404] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (t, J= Hz, 1H), 8.02 (m, J=Hz, 1H), 7.44 – 7.37 (m, 2H), 7.22 (q, J = 7.9 Hz, 4H), 6.95 (s, 0H), 6.73 (s, 1H), 6.43 (s, 1H), 5.44 (d, J = 3.4 Hz, 2H), 5.29 (d, J = 2.7 Hz, 2H), 3.65 (dm, 2H), 3.47 (s, 2H), 3.24 (q, J = 6.6 Hz, 2H), 3.08 (d, J = 7.8 Hz, 2H), 2.97 (m, 2.30 (m, 1H),2.20 (m, 1H), 2.13 (q, J = 7.4 Hz, 2H), 1.33 – 1.20 (m, J=7.8 Hz 3H), 1.08 (q, J = 6.9 Hz, 3H), 0.90 (dd, J = 6.9, 3.3 Hz, 6H). ESMS calculated for $C_{49}H_{50}N_{6}O_{1}0$: 882.4; found: 883.8 (M+H^{+}).

[001405] SDC-TRAP-0239

[001406] 4-(4-((4-(4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)piperazin-1-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethylisoxazole-3-carboxamide



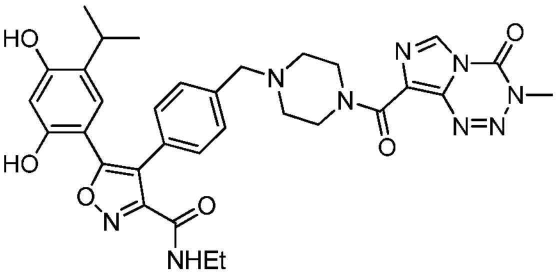


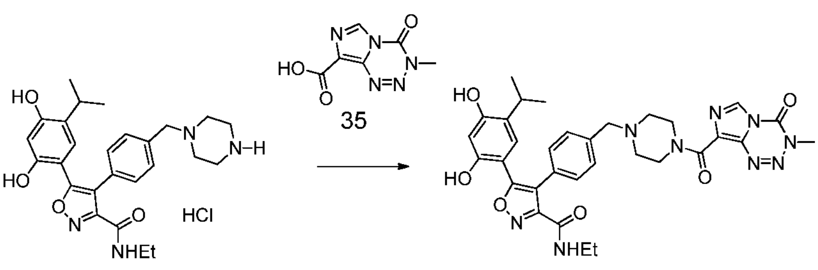
41 42 43

[001407] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.63 (d, J = 2.2 Hz, 1H), 10.14 (s, 1H), 9.77 (s, 1H), 9.65 (s, 1H), 8.84 (t, J = 5.6 Hz, 1H), 7.32 – 7.15 (m, 8H), 6.73 (s, 1H), 6.43 (s, 1H), 6.33 (d, J = 2.2 Hz, 1H), 6.00 (s, 2H), 3.56 (s, 4H), 3.46 (d, J = 9.4 Hz, 2H), 3.34 (d, J = 17.5 Hz, 2H), 3.03 – 2.89 (m, 3H), 2.84 (dd, J = 9.5, 5.7 Hz, 2H), 2.36 (s, 4H), 1.07 (t, J = 7.2 Hz, 3H), 0.90 (d, J = 6.9 Hz, 6H).ESMS calculated for $C_{41}H_{44}N_8O_6$: 744.3; found: 745.7 (M+H^{+}).

[001408] SDC-TRAP-0240

[001409] 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-((4-(3-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carbonyl)piperazin-1-yl)methyl)phenyl)isoxazole-3-carboxamide





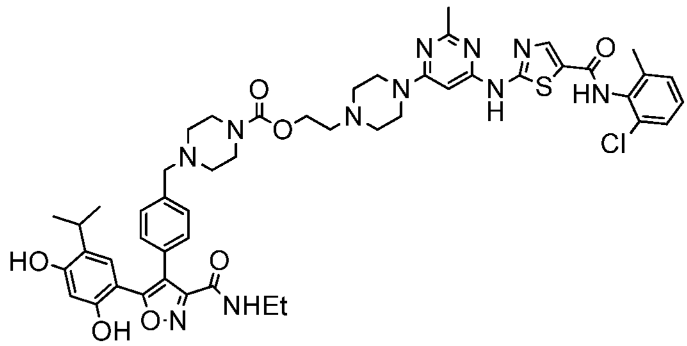
34 36

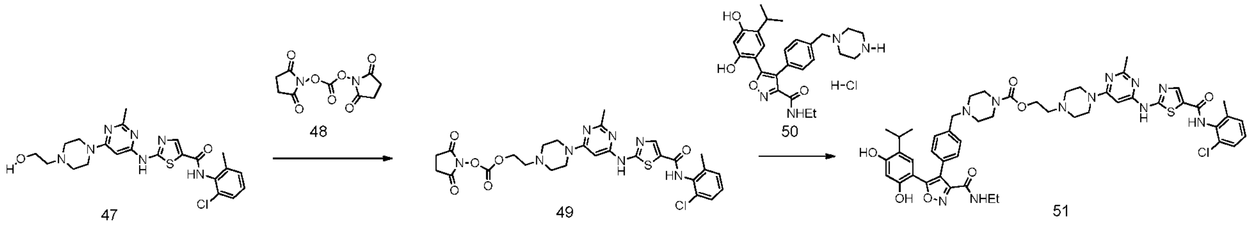
[001410] ^{1}H NMR (400 MHz, DMSO-d6) δ 9.75 (s, 1H), 9.65 (s,1H), 8.82 (s, 1H), 7.25 (d, J=8.2 2H), 7.20 (d, J=8.2, 2H), 3.84 (s, 3H), 3.67 (s, 2H), 3.55 (s, 2H), 3.49 (s, 2H), 3.22 (m, 2H) 2.97 (m, 1H) 2.44 (m, 2H), 2.39 (m, 2H) 1.07 (t, J=7.3 Hz, 3H) 0.90 d J= 7.0Hz, 6H)

[001411] ESMS calculated for $C_{32}H_{35}N_9O_6$: 641.3; found: 642.6 (M+H$^+$).

[001412] SDC-TRAP-0241

[001413] 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)ethyl 4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazine-1-carboxylate

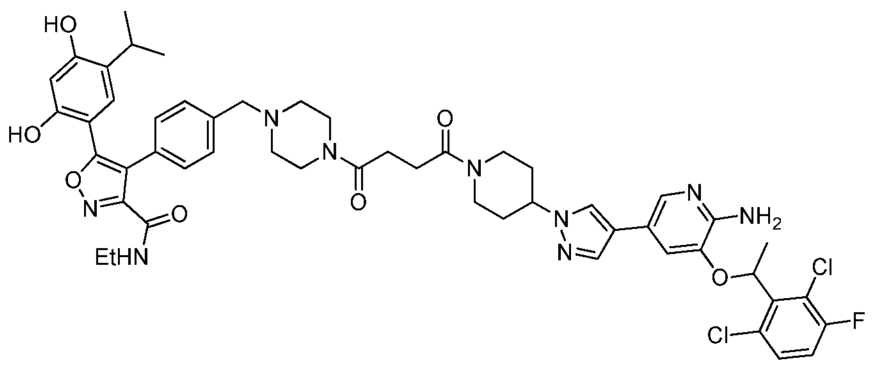


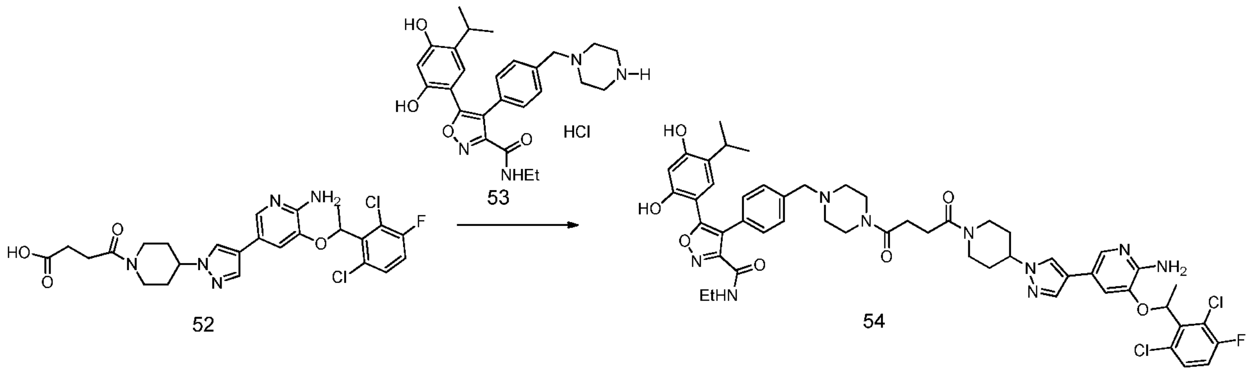


[001414] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.46 (s, 1H), 9.87 (s, 1H), 9.76 (s, 1H), 9.65 (s, 1H), 8.82 (t, J = 5.7 Hz, 1H), 8.22 (s, 1H), 7.40 (dd, J = 7.9, 1.9 Hz, 1H), 7.33 – 7.15 (m, 6H), 6.72 (s, 1H), 6.44 (s, 1H), 6.05 (s, 1H), 4.13 (t, J = 5.9 Hz, 2H), 3.48 (d, J = 20.4 Hz, 4H), 3.36 (d, J = 7.7 Hz, 4H), 3.21 (dq, J = 14.8, 7.8, 7.3 Hz, 2H), 2.97 (p, J = 7.1 Hz, 1H), 2.59 (t, J = 5.7 Hz, 2H), 2.40 (s, 3H), 2.32 (t, J = 4.8 Hz, 4H), 2.24 (s, 3H), 1.08 (q, J = 7.6 Hz, 3H), 0.90 (d, J = 6.8 Hz, 6H). ESMS calculated for $C_{49}H_{56}ClN_{11}O_7S$:977.8; found: 978.8 (M+H$^+$).

[001415] SDC-TRAP-0242

[001416] 4-(4-((4-(4-(4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-4-oxobutanoyl)piperazin-1-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethylisoxazole-3-carboxamide



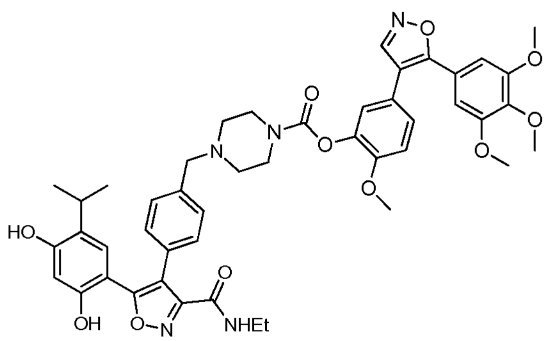


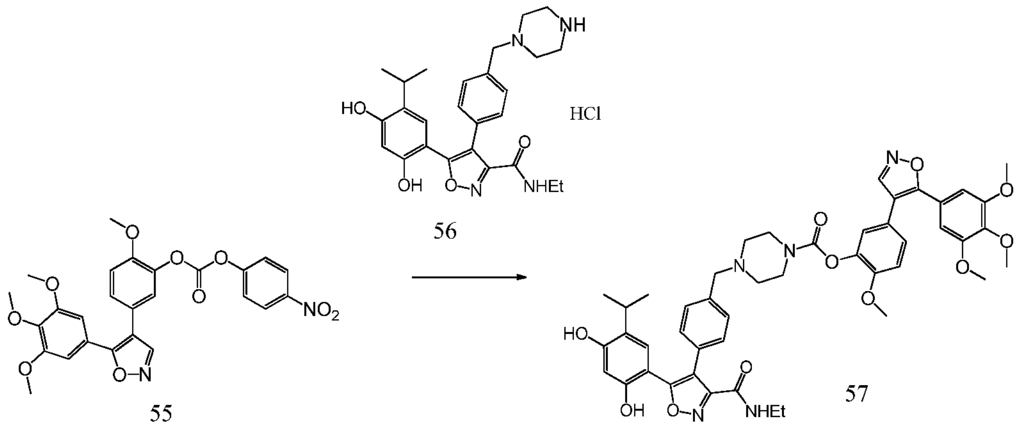
[001417] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (t, J = 5.7 Hz, 1H), 8.08 (s, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.51 – 7.42 (m, 3H), 7.38 – 7.31 (m, 2H), 7.13 (d, J = 1.7 Hz, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.45 (s, 1H), 6.29 (q, J = 6.7 Hz, 1H), 4.44 (d, J = 13.2 Hz, 2H), 4.34 (s, 2H), 4.03 (d, J = 13.1 Hz, 1H), 3.30 – 3.16 (m, 4H), 3.00 (p, J = 6.9 Hz, 1H), 2.61 (m, 4H), 2.06 (dd, J = 24.5, 12.2 Hz, 2H), 1.87 (d, J = 6.6 Hz, 3H), 1.69 (d, J = 12.1 Hz, 1H), 1.09 (t, J = 7.2 Hz, 3H), 0.97 – 0.90 (m, 6H).

ESMS calculated for $C_{51}H_{56}Cl_2FN9O$: 995.4; found 532/534 fragment (weak 996?) (M+H$^+$).

[001418] SDC-TRAP-0243

[001419] 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl 4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazine-1-carboxylate





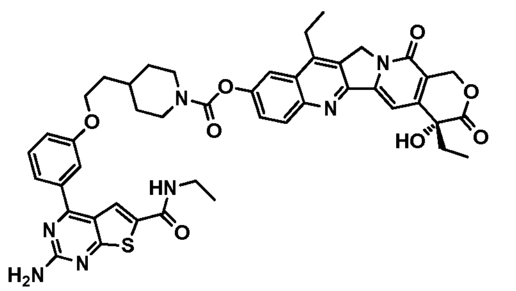
[001420] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 9.68 (s, 1H), 8.85 (s, 1H), 7.36 – 7.14 (m, 7H), 6.87 (d, J = 3.4 Hz, 2H), 6.74 (s, 1H), 6.44 (s, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 3.53 (d, J = 9.3 Hz, 3H), 3.53 – 3.45 (m, 2H), 3.39 (m, 2H), 3.29 – 3.15 (m, 2H), 2.97 (p, J = 6.7 Hz, 1H), 2.39 (s, 4H), 1.09 (t, J=6.8 Hz, 3H),0.91 (d, J= Hz,6H).
ESMS calculated for $C_{46}H_{49}N_5O_{11}$: 847.3; found 848.8 (M+H$^+$).

[001421] Example 46

[001422] SDC-TRAPs comprising a VER-82160 (NVP-BEP795, available from Novartis International AG)

[001423] SDC-TRAP-0244

[001424] (R)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate



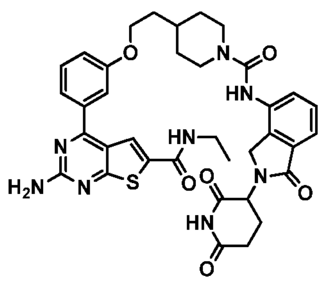
[001425] (R)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (4-nitrophenyl) carbonate (0.1 mmol) was dissolved in DMF (1 mL), followed by the addition of 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxam

ide (0.1 mmol) (for preparation, see: *J. Med. Chem.*, 2009, *52*, 4794 – 4809) and Et_3N (0.2 mmol). The solution was stirred at room temperature for 30 min. Removal of solvents followed by silica gel chromatography purification (CH_2Cl_2/MeOH) afforded the desired product as a white solid.

[001426] ^{1}H NMR (400 MHz, DMSO-d*6*), δ 8.73 (t, *J* = 5.6 Hz, 1H), 8.17 (d, *J* = 9.2 Hz, 1H), 8.05 (s, 1H), 7.98 (d, 2.8 Hz, 1H), 7.66 (dd, *J* = 9.2, 2.4 Hz, 1H), 7.52 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.32 (s, 1H), 7.19 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.14 (s, 2H), 6.54 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.27 (d, *J* = 12 Hz, 1H), 4.17 (t, *J* = 5.6 Hz, 2H), 4.11 (q, *J* = 5.2 Hz, 2H), 3.30 – 3.23 (m, 4H), 3.22 – 3.16 (m, 2H), 2.99 – 2.94 (m, 2H), 1.91 – 1.80 (m, 9H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm; ESMS calculated for $C_{45}H_{45}N_7O_8S$: 843.3; found: 844.5 ($M + H^+$).

[001427] SDC-TRAP-0245

[001428] 2-amino-4-(3-(2-(1-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)piperidin-4-yl)ethoxy)phenyl)-N-ethylthieno[2,3-d]pyrimidine-6-carboxamide



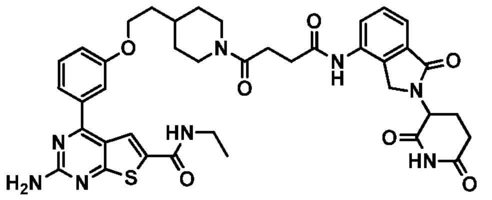
[001429] Lenalidomide (3.9 mmol) was added to round-bottomed flask containing THF (150 mL) and 4-nitrophenyl chloroformate (4.6 mmol). The mixture was stirred in a 70 ^{0}C oil bath for 3 h. The resulting precipitate was isolated by vacuum filtration and the filter cake was washed with EtOAc (100 mL × 2) and dried under high vacuum, to yield 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (973 mg) as a white solid.

[001430] Compound SDC-TRAP-0245 was synthesized in a similar manner as described for SDC-TRAP-0244, using 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate.

[001431] ^{1}H NMR (400 MHz, DMSO-d*6*), δ 11.00 (s, 1H), 8.71 (t, *J* = 4.0 Hz, 1H), 8.53 (s, 1H), 8.04 (s, 1H), 7.53 – 7.38 (m, 6H), 7.18 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.13 (s, 2H), 5.12 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.34 (d, *J* = 16.0 Hz, 2H), 4.15 – 4.09 (m, 5H), 3.26 – 3.23 (m, 2), 2.95 – 2.79 (m, 3H), 2.59 (d, *J* = 16.0 Hz, 1H), 2.39 (qd, *J* = 12.0, 4.0 Hz, 1H), 2.01 – 1.97 (m, 1H), 1.83 – 1.72 (m, 5H), 1.25 – 1.18 (m, 2H), 1.11 (t, *J* = 8.0 Hz, 3H) ppm; ESMS calculated for $C_{36}H_{38}N_8O_6S$: 710.3; found: 711.6 ($M + H^+$).

[001432] SDC-TRAP-0246

[001433] 2-amino-4-(3-(2-(1-(4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-oxobutanoyl)piperidin-4-yl)ethoxy)phenyl)-N-ethylthieno[2,3-d]pyrimidine-6-carboxamide

[001434] 

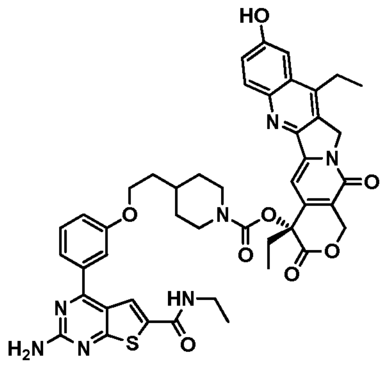
[001435] Lenalidomide (2.8 mmol) was added to a round-bottom flask containing a solution of succinic anhydride (3.4 mmol) in toluene (7 mL), and equipped with a reflux condenser. The mixture was stirred for 3 h, then the precipitate was isolated by vacuum filtration and the filter cake was washed with EtOAc (20 mL × 2) and dried under high vacuum, to yield 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-oxobutanoic acid (802 mg) as a white solid.

[001436] A round-bottomed flask was charged with 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide (0.10 mmol), 4-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-4-oxobutanoic acid (0.12 mmol), DMF (1 mL), HATU (0.14 mmol) and diisopropyl ethylamine (0.23 mmol). The solution was stirred at 22 ^{0}C for 21 h then H_2O (20 mL) was added. The resulting precipitate was isolated by vacuum filtration and purified by silica gel chromatography (CH_2Cl_2/MeOH) to afford the desired product as a white solid.

[001437] ^{1}H NMR (400 MHz, DMSO-*d6*), δ 11.03 (s, 1H), 9.85 (s, 1H), 8.71 (t, *J* = 5.2 Hz, 1H), 8.03 (s, 1H), 7.82 (dd, *J* = 6.4, 2.4 Hz, 1H), 7.52 – 7.46 (m, 3H), 7.42 – 7.37 (m, 2H), 7.17 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.03 (s, 2H), 5.15 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.35 (d, *J* = 17.6 Hz, 2H), 4.14 – 4.34 (m, 1H), 4.14 – 4.08 (m, 3H), 3.90 (d, *J* = 13.2 Hz, 1H), 3.29 – 3.22 (m, 3H), 3.04 – 2.97 (m, 1H), 2.93 (ddd, *J* = 17.6, 13.6, 5.2 Hz, 1H), 2.68 – 2.60 (m, 6H), 2.31 (dd, *J* = 13.2, 4.4 Hz, 1H), 2.09 – 2.02 (m, 1H), 1.81 – 1.72 (m, 5H), 1.11 (t, *J* = 7.2 Hz, 3H) ppm; ESMS calculated for $C_{39}H_{42}N_8O_7S$: 766.3; found: 767.6 ($M + H^+$).

[001438] SDC-TRAP-0247

[001439] (R)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate



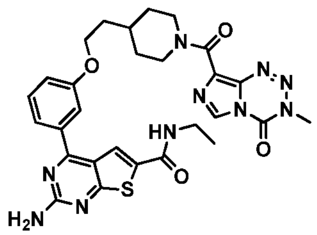
[001440] (R)-tert-butyl (4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-4,9-diyl) (4-nitrophenyl) dicarbonate (0.2 mmol) was dissolved in DMF (2 mL), followed by the addition of 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide (0.2 mmol) and Et_3N (0.4 mmol). The solution was stirred at room temperature for 30 min. Removal of solvents followed by silica gel chromatography purification (CH_2Cl_2/MeOH) afforded the desired product (R)-9-((tert-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate as a white solid.

[001441] CH_2Cl_2 (4 mL) was added to (R)-9-((tert-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate was (0.12 mmol), followed by the addition of HCl (4M in dioxane, 1 mL) at room temperature. The mixture was stirred at room temperature for 15 h, followed by adding additional HCl (4M in dioxane, 1 mL) at room temperature. The mixture was stirred for an additional 3 h, and then concentrated under reduced pressure. The resulting crude solid was purified by silica gel chromatography (CH_2Cl_2/MeOH) to afford the desired product as a pale-yellow solid.

[001442] ^{1}H NMR (400 MHz, DMSO-d*6*), δ 10.32 (s, 1H), 8.70 (t, *J* = 6.0 Hz), 8.04 (s, 1H), 7.98 (d, *J* = 9.3 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.42 – 7.38 (m, 4H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.12 (s, 2H), 6.94 (d, *J* = 18.4 Hz), 5.49 (s, 2H), 5.30 (s, 2H), 4.28 – 4.22 (m, 1H), 4.18 – 4.11 (m, 2H), 3.80 – 3.72 (m, 1H), 3.27 – 3.23 (m, 3H), 3.17 (s, 1H), 3.08 (q, *J* = 7.6 Hz, 2H), 2.79 – 2.72 (m, 1H), 2.13 (q, *J* = 7.6 Hz, 2H), 1.84 – 1.74 (m, 6H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm; ESMS calculated for $C_{45}H_{45}N_7O_8S$: 843.3; found: 844.7 ($M + H^+$).

[001443] SDC-TRAP-0248

[001444] 2-amino-N-ethyl-4-(3-(2-(1-(3-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carbonyl)piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide

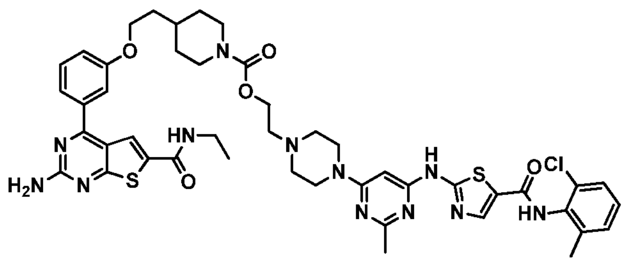


[001445] A round-bottomed flask was charged with 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide (0.10 mmol), 3-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxylic acid (0.12 mmol), DMF (1 mL), HATU (0.14 mmol) and diisopropyl ethylamine (0.23 mmol). The solution was stirred at 22 ^{0}C for 7 h then H_2O (20 mL) was added. The resulting precipitate was isolated by vacuum filtration and purified by silica gel chromatography (CH_2Cl_2/MeOH) to afford the desired product as a white solid.

[001446] ^{1}H NMR (400 MHz, Chloroform-*d*), δ 8.42 (s, 1H), 7.78 (s, 1H), 7.45 – 7.35 (m, 3H), 7.06 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.25 (t, *J* = 8.0 Hz, 1H), 4.80 (d, *J* = 16.0 Hz, 1H), 4.18 (d, *J* = 16.0 Hz, 1H), 4.11 (t, *J* = 6.2 Hz, 2H), 4.01 (s, 3H), 3.48 (dq, *J* = 12.0, 8.0 Hz, 2H), 3.17 (t, *J* = 12.0 Hz, 1H), 2.84 (dd, *J* = 8.0, 8.0 Hz, 1H), 1.94 – 1.90 (m, 2H), 1.84 – 1.80 (m, 5H), 1.45 – 1.35 (m, 2H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm; ESMS calculated for $C_{28}H_{30}N_{10}O_4S$: 602.2; found: 603.5 ($M + H^+$).

[001447] SDC-TRAP-0249

[001448] 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)ethyl 4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate

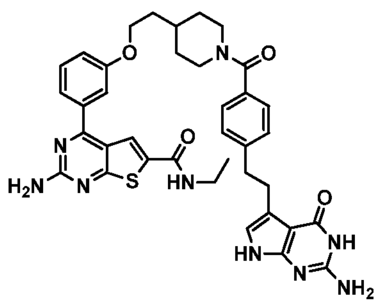


[001449] A round-bottomed flask was charged with Dasatinib (0.18 mmol), DMF (1.5 mL), diisopropyl ethylamine (0.45 mmol), and *N*,*N*''-disuccinimidyl carbonate (0.30 mmol) at 22 ^{0}C. The solution was stirred at 22 ^{0}C, then 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide (0.15 mmol) was added. The solution as stirred for an additional 19 h, then concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (CH_2Cl_2/MeOH) to afford the desired product as a white solid.

[001450] ^{1}H NMR (400 MHz, DMSO-d*6*), δ 11.50 (s, 1H), 9.89 (s, 1H), 8.71 (t, *J* = 6.0 Hz, 1H), 8.22 (s, 1H), 8.03 (s, 1H), 7.49 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.41 – 7.36 (m, 3H), 7.30 – 7.24 (m, 2H), 7.16 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.13 (s, 2H), 6.04 (s, 1H), 4.13 – 4.10 (m, 4H), 3.99 (s, 1H), 3.96 (s, 1H), 3.53 – 3.47 (m, 4H), 3.39 – 3.29 (m, 8H), 3.25 (dq, *J* = 12.8, 6.8 Hz, 2H), 2.62 – 2.57 (m, 2H), 2.40 (s, 3H), 2.24 (s, 3H), 1.75 – 1.70 (m, 5H), 1.11 (t, *J* = 7.2 Hz, 3H) ppm; ESMS calculated for $C_{45}H_{51}ClN_{12}O5S_2$: 938.3; found: 939.6 (M + H$^+$).

[001451] SDC-TRAP-0250

[001452] 2-amino-4-(3-(2-(1-(4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)piperidin-4-yl)ethoxy)phenyl)-N-ethylthieno[2,3-d]pyrimidine-6-carboxamide

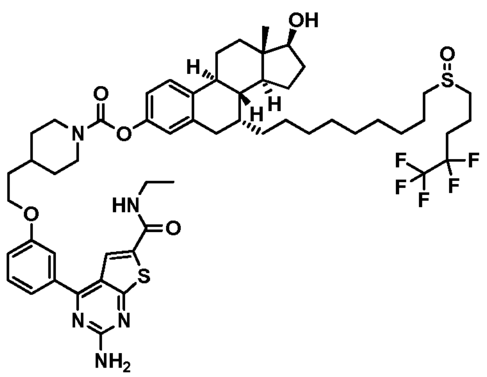


[001453] Compound SDC-TRAP-0250 was synthesized in a similar manner as described for compound SDC-TRAP-0248, using 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide as the amine partner and 4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoic acid as the acid partner.

[001454] ^{1}H NMR (400 MHz, DMSO-d*6*), δ 10.64 (d, *J* = 1.2 Hz, 1H), 10.15 (s, 1H), 8.71 (t, *J* = 8.0 Hz, 1H), 8.04 (s, 1H), 7.50 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.41 – 7.37 (m, 2H), 7.29 – 7.24 (m, 5H), 7.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.14 (s, 2H), 6.34 (s, 1H), 6.01 (s, 2H), 4.12 (t, *J* = 6.0 Hz, 2H), 3.34 – 3.31 (m, 4H), 3.26 – 3.23 (m, 2H), 2.96 – 2.92 (m, 2H), 2.86 – 2.82 (m, 2H), 1.83 – 1.74 (m, 6H), 1.09 (t, *J* = 7.2 Hz, 3H) ppm; ESMS calculated for $C_{37}H_{39}N_9O_4S$: 705.3; found: 706.6 (M + H$^+$).

[001455] SDC-TRAP-0251

[001456] (7R,8R,9S,13S,14S,17S)-17-hydroxy-13-methyl-7-(9-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate



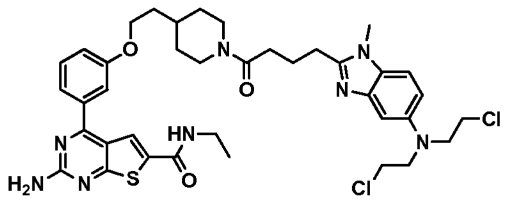
[001457] Compound SDC-TRAP-0251 was synthesized in a similar manner as described for compound SDC-TRAP-0249, using

2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide as the amine partner and Fulvestrant as the alcohol partner.

[001458] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.75 (s, 1H), 7.50 – 7.33 (m, 5H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.08 (ddd, *J* = 8.1, 2.6, 1.1 Hz, 1H), 6.88 – 6.78 (m, 3H), 6.07 (s, 1H), 4.27 (s, 2H), 4.12 (d, *J* = 4.0 Hz, 2H), 3.74 (t, *J* = 8.6 Hz, 1H), 3.49 (qd, *J* = 7.3, 5.6 Hz, 2H), 2.97 (s, 1H), 2.88 (dd, *J* = 17.0, 5.7 Hz, 2H), 2.80 – 2.58 (m, 6H), 2.39 – 2.08 (m, 8H), 1.96 – 1.69 (m, 10H), 1.68 – 1.54 (m, 5H), 1.53 – 1.30 (m, 18H), 1.25 (t, *J* = 8.0 Hz, 3H), 0.77 (s, 3H) ppm; ESMS calculated for $C_{55}H_{72}F_5N_5O_6S_2$: 1057.5; found: 1058.9 (M + H$^+$).

[001459] SDC-TRAP-0252

[001460] 2-amino-4-(3-(2-(1-(4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)butanoyl)piperidin-4-yl)ethoxy)phenyl)-N-ethylthieno[2,3-d]pyrimidine-6-carboxamide



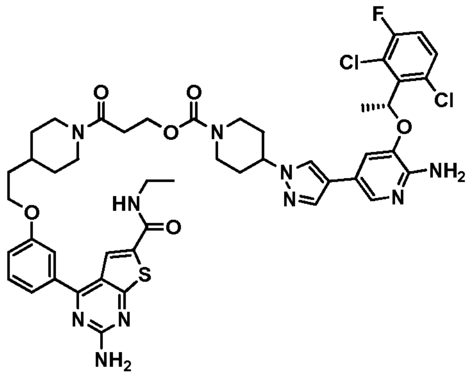
[001461] A round-bottomed flask was charged with 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide (0.05 mmol), Bendamustine (0.06 mmol), DMF (1 mL), HATU (0.07 mmol) and diisopropyl ethylamine (0.12 mmol). The solution was stirred at 22 ^{0}C for 7 h then concentrated under reduced pressure. The resulting crude oil was purified by silica gel chromatography (CH_2Cl_2/MeOH) to afford the desired product as a white solid.

[001462] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 (s, 1H), 7.48 – 7.31 (m, 3H), 7.22 (d, *J* = 8.9 Hz, 1H), 7.10 – 7.01 (m, 2H), 6.81 (dd, *J* = 8.9, 2.4 Hz, 1H), 6.02 (t, *J* = 5.6 Hz, 1H), 4.58 (d, *J* = 13.4 Hz, 1H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.88 (d, *J* = 13.6 Hz, 1H), 3.79 – 3.59 (m, 12H), 3.49 (qd, *J* = 7.3, 5.7 Hz, 2H), 3.07 – 2.93 (m, 3H), 2.61 – 2.49 (m, 3H), 2.24 – 2.12 (m, 2H), 2.01 – 1.72 (m, 5H), 1.33 – 1.13 (m, 6H), 1.25 (t, *J* = 8.0 Hz, 3H) ppm; ESMS calculated for $C_{38}H_{46}Cl_2N_8O_3S$: 764.3; found: 765.6 (M + H$^+$).

[001463] SDC-TRAP-0253

[001464] (R)-3-(4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidin-1-yl)-3-oxopropyl

4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



[001465] (R)-3-(tert-butoxy)-3-oxopropyl 4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate was prepared using a similar procedure to SDC-TRAP-0249.

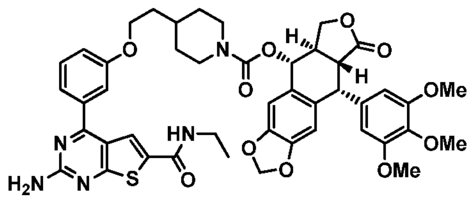
[001466] (R)-3-(tert-butoxy)-3-oxopropyl 4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (0.04 mmol) was treated with HCl (4M in dioxane, 0.5 mL) at 22 ^{0}C for 1 h, then concentrated under reduced pressure to yield the (R)-3-((4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carbonyl)oxy)propanoic acid.

[001467] SDC-TRAP-0253 was synthesized in a similar manner as described for SDC-TRAP-0252, from (R)-3-((4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carbonyl)oxy)propanoic acid and 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide.

[001468] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (s, 1H), 7.70 (d, *J* = 1.8 Hz, 1H), 7.55 (d, *J* = 0.8 Hz, 1H), 7.51 – 7.26 (m, 5H), 7.05 (dd, *J* = 8.9, 7.8 Hz, 2H), 6.87 (d, *J* = 1.8 Hz, 1H), 6.07 (q, *J* = 6.7 Hz, 2H), 5.05 (s, 2H), 4.63 (d, *J* = 13.3 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.31 – 4.20 (m, 1H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.89 (d, *J* = 13.6 Hz, 1H), 3.49 (qd, *J* = 7.2, 5.6 Hz, 2H), 3.05 (dd, *J* = 12.6, 12.6 Hz, 1H), 2.94 (s, 3H), 2.72 (d, *J* = 3.8 Hz, 3H), 2.58 (dd, *J* = 12.2, 12.2 Hz, 1H), 2.18 – 2.09 (m, 3H), 1.97 – 1.82 (m, 5H), 1.82 – 1.74 (m, 2H), 1.25 (t, *J* = 8.0 Hz, 9H) ppm; ESMS calculated for $C_{47}H_{51}Cl_2FN_{10}O_6S$: 972.3; found: 973.7 (M + H^{+}).

[001469] SDC-TRAP-0254

[001470] (5R,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate

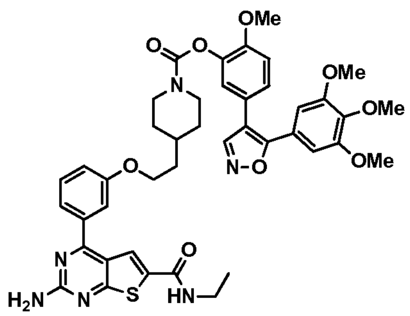


[001471] SDC-TRAP-0254 was synthesized in a similar manner as described for SDC-TRAP-0249, using 2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide as the amine partner and Podophyllotoxin as the alcohol partner.

[001472] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.77 (s, 1H), 7.47 – 7.33 (m, 2H), 7.06 (s, 1H), 6.84 (s, 1H), 6.54 (s, 1H), 6.40 (s, 1H), 6.02 – 5.95 (m, 1H), 5.80 (d, *J* = 8.9 Hz, 1H), 4.60 (d, *J* = 4.3 Hz, 1H), 4.47 – 4.42 (m, 1H), 4.24 (t, *J* = 9.9 Hz, 1H), 4.11 (s, 1H), 3.81 (d, *J* = 1.2 Hz, 2H), 3.75 (s, 3H), 3.56 – 3.44 (m, 1H), 2.98 – 2.79 (m, 2H), 1.89 – 1.70 (m, 2H), 1.58 – 1.55 (m, 6H), 1.26 (t, *J* = 7.3 Hz, 3H) ppm; ESMS calculated for $C_{45}H_{47}N_5O_{11}S$: 865.3; found: 866.6 (M + H$^+$).

[001473] SDC-TRAP-0255

[001474] 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl 4-(2-(3-(2-amino-6-(ethylcarbamoyl)thieno[2,3-d]pyrimidin-4-yl)phenoxy)ethyl)piperidine-1-carboxylate



[001475] SDC-TRAP-0255 was synthesized in a similar manner as described for SDC-TRAP-0249, using

2-amino-N-ethyl-4-(3-(2-(piperidin-4-yl)ethoxy)phenyl)thieno[2,3-d]pyrimidine-6-carboxamide as the amine partner, and 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenol as the alcohol partner.

[001476] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 7.76 (s, 1H), 7.50 – 7.33 (m, 3H), 7.26 – 7.13 (m, 2H), 7.08 (ddd, *J* = 8.0, 2.6, 1.1 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.91 (s, 2H), 5.97 – 5.92 (m, 1H), 4.13 (t, *J* = 8.0 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H) 3.76 (s, 6H), 3.50 (qd, *J* = 7.3, 5.6 Hz, 2H), 3.04 – 2.99 (m, 1H), 2.89 – 2.84 (m, 1H), 1.85 – 1.80 (m, 6H), 1.30 – 1.22 (m, 9H) ppm; ESMS calculated for $C_{42}H_{44}N_6O_9S$: 808.3; found: 809.6 (M + H^+).

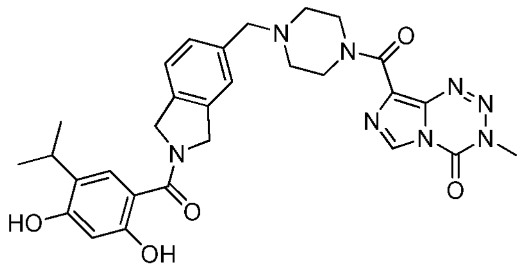
[001477] **Example 47**

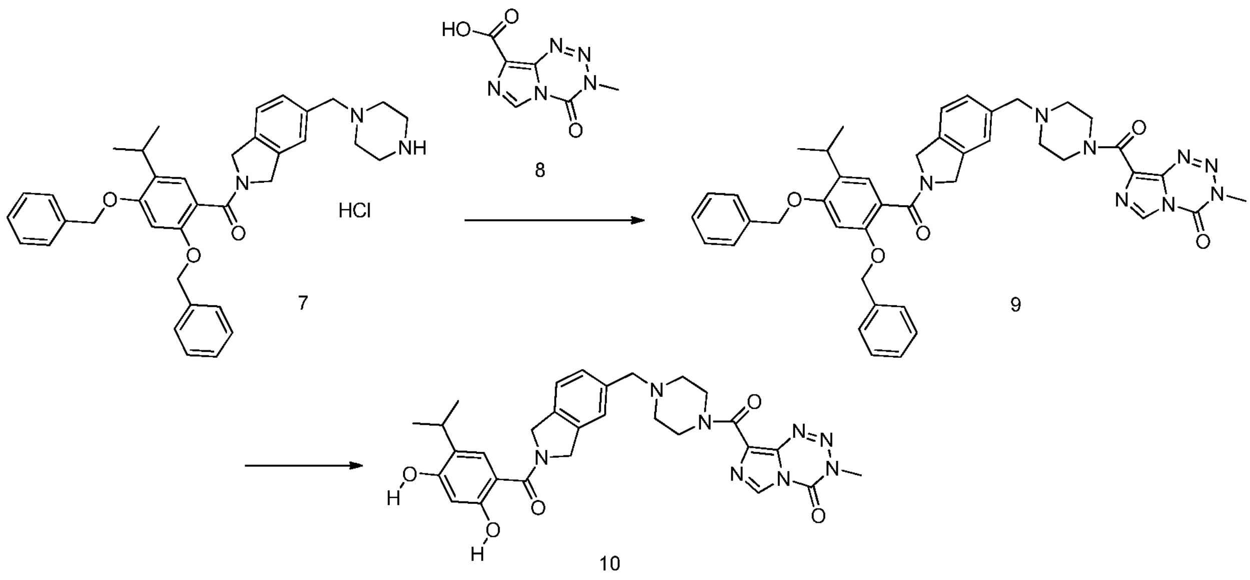
[001478] **SDC-TRAPs comprising AT-13387AU (available from Astex Pharmaceuticals, Inc.)**

[001479] Unless otherwise indicated, compounds in this example were produced in a similar manner as described for SDC-TRAP-0256 and/or according to the given reaction schemes.

[001480] SDC-TRAP-0256

[001481] 8-(4-((2-(2,4-dihydroxy-5-isopropylbenzoyl)isoindolin-5-yl)methyl)piperazine-1-carbonyl)-3-methylimidazo[5,1-d][1,2,3,5]tetrazin-4(3H)-one





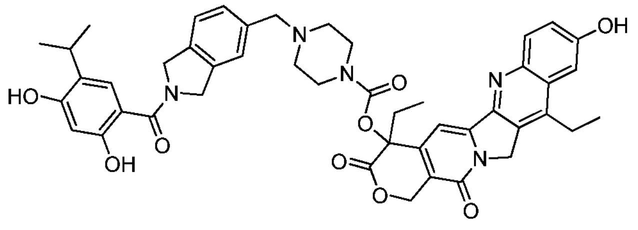
[001482] 3-Methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxylic acid 8 (prepared by literature method from temozolamide) (36mgs, 0.184 mmoles) was combined with 3 mls of anhydrous N,N-dimethylformamide, 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate coupling agent (76 mgs, 0.199 mmoles), N,N- diisopropylethylamine (88 μl, 0.49 mmoles), and (2,4-bis(benzyloxy)-5-isopropylphenyl)(5-(piperazin-1-ylmethyl)isoindolin-2-yl)methanone hydrochloride 7 (100 mgs, 0.168 mmoles) were combined in a sealed vial and stirred at room temperature for one day. The reaction was taken up in 10 mls of water and extracted twice with 20 mls of ethyl acetate. The organic phases were dried over sodium sulfate and evaporated *in vacuo*. The crude product was purified on a medium pressure silica column, eluting with 0-15% methanol/ dichloromethane. This yielded 8-(4-((2-(2,4-bis(benzyloxy)-5-isopropylbenzoyl)isoindolin-5-yl)methyl)piperazine-1-carbonyl)-3-methylimidazo[5,1-d][1,2,3,5]tetrazin-4(3H)-one (102 mgs, 81%) as a pale yellow solid.

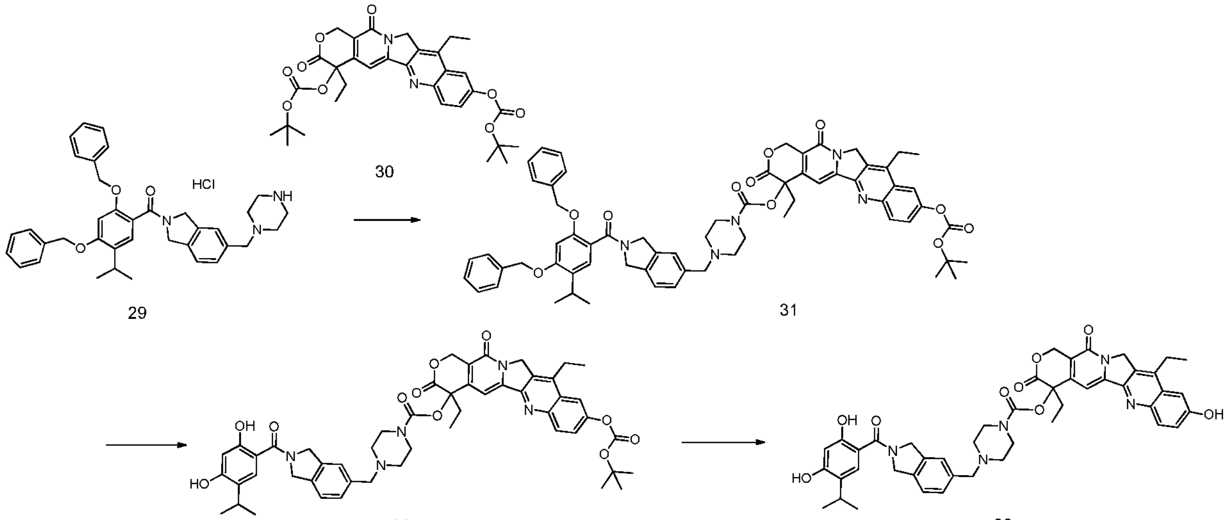
[001483] This was deprotected under standard hydrogenolysis conditions to yield the final product.

[001484] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.05 (s, 1H), 9.62 (s, 1H), 8.82 (s, 1H), 7.32 (s, 1H), 7.24 (s, 2H), 7.04 (s, 1H), 6.39 (s, 1H), 4.77 (s, 4H), 3.84 (s, 3H), 3.67 (s, 2H), 3.52 (s, 4H), 3.09 (p, J = 6.9 Hz, 1H), 2.45-2.30 (m, 4H), 1.08 (d, 6H). ESMS calculated for $C_{29}H_{32}N_8O_5$: 572.3; found: 573.5 (M+H$^+$).

[001485] SDC-TRAP-0257

[001486] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-((2-(2,4-dihydroxy-5-isopropylbenzoyl)isoindolin-5-yl)methyl)piperazine-1-carboxylate

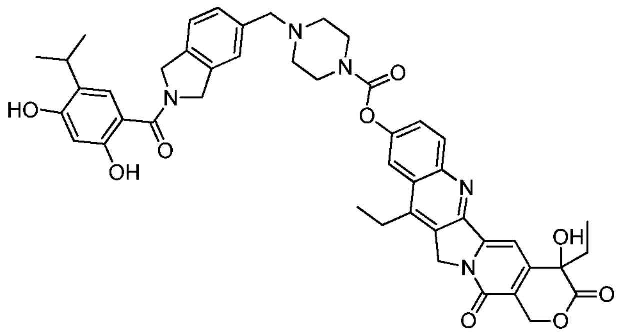


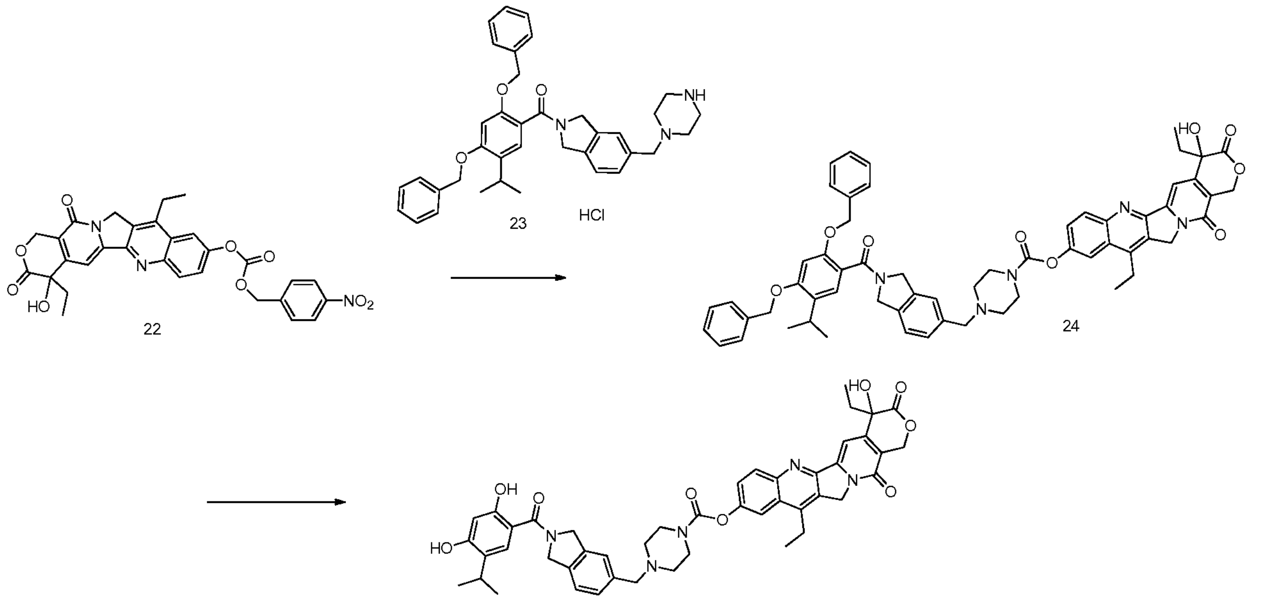


[001487] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 2H), 10.08 (s, 1H), 9.64 (s, 1H), 8.04 (d, J = 8.9 Hz, 1H), 7.43 (d, J = 9.1 Hz, 2H), 7.31 (s, 1H), 7.22 (d, J = 7.6 Hz, 2H), 7.04 (s, 1H), 6.95 (s, 1H), 6.39 (s, 1H), 5.44 (d, J = 3.4 Hz, 2H), 5.32 – 5.27 (m, 2H), 4.77 (d, J = 6.3 Hz, 4H), 3.71 (s, 1H), 3.61 (s, 1H), 3.50 (d, J = 2.7 Hz, 2H), 3.25 (m, 2H), 3.15 – 3.03 (m, 2H), 2.49 (m, 1H), 2.22 (m, 1H), 2.13 (q, J = 7.1 Hz, 2H), 1.27 (t, J=10 Hz,3H) 1.13 (d, 6H), 0.90 (t, J = 7.4 Hz, 3H). ESMS calculated for $C_{46}H_{47}N_5O_9$: 813.3; found: 814.7 (M+H$^+$).

[001488] SDC-TRAP-0258

[001489] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((2-(2,4-dihydroxy-5-isopropylbenzoyl)isoindolin-5-yl)methyl)piperazine-1-carboxylate





22 23 24 25

[001490] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 (s, 1H), 8.18 (d, J = 9.4 Hz, 1H), 8.00 (s, 1H), 7.67 (d, J = 9.1 Hz, 1H), 7.32 (s, 1H), 7.27 (s, 2H), 7.05 (s, 1H), 6.54 (s, 1H), 6.40 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.79 (s, 4H), 3.68 (m, 2H), 3.56 (m, 2H), 3.30 (d, J = 11.6 Hz, 2H), 3.19 (m, 2H), 3.09 (d, J = 9.3 Hz, 1H), 1.87 (m, 2H), 1.29 (t, J=7.2 Hz, 3H), 1.14 (d, J=9.9 Hz, 6H), 0.88 (t, J = 7.4 Hz, 3H). ESMS calculated for $C_{46}H_{47}N_5O_9$: 813.3; found: 814.7 (M+H$^+$).

[001491] **Example 48**

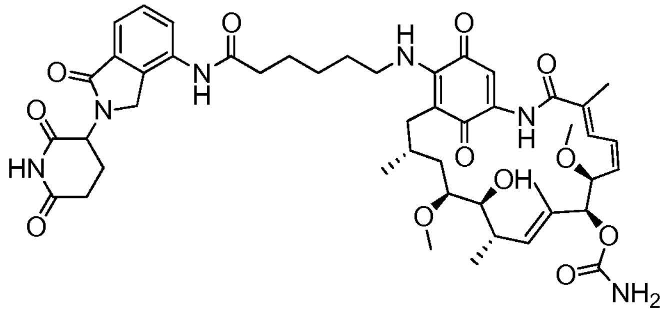
[001492] **SDC-TRAPs comprising GELDANAMYCIN (available from InvivoGen)**

[001493] Unless otherwise indicated, compounds in this example were prepared in a manner analogous to SDC-TRAP-0259, SDC-TRAP-0260 or SDC-TRAP-0266.

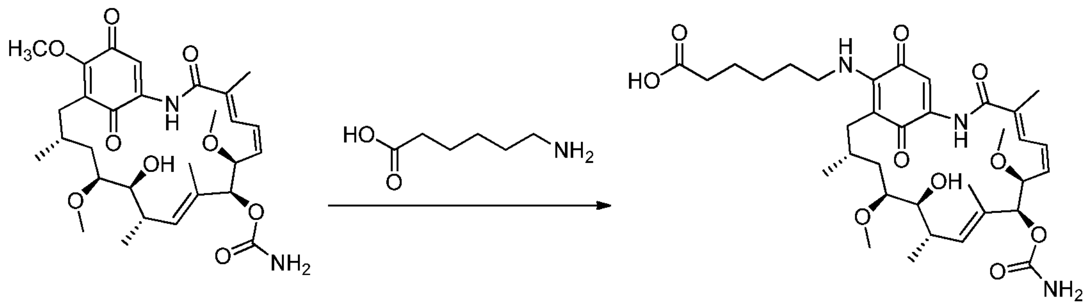
[001494] SDC-TRAP-0259

[001495] (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-19-((6-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-6-oxohexyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetrameth

yl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

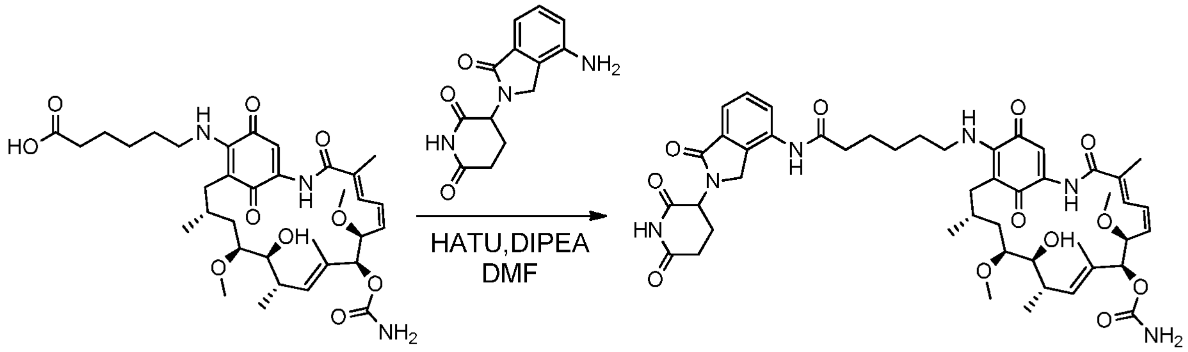


[001496] Step1: Synthesis of 6-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)hexanoic acid



[001497] To a solution of geldanamycin (448 mg, 0.80 mmol) in DMSO (6.0 mL) was added 6-aminohexanoic acid (525 mg, 4.0 mmol) and triethylamine (0.70 mL). The mixture was stirred at 45 °C for 6.5 hours. The reaction mixture was poured into 0.5 N HCl and extracted with dichloromethane. After drying with Na_2SO_4, solvent was evaporated under reduced pressure to give a residue. The residue was purified by ISCO over silica gel to afford 6-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)hexanoic acid (586 mg, 100%) as a purple solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.20 (s, 1H), 7.27 (s, 1H), 6.95 (d, J = 11.6 Hz, 1H), 6.59 (t, J = 11.3 Hz, 1H), 6.30 (t, J = 5.6 Hz, 1H), 5.93 – 5.81 (m, 2H), 5.19 (s, 1H), 4.97 (brs, 2H), 4.32 (d, J = 9.8 Hz, 1H), 3.62 – 3.44 (m, 5H), 3.37 (s, 3H), 3.27 (s, 3H), 2.80-2.35 (m, 10H), 2.03 (s, 3H), 1.79-1.40 (m, 8H), 1.00 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H). ESMS calculated for $C_{34}H_{49}N_3O_{10}$: 659.3; found: 567.5 $(M - 92)^+$.

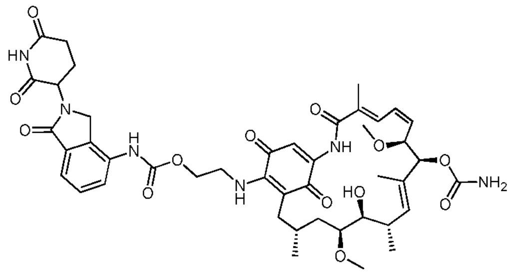
[001498] Step 2: Synthesis of (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-19-((6-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-6-oxohexyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate



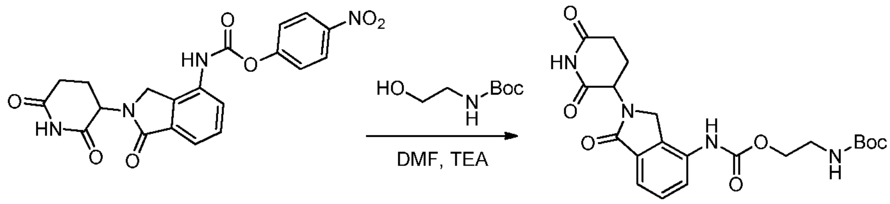
[001499] To a solution of 6-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)hexanoic acid (40.7 mg, 0.062 mmol) in DMF (3.0 mL) was added HATU (27 mg, 0.072 mmol), lenalidomide (24 mg, 0.093 mmol) and DIPEA (0.05 mL). The reaction mixture was stirred at 40 °C under nitrogen for 6 hrs and at room temperature for overnight. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-19-((6-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)amino)-6-oxohexyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate (16.3 mg, 29%) as a purple solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.20 (d, *J* = 6.3 Hz, 1H), 7.81 – 7.61 (m, 2H), 7.46 (td, *J* = 7.7, 2.1 Hz, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 6.95 (d, *J* = 11.6 Hz, 1H), 6.57 (td, *J* = 11.4, 4.5 Hz, 1H), 6.28 (d, *J* = 5.9 Hz, 1H), 5.92 – 5.81 (m, 2H), 5.27 – 5.06 (m, 2H), 4.86 (s, 2H), 4.41 – 4.28 (m, 3H), 3.61 – 3.41 (m, 5H), 3.39 – 3.33 (m, 3H), 3.30 – 3.25 (m, 3H), 2.91 – 2.60 (m, 4H), 2.51 – 2.22 (m, 4H), 2.17 (ddt, *J* = 10.5, 7.8, 3.8 Hz, 1H), 2.09 (s, 1H), 2.02 (d, *J* = 1.2 Hz, 3H), 1.87 – 1.76 (m, 5H), 1.71 (d, *J* = 7.4 Hz, 3H), 1.57 – 1.41 (m, 3H), 1.30 – 1.23 (m, 2H), 1.04 – 0.83 (m, 6 H) ppm. ESMS calculated for $C_{47}H_{60}N_6O_{12}$: 900.4; found: 808.7 $(M - 92)^+$.

[001500] SDC-TRAP-0260

[001501] 2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate

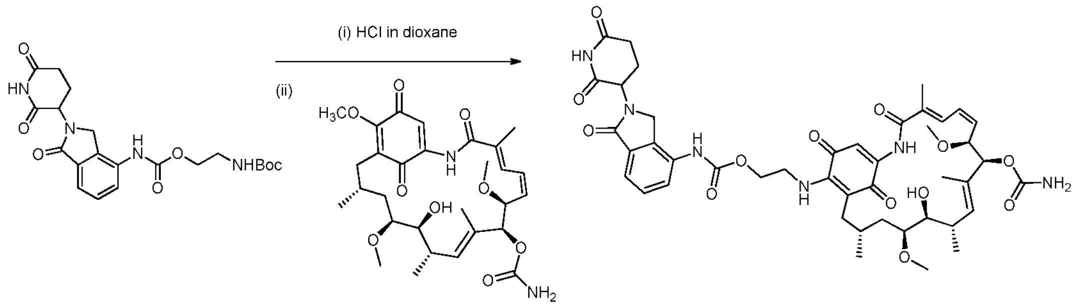


[001502] Step 1: Synthesis of 2-((*tert*-butoxycarbonyl)amino)ethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[001503] To a solution of *tert*-butyl (2-hydroxyethyl)carbamate (79 mg, 0.49 mmol) in DMF (4.0 mL) was added 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (148 mg, 0.35 mmol) and triethylamine (0.10 mL). The mixture was stirred at room temperature for 1.5 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford 2-((*tert*-butoxycarbonyl)amino)ethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (174 mg, 100%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.55 (s, 1H), 8.02 (s, 2H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 5.20 (dd, *J* = 13.2, 5.2 Hz, 1H), 4.99 (s, 2H), 4.23 (t, *J* = 5.2 Hz, 2H), 3.46-3.42 (m, 2H), 2.88-2.26 (m, 4H), 1.42 (s, 9H). ESMS calculated for $C_{21}H_{26}N_4O_7$: 446.2; found: 447.4 $(M + H)^+$.

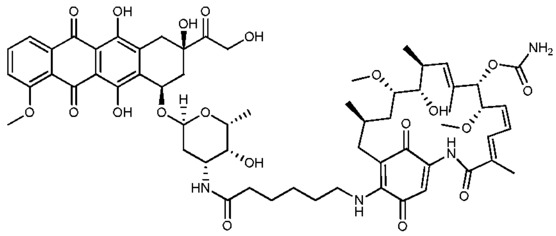
[001504] Step 2: Synthesis of 2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[001505] To a solution of 2-((*tert*-butoxycarbonyl)amino)ethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (170 mg) in DCM (8.0 mL) was added 4.0M HCl in dioxane (2.0 mL). The reaction mixture was stirred at room temperature for 1.5 hours. Solvent was evaporated to give 2-aminoethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (173 mg) as a yellow solid. A solution of 2-aminoethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (173 mg), geldanamycin (84 mg, 0.15 mmol) and triethylamine (0.20 mL) in DMSO was stirred at room temperature for overnight. The reaction mixture was poured into 0.5 N HCl and extracted with dichloromethane. After drying with Na_2SO_4, solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford 2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (62 mg) as a purple solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.14 (d, J = 2.5 Hz, 1H), 9.01 (s, 1H), 7.70 – 7.57 (m, 1H), 7.52 – 7.40 (m, 1H), 7.14 (d, J = 11.1 Hz, 1H), 6.95 (d, J = 11.5 Hz, 1H), 6.64 – 6.48 (m, 2H), 5.86 (td, J = 11.0, 5.4 Hz, 2H), 5.26 – 5.14 (m, 2H), 4.90 (s, 2H), 4.53 (s, 1H), 4.47 – 4.27 (m, 4H), 4.18 (s, 1H), 3.86 (s, 2H), 3.56 (d, J = 8.4 Hz, 1H), 3.44 (dd, J = 8.5, 4.2 Hz, 1H), 3.35 (s, 3H), 3.27 (d, J = 2.0 Hz, 3H), 2.89 – 2.59 (m, 5H), 2.37 (dt, J = 17.0, 11.8 Hz, 2H), 2.17 (s, 2H), 2.00 (dd, J = 2.7, 1.3 Hz, 3H), 1.82 – 1.67 (m, 6H), 1.03 – 0.93 (m, 6H) ppm. ESMS calculated for $C_{44}H_{54}N_6O_{13}$: 874.4; found: 782.6 (M - 92)$^+$.

[001506] SDC-TRAP-0261

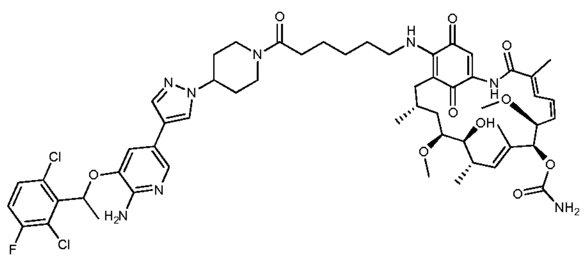
[001507] (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-13-hydroxy-19-((6-(((2R,3R,4R,6S)-3-hydroxy-2-methyl-6-(((1R,3R)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2H-pyran-4-yl)amino)-6-oxohexyl)amino)-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate



[001508] Using doxorubicin as starting material, the title compound was prepared analogously to SDC-TRAP-0259 (step 2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 13.99 (s, 1H), 13.27 (s, 1H), 9.17 (s, 1H), 8.05 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.80 (t, *J* = 8.5 Hz, 1H), 7.40 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.25 (s, 1H), 6.95 (d, *J* = 11.7 Hz, 1H), 6.58 (t, *J* = 11.2 Hz, 1H), 6.26 (t, *J* = 5.5 Hz, 1H), 5.96 – 5.79 (m, 3H), 5.50 (d, *J* = 3.9 Hz, 1H), 5.29 (dd, *J* = 4.3, 2.2 Hz, 1H), 5.19 (s, 1H), 4.76 (dd, *J* = 4.9, 1.8 Hz, 2H), 4.56 (s, 1H), 4.31 (d, *J* = 9.9 Hz, 1H), 4.16 (dt, *J* = 14.6, 7.3 Hz, 1H), 4.09 (s, 3H), 3.63 (brs, 1H), 3.60 – 3.39 (m, 3H), 3.35 (s, 3H), 3.27 (s, 3H), 3.10 – 2.99 (m, 2H), 2.81 (s, 3H), 2.77 – 2.65 (m, 1H), 2.45 – 2.25 (m, 3H), 2.23 – 2.10 (m, 3H), 2.03 (s, 3H), 1.91 – 1.73 (m, 7H), 1.53 – 1.35 (m, 6H), 1.34 – 1.17 (m, 8H), 0.97 (dd, *J* = 23.7, 6.7 Hz, 6H). ESMS calculated for $C_{61}H_{76}N_4O_{20}$: 1184.5; found: 771.7 (M - 413)$^{+}$.

[001509] SDC-TRAP-0262

[001510] (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-19-((6-(4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidin-1-yl)-6-oxohexyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

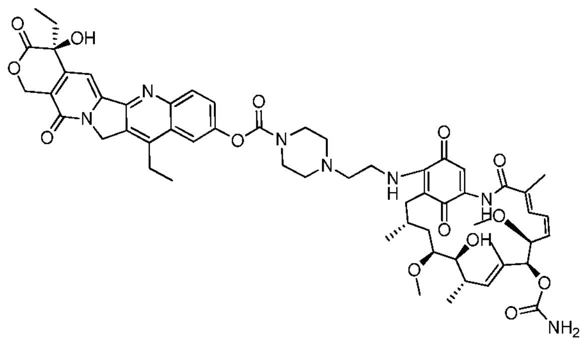


[001511] Using crizotinib as starting material, the title compound was prepared analogously to SDC-TRAP-0259 (step 2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 8.02 (s, 1H), 7.75 (d, *J* = 1.7 Hz, 1H), 7.57 (d, *J* = 0.8 Hz, 1H), 7.49 (d, *J* = 0.8 Hz, 1H), 7.30 (dd, *J* = 8.9, 4.8 Hz, 1H), 7.28 (s, 1H), 7.06 (dd, *J* = 8.9, 7.9 Hz, 1H), 6.96 (d, *J* = 11.7 Hz, 1H), 6.86 (d, *J* = 1.9 Hz, 1H), 6.64 – 6.53 (m, 1H), 6.29 (t, *J* = 5.4 Hz, 1H), 6.07 (q, *J* = 6.7 Hz, 1H),), 5.91 (d, *J* = 10.9 Hz, 1H), 5.85 (d, *J* = 10.6 Hz, 1H), 5.19 (s, 1H), 4.79 (s, 2 H), 4.31 (d, *J* = 10.1 Hz, 2H), 4.00 (d, *J* = 14.1 Hz, 1H), 3.59– 3.41 (m, 3H), 3.37 (s, 3H), 3.27 (s, 3H), 3.18 -1.72 (m, 27H),

1.50-1.43 (m, 6 H), 1.00 (d, J = 6.9 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H). ESMS calculated for $C_{55}H_{69}Cl_2FN_8O_{10}$: 1090.5; found: 1091.7 $(M + H)^+$.

[001512] SDC-TRAP-0263

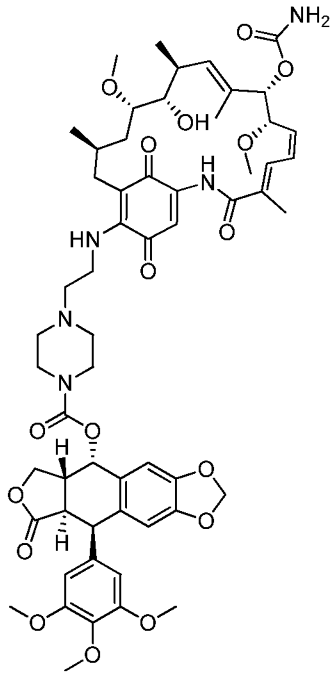
[001513] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl)piperazine-1-carboxylate



[001514] ^{1}H NMR (400 MHz, Chloroform-d) δ 9.20 (s, 1H), 8.22 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 2.5 Hz, 1H), 7.64 (s, 1H), 7.60 (dd, J = 9.2, 2.5 Hz, 1H), 7.30 (s, 1H), 7.13 (s, 1H), 6.97 (d, J = 11.7 Hz, 1H), 6.60 (t, J = 11.4 Hz, 1H), 5.97 – 5.81 (m, 2H), 5.75 (d, J = 16.2 Hz, 1H), 5.35 – 5.28 (m, 1H), 5.27 (s, 2H), 5.20 (s, 1H),4.68 (brs, 2H), 4.37 (s, 1H), 4.32 (d, J = 10.0 Hz, 1H), 3.96 – 3.43 (m, 8H), 3.38 (s, 3H), 3.28 (s, 3H), 3.17 (q, J = 7.7 Hz, 2H), 2.85 – 2.67 (m, 4H), 2.49 – 2.34 (m, 1H), 2.04 (d, J = 1.2 Hz, 3H), 1.98 – 1.71 (m, 9H), 1.46 – 1.34 (m, 3H), 1.06-1.00 (m, 12H) ppm. ESMS calculated for $C_{57}H_{69}N_7O_{14}$: 1075.5; found: 1076.8 $(M + H)^+$.

[001515] SDC-TRAP-0264

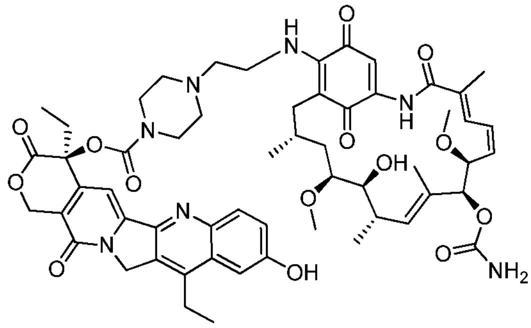
[001516] (5S,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 4-(2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl)piperazine-1-carboxylate



[001517] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 7.28 (s, 1H), 7.09 (s, 1H), 6.97 (d, *J* = 11.8 Hz, 1H), 6.83 (s, 1H), 6.65 – 6.52 (m, 2H), 6.40 (s, 2H), 5.99 (dd, *J* = 6.4, 1.4 Hz, 2H), 5.95 – 5.78 (m, 3H), 5.20 (s, 1H), 4.77 (brs, 2H), 4.61 (d, *J* = 4.3 Hz, 1H), 4.47 (dd, *J* = 9.4, 6.8 Hz, 1H), 4.42 – 4.20 (m, 3H), 3.81(s, 3 H), 3.75 (s, 6H), 3.58 (d, *J* = 7.6 Hz, 6H), 3.46 (d, *J* = 9.1 Hz, 1H), 3.37 (s, 3H), 3.28 (s, 3H), 2.95 – 2.87 (m, 1H), 2.81 – 2.66 (m, 4H), 2.56 – 2.35 (m, 7H), 2.03 (d, *J* = 1.3 Hz, 3H), 1.81 (d, *J* = 1.4 Hz, 6H), 0.99 (dd, *J* = 11.8, 6.7 Hz, 6H). ESMS calculated for $C_{57}H_{71}$ N_5O_{17}: 1097.5; found: 1098.3 $(M + H)^+$.

[001518] SDC-TRAP-0265

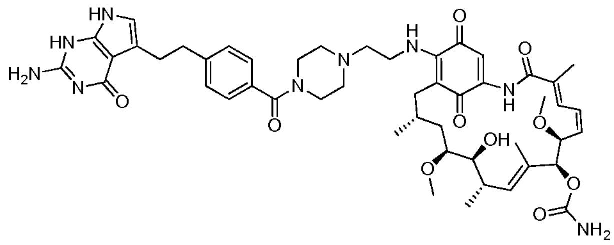
[001519] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl)piperazine-1-carboxylate



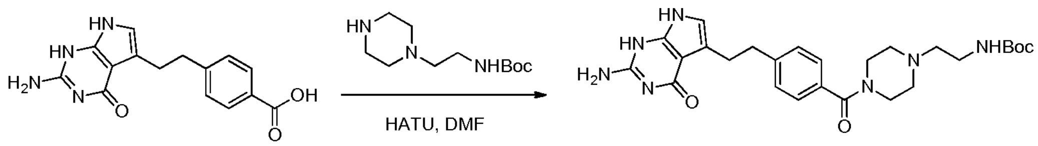
[001520] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.20 (s, 1H), 8.02 (d, *J* = 9.2 Hz, 1H), 7.35 (dd, *J* = 9.2, 2.6 Hz, 1H), 7.28 (s, 1H), 7.15 (d, *J* = 19.1 Hz, 1H), 7.06 (s, 1H), 6.97 (d, *J* = 11.6 Hz, 1H), 6.59 (t, *J* = 11.3 Hz, 1H), 5.94 – 5.83 (m, 2H), 5.71 (d, *J* = 17.0 Hz, 1H), 5.40 (d, *J* = 17.0 Hz, 1H), 5.21 (s, 1H), 4.95 (s, 2H), 4.70 (brs, 2 H), 4.33 (d, *J* = 9.8 Hz, 2H), 3.95 (s, 1H), 3.67 (d, *J* = 14.9 Hz, 4H), 3.63 – 3.54 (m, 2H), 3.44 (d, *J* = 8.8 Hz, 1H), 3.32 (s, 3H), 3.28 (s, 3 H), 2.95 (q, *J* = 7.8 Hz, 2H), 2.79 – 2.58 (m, 7H), 2.52 (s, 1H), 2.43 – 2.23 (m, 3H), 2.20 – 2.09 (m, 1H), 2.07 – 2.01 (m, 4H), 1.83 – 1.74 (m, 6H), 1.46 (s, 1H), 1.27 (dt, *J* = 8.1, 7.3 Hz, 4H), 1.03-0.98 (m, 9H). ESMS calculated for $C_{57}H_{71}N_5O_{17}$: 1097.5; found: 1098.3 $(M + H)^+$.

[001521] SDC-TRAP-0266

[001522] (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-19-((2-(4-(4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)piperazin-1-yl)ethyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate

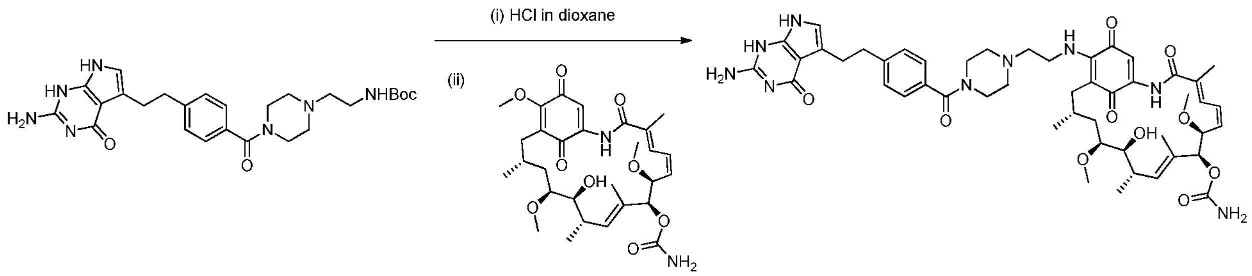


[001523] Step1: Synthesis of tert-butyl (2-(4-(4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)piperazin-1-yl)ethyl)carbamate



[001524] To a solution of 4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoic acid (171 mg, 0.80 mmol) in DMF (5.0 mL) was added HATU (228 mg, 0.60 mmol), tert-butyl (2-(piperazin-1-yl)ethyl)carbamate (138 mg, 0.60 mmol) and DIPEA (0.20 mL). The mixture was stirred at rt for overnight. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford tert-butyl (2-(4-(4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)pipe razin-1-yl)ethyl)carbamate (284 mg, 97%) as a yellow solid. ESMS calculated for $C_{26}H_{35}N_7O_4$: 509.3; found: 510.4 $(M + H)^+$.

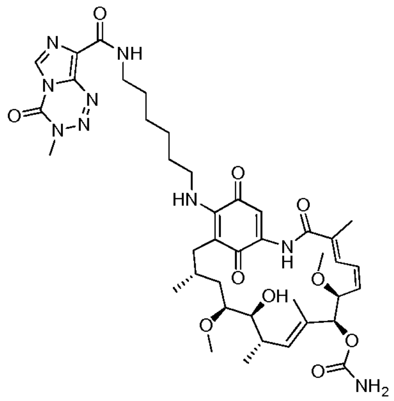
[001525] Step 2: Synthesis of (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-19-((2-(4-(4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)piperazin-1-yl)ethyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate



[001526] Using tert-butyl (2-(4-(4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoyl)piperazin-1-yl)ethyl)carbamate as starting material, the title compound was prepared analogously to SDC-TRAP-0260 (step 2). ^{1}H NMR (400 MHz, Chloroform-*d*+CD_3OD) δ 7.30 – 7.23 (m, 4H), 6.97 (d, *J* = 11.7 Hz, 1H), 6.66 – 6.54 (m, 1H), 6.30 (s, 1H), 5.94 – 5.80 (m, 2H), 5.14 (s, 1H), 4.32 (d, *J* = 9.9 Hz, 1H), 3.94 – 3.67 (m, 3H), 3.63 – 3.38 (m, 6H), 3.37 (s, 3H), 3.28 (s, 3H), 3.02 (d, *J* = 3.6 Hz, 4H), 2.77-2.40 (m, 11H), 2.03 (d, *J* = 1.3 Hz, 3H), 1.86 – 1.64 (m, 6H), 0.99 (dd, *J* = 11.0, 6.7 Hz, 6H) ppm. ESMS calculated for $C_{49}H_{63}N_9O_{10}$: 937.5; found: 845.8 $(M - 92)^+$.

[001527] SDC-TRAP-0267

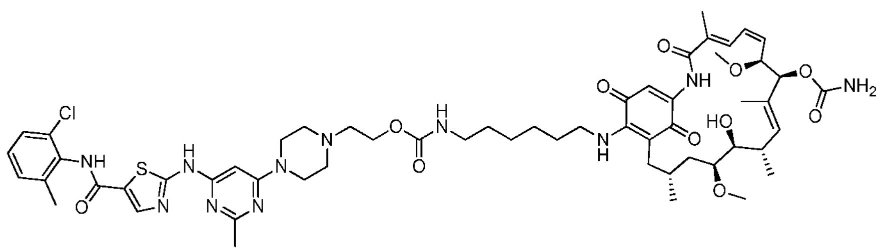
[001528] (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-19-((6-(3-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamido)hexyl)amino)-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate



[001529] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 8.40 (s, 1H), 7.36 (t, *J* = 6.0 Hz, 1H), 7.27 (s, 1H), 6.96 (d, *J* = 11.8 Hz, 1H), 6.64 – 6.54 (m, 1H), 6.28 (t, *J* = 5.4 Hz, 1H), 5.94 – 5.81 (m, 2H), 5.20 (s, 1H),4.53(brs, 2H), 4.32 (d, *J* = 10.0 Hz, 2H), 4.04 (s, 3H), 3.61 – 3.42 (m, 9H), 3.37 (s, 3H), 3.27 (s, 3H), 2.79 – 2.59 (m, 2H), 2.41 (dd, *J* = 14.0, 10.8 Hz, 1H), 2.03 (d, *J* = 1.3 Hz, 3H), 1.83 – 1.75 (m, 9H), 1.70 (t, *J* = 7.1 Hz, 6H), 1.51 – 1.44 (m, 4H), 0.98 (dd, *J* = 17.5, 6.7 Hz, 6H). ESMS calculated for $C_{49}H_{63}N_9O_{10}$: 937.5; found: 845.8 (M - 92)$^+$.

[001530] SDC-TRAP-0268

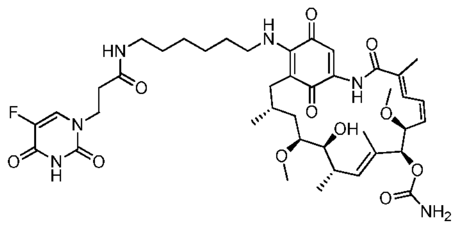
[001531] 2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)ethyl (6-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)hexyl)carbamate



[001532] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.65 (s, 1H), 9.19 (s, 1H), 7.96 (s, 1H), 7.34 – 7.27 (m, 3H), 7.24 – 7.12 (m, 2H), 6.97 (d, *J* = 11.8 Hz, 1H), 6.60 (t, *J* = 11.4 Hz, 1H), 6.43 (s, 1H), 6.00 – 5.87 (m, 2H), 5.82 (s, 1H), 5.18 (s, 1H), 4.79 (s, 1H), 4.53 (s, 1H), 4.33 (d, *J* = 10.0 Hz, 1H), 4.20 (s, 2H), 3.65-3.40 (m, 8H), 3.37 (s, 3H), 3.29 (s, 3H), 3.12 (dd, *J* = 13.4, 6.1 Hz, 1H), 2.80 – 2.40 (m, 14H), 2.35 (s, 3H), 2.03 (d, *J* = 1.3 Hz, 3H), 1.87 – 1.79 (m, 5H), 1.70 – 1.35 (m, 10H), 0.97 (d, *J* = 6.7 Hz, 6H). ESMS calculated for $C_{57}H_{76}ClN_{11}O_{11}S$: 1157.5; found: 1158.4 (M + H)$^+$.

[001533] SDC-TRAP-0269

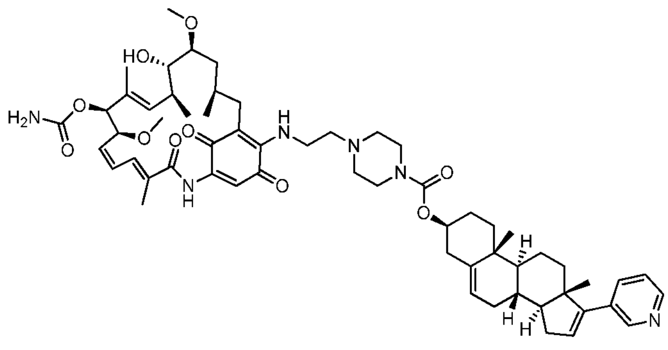
[001534] (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-19-((6-(3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanamido)hexyl)amino)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate



[001535] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.23 (s, 1H), 8.94 (s, 1H), 7.57 (d, *J* = 5.7 Hz, 1H), 6.97 (d, *J* = 11.7 Hz, 1H), 6.64 – 6.53 (m, 1H), 6.29 (t, *J* = 5.5 Hz, 1H), 5.92 – 5.76 (m, 3H), 5.24 (s, 1H), 4.81 (brs, 2 H), 4.38 – 4.26 (m, 2H), 4.00 (dd, *J* = 6.4, 5.1 Hz, 2H), 3.63 – 3.41 (m, 4H), 3.38 (s, 3H), 3.33 – 3.18 (m, 5H), 2.73 (dd, *J* = 16.7, 10.4 Hz, 2H), 2.62 (dd, *J* = 6.4, 5.1 Hz, 2H), 2.42 – 2.31 (m, 1H), 2.06 – 2.00 (m, 3H), 1.82 – 1.62 (m, 8H), 1.51 (p, *J* = 7.1 Hz, 2H), 1.44 – 1.29 (m, 5H), 0.99 (dd, *J* = 18.9, 6.6 Hz, 6H). ESMS calculated for $C_{41}H_{57}FN_6O_{11}$: 828.4; found: 736.7 (M - 92)$^+$.

[001536] SDC-TRAP-0270

[001537] (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-(2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl)piperazine-1-carboxylate

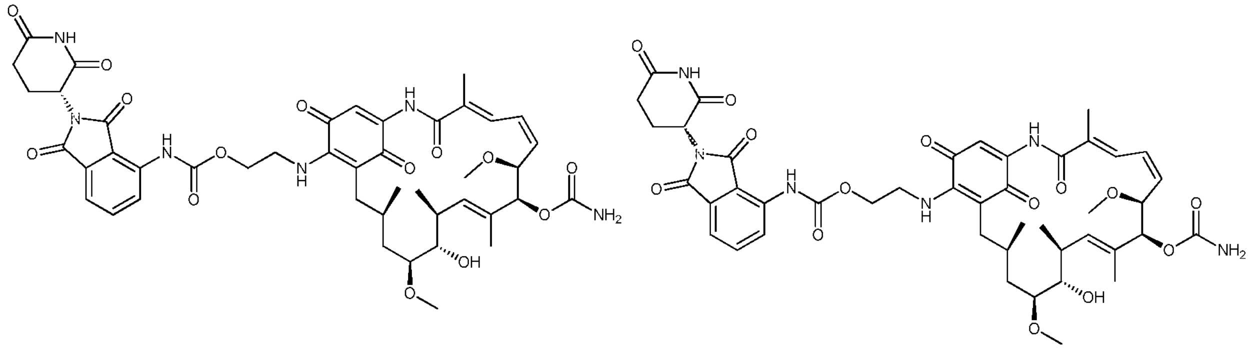


[001538] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 8.62 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.65 (dt, *J* = 8.0, 1.9 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.09 (s, 1H), 6.96 (d, *J* = 11.7 Hz, 1H), 6.65 – 6.54 (m, 1H), 6.00 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.96 – 5.81 (m, 2H), 5.46 – 5.39 (m, 1H), 5.19 (s, 1H), 4.76 (s, 2H), 4.60 – 4.47 (m, 1H), 4.43 (s, 1H), 4.32 (d, *J* = 9.9 Hz, 1H), 3.73 (dd, *J* = 13.9, 5.8 Hz, 1H), 3.63 – 3.42 (m, 7H), 3.37 (s, 3H), 3.27 (s, 3H), 2.80 – 2.64 (m, 4H), 2.49 – 2.22 (m, 8H), 2.13 – 2.01 (m, 6H), 1.96 – 1.41 (m, 16H), 1.23 – 0.94 (m, 14H). ESMS calculated for $C_{59}H_{80}N_6O_{10}$: 1032.6; found: 1033.7 $(M + H)^+$.

[001539] SDC-TRAP-0271

[001540] 2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl (2-((R)-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)carbamate and

2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl (2-((S)-2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)carbamate (diastereomer ratio 1 : 1).

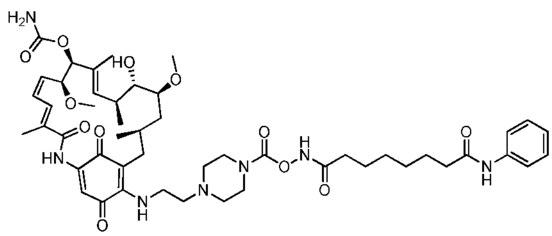


(Diastereomer ratio 1 : 1)

[001541] HPLC: 15.484 min (50%) and 15.721 min (50%). ESMS calculated for $C_{44}H_{52}N_6O_{14}$: 888.4; found: 796.7 $(M - 92)^+$.

[001542] SDC-TRAP-0272

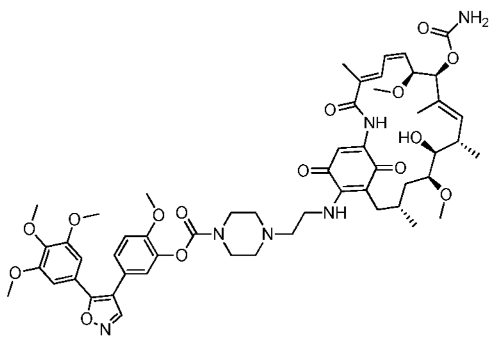
[001543] (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-19-((2-(4-(((8-oxo-8-(phenylamino)octanamido)oxy)carbonyl)piperazin-1-yl)ethyl)amino)-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate



[001544] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.18 (s, 1H), 8.90 (s, 1H), 7.56 – 7.49 (m, 2H), 7.36 – 7.24 (m, 3H), 7.12-7.06 (m, 2H), 6.96 (d, J = 11.7 Hz, 1H), 6.65 – 6.54 (m, 1H), 5.95 – 5.81 (m, 2H), 5.19 (s, 1H), 4.75 (brs, 2H), 4.41 (s, 1H), 4.31 (d, J = 10.0 Hz, 1H), 3.76 – 3.42 (m, 9H), 3.37 (s, 3H), 3.27 (s, 3H), 2.75-2.18 (m, 12H), 2.00 (s, 3H), 1.80-1.40 (m, 15H), 0.99 (dd, J = 15.3, 6.6 Hz, 6H). ESMS calculated for $C_{49}H_{69}N_7O_{12}$: 947.5; found: 949.0 $(M + H)^+$.

[001545] SDC-TRAP-0273

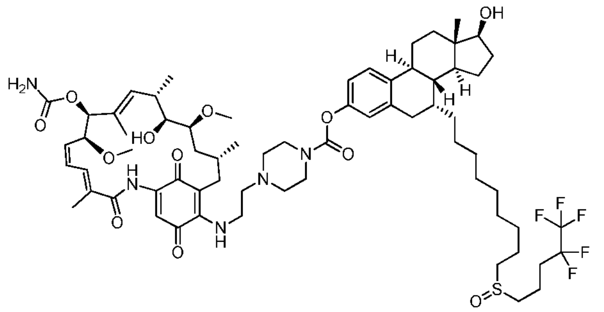
[001546] 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl 4-(2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl)piperazine-1-carboxylate



[001547] ^{1}H NMR (400 MHz, Chloroform-d) δ 9.19 (s, 1H), 8.31 (s, 1 H), 7.28 (s, 1H), 7.25-7.22 (m, 1 H), 7.16 (d, 1H), 7.12-7.08 (m, 1H), 7.03 – 6.93 (m, 2H), 6.90 (s, 2H), 5.95 – 5.84 (m, 2H), 5.20 (s, 1H), 4.78 (s, 2H), 4.32 (d, J = 9.9 Hz, 1H), 3.88 (d, J = 2.2 Hz, 6H), 3.76 (s, 6H), 3.58 (dd, J = 16.7, 8.7 Hz, 4H), 3.46 (d, J = 8.9 Hz, 1H), 3.37 (s, 3H), 3.28 (s, 3H), 2.80 – 2.40 (m, 14H), 2.01 (s, 3 H), 1.83-1.79 (m, 6H), 1.00 (dd, J = 9.3, 6.5 Hz, 6H). ESMS calculated for $C_{54}H_{68}N_6O_{15}$: 1040.5; found: 1042.0 $(M + H)^+$.

[001548] SDC-TRAP-0274

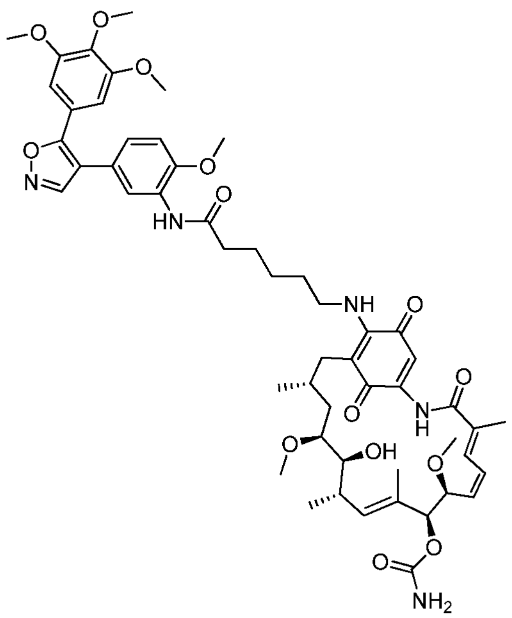
[001549] (7R,8R,9S,13S,14S,17S)-17-hydroxy-13-methyl-7-(9-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-(2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl)piperazine-1-carboxylate



[001550] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.19 (s, 1H), 7.28 (s, 1H), 7.09 (s, 1H), 6.97 (d, *J* = 11.5 Hz, 1H), 6.92 – 6.79 (m, 2H), 6.59 (t, *J* = 11.4 Hz, 1H), 5.95 – 5.82 (m, 2H), 5.20 (s, 1H), 4.76 (s, 2H), 4.32 (d, *J* = 10.0 Hz, 1H), 3.79 – 3.47 (m, 7H), 3.37 (s, 3H), 3.28 (s, 3H), 2.90 -2.08 (m, 22H), 2.03 (s, 3H), 1.92 -1.17 (m, 36H), 1.00 (dd, *J* = 9.3, 6.6 Hz, 6H), 0.78 (s, 3H). ESMS calculated for $C_{67}H_{96}F_5N_5O_{12}S$: 1289.7; found: 1290.8 $(M + H)^+$.

[001551] SDC-TRAP-0275

[001552] (4E,6Z,8S,9S,10E,12S,13S,14S,16R)-13-hydroxy-8,14-dimethoxy-19-((6-((2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)amino)-6-oxohexyl)amino)-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-9-yl carbamate



[001553] Using 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline as starting material, the title compound was prepared analogously to SDC-TRAP-0259 (step 2). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.18 (s, 1H), 8.55 (d, *J* = 2.2 Hz, 1H), 8.34 (s, 1H), 8.02 (s, 1H), 7.79 (s, 1H), 7.28 (s, 1H), 7.08 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.96-6.88 (m, 2H), 6.59 (t, *J* = 11.4 Hz, 1H), 6.28 (t, *J* = 5.8 Hz, 1H), 5.88 (q, *J* = 10.5 Hz, 2H), 5.19 (s, 1H), 4.75 (brs, 2H), 4.31 (d,

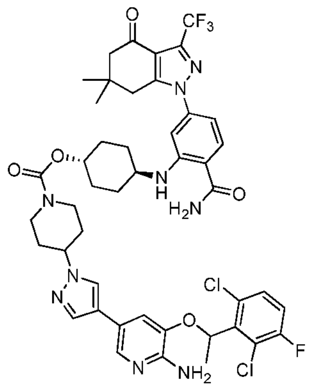
J = 9.9 Hz, 2H), 3.93 (s, 3H), 3.88 (s, 3H), 3.73 (s, 6H), 3.62 – 3.43 (m, 4H), 3.36 (s, 3H), 3.27 (s, 3H), 2.96 (s, 3H), 2.89 (s, 3H), 2.83 – 2.63 (m, 2H), 2.49 – 2.33 (m, 3H), 2.03 (s, 3H), 1.83 – 1.45 (m, 7H), 0.98 (dd, J = 15.6, 6.8 Hz, 6H). ESMS calculated for $C_{53}H_{67}N_5O_{14}$: 997.5; found: 998.8 $(M + H)^+$.

[001554] **Example 49**

[001555] **SDC-TRAPs comprising SNX-5422 (PF-04929113, available from Esanex, Inc.)**

[001556] SDC-TRAP-0276

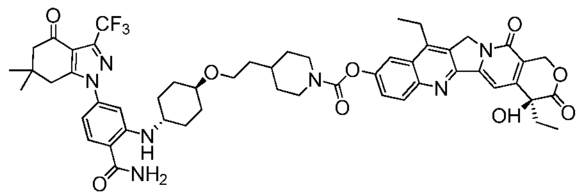
[001557] (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl 4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate



[001558] A solution of 4-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)-2-(((1r,4r)-4-hydroxycyclohexyl)amino)benzamide (46.4 mg, 0.10 mmol), disuccinimidyl carbonate (38.4 mg, 0.15 mmol) and triethylamine (0.10 mL) in DMF (2.0 mL) was stirred at room temperature for 4 hrs. After 3-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)-5-(1-(piperidin-4-yl)-1H-pyrazol-4-yl)pyridin-2-amine (crizotinib) (90 mg, 0.20 mmol) was added, the reaction mixture was continually stirred at room temperature for overnight. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl

4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate (14.1 mg) as a white solid. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.84 (d, J = 0.8 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.58 – 7.47 (m, 2H), 7.41 (dd, J = 9.0, 4.8 Hz, 1H), 7.24 – 7.15 (m, 1H), 7.06 (d, J = 1.7 Hz, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.65 (dd, J = 8.5, 2.1 Hz, 1H), 6.26 (q, J = 6.6 Hz, 1H), 4.63-4.59 (m, 2H), 4.33-4.28 (m, 1H), 4.16 (d, J = 13.6 Hz, 2H), 3.48 – 3.38 (m, 1H), 3.00-2.86 (m, 6H), 2.40 (s, 2H), 2.12 – 1.74 (m, 11H), 1.59-1.34 (m, 4H), 1.01 (s, 6H). ESMS calculated for $C_{45}H_{47}Cl_2F_4N_9O_5$: 939.3; found: 940.7 $(M + H)^+$.

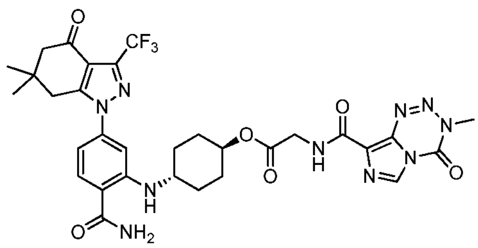
[001559] SDC-TRAP-0277



[001560]

[001561] SDC-TRAP-0278

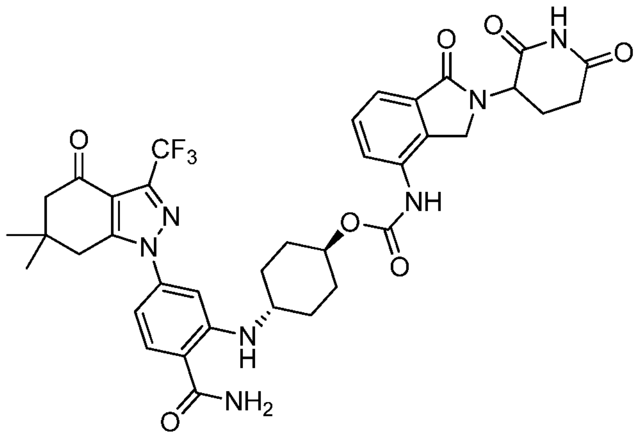
[001562] (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl 2-(3-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamido)acetate



[001563] Using temozolomide as starting material, the title compound was prepared analogously to SDC-TRAP-0280. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.78 (t, J = 6.1 Hz, 1H), 8.46 (d, J = 7.7 Hz, 1H), 7.95 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.35 (s, 1H), 6.89 (d, J = 2.1 Hz, 1H), 6.73 (dd, J = 8.4, 2.0 Hz, 1H), 4.78-4.76 (m, 1H), 4.04 (d, J = 6.1 Hz, 2H), 3.87 (s, 3H), 3.52-3.48 (m, 1 H), 2.98 (s, 2H), 2.45 (s, 2H), 2.04-1.90 (m, 4H), 1.58-1.32 (m, 4H), 1.04 (s, 6H). ESMS calculated for $C_{31}H_{33}F_3N_{10}O_6$: 698.3; found: 699.6 $(M + H)^+$.

[001564] SDC-TRAP-0279

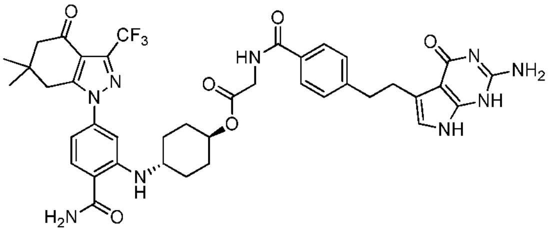
[001565] (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[001566] A solution of 4-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)-2-(((1r,4r)-4-hydroxycyclohexyl)amino)benzamide (46.4 mg, 0.10 mmol), 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (42.4 mg, 0.10 mmol) and triethylamine (0.05 mL) in DMF (1.5 mL) was stirred at room temperature for 1.5 hrs and at 45 °C for 4 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (19.2 mg) as an yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 9.52 (s, 1H), 8.45 (d, J = 7.6 Hz, 1H), 7.82-7.76 (m, 3H), 7.53 – 7.43 (m, 3H), 6.92 (d, J = 2.0 Hz, 1H), 6.78 – 6.70 (m, 1H), 5.13 (dd, J = 13.3, 5.1 Hz, 1H), 4.72-4.68 (m, 1H), 4.44 (d, J = 17.6 Hz, 1H), 4.36 (d, J = 17.6 Hz, 1H), 3.52-3.47 (m, 1H), 2.99 (s, 2 H), 2.64-2.60 (m, 2H), 2.45(s, 2H), 2.11 – 1.99 (m, 6H), 1.60-1.34 (m, 4H), 1.04 (s, 6H). ESMS calculated for $C_{37}H_{38}F_3N_7O_7$: 749.3; found: 750.6 $(M + H)^+$.

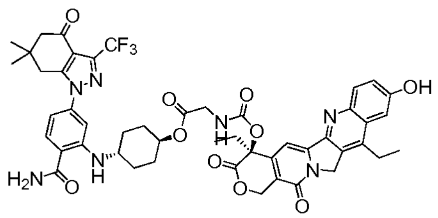
[001567] SDC-TRAP-0280

[001568] (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl 2-(4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzamido)acetate

[001569] 

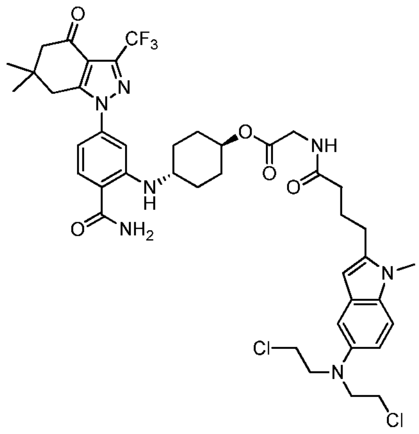
[001570] To a solution of 4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoic acid (29.8 mg, 0.10 mmol) in DMF (2.0 mL) was added HATU (38 mg, 0.10 mmol), (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl 2-aminoacetate (52.1 mg, 0.10 mmol) and DIPEA (0.05 mL). The reaction mixture was stirred at room temperature under nitrogen for 6 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl 2-(4-(2-(2-amino-4-oxo-4,7-dihydro-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzamido)acetate (69.7 mg) as an yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (s, 1H), 10.15 (s, 1H), 8.85 (t, J = 5.9 Hz, 1H), 8.49 – 8.39 (m, 1H), 8.00 (s, 1H), 7.83 – 7.73 (m, 3H), 7.38 – 7.26 (m, 3H), 6.90 (d, J = 2.1 Hz, 1H), 6.73 (dd, J = 8.4, 2.0 Hz, 1H), 6.31 (d, J = 1.7 Hz, 1H), 6.00 (s, 2H), 4.76 (dt, J = 10.2, 5.7 Hz, 1H), 3.96 (t, J = 2.9 Hz, 2H), 3.45 (d, J = 11.4 Hz, 1H), 2.98 (s, 2H), 2.97-2.83 (m, 4H), 2.45 (s, 2H), 2.09-1.89 (m, 4H), 1.58-1.35 (m, 4H), 1.03 (s, 6H). ESMS calculated for $C_{40}H_{42}F_3N_9O_6$: 801.3; found: 802.7 $(M + H)^+$.

[001571] SDC-TRAP-0281



[001572] SDC-TRAP-0282

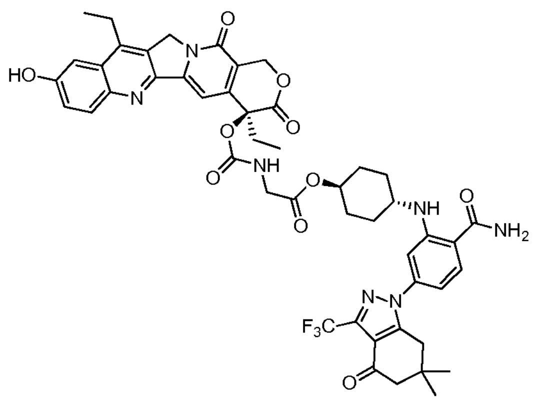
[001573] (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl 2-(4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-indol-2-yl)butanamido)acetate



[001574] Using bendamustine as starting material, the title compound was prepared analogously to SDC-TRAP-0280. ^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.33 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 7.20 (t, J = 5.8 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.89 – 6.80 (m, 2H), 6.76 (dd, J = 8.4, 2.1 Hz, 1H), 6.05 (s, 1H), 4.87-4.83 (m, 1H), 3.91 (d, J = 5.9 Hz, 2H), 3.79 – 3.66 (m, 11H), 3.52 – 3.43 (m, 1H), 3.00 – 2.90 (m, 4H), 2.46 (s, 2H), 2.36 (t, J = 7.1 Hz, 2H), 2.19 – 2.00 (m, 6H), 1.69 – 1.55 (m, 2H), 1.54 – 1.39 (m, 2H), 1.11 (s, 6H). ESMS calculated for $C_{42}H_{50}Cl_2F_3N_7O_5$: 859.3; found: 860.7 $(M + H)^+$.

[001575] SDC-TRAP-0283

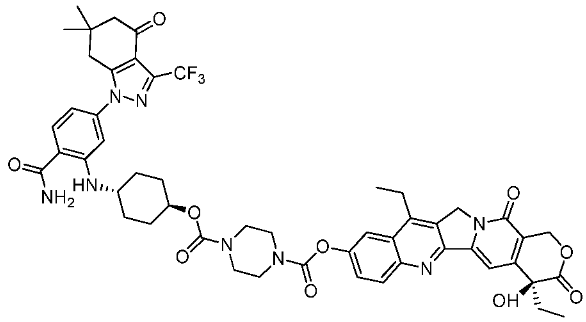
[001576] (1r,4S)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl 2-(((((S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl)oxy)carbonyl)amino)acetate



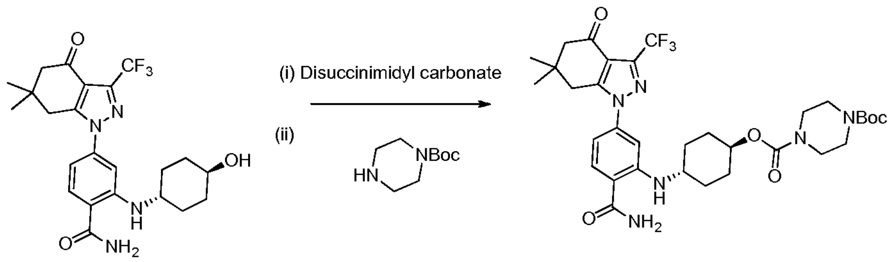
[001577] The title compound was prepared according to the procedure of SDC-TRAP-0284 (Step 3). ESMS calculated for $C_{48}H_{48}F_3N_7O_{10}$: 939.3; found: 940.7 $(M + H)^+$.

[001578] SDC-TRAP-0284

[001579] 1-((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) 4-((S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl) piperazine-1,4-dicarboxylate

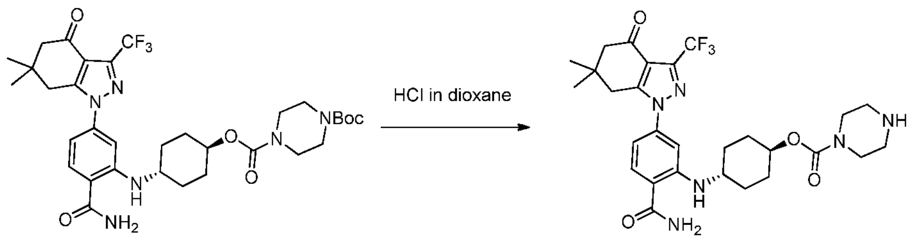


[001580] Step 1: Synthesis of 1-tert-butyl 4-((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) piperazine-1,4-dicarboxylate



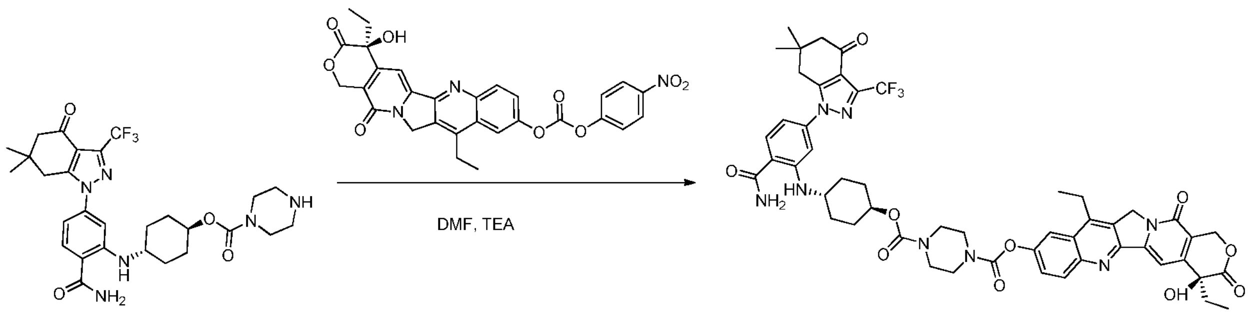
[001581] A solution of 4-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)-2-(((1r,4r)-4-hydroxycyclohexyl)amino)benzamide (557 mg, 1.2 mmol), disuccinimidyl carbonate (460 mg, 1.8 mmol) and triethylamine (0.40 mL) in DMF (10 mL) was stirred at room temperature for overnight. *tert*-Butyl piperazine-1-carboxylate (452 mg, 2.40 mmol) was added and the reaction mixture was continually stirred at room temperature for 4 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford 1-tert-butyl 4-((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) piperazine-1,4-dicarboxylate (469 mg, 58%) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.19 (d, J = 7.3 Hz, 1H), 7.50 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 6.61 (dd, J = 8.4, 2.0 Hz, 1H), 5.68 (s, 2H), 4.74 (s, 1H), 3.44-3.40 (m, 9 H), 2.85 (s, 2H), 2.49 (s, 2H), 2.15-2.08 (m, 4H), 1.57-1.51 (m, 4H), 1.47 (s, 9H), 1.14 (s, 6H). ESMS calculated for $C_{33}H_{43}F_3N_6O_6$: 676.3; found: 677.5 $(M + H)^+$.

[001582] Step 2: Synthesis of (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl piperazine-1-carboxylate



[001583] To a solution of 1-tert-butyl 4-((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) piperazine-1,4-dicarboxylate (469 mg) in 1,4-dioxane (10.0 mL) and methanol (1.0 mL) was added 4.0M HCl in dioxane (2.0 mL). The reaction mixture was stirred at room temperature for 2.5 hours. Solvent was evaporated to give 2-aminoethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate HCl salt (552 mg, 100%) as a yellow solid. ESMS calculated for $C_{28}H_{35}F_3N_6O_4$: 576.3; found: 577.5 $(M + H)^+$.

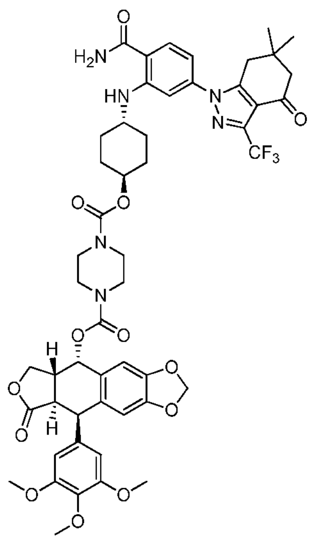
[001584] Step3: Synthesis of 1-((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) 4-((S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl) piperazine-1,4-dicarboxylate



[001585] A solution of 2-aminoethyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate HCl salt (70 mg), (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (4-nitrophenyl) carbonate (39 mg, 0.07 mmol) and triethylamine (0.10 mL) in DMF (2.0 mL) was stirred at room temperature for 3hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford 1-((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) 4-((S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl) piperazine-1,4-dicarboxylate (68.4 mg, 98%) as an yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 7.6 Hz, 1H), 8.20 (d, J = 9.1 Hz, 1H), 8.04-8.01 (m, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.70 (dd, J = 9.2, 2.4 Hz, 1H), 7.35 (s, 1H), 6.90 (d, J = 2.1 Hz, 1H), 6.74 (dd, J = 8.4, 2.0 Hz, 1H), 6.55 (s, 1H), 5.45 (s, 2H), 5.35 (s, 2H), 4.67-4.63 (m, 1H), 3.70-3.50 (m, 9H), 3.19-3.15 (m, 3H), 2.99 (s, 2H), 2.46 (s, 2H), 2.05-1.86 (m, 6H), 1.60-1.35(m, 4H), 1.30 (t, J = 7.6 Hz, 3H), 1.05 (s, 6H), 0.89 (t, J = 7.3 Hz, 3H). ESMS calculated for $C_{51}H_{53}F_3N_8O_{10}$: 994.4; found: 995.8 $(M + H)^+$.

[001586] SDC-TRAP-0285

[001587] 1-((1r,4S)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) 4-((5S,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl) piperazine-1,4-dicarboxylate

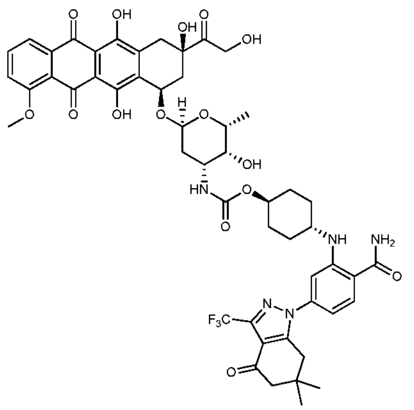


[001588] The title compound was prepared according to the procedure of SDC-TRAP-0284 (Step 3). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (d, J = 7.6 Hz, 1H), 8.01 (s, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.36 (s, 1H), 6.95 (s, 1H), 6.89 (d, J = 2.0 Hz, 1H), 6.73 (dd, J = 8.4, 2.0 Hz, 1H), 6.61 (s, 1H), 6.33 (s, 2H), 6.06 – 6.00 (m, 2H), 5.80 (d, J = 8.0 Hz, 1H), 4.58-4.54 (m, 2H), 4.39 (t, J = 7.8 Hz, 1H), 4.18 (t, J = 7.8 Hz, 1H), 3.64 (s, 6H), 3.61 (s, 3H), 3.55-3.35 (m, 9H), 2.98

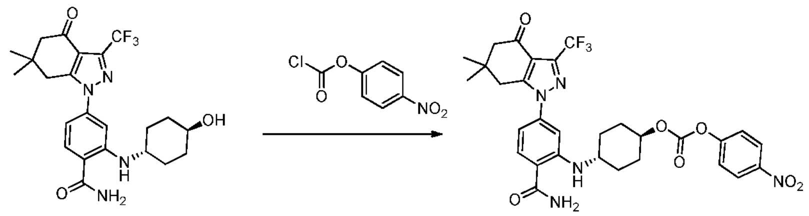
(s, 2H), 2.80-2.65 (m, 2H), 2.45 (s, 2H), 2.05-1.92 (m, 4H), 1.58-1.35 (m, 4H), 1.04 (s, 6H). ESMS calculated for $C_{51}H_{55}F_3N_6O_{13}$: 1016.4; found: 1017.7 $(M + H)^+$.

[001589] SDC-TRAP-0286

[001590] (1r,4R)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl ((2R,3R,4R,6S)-3-hydroxy-2-methyl-6-(((1R,3R)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2H-pyran-4-yl)carbamate

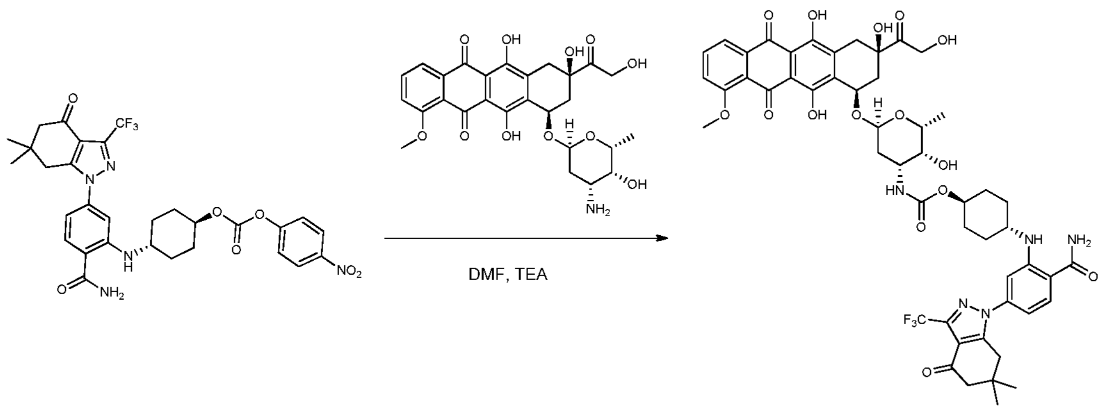


[001591] Step 1: Synthesis of (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl (4-nitrophenyl) carbonate

[001592] 

[001593] A solution of 4-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)-2-(((1r,4r)-4-hydroxycyclohexyl)amino)benzamide (464 mg, 1.0 mmol), 4-nitrophenylchloroformate (240 mg, 1.2 mmol) and DMAP (366 mg, 3.0 mmol) in DCM was stirred at room temperature for 1.5 hrs. The reaction mixture was diluted with DCM, washed with 0.1 N HCl and dried with Na2SO4. Solvent was evaporated under reduced pressure to give (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl (4-nitrophenyl) carbonate (702 mg, 90% purity) as a yellow solid. ESMS calculated for $C_{30}H_{30}F_3N_5O_7$: 629.2; found: 630.5 $(M + H)^+$.

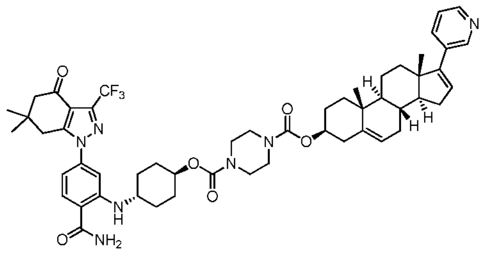
[001594] Step 2: Synthesis of(1r,4R)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl ((2R,3R,4R,6S)-3-hydroxy-2-methyl-6-(((1R,3R)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2H-pyran-4-yl)carbamate.



[001595] A solution of (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl (4-nitrophenyl) carbonate (67 mg), doxorubicin (58 mg, 0.106 mmol) and triethylamine (0.10 mL) in DMF (2.0 mL) was stirred at room temperature for overnight. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford the desired product (27.6 mg) as an organge solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.05 (s, 1H), 13.30 (s, 1H), 8.40 (d, J = 7.7 Hz, 1H), 8.00 – 7.87 (m, 3H), 7.77 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.33 (s, 1H), 6.87 (d, J = 2.2 Hz, 1H), 6.75 – 6.62 (m, 2H), 5.47 (s, 1H), 5.21 (d, J = 3.6 Hz, 1H), 4.95 (t, J = 4.6 Hz, 1H), 4.86 (t, J = 6.0 Hz, 1H), 4.68 (d, J = 5.7 Hz, 1H), 4.57 (d, J = 6.0 Hz, 2H), 4.48-4.44 (m, 1H), 4.19 – 4.11 (m, 1H), 3.99 (s, 3H), 3.70-3.67 (m, 1H), 3.45-3.40 (m, 2H), 2.99-2.95 (m, 4H), 2.43 (s, 2H), 2.24 – 1.80 (m, 8H), 1.51 – 1.21 (m, 4H), 1.12 (d, J = 6.4 Hz, 3H), 1.01 (s, 6H). ESMS calculated for $C_{51}H_{54}F_3N_5O_{15}$: 1033.4; found: 1034.9 $(M + H)^+$.

[001596] SDC-TRAP-0287

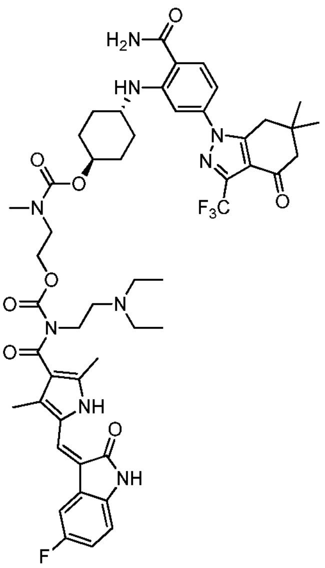
[001597] 1-((1r,4S)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) 4-((3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl) piperazine-1,4-dicarboxylate



[001598] The title compound was prepared according to the procedure of SDC-TRAP-0284 (Step 3). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 1.7 Hz, 1H), 8.46 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.19 (d, *J* = 7.3 Hz, 1H), 7.65 (dt, *J* = 8.1, 1.9 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.22 (ddd, *J* = 8.0, 4.8, 0.9 Hz, 1H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.60 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.99 (dd, *J* = 3.3, 1.7 Hz, 1H), 5.69 (s, 2H), 5.46 – 5.39 (m, 1H), 4.75 (dq, *J* = 9.9, 5.6, 4.7 Hz, 1H), 4.61 – 4.48 (m, 1H), 3.46 (s, 8H), 2.85 (s, 2H), 2.49 (s, 2H), 2.46 – 1.43 (m, 24H), 1.23 – 1.02 (m, 14H). ESMS calculated for $C_{53}H_{64}F_3N_7O_6$: 951.5; found: 952.9 $(M + H)^+$.

[001599] SDC-TRAP-0288

[001600] 2-(((((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl)oxy)carbonyl)(methyl)amino)ethyl (2-(diethylamino)ethyl)(5-((Z)-(5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamate

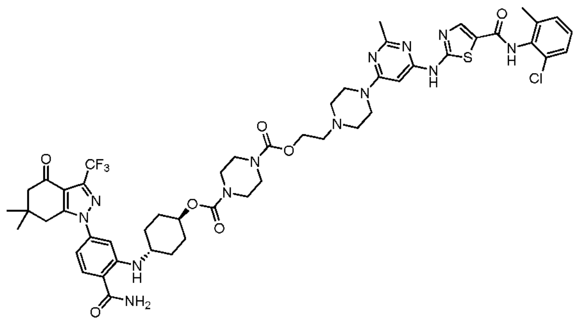


[001601] The title compound was prepared according to the procedure of SDC-TRAP-0286 (Step 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.78 (s, 1H), 10.93 (s, 1H), 8.46 (d, *J* = 7.6 Hz, 1H), 7.99 (s, 1H), 7.83 – 7.69 (m, 3H), 7.35 (s, 1H), 6.94 – 6.79 (m, 3H), 6.73 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.54-4.50 (m, 1H), 4.13 (s, 2H), 3.89-3.77 (m, 2H), 3.55-3.45 (m, 2H), 3.30 (s, 3H), 2.97 (s, 2H), 2.70 (s, 2H), 2.63-2.60 (m, 1H), 2.50 – 2.41 (m, 6H), 2.35 (s, 3H), 2.31 (s, 3H),

1.97-1.87 (m, 4H), 1.51-1.28 (m, 4H), 1.02 (s, 6H), 0.91 (t, *J* = 6.9 Hz, 6H). ESMS calculated for $C_{50}H_{59}F_4N_9O_8$: 989.4; found: 990.8 $(M + H)^+$.

[001602] SDC-TRAP-0289

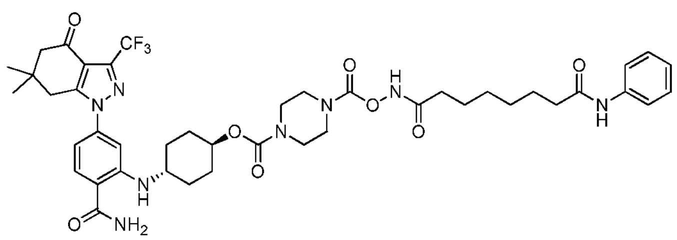
[001603] 1-((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl) 4-(2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)ethyl) piperazine-1,4-dicarboxylate



[001604] The title compound was prepared according to the procedure of SDC-TRAP-0284 (Step 3). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.20 (s, 1H), 8.18 (d, *J* = 7.4 Hz, 1H), 7.97 (s, 1H), 7.51 (d, *J* = 8.3 Hz, 1H), 7.42 (s, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.24 – 7.13 (m, 2H), 6.77 (d, *J* = 2.1 Hz, 1H), 6.60 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.90 (s, 1H), 5.79 (s, 2H), 4.75-4.71 (m, 1H), 4.29 (t, *J* = 5.7 Hz, 2H), 3.69-3.63 (m, 6H), 3.47 (s, 8H), 3.12-3.07 (m, 2H), 2.85 (s, 2H), 2.77-2.71 (m, 3H), 2.51 (s, 3H), 2.49 (s, 2H), 2.35 (s, 3H), 2.15-2.10 (m, 4H), 1.60 – 1.41 (m, 4H), 1.13 (s, 6H). ESMS calculated for $C_{51}H_{59}ClF_3N_{13}O_7S$: 1089.4; found: 1090.9 $(M + H)^+$.

[001605] SDC-TRAP-0290

[001606] (1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl 4-(((8-oxo-8-(phenylamino)octanamido)oxy)carbonyl)piperazine-1-carboxylate

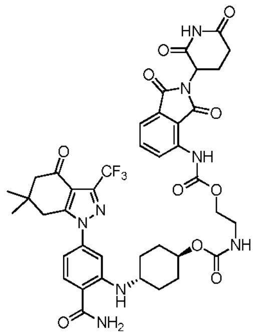


[001607] The title compound was prepared according to the procedure of SDC-TRAP-0284 (Step 3). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.48 (s, 1H), 9.85 (s, 1H), 8.48 (d, *J* = 7.6 Hz, 1H), 8.01 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.58 (dt, *J* = 7.0, 1.3 Hz, 2H), 7.36 (s, 1H), 7.32 –

7.23 (m, 2H), 7.01 (tt, *J* = 7.3, 1.2 Hz, 1H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.0 Hz, 1H), 4.62 (dt, *J* = 9.7, 5.5 Hz, 1H), 3.44-3.38 (m, 9H), 2.98 (s, 2H), 2.45 (s, 2H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.12 – 1.90 (m, 6H), 1.60-1.21 (m, 12H), 1.03 (s, 6H). ESMS calculated for $C_{43}H_{53}F_3N_8O_8$: 866.4; found: 867.7 $(M + H)^+$.

[001608] SDC-TRAP-0291

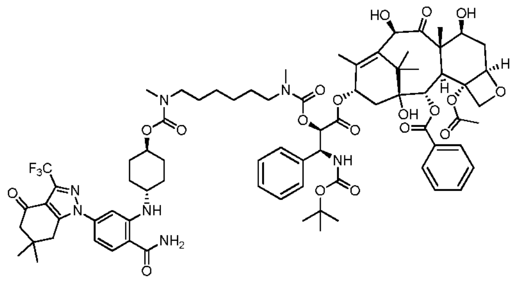
[001609] 2-(((((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl)oxy)carbonyl)amino)ethyl (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)carbamate



[001610] The title compound was prepared according to the procedure of SDC-TRAP-0286 (Step 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.14 (s, 1H), 9.02 (s, 1H), 8.42 (d, *J* = 7.7 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.00 (s, 1H), 7.89 – 7.75 (m, 2H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.38 – 7.27 (m, 2H), 6.88 (d, *J* = 2.1 Hz, 1H), 6.73 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.14 (dd, *J* = 12.7, 5.4 Hz, 1H), 4.56-4.53 (m, 1H), 4.16 (t, *J* = 5.5 Hz, 2H), 3.53-3.49 (m, 2H), 3.29 (q, *J* = 5.4 Hz, 2H), 2.97 (s, 2H), 2.95 – 2.81 (m, 1H), 2.65 – 2.50 (m, 2H), 2.44 (s, 2H), 2.10 -1.88 (m, 4H), 1.55 – 1.25 (m, 4H), 1.03 (s, 6H). ESMS calculated for $C_{40}H_{41}F_3N_8O_{10}$: 850.3; found: 851.7 $(M + H)^+$.

[001611] SDC-TRAP-0292

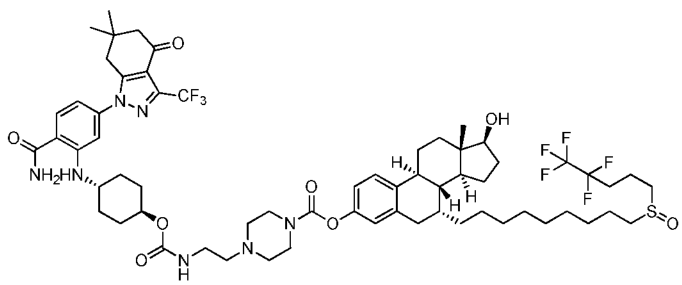
[001612] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(((6-(((((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl)oxy)carbonyl)(methyl)amino)hexyl)(methyl)carbamoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate



[001613] The title compound was prepared according to the procedure of SDC-TRAP-0286 (Step 2). ESMS calculated for $C_{76}H_{96}F_3N_7O_{19}$: 1467.7; found: 1469.0 $(M + H)^+$.

[001614] SDC-TRAP-0293

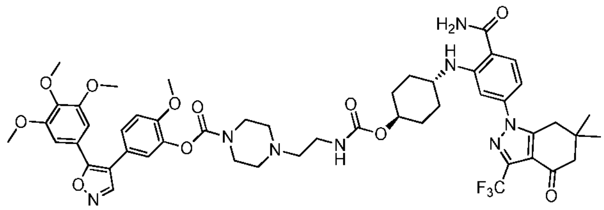
[001615] (7R,8R,9S,13S,14S,17S)-17-hydroxy-13-methyl-7-(9-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl 4-(2-(((((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl)oxy)carbonyl)amino)ethyl)piperazine-1-carboxylate



[001616] The title compound was prepared according to the procedure of SDC-TRAP-0286 (Step 2). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.99 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 6.92 – 6.77 (m, 4H), 4.56-4.54 (m, 2H), 3.55 (t, J = 8.3 Hz, 2H), 3.45-3.41 (m, 1H), 3.12-1.10 (m, 64H), 1.03 (s, 6H),. ESMS calculated for $C_{63}H_{85}F_8N_7O_8S$: 1251.6; found: 1252.6 $(M + H)^+$.

[001617] SDC-TRAP-0294

[001618] 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl 4-(2-(((((1r,4r)-4-((2-carbamoyl-5-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)phenyl)amino)cyclohexyl)oxy)carbonyl)amino)ethyl)piperazine-1-carboxylate



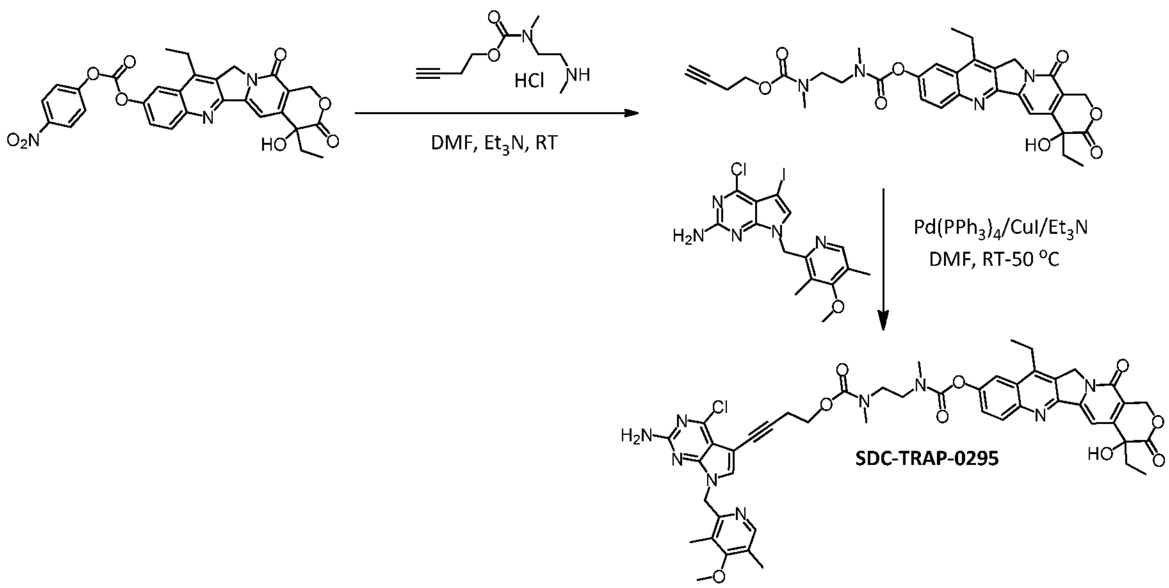
[001619] The title compound was prepared according to the procedure of SDC-TRAP-0286 (Step 2). [1]H NMR (400 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.43 (d, J = 7.7 Hz, 1H), 8.00 (s, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.38 – 7.28 (m, 2H), 7.25 – 7.15 (m, 2H), 7.00 (s, 1H), 6.91-6.87 (m, 3H), 6.73 (dd, J = 8.4, 2.0 Hz, 1H), 4.55-4.51 (m, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.69(s, 6H), 3.58-3.38 (m, 6H), 3.13-3.09 (m, 2H), 2.98 (s, 2H), 2.46-2.40 (m, 7H), 2.10-1.88 (m, 4H), 1.52-1.28 (m, 4H), 1.03 (s, 6H). ESMS calculated for $C_{50}H_{57}F_3N_8O_{11}$: 1002.4; found: 1003.9 $(M + H)^+$.

[001620] **Example 50**

[001621] **SDC-TRAPs comprising BIIB028 (CNF2024, available from Biogen Idec International GmbH)**

[001622] SDC-TRAP-0295

[001623] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo [2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl) ethane-1,2-diylbis(methylcarbamate)



[001624] Step 1: But-3-yn-1-yl (4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl) ethane-1,2-diylbis(methylcarbamate)

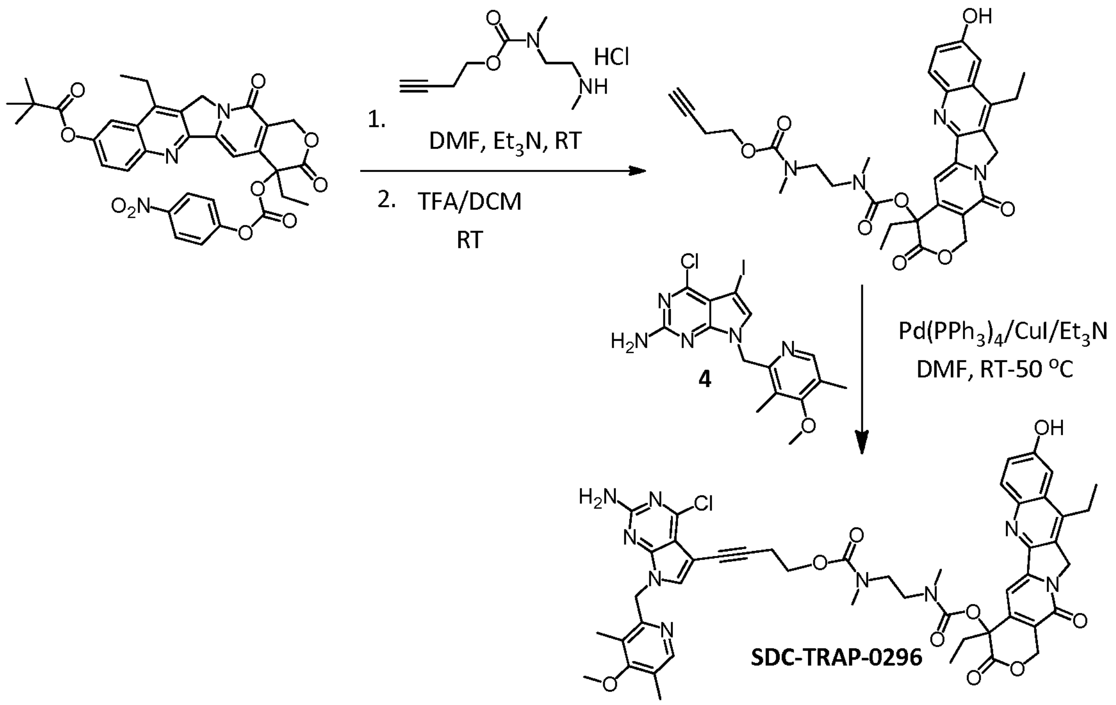
[001625] To the suspension of but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate hydrochloride (53 mg, 0.24 mmol) and 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (4-nitrophenyl) carbonate (136 mg, 0.24 mmol) in dry DMF was added Et_3N (0.12 mL, 0.81 mmol). The reaction mixture was stirred at room temperature until the reaction completion (2 h to 15 h). The solvent was removed and the residue partitioned between water and ethyl acetate. The organic layer was separated, dried over Na_2SO_4 and concentrated. The crude product was purified by ISCO using DCM/MeOH as eluent to afford 97 mg (67%) of product.

[001626] Step 2: A mixture of 4-chloro-5-iodo-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (22 mg, 0.05 mmol, prepared by following patent WO 2006/105372), CuI (1 mg, 0.005 mmol, 11 mol%), $Pd(PPh_3)_4$ (3 mg, 0.0025 mmol, 5 mol%) were taken in dry DMF (0.5 mL). The reaction mixture was degassed by bubbling N_2 into the mixture for 2 min then Et_3N (0.042 mL, 0.3 mmol, 5 eq.) and but-3-yn-1-yl (4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl) ethane-1,2-diylbis(methylcarbamate) (30 mg, 0.05 mmol) were added. The mixture was further stirred at room temperature for 10 min then heated at 50 °C until the reaction completion (1 – 2 h). The solvent was removed and the residue partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried (Na_2SO_4), concentrated. The crude product was purified by ISCO using DCM/MeOH as eluent to afford 13 mg of title compound.

[001627] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.45 (d, *J* = 7.1 Hz, 1H), 8.22 – 8.08 (m, 1H), 7.85-7.75 (m, 1H), 7.65 (d, *J* = 3.0 Hz, 1H), 7.61 – 7.51 (m, 1H), 7.06 – 6.96 (m, 1H), 6.13 (broad s, 2H), 5.76 (d, *J* = 16.3 Hz, 1H), 5.6-5.45 (m, 2H), 5.36 – 5.23 (m, 3H), 4.31 (ddd, *J* = 18.7, 9.8, 5.1 Hz, 2H), 3.94 (d, *J* = 10.7 Hz, 1H), 3.76 (s, 3H), 3.72 – 3.51 (m, 4H), 3.24 (s, 1H), 3.20 – 2.98 (m, 7H), 2.78 (dt, *J* = 12.9, 6.9 Hz, 2H), 2.38 (s, 3H), 2.20 (s, 3H), 1.89 (td, *J* = 15.5, 14.6, 7.1 Hz, 2H), 1.38 (td, *J* = 8.2, 7.6, 5.0 Hz, 3H), 1.03 (t, *J* = 7.3 Hz, 3H). ppm; ESMS calculated for $C_{47}H_{48}ClN_9O_9$: 917.3; found: 918.7 ($M + H^+$).

[001628] SDC-TRAP-0296

[001629] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo [2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl) ethane-1,2-diylbis(methylcarbamate)



[001630] Step 1: But-3-yn-1-yl (9-((tert-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4': 6,7]indolizino[1,2-b]quinolin-4-yl) ethane-1,2-diylbis(methylcarbamate)

[001631] The compound was obtained (according to SDC-TRAP-0295) by reaction of but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate hydrochloride (44 mg, 0.2 mmol) with but-3-yn-1-yl (9-((tert-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4': 6,7]indolizino[1,2-b]quinolin-4-yl) ethane-1,2-diylbis(methylcarbamate) (128 mg, 0.2 mmol) in the presence of Et_3N (0.1 mL, 0.68 mmol) in dry DMF (4 mL). Yield: 82 mg (58%).

[001632] Step 2: But-3-yn-1-yl (4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl) ethane-1,2-diylbis(methylcarbamate)

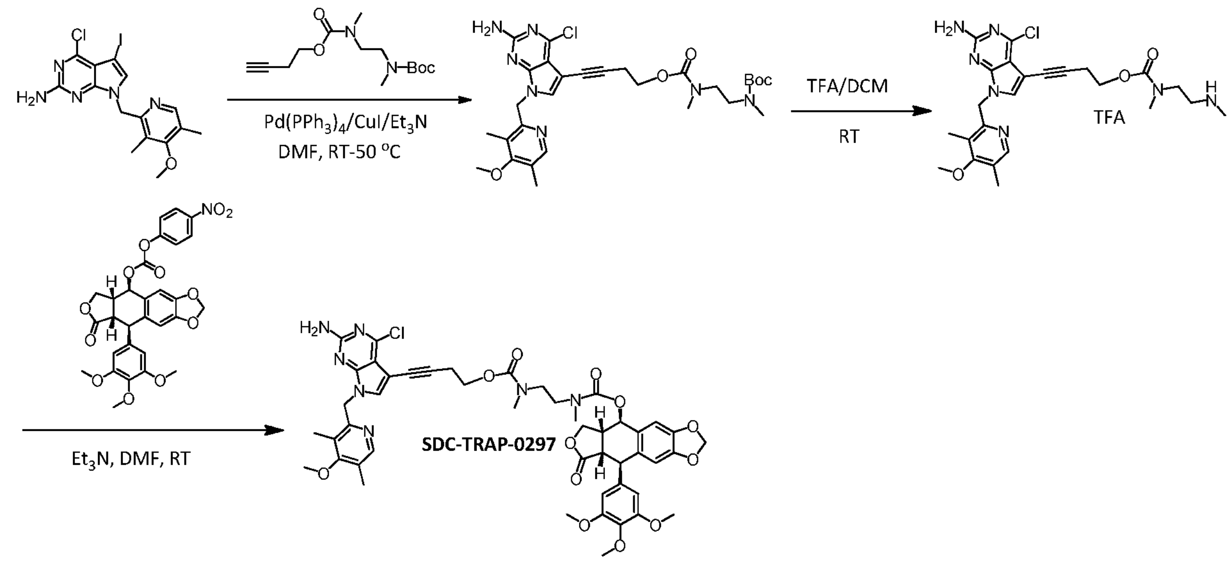
[001633] To a solution of but-3-yn-1-yl (9-((tert-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':

6,7]indolizino[1,2-b]quinolin-4-yl) ethane-1,2-diylbis(methylcarbamate) (82 mg, 0.11 mmol) in DCM (2 mL) was added TFA (0.27 mL, 3.5 mmol). The reaction mixture was stirred at room temperature for 6 h then concentrated. The residue was dissolved in DCM, washed with aq. $NaHCO_3$, dried over Na_2SO_4 and concentrated to get 57 mg of product.

[001634] Step 3: The title compound was obtained (according to the procedure SDC-TRAP-0295) by Sonogashira coupling of 4-chloro-5-iodo-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (38 mg, 0.86 mmol), CuI (2 mg, 0.0095 mmol, 11 mol%), $Pd(PPh_3)_4$ (5 mg, 0.0043 mmol, 5 mol%), dry DMF (1 mL), Et_3N (0.06 mL, 0.43 mmol, 5 eq.) and but-3-yn-1-yl (4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl) ethane-1,2-diylbis(methylcarbamate) (52 mg, 0.86 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (d, J = 5.0 Hz, 1H), 8.08-7.92(m, 2H), 7.43 – 7.35 (m, 2H), 7.22 (dd, J = 17.0, 4.9 Hz, 1H), 6.98-6.94 (m, 1H), 6.72 (broad s, 2H), 5.43 (s, 2H), 5.32 – 5.16 (m, 4H), 4.28-4.0 (m, 2H), 3.73 – 3.4 (m, 5H), 3.13 – 3.04 (m, 6H), 2.83 – 2.71 (m, 5H), 2.23 (s, 2H), 2.19 – 2.06 (m, 6H), 1.33 – 1.21 (m, 4H), 0.89 (p, J = 8.4 Hz, 3H). ppm; ESMS calculated for $C_{47}H_{48}ClN_9O_9$: 917.3; found: 918.7 ($M + H^+$).

[001635] SDC-TRAP-0297

[001636] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl ((5R,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl) ethane-1,2-diylbis(methylcarbamate)



[001637] Step 1:
4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl tert-butyl ethane-1,2-diylbis(methylcarbamate)

[001638] The compound was obtained (according to the procedure SDC-TRAP-0295) by Sonogashira coupling of 4-chloro-5-iodo-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (0.22 g, 0.5 mmol), CuI (11 mg, 0.055 mmol), $Pd(PPh_3)_4$ (29 mg, 0.025 mmol), dry DMF (5 mL), Et_3N (0.35 mL, 2.5 mmol) and but-3-yn-1-yl tert-butyl ethane-1,2-diylbis(methylcarbamate) (156 mg, 0.55 mmol). Yield: 145 mg (48%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 7.02 (s, 1H), 5.29 (s, 2H), 4.94 (s, 2H), 4.27 -4.22 (m, 2H), 3.74 (s, 3H), 3.36 (broad s, 4H), 2.93 (s, 3H), 2.90 – 2.70 (m, 5H), 2.25 (s, 3H), 2.19 (s, 3H), 1.44 (s, 9H). ppm; ESMS calculated for $C_{47}H_{48}ClN_9O_9$: 599.2; found: 600.6 (M + H^+).

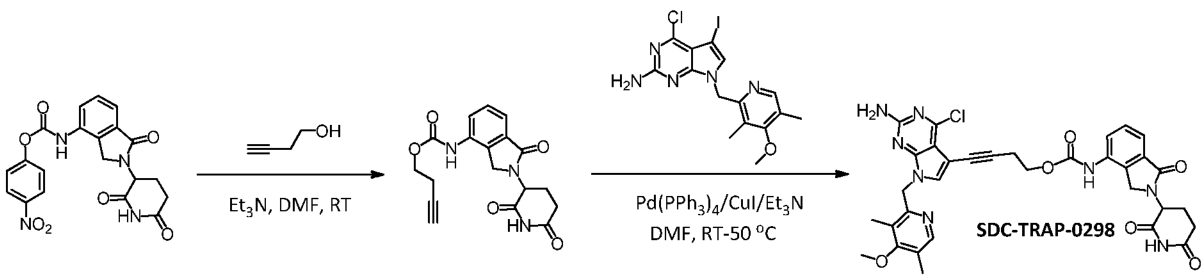
[001639] Step 2:
4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt

[001640] To a solution of 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl *tert*-butyl ethane-1,2-diylbis(methylcarbamate) (20 mg, 0.032 mmol) in DCM (1 mL) was added TFA (0.1 mL). The reaction mixture was stirred at room temperature for 10 min, concentrated and dried on high vacuum. The crude amine TFA salt was used in the next step without further purification.

[001641] Step 3: The title compound was prepared (according to the procedure SDC-TRAP-0295) by coupling of 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (20 mg, 0.032 mmol) with 4-nitrophenyl ((5R,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl) carbonate (19 mg, 0.035 mmol) in the presence of Et_3N (0.023 mL, 0.16 mmol) in dry DMF (1 mL). Yield: 17 mg (58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.25 (s, 1H), 6.95 – 6.81 (m, 1H), 6.71 (broad s, 2H), 6.59 (broad s, 1H), 6.39 – 6.30 (m, 2H), 6.05 - 5.95 (m, 2H), 5.87 – 5.74 (m, 1H), 5.26 (s, 2H), 4.6 – 4.5 (m, 1H), 4.4-4.3 (m, 1H), 4.2 – 4.1 (m, 1H), 4.08-4.00 (m, 2H), 3.72 (s, 3H), 3.67 – 3.57 (m, 9H), 3.44 – 3.34 (m, 3H), 2.90 – 2.83 (m, 5H), 2.76 (s, 1H), 2.72 – 2.60 (m, 3H), 2.24 (s, 3H), 2.15 (s, 3H), 2.09 (s, 2H). ppm; ESMS calculated for $C_{47}H_{50}ClN_7O_{12}$: 939.2; found: 940.8 (M + H$^+$).

[001642] SDC-TRAP-0298

[001643] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



[001644] **Step 1:** But-3-yn-1-yl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate

[001645] The compound was prepared (according to the procedure described for SDC-TRAP-0295) by coupling of 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (43 mg, 0.1 mmol) with but-3-yn-1-ol (14 mg, 0.2 mmol) in the presence of Et_3N (0.028 mL, 0.2 mmol) in dry DMF (0.5 mL).

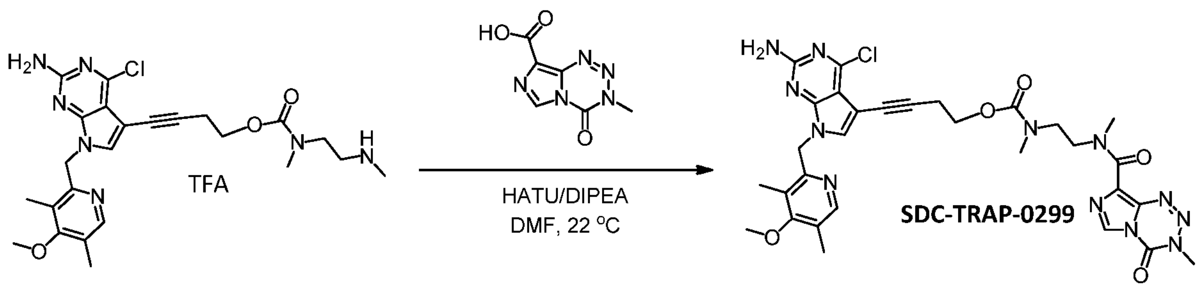
[001646] **Step 2:** The title compound was obtained (according to the procedure described for SDC-TRAP-0295) by Sonogashira coupling of

4-chloro-5-iodo-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (45 mg, 0.1 mmol) with but-3-yn-1-yl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (45 mg, 0.1 mmol) in the presence of CuI (2 mg, 0.0095 mmol), $Pd(PPh_3)_4$ (6 mg, 0.005 mmol), Et_3N (0.07 mL, 0.5 mmol) in dry DMF (1 mL).

[001647] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.01 (s, 1H), 9.69 (s, 1H), 8.04 (s, 1H), 7.75 (p, J = 3.8 Hz, 1H), 7.53 – 7.42 (m, 2H), 7.28 (s, 1H), 6.71 (s, 2H), 5.27 (s, 2H), 5.11 (dd, J = 13.2, 5.1 Hz, 1H), 4.47 – 4.32 (m, 2H), 4.27 (t, J = 6.4 Hz, 2H), 3.72 (s, 3H), 2.91 (td, J = 13.0, 12.5, 6.8 Hz, 1H), 2.83 (t, J = 6.4 Hz, 2H), 2.59 (d, J = 16.9 Hz, 1H), 2.41 – 2.26 (m, 1H), 2.25 (s, 3H), 2.16 (s, 3H), 2.05 – 1.95 (m, 1H). ppm; ESMS calculated for $C_{33}H_{31}ClN_8O_6$: 670.2; found: 671.6 (M + H$^+$).

[001648] SDC-TRAP-0299

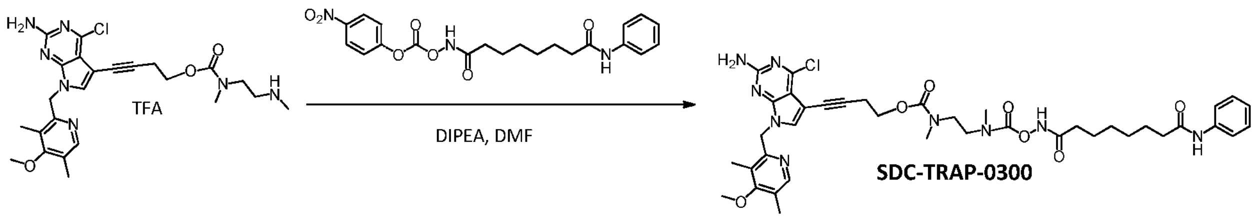
[001649] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (2-(N,3-dimethyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamido)ethyl)(methyl)carbamate



[001650] To a mixture of 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (41 mg, 0.068 mmol) and 3-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxylic acid (16 mg, 0.0816 mmol) in DMF (1 mL) was added HATU (36 mg, 0.096 mmol) followed by DIPEA (0.060 mL, 0.34 mmol). The reaction mixture was stirred at room temperature overnight then concentrated. The residue was partitioned between ethyl acetate and water. The organic phase was separated, washed with brine, dried (Na_2SO_4) and concentrated. The crude product was purified by ISCO using DCM/MeOH as eluent to afford 22 mg (44%) of title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (d, J = 13.7 Hz, 1H), 8.05 (s, 1H), 7.25 (s, 1H), 6.71 (s, 2H), 5.27 (s, 2H), 4.15 (t, J = 6.6 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.83 (s, 3H), 3.72 (s, 3H), 3.70 – 3.60 (m, 2H), 3.56 – 3.46 (m, 2H), 3.07 – 3.00 (m, 3H), 2.93 (d, J = 16.8 Hz, 1H), 2.76 – 2.64 (m, 4H), 2.25 (s, 3H), 2.15 (s, 3H). ppm; ESMS calculated for $C_{30}H_{33}ClN_{12}O_5$: 676.2; found: 677.6 (M + H$^+$).

[001651] SDC-TRAP-0300

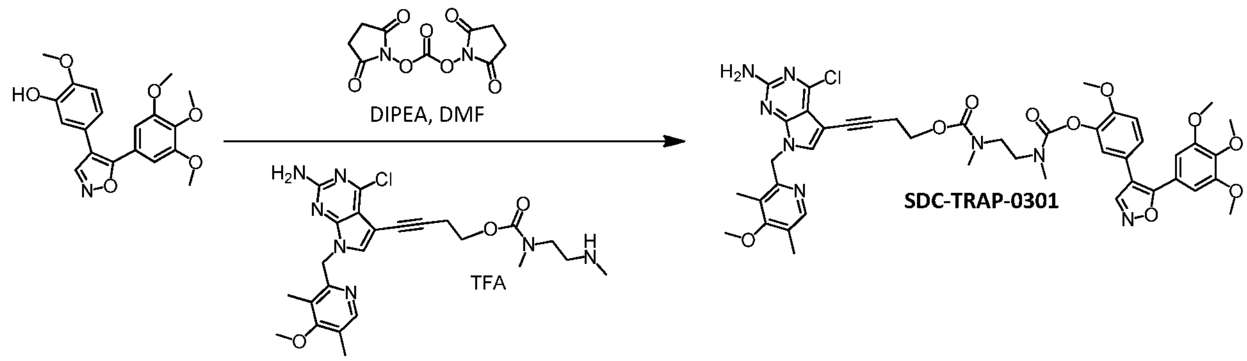
[001652] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo [2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methyl(((8-oxo-8-(phenylamino)octanamido)oxy)carbonyl)amino)ethyl)carbamate



[001653] The title compound was prepared (according to the procedure described for SDC-TRAP-0295) by coupling of 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (51 mg, 0.086 mmol) with N^1-(((4-nitrophenoxy)carbonyl)oxy)-N^8-phenyloctanediamide (40 mg, 0.09 mmol) in the presence of DIPEA (0.075 ml, 0.43 mmol) in dry DMF (1.5 mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.44 (s, 1H), 9.84 (s, 1H), 8.05 (s, 1H), 7.61 – 7.54 (m, 2H), 7.32 – 7.22 (m, 3H), 7.01 (tt, J = 7.4, 1.2 Hz, 1H), 6.71 (s, 2H), 5.27 (s, 2H), 4.13 (t, J = 6.6 Hz, 2H), 3.72 (s, 3H), 3.47 – 3.34 (m, 2H), 2.91 – 2.80 (m, 6H), 2.74 (t, J = 6.8 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 2.24 (s, 3H), 2.15 (s, 3H), 2.07 (t, J = 7.3 Hz, 2H), 1.56 -1.46 (m, 4H), 1.33 – 1.21 (m, 6H). ppm; ESMS calculated for $C_{39}H_{48}ClN_9O_7$: 789.3; found: 790.7 (M + H$^+$).

[001654] SDC-TRAP-0301

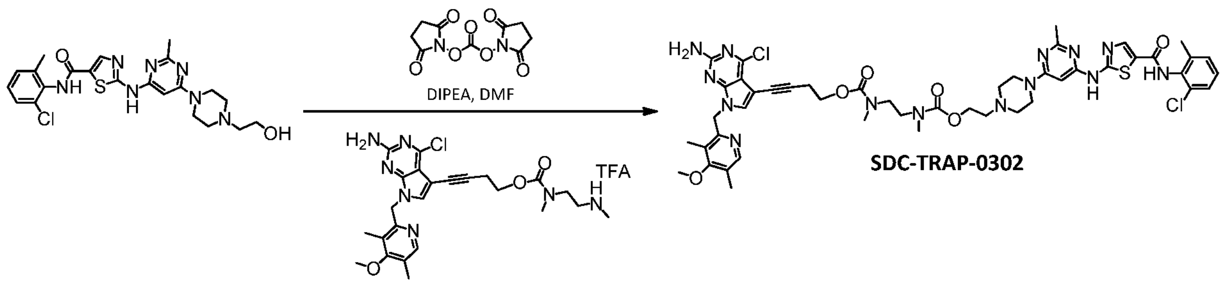
[001655] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo [2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl) ethane-1,2-diylbis(methylcarbamate)



[001656] To a mixture of 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenol (42 mg, 0.11 mmol) and bis(2,5-dioxopyrrolidin-1-yl) carbonate (38 mg, 0.146 mmol) in dry DMF (1 mL) was added DIPEA (0.064 mL, 0.36 mmol). It was stirred at room temperature for 3 h. To this 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (44 mg, 0.073 mmol) in dry DMF (0.5 mL) was added then further stirred at room temperature for 3 h. The reaction mixture was concentrated and the residue partitioned between water and ethyl acetate. The organic layer was separated, dried over Na_2SO_4 and concentrated. The crude product was purified by ISCO using DCM/MeOH as eluent to afford 25 mg (39%) of product. ^1H NMR (400 MHz, Chloroform-*d*) δ 8.31 (s, 1H), 8.20 (s, 1H), 7.22 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.20 – 7.14 (m, 1H), 7.02 (s, 1H), 7.00 – 6.94 (m, 1H), 6.90 (s, 2H), 5.28 (s, 2H), 4.93 (s, 2H), 4.32 - 4.20 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.75 (s, 6H), 3.73 (s, 3H), 3.60- 3.50 (m, 2H), 3.48 (s, 2H), 3.12 – 2.96 (m, 6H), 2.80 – 2.68 (m, 2H), 2.24 (s, 3H), 2.19 (s, 3H). ppm; ESMS calculated for $C_{44}H_{47}ClN_8O_{10}$: 882.3; found: 883.7 (M + H^+).

[001657] SDC-TRAP-0302

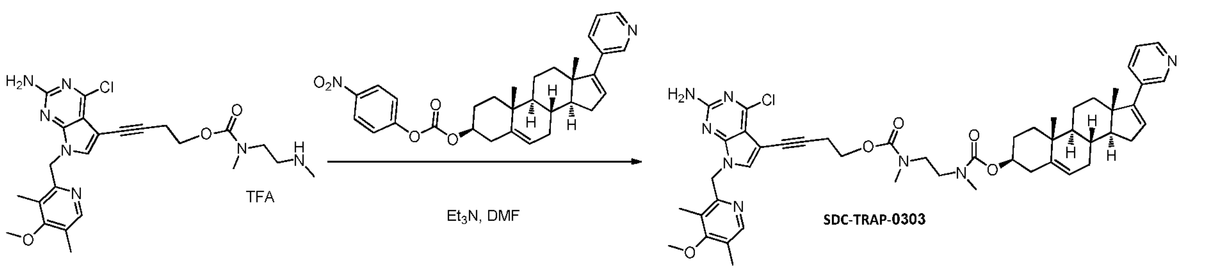
[001658] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (2-(4-(6-((5-((2-chloro-6-methylphenyl)carbamoyl)thiazol-2-yl)amino)-2-methylpyrimidin-4-yl)piperazin-1-yl)ethyl) ethane-1,2-diylbis(methylcarbamate)



[001659] The title compound was prepared (according to the procedure described for SDC-TRAP-0301) by using *N*-(2-chloro-6-methylphenyl)-2-((6-(4-(2-hydroxyethyl)piperazin-1-yl)-2-methylpyrimidin-4-yl)amino)thiazole-5-carboxamide (36 mg, 0.073 mmol), 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (44 mg, 0.073 mmol), bis(2,5-dioxopyrrolidin-1-yl) carbonate (19 mg, 0.073 mmol), DIPEA (0.13 mL, 0.73 mmol) in dry DMF (1 mL). Yield: 30 mg (41%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.99 (s, 1H), 8.19 – 8.17 (m, 1H), 7.97 (s, 1H), 7.35 – 7.28 (m, 2H), 7.24 – 7.12 (m, 2H), 7.08 – 7.03 (m, 1H), 5.83 – 5.76 (m, 1H), 5.64 (s, 1H), 5.55 (s, 1H), 5.30 (s, 2H), 4.28 – 4.17 (m, 4H), 3.73 (s, 3H), 3.53 (broad s, 4H), 3.47 – 3.38 (m, 4H), 2.94 – 2.89 (m, 6H), 2.80 -2.70 (m, 2H), 2.68 – 2.60 (m, 2H), 2.58 – 2.48 (m, 7H), 2.36 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H). ppm; ESMS calculated for $C_{47}H_{54}Cl_2N_{14}O_6S$: 1012.3; found: 1013.8 (M + H^+).

[001660] SDC-TRAP-0303

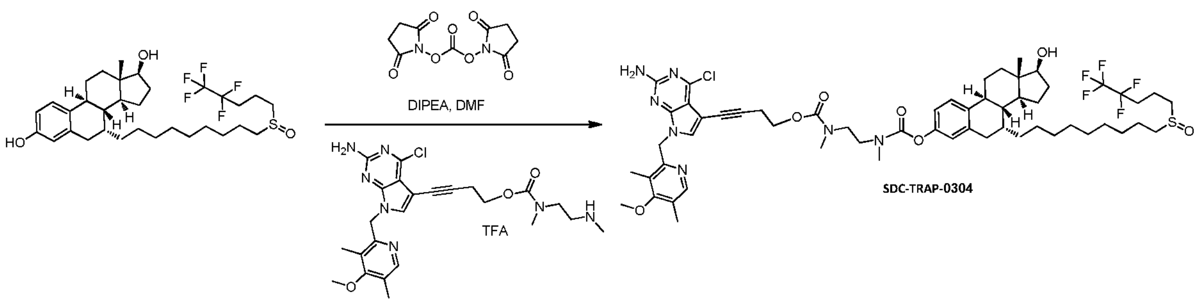
[001661] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl ((3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl) ethane-1,2-diylbis(methylcarbamate)



[001662] The title compound was prepared (according to the procedure described for SDC-TRAP-0295) by coupling of 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (44 mg, 0.073 mmol) with (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl (4-nitrophenyl) carbonate (47 mg, 0.090 mmol) in the presence of Et_3N (0.051 ml, 0.37 mmol) in dry DMF (2 mL). Yield: 36 mg (57%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.62 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.21 (s, 1H), 7.64 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.23 – 7.20 (m, 1H), 7.03 (s, 1H), 6.00 - 5.98 (m, 1H), 5.40 (s, 1H), 5.29 (s, 2H), 4.93 (s, 2H), 4.55 – 4.40 (m, 2H), 4.25 (t, *J* = 6.8 Hz, 2H), 3.74 (s, 3H), 3.40 (broad s, 4H), 2.94 (s, 4H), 2.87 (s, 2H), 2.78 – 2.70 (m, 2H), 2.43 – 2.27 (m, 3H), 2.25 (s,3H), 2.19 (s, 3H), 2.10 – 2.00 (m, 3H), 1.94 – 1.6 (m, 7H), 1.51 – 1.49 (m, 1H), 1.20-1.10 (m, 2H), 1.07 (s, 3H), 1.05 (s, 3H). ppm; ESMS calculated for $C_{49}H_{59}ClN_8O_5$: 874.4; found: 875.7 ($M + H^+$).

[001663] SDC-TRAP-0304

[001664] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl ((7R,8R,9S,13S,14S,17S)-17-hydroxy-13-methyl-7-(9-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl) ethane-1,2-diylbis(methylcarbamate)



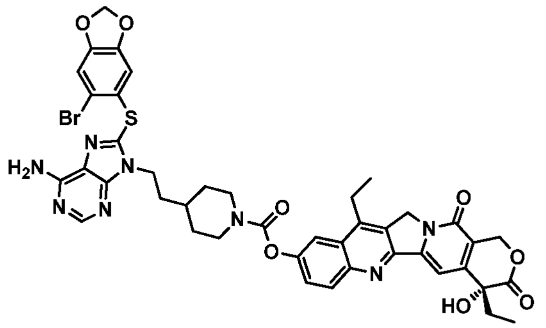
[001665] The title compound was prepared (according to the procedure described for SDC-TRAP-0301) by using (7R,8R,9S,13S,14S,17S)-13-methyl-7-(9-((4,4,5,5,5-pentafluoropentyl)sulfinyl)nonyl)-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol (58 mg, 0.094 mmol) with 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyri midin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (36 mg, 0.06 mmol), bis(2,5-dioxopyrrolidin-1-yl) carbonate (38 mg, 0.14 mmol), DIPEA (0.08 mL, 0.45 mmol) in dry DMF (1 mL). Yield: 41 mg (61%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (s, 1H), 7.24 (s, 1H), 7.03 (s, 1H), 6.87 – 6.82 (m, 1H), 6.79 (s, 1H), 5.28 (s, 2H), 4.97 (s, 2H), 4.30 - 4.22 (m, 2H), 3.74 (s, 4H), 3.60 – 3.45 (m, 4H), 3.10 (s, 1H), 3.03 (s, 1H), 2.98 – 2.95 (m, 4H), 2.92 -2.86 (m, 1H), 2.82 – 2.60 (m, 6H), 2.67 – 2.60 (m, 1H), 2.36 – 2.06 (m, 13H), 1.90 (d, *J* = 12.1 Hz, 1H), 1.80 – 1.71 (m, 3H), 1.52 – 1.15 (m, 19H), 1.05 – 0.95 (m, 1H), 0.90 -0.80 (m, 2H), 0.76 (s, 3H). ppm; ESMS calculated for $C_{57}H_{75}ClF_5N_7O_7S$: 1131.5; found: 1132.6 (M + H^+).

[001666] Example 51

[001667] SDC-TRAPs comprising MPC-3100 (available from Myrexis, Inc.)

[001668] SDC-TRAP-0305

[001669] (R)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidine-1-carboxylate



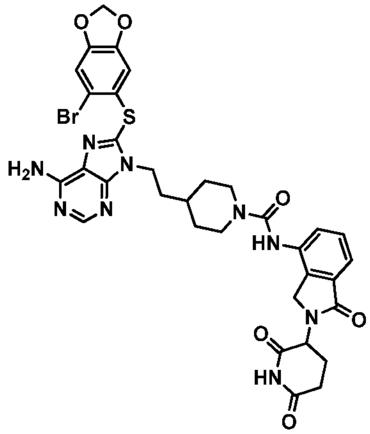
[001670] SDC-TRAP-0305 was synthesized in a similar manner as described for SDC-TRAP-0244, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner.

[001671] ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.22 – 8.15 (m, 2H), 7.97 (d, *J* = 2.5 Hz, 1H), 7.65 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.44 (s, 1H), 7.33 (s, 1H), 6.94 (s, 1H), 6.09 (s, 2H), 5.51 (d, *J* = 16.2 Hz, 2H), 5.38 (s, 2H), 4.33 – 4.23 (m, 2H), 4.13 – 4.06 (m, 4H), 1.98 – 1.84 (m, 4H), 1.75

(q, $J = 7.2$ Hz, 2H), 1.35 (t, $J = 7.6$ Hz, 3H), 1.28 – 1.17 (m, 5H), 0.94 (t, $J = 7.3$ Hz, 3H).ppm; ESMS calculated for $C_{42}H_{39}BrN_8O_8S$: 896.2; found: 897.7 ($M + H^+$).

[001672] SDC-TRAP-0306

[001673] 4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)piperidine-1-carboxamide

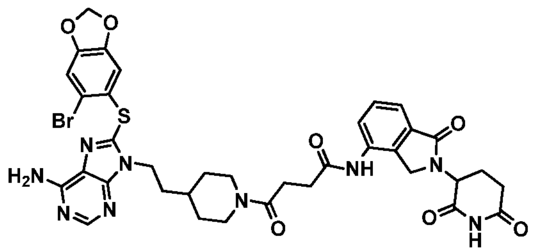


[001674] SDC-TRAP-0306 was synthesized in a similar manner as described for SDC-TRAP-0245, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner.

[001675] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 8.48 (s, 1H), 8.17 (s, 1H), 7.55 – 7.35 (m, 5H), 6.82 (s, 1H), 6.09 (s, 2H), 5.11 (dd, $J = 13.3$, 5.1 Hz, 1H), 4.40 – 4.26 (m, 2H), 4.21 (t, $J = 7.3$ Hz, 2H), 3.41 – 3.16 (m, 4H), 2.90 (ddd, $J = 17.3$, 13.6, 5.4 Hz, 1H), 2.76 – 2.65 (m, 2H), 2.59 (ddd, $J = 17.2$, 4.3, 2.3 Hz, 1H), 2.47 – 2.32 (m, 1H), 1.98 (td, $J = 7.4$, 6.7, 3.7 Hz, 1H), 1.76 – 1.59 (m, 4H), 1.16 – 1.02 (m, 1H).ppm; ESMS calculated for $C_{33}H_{32}BrN_9O_6S$: 763.1; found: 764.6 ($M + H^+$).

[001676] SDC-TRAP-0307

[001677] 4-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-4-oxobutanamide

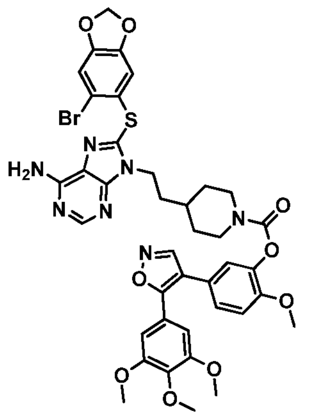


[001678] SDC-TRAP-0307 was synthesized in a similar manner as described for SDC-TRAP-0246, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner.

[001679] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (d, J = 5.4 Hz, 1H), 9.84 (s, 1H), 8.16 (s, 1H), 7.82 (dd, J = 6.4, 2.5 Hz, 1H), 7.53 – 7.43 (m, 2H), 7.43 – 7.36 (m, 3H), 6.82 (s, 1H), 6.09 (s, 2H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.44 – 4.26 (m, 2H), 4.19 (t, J = 7.3 Hz, 2H), 3.86 (d, J = 13.2 Hz, 1H), 3.41 – 3.16 (m, 4H), 2.99 – 2.85 (m, 1H), 2.66 – 2.57 (m, 4H), 2.49 – 2.24 (m, 2H), 2.04 (dd, J = 10.2, 4.8 Hz, 1H), 1.73 (d, J = 14.8 Hz, 1H), 1.69 – 1.56 (m, 3H), 1.45 – 1.40 (m, 1H), 1.14 – 1.04 (m, 1H), 0.99 – 0.86 (m, 1H).ppm; ESMS calculated for $C_{36}H_{36}BrN_9O_7S$: 819.2; found: 820.5 (M + H$^+$).

[001680] SDC-TRAP-0308

[001681] 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl 4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidine-1-carboxylate



[001682] SDC-TRAP-0308 was synthesized in a similar manner as described for SDC-TRAP-0249, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner, and 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenol as the alcohol partner.

[001683] ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.17 (s, 1H), 7.40 (d, J = 12.1 Hz, 3H), 7.31 (dd, J = 8.4, 2.2 Hz, 1H), 7.20 (d, J = 4.0 Hz, 3H), 7.18 (d, J = 8.0 Hz, 1H), 6.88 (s, 2H), 6.82 (s, 1H), 6.09 (s, 2H), 4.20 (t, J = 7.3 Hz, 2H), 3.79 (s, 3H), 3.70 (s, 9H), 3.34 – 3.35

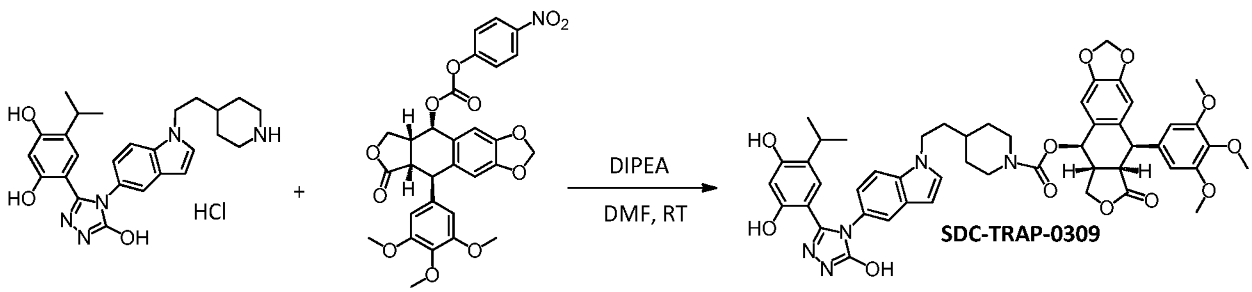
(m, 4H), 1.74 (d, *J* = 12.0 Hz, 2H), 1.70 – 1.60 (m, 2H), 1.49 – 1.37 (m, 1H), 1.19 – 1.07 (m, 2H).ppm; ESMS calculated for $C_{39}H_{38}BrN_7O_9S$: 861.2; found: 862.7 (M + H^+).

[001684] Example 52

[001685] Unless otherwise indicated, the compounds presented in this example were produced using techniques known to one of ordinary skill in the art.

[001686] SDC-TRAP-0309

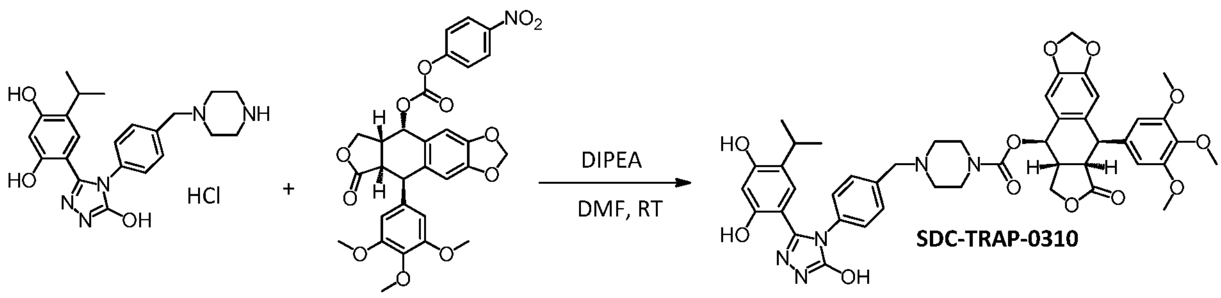
[001687] (5R,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate



[001688] The title compound was prepared (according to the procedure SDC-TRAP-0295) by coupling of 4-(5-hydroxy-4-(1-(2-(piperidin-4-yl)ethyl)-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol hydrochloride (75 mg, 0.15 mmol) with 4-nitrophenyl ((5R,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl) carbonate (87 mg, 0.15 mmol) in the presence of DIPEA (0.092 mL, 0.53 mmol) in dry DMF (2 mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 9.53 (d, *J* = 14.1 Hz, 2H), 7.52 – 7.40 (m, 3H), 6.98 – 6.85 (m, 2H), 6.68 (s, 1H), 6.60 (s, 1H), 6.46 – 6.40 (m, 1H), 6.33 (s, 2H), 6.23 (s, 1H), 6.02 -6.00 (m, 2H), 5.76 (s, 1H), 4.55 (d, *J* = 4.6 Hz, 1H), 4.37 (t, *J* = 7.8 Hz, 1H), 4.25 - 4.12 (m, 3H), 3.95 (broad s, 2H), 3.64 (s, 6H), 3.62 (s, 3H), 3.42-3.32 (m, 1H), 2.88 (p, *J* = 6.9 Hz, 1H), 2.80 – 2.70 (m, 3H), 1.80 – 1.63 (m, 4H), 1.40 (broad s, 1H), 1.14 (broad s, 2H), 0.78 (d, *J* = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{49}H_{51}N_5O_{12}$: 901.3; found: 902.7 (M + H^+).

[001689] SDC-TRAP-0310

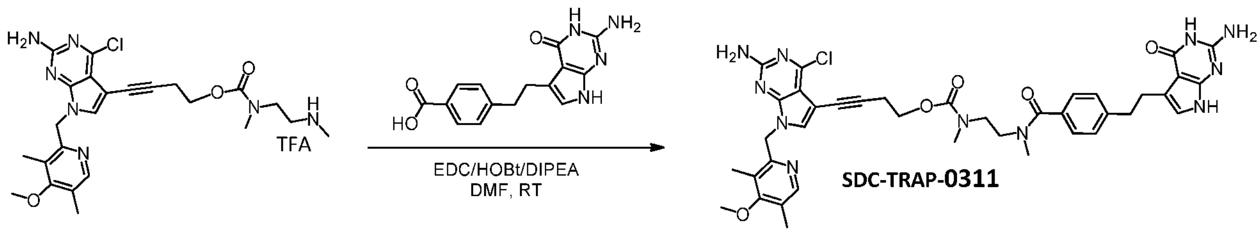
[001690] (5R,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate



[001691] The title compound was prepared (according to the procedure SDC-TRAP-0295) by coupling 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol hydrochloride (67 mg, 0.15 mmol) with 4-nitrophenyl ((5R,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl) carbonate (87 mg, 0.15 mmol) in the presence of DIPEA (0.092 mL, 0.53 mmol) in dry DMF (2 mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.59 (s, 1H), 9.40 (s, 1H), 7.35 – 7.28 (m, 2H), 7.19 – 7.10 (m, 2H), 6.88 (s, 1H), 6.76 (s, 1H), 6.60 (s, 1H), 6.33 (s, 2H), 6.26 (s, 1H), 6.03 – 6.02 (m, 2H), 5.78 (d, J = 5.78 Hz, 1H), 5.75 (s, 1H), 4.55 (d, J = 4.6 Hz, 1H), 4.37 (dd, J = 8.5, 7.1 Hz, 1H), 4.17 (dd, J = 10.6, 8.6 Hz, 1H), 3.63 (s, 6H), 3.62 (s, 3H), 3.48 (s, 2H), 3.45 – 3.31 (m, 4H), 2.96 (p, J = 6.8 Hz, 1H), 2.80 – 2.68 (m, 1H), 2.40 – 2.34 (m, 4H), 0.93 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{45}H_{47}N_5O_{12}$: 849.32; found: 850.7 (M + H$^+$).

[001692] SDC-TRAP-0311

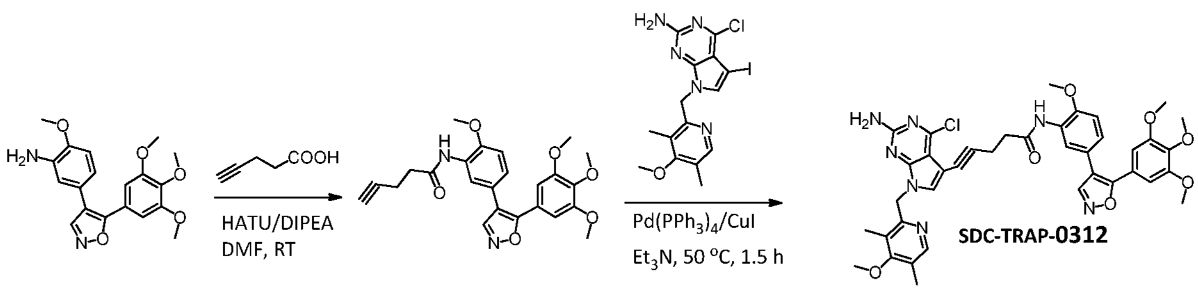
[001693] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (2-(4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)-N-methylbenzamido)ethyl)(methyl)carbamate



[001694] The title compound was prepared (according to the procedure described for SDC-TRAP-0299) by coupling of 4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzoic acid (24 mg, 0.08 mmol) with 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (48 mg, 0.08 mmol) in the presence of EDC (16 mg, 0.08 mmol), HOBt (11 mg, 0.08 mmol), DIPEA (0.046 mL, 0.26 mmol) in dry DMF (2 mL). Yield: 25 mg (40%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.61 (s, 1H), 10.14 (s, 1H), 8.03 (s, 1H), 7.30 – 7.15 (m, 5H), 6.71 (s, 2H), 6.32 (broad s, 1H), 6.00 (s, 2H), 5.26 (s, 2H), 4.20 – 3.85 (m, 2H), 3.71 (s, 3H), 3.65 - 3.45 (m, 4H), 3.00 – 2.60 (m, 12H), 2.23 (s, 3H), 2.14 (s, 3H). ppm; ESMS calculated for $C_{39}H_{42}ClF_5N_{11}O_5$: 779.3; found: 780.8 (M + H$^+$).

[001695] SDC-TRAP-0312

[001696] 5-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)pent-4-ynamide



[001697] Step 1: *N-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)pent-4-ynamide*

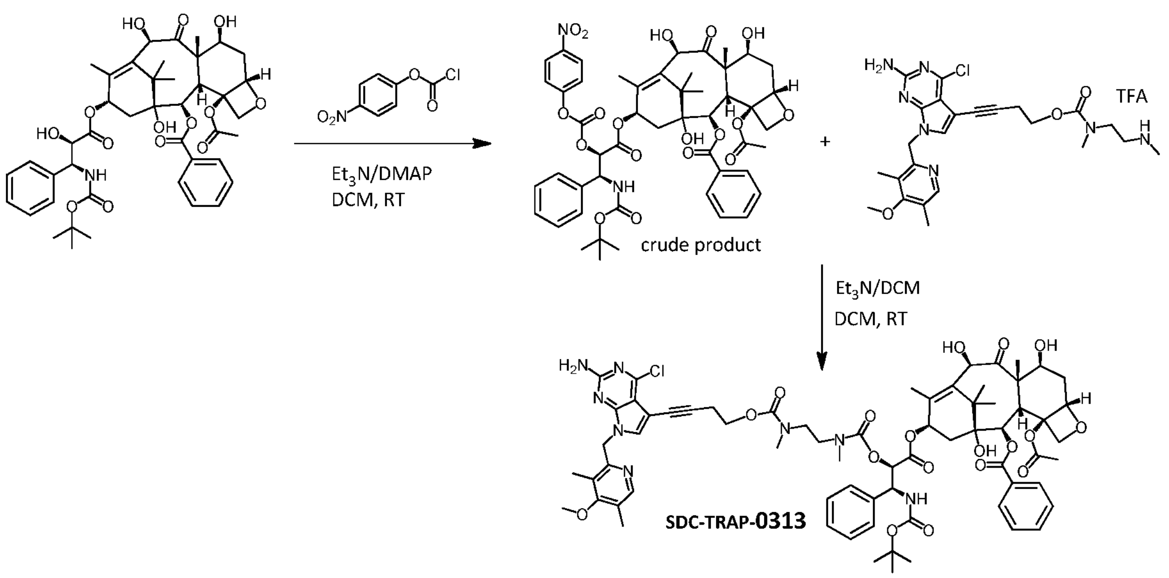
[001698] The compound was prepared (according to the procedure described for SDC-TRAP-0299) by coupling of 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline (178 mg, 0.5 mmol) with

pent-4-ynoic acid (54 mg, 0.55 mmol) in the presence of HATU (0.22 g, 0.6 mmol), DIPEA (0.29 mL, 1.65 mmol) in dry DMF (4 mL). Yield: 230 mg (crude product, 98%). The crude product was used in the next step without further purification.

[001699] Step 2: The title compound was obtained (according to the procedure described for SDC-TRAP-0295) by Sonogashira coupling of 4-chloro-5-iodo-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-2-amine (45 mg, 0.1 mmol) with *N*-(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)pent-4-ynamide (66 mg, 0.15 mmol) in the presence of CuI (2 mg, 0.011 mmol), $Pd(PPh_3)_4$ (6 mg, 0.005 mmol), Et_3N (0.07 mL, 0.5 mmol) in dry DMF (1 mL). Yield: 38 mg (50%). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 8.32 (s, 1H), 8.19 (s, 1H), 8.04 (s, 1H), 7.06 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.03 (s, 1H), 6.92 (s, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 5.28 (s, 2H), 4.93 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H), 3.73 (s, 3H), 3.72 (s, 6H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.70 (t, *J* = 6.8 Hz, 2H), 2.24 (s, 3H), 2.19 (s, 3H). ppm; ESMS calculated for $C_{39}H_{38}ClN_7O_7$: 751.2; found: 752.7(M + H^+).

[001700] SDC-TRAP-0313

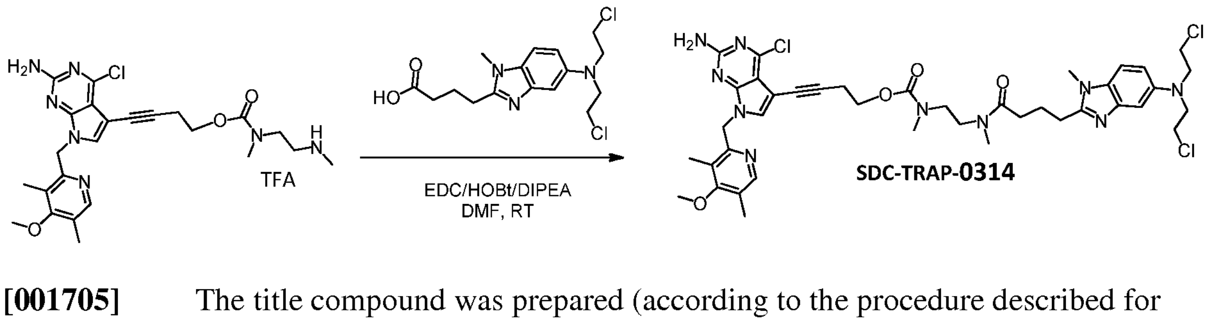
[001701] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((R)-14-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)-2-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-5,8-dimethyl-4,9-dioxo-3,10-dioxa-5,8-diazatetradec-13-yn-1-oyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate



[001702] To a solution of (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-hydroxy-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate (97 mg, 0.12 mmol) and 4-nitrophenyl carbonochloridate (29 mg, 0.12 mmol) in DCM (10 mL) was added DMAP (10 mg) followed by Et_3N (0.034 mL, 0.24 mmol). The reaction mixtutre was stirred at room temperature for 2.5 h, then treated with 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (60 mg, 0.1 mmol) with Et_3N (0.056 mL, 0.4 mmol) in DCM (2 mL). After stirring at room temperature for 3h, the mixture was diluted with DCM, washed with water, dried (Na_2SO_4), concentrated. The crude product was purified by ISCO using DCM/MeOH as eluent to afford 15 mg of title compound. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.18 (m, 1H), 8.13 – 8.09 (m, 2H), 7.63 – 7.57 (m, 1H), 7.54 – 7.45 (m, 2H), 7.41 – 7.27 (m, 5H), 7.04 (s, 1H), 6.35 -6.10 (m, 1H), 5.69 (t, *J* = 7.6 Hz, 1H), 5.60 – 5.45 (m, 1H), 5.42 – 5.41 (m, 1H), 5.37 – 5.30 (m, 1H), 5.27 – 5.23 (m, 2H), 5.05 – 5.90 (m, 3H), 4.38 – 4.15 (m, 6H), 3.99 – 3.89 (m, 1H), 3.73 (s, 3H), 3.66 – 3.50 (m, 1H), 3.45 – 3.00 (m, 2H), 2.98 – 2.82 (m, 6H), 2.75 (dt, *J* = 23.0, 6.7 Hz, 2H), 2.65 – 2.53 (m, 1H), 2.50 (s, 1H), 2.43 – 2.32 (m, 2H), 2.24 – 2.23 (m, 3H), 2.18 (s, 3H), 2.15 – 2.05 (m, 1H), 1.98 (s, 1H), 1.95 – 1.82 (m, 3H), 1.74 (s, 2H), 1.65 (broad s, 5H), 1.33 – 1.12 (m, 16H). ppm; ESMS calculated for $C_{68}H_{81}ClN_8O_{18}$: 1332.5; found: 1333.6(M + H$^+$).

[001703] SDC-TRAP-0314

[001704] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl(2-(4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-N-methylbutanamido)ethyl)(methyl)carbamate

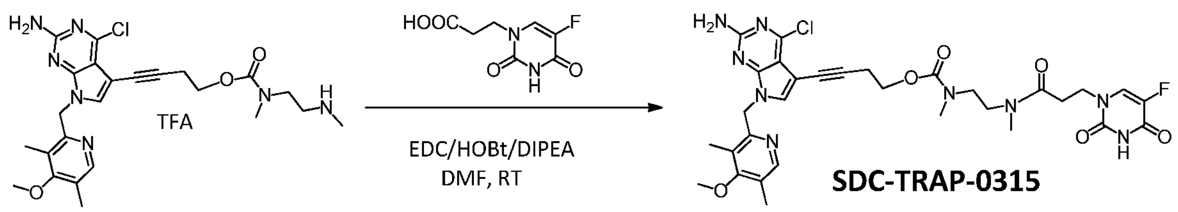


[001705] The title compound was prepared (according to the procedure described for SDC-TRAP-0299) by coupling of

4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)butanoic acid (24 mg, 0.08 mmol) with 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (42 mg, 0.07 mmol) in the presence of EDC (14 mg, 0.07 mmol), HOBt (10 mg, 0.07 mmol), DIPEA (0.062 mL, 0.35 mmol) in dry DMF (1 mL). Yield: 22 mg (38%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 (s, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.76 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.27 (s, 2H), 4.98 (s, 2H), 4.19 (t, *J* = 6.6 Hz, 2H), 3.77 – 3.67 (m, 10H), 3.65 – 3.60 (m, 4H), 3.56 – 3.30 (m, 4H), 3.00 (s, 1H), 2.96 – 2.85 (m, 7H), 2.71 (t, *J* = 6.6 Hz, 2H), 2.55 – 2.40 (m, 2H), 2.24 (s, 3H), 2.19 (s, 3H), 2.18 – 2.09 (m, 2H). ppm; ESMS calculated for $C_{40}H_{49}Cl_3N_{10}O_4$: 838.3; found: 841.7 (M + H$^+$).

[001706] SDC-TRAP-0315

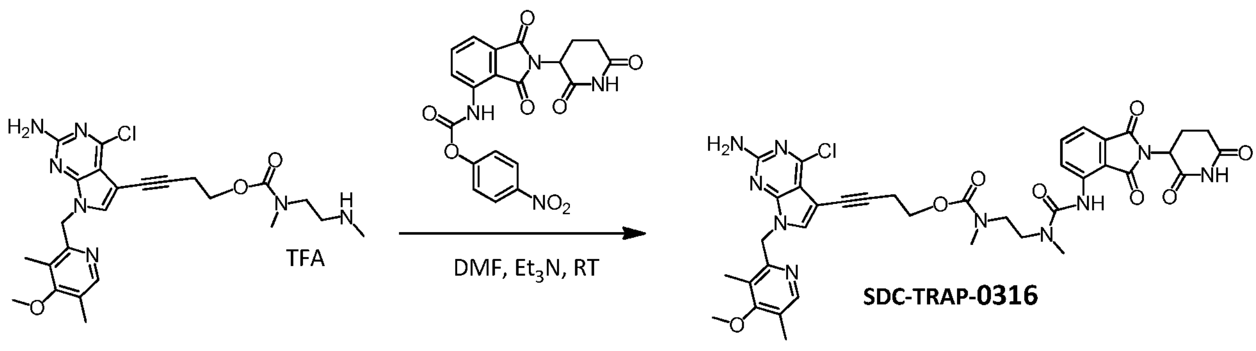
[001707] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (2-(3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-N-methylpropanamido)ethyl)(methyl)carbamate



[001708] The title compound was prepared (according to the procedure described for SDC-TRAP-0299) by coupling of 3-(5-fluoro-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)propanoic acid (15 mg, 0.07 mmol) with 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (42 mg, 0.07 mmol) in the presence of EDC (20 mg, 0.1 mmol), HOBt (12 mg, 0.09 mmol), DIPEA (0.05 mL, 0.28 mmol) in dry DMF (1 mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.09 – 7.96 (m, 2H), 7.7 (s, 1H), 6.72 (s, 2H), 5.27 (s, 2H),4.14 - 4.08 (m, 2H), 3.84 – 3.75 (m, 2H), 3.72 (s, 3H), 3.44 – 3.37 (m, 2H), 2.94 – 2.70 (m, 12H), 2.25 (s, 3H), 2.15 (s, 3H). ppm; ESMS calculated for $C_{31}H_{35}ClFN_9O_6$: 683.2; found: 684.6 (M + H$^+$).

[001709] SDC-TRAP-0316

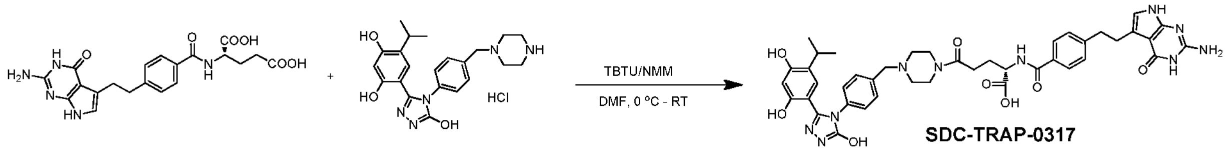
[001710] 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl (2-(3-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-1-methylureido)ethyl)(methyl)carbamate



[001711] The title compound was prepared (according to the procedure described for SDC-TRAP-0295) by coupling of 4-(2-amino-4-chloro-7-((4-methoxy-3,5-dimethylpyridin-2-yl)methyl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)but-3-yn-1-yl methyl(2-(methylamino)ethyl)carbamate TFA salt (42 mg, 0.07 mmol) with 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)carbamate (43 mg, 0.1 mmol) in the presence of Et_3N (0.05 ml, 0.35 mmol) in dry DMF (2 mL). ^1H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 8.93 (s, 1H), 8.50 (t, J = 9.0 Hz, 1H), 8.04 (s, 1H), 7.76 -7.70 (m, 1H), 7.46 -7.41 (m, 1H), 7.23 (s, 1H), 6.70 (s, 2H), 5.26 (s, 2H), 5.14 (dd, J = 13.0, 5.4 Hz, 1H), 4.10 – 4.07 (m, 2H), 3.71 (s, 3H), 3.55 – 3.40 (m, 5H), 3.04 -3.01 (m, 3H), 2.90 -2.80 (m, 4H), 2.74 – 2.53 (m, 4H), 2.24 (s, 3H), 2.15 (s, 3H). ppm; ESMS calculated for $C_{38}H_{39}ClN_{10}O_8$: 798.2; found: 799.7(M + H^+).

[001712] SDC-TRAP-0317

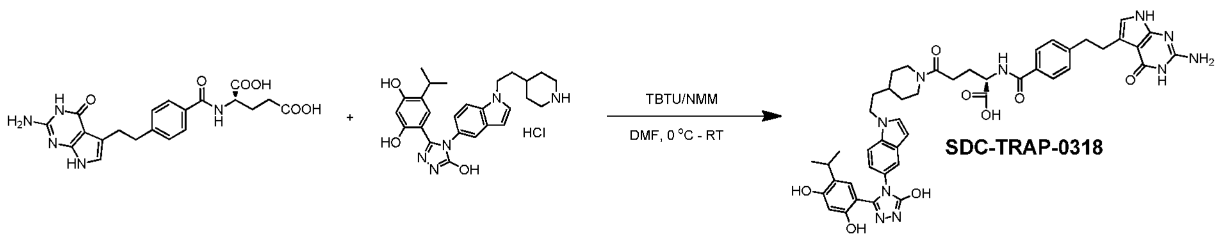
[001713] (*S*)-2-(4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzamido)-5-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-5-oxopentanoic acid



[001714] To a solution of (*S*)-2-(4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzamido)pentanedioic acid (0.17 g, 04 mmol) in dry DMF (3 mL) at 0 °C was added NMM (0.1 mL, 0.8 mmol) followed by TBTU (128 mg, 0.4 mmol). The mixture was stirred at this temperature for 45 min, then treated with 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol hydrochloride (178 mg, 0.4 mmol) and NMM (0.05 mL, 0.4 mmol). The reaction mixture was further allowed to stir overnight. The solvent was removed and the resulting solid was stirred in water, filtered, dried (300 mg crude product). The crude product (100 mg) was purified by ISCO to afford 25 mg of pure product. ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.68 – 7.62 (m, 2H), 7.35 – 7.30 (m, 2H), 7.23 – 7.18 (m, 2H), 7.18 – 7.13 (m, 2H), 6.65 (s, 1H), 6.22 (s, 1H), 6.15 (s, 1H), 4.51 – 4.48 (m, 1H), 3.57 – 3.34 (m, 6H), 2.97 – 2.83 (m, 5H), 2.53 – 1.97 (m, 8H), 0.82 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{42}H_{46}N_{10}O_8$: 818.3; found: 819.3 (M + H$^+$).

[001715] SDC-TRAP-0318

[001716] (S)-2-(4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzamido)-5-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-5-oxopentanoic acid

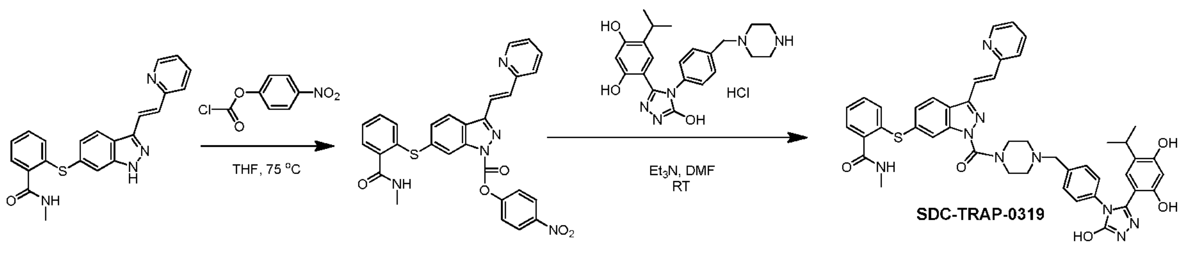


[001717] The title compound was prepared (according to the procedure described for SDC-TRAP-0317) by coupling of (S)-2-(4-(2-(2-amino-4-oxo-4,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl)benzamido)pentanedioic acid (86 mg , 0.2 mmol) with 4-(5-hydroxy-4-(1-(2-(piperidin-4-yl)ethyl)-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol hydrochloride (124 mg, 0.25 mmol) in the presence of TBTU (65 mg, 0.2 mmol), NMM (0.05 mL + 0.022 mL, 0.4 mmol + 0.2 mmol) in dry DMF (5 mL). ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.72 – 7.70 (m, 2H), 7.48 – 7.45 (m, 2H), 7.38 – 7.24 (m, 3H), 7.07 – 6.96 (m, 1H), 6.46 (broad s, 2H), 6.24 (d, J = 12.0 Hz, 2H), 4.64 – 4.33 (m, 2H), 4.24 -4.39

(m, 2H), 3.92 – 3.80 (m, 1H), 3.06 – 2.74 (m, 6H), 2.52 – 2.40 (m, 3H), 2.34 – 1.99 (m, 2H), 1.75 - 1.60 (m, 4H), 1.18 – 0.74 (m, 4H), 0.56 (d, J = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{46}H_{50}N_{10}O_8$: 870.3; found: 871.3 (M + H^+).

[001718] SDC-TRAP-0319

[001719] (*E*)-2-((1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carbonyl)-3-(2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)thio)-N-methylbenzamide



[001720]

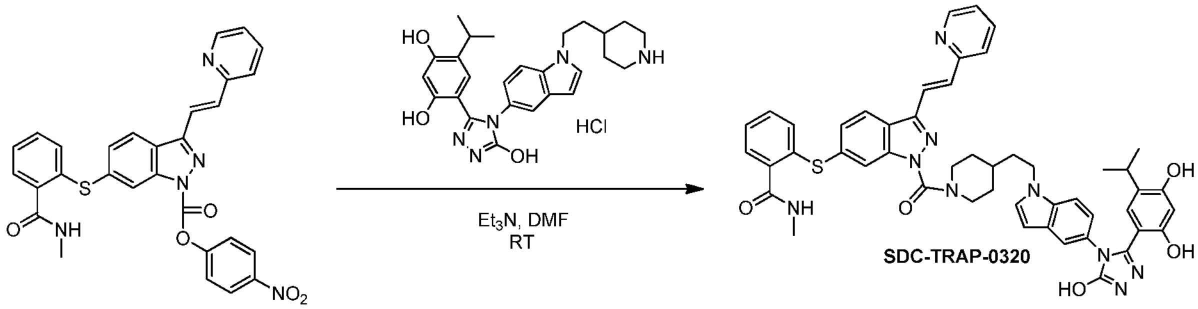
[001721] Step 1: *(E)-4-nitrophenyl 6-((2-(methylcarbamoyl)phenyl)thio)-3-(2-(pyridin-2-yl)vinyl)-1H-indazole-1-carboxylate*

[001722] (*E*)-N-methyl-2-((3-(2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)thio)benzamide (100 mg, 0.258 mmol) and 4-nitrophenyl carbonochloridate (63 mg, 0.31 mmol) were taken in THF (8 mL). The suspension was heated to reflux overnight. The resulting yellow solid was filtered, washed with ethyl acetate and dried to get the product (110 mg, 75%).

[001723] Step 2: To a suspension of (*E*)-4-nitrophenyl 6-((2-(methylcarbamoyl)phenyl)thio)-3-(2-(pyridin-2-yl)vinyl)-1H-indazole-1-carboxylate (56 mg, 0.1 mmol) and 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol hydrochloride (46 mg, 0.1 mmol) in DMF (1 mL) was added Et_3N (0.07 mL, 0.5 mmol). The reaction mixture was stirred at room temperature for 5 h. The solvent was removed and the residue partitioned between water and ethyl acetate. The organic layer was separated, dried over Na_2SO_4 and concentrated. The crude product was purified by ISCO using DCM/MeOH as eluent to afford the product. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 8.66 – 8.61 (m, 1H), 8.44 (q, J = 4.6 Hz, 1H), 8.26 (d, J = 8.5 Hz, 1H), 7.94 (s, 1H), 7.92 – 7.84 (m, 2H), 7.78 – 7.67 (m, 2H), 7.55 – 7.47 (m, 1H), 7.41 - 7.34 (m, 6H), 7.21 – 7.13 (m, 3H), 6.75 (s, 1H), 6.28 (s, 1H), 3.90 (s, 4H), 3.74 (broad s, 4H), 3.57 (s, 2H), 2.93 (p, J = 6.9 Hz, 1H), 2.77 (d, *J* = 4.5 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 6H). ppm; ESMS calculated for $C_{45}H_{43}N_9O_5S$: 821.3; found: 822.1 (M + H^+).

[001724] SDC-TRAP-0320

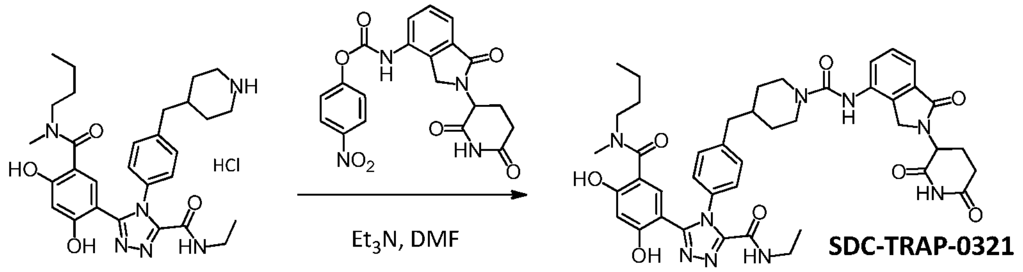
[001725] (*E*)-2-((1-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carbonyl)-3-(2-(pyridin-2-yl)vinyl)-1H-indazol-6-yl)thio)-N-methylbenzamide



[001726] The title compound was prepared (according to the procedure described for SDC-TRAP-0319) by coupling of 4-(5-hydroxy-4-(1-(2-(piperidin-4-yl)ethyl)-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol hydrochloride (50 mg, 0.1 mmol) with (*E*)-4-nitrophenyl 6-((2-(methylcarbamoyl)phenyl)thio)-3-(2-(pyridin-2-yl)vinyl)-1H-indazole-1-carboxylate (56 mg, 0.1 mmol) in the presence of Et_3N (0.07 ml, 0.5 mmol) in dry DMF (1 mL). ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.51 – 8.45 (m, 1H), 7.98 – 7.96 (m, 1H), 7.66 – 7.81 (m, 1H), 7.80 – 7.73 (m, 2H), 7.66 – 7.62 (m, 1H), 7.60 – 7.58 (m, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.44 – 7.43 (m, 1H), 7.41 – 7.36 (m, 1H), 7.32 – 7.21 (m, 7H), 6.98 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.46 – 6.40 (m, 2H), 6.17 (s, 1H), 4.34 - 4.30 (m, 2H), 4.24 (t, *J* = 7.1 Hz, 2H), 3.06 – 2.89 (m, 2H), 2.79 - 2.71 (m, 4H), 1.87 – 1.70 (m, 4H), 1.62 – 1.26 (m, 3H), 0.51 (d, *J* = 6.9 Hz, 6H). ppm; ESMS calculated for $C_{49}H_{47}N_9O_5S$: 873.3; found: 874.1 (M + H^+).

[001727] SDC-TRAP-0321

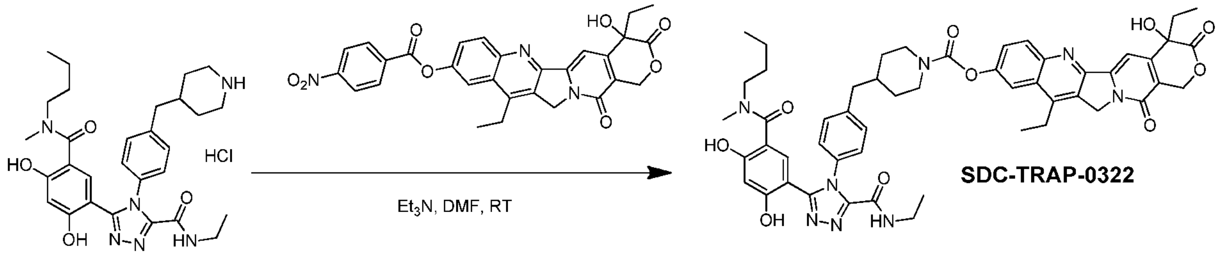
[001728] 4-(4-(3-(5-(butyl(methyl)carbamoyl)-2,4-dihydroxyphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)piperidine-1-carboxamide



[001729] The title compound was prepared (according to the procedure described for SDC-TRAP-0319) by coupling of 5-(5-(butyl(methyl)carbamoyl)-2,4-dihydroxyphenyl)-N-ethyl-4-(4-(piperidin-4-ylmethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide hydrochloride (28.5 mg, 0.05 mmol) with 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (30 mg, 0.07 mmol) in the presence of Et_3N (0.021 ml, 0.15 mmol) in dry DMF (1 mL). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.00 (s, 1H), 10.37 (s, 1H), 10.13 (s, 1H), 8.97 (t, J = 5.9 Hz, 1H), 8.52 (s, 1H), 7.54 – 7.39 (m, 3H), 7.17 (s, 4H), 6.79 (s, 1H), 6.33 (s, 1H), 5.12 (dd, J = 13.3, 5.2 Hz, 1H), 4.38 – 4.30 (m, 2H), 4.08 (d, J = 13.2 Hz, 2H), 3.23 – 3.11 (m, 3H), 2.94 – 2.86 (m, 1H), 2.76 – 2.67 (m, 5H), 2.64 – 2.51 (m, 3H), 2.46 – 2.34 (m, 1H), 2.03 – 1.95 (m, 1H), 1.75 (broad s, 1H), 1.60 – 1.52 (m, 2H), 1.39 (broad s, 2H), 1.25 – 1.07 (m, 5H), 1.06 – 1.02 (m, 3H), 0.81 (broad s, 3H). ppm; ESMS calculated for $C_{43}H_{49}N_9O_8$: 819.3; found: 820.2 (M + H^+).

[001730] SDC-TRAP-0322

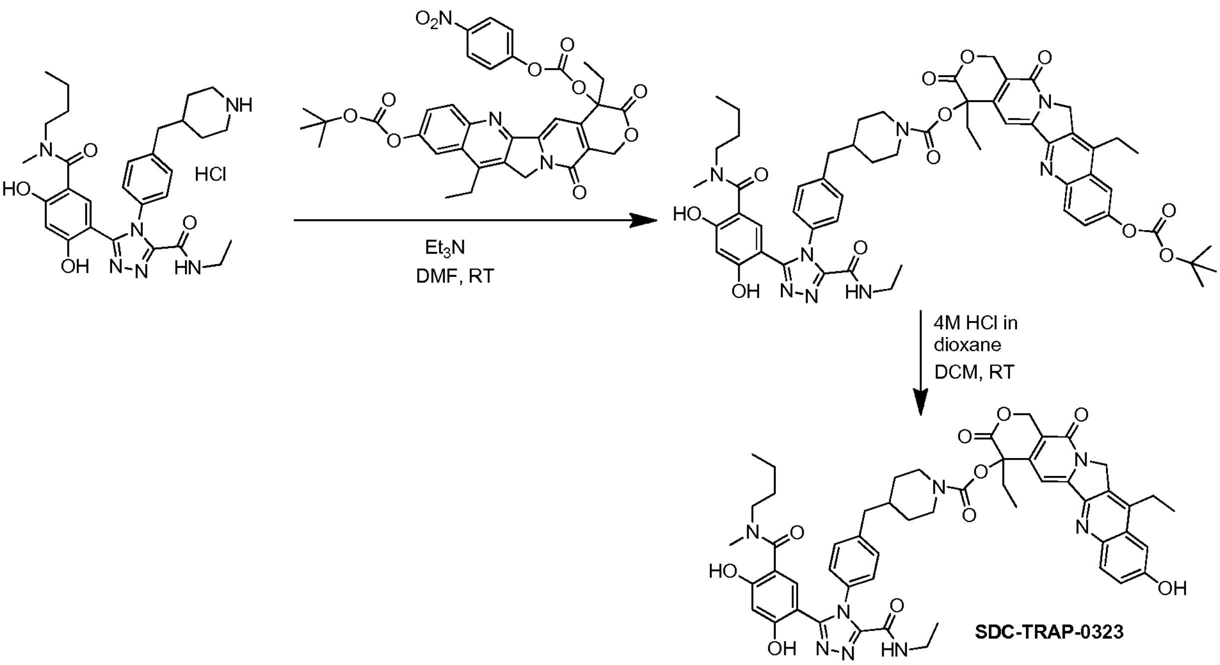
[001731] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(5-(butyl(methyl)carbamoyl)-2,4-dihydroxyphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-1-carboxylate



[001732] The title compound was prepared (according to the procedure described for SDC-TRAP-0295) by coupling of 5-(5-(butyl(methyl)carbamoyl)-2,4-dihydroxyphenyl)-N-ethyl-4-(4-(piperidin-4-ylmethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide hydrochloride (40 mg, 0.07 mmol) with 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-nitrobenzoate (39 mg, 0.071 mmol) in the presence of Et_3N (0.034 mL, 0.23 mmol) in dry DMF (2 mL). ^1H NMR (400 MHz, Chloroform-*d*) δ 10.54 (s, 1H), 8.23 (d, *J* = 9.2 Hz, 1H), 7.85 (s, 1H), 7.65 (s, 1H), 7.60 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.41 – 7.31 (m, 5H), 6.76 (s, 1H), 6.66 (s, 1H), 5.76 (d, *J* = 16.3 Hz, 1H), 5.35 – 5.28 (m, 1H), 5.27 (s, 2H), 4.38 (dd, *J* = 34.3, 13.4 Hz, 2H), 3.75 (s, 1H), 3.43 -3.37 (m, 2H), 3.27 – 3.11 (m, 4H), 3.11 – 2.85 (m, 2H), 2.73 (t, *J* = 7.3 Hz, 2H), 2.67 (s, 3H), 1.98 – 1.79 (m, 5H), 1.50 – 1.35 (m, 7H), 1.23 – 1.20 (m, 6H), 1.05 (t, *J* = 7.4 Hz, 3H), 0.92 (t, *J* = 7.3 Hz, 3H). ppm; ESMS calculated for $C_{52}H_{56}N_8O_{10}$: 952.4; found: 953.4 $(M + H^+)$.

[001733] SDC-TRAP-0323

[001734] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(3-(5-(butyl(methyl)carbamoyl)-2,4-dihydroxyphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-1-carboxylate



[001735] Step 1: 9-((tert-butoxycarbonyl)oxy)-4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6

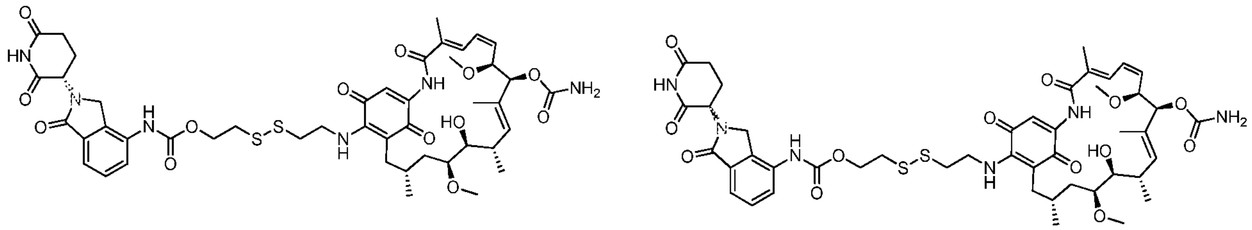
,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(3-(5-(butyl(methyl)carbamoyl)-2,4-dihydroxyphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-1-carboxylate

[001736] The compound was prepared (according to the procedure described for SDC-TRAP-0295) by coupling of 5-(5-(butyl(methyl)carbamoyl)-2,4-dihydroxyphenyl)-N-ethyl-4-(4-(piperidin-4-ylmethyl)phenyl)-4H-1,2,4-triazole-3-carboxamide hydrochloride (40 mg, 0.07 mmol) with *tert*-butyl (4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-4,9-diyl) (4-nitrophenyl) dicarbonate (57 mg, 0.088 mmol) in the presence of Et_3N (0.034 mL, 0.23 mmol) in dry DMF (1.2 mL). The crude product was purified by ISCO to get 40 mg of impure product.

[001737] Step 2: The above product was dissolved in DCM (2.5 mL) and treated with 4M HCl in dioxane (2.5 mL). The reaction mixture was stirred at room temperature for 4 h. The solvent was removed and the residue purified by ISCO to get 23 mg of product. ^1H NMR (400 MHz, DMSO-d_6) δ 10.42 (broad s, 1H), 10.32 (s, 1H), 10.12 (s, 1H), 8.96 (t, J = 5.9 Hz, 1H), 8.07 - 8.00 (m, 1H), 7.45 – 7.39 (m, 2H), 7.29 – 7.06 (m, 4H), 6.97 – 6.90 (m, 1H), 6.75 (s, 1H), 6.32 (s, 1H), 5.53 – 5.37 (m, 2H), 5.31 – 5.25 (m, 2H), 4.30 – 4.18 (m, 1H), 3.82 - 3.70 (m, 1H), 3.25 – 2.90 (m, 6H), 2.85 – 2.60 (m, 4H), 2.20 - 2.07 (m, 2H), 1.85 - 1.55 (m, 2H), 1.54 – 1.11 (m, 10H), 1.04 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H), 0.85 – 0.60 (broad s, 6H). ppm; ESMS calculated for $C_{52}H_{56}N_8O_{10}$: 952.4; found: 953.4 ($M + H^+$).

[001738] SDC-TRAP-0324

[001739] 2-((2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl)disulfanyl)ethyl (2-((S)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate and 2-((2-(((4E,6Z,8S,9S,10E,12S,13S,14S,16R)-9-(carbamoyloxy)-13-hydroxy-8,14-dimethoxy-4,10,12,16-tetramethyl-3,20,22-trioxo-2-azabicyclo[16.3.1]docosa-1(21),4,6,10,18-pentaen-19-yl)amino)ethyl)disulfanyl)ethyl (2-((R)-2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (diastereomer ratio 1 : 1)

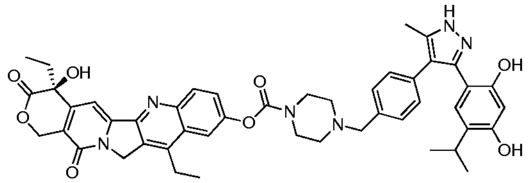


diastereomer ratio 1 : 1

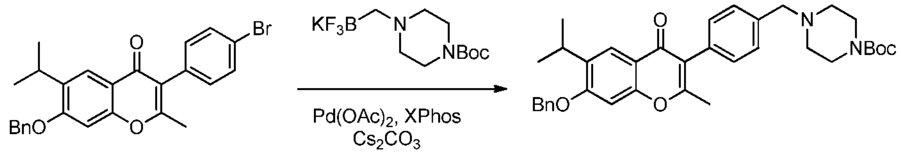
[001740] HPLC: 15.349 min. (50%), 15.480 min. (50%). ESMS calculated for $C_{46}H_{58}N_6O_{13}S_2$: 966.4; found: 874.7 $(M - 92)^+$.

[001741] SDC-TRAP-0325

[001742] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



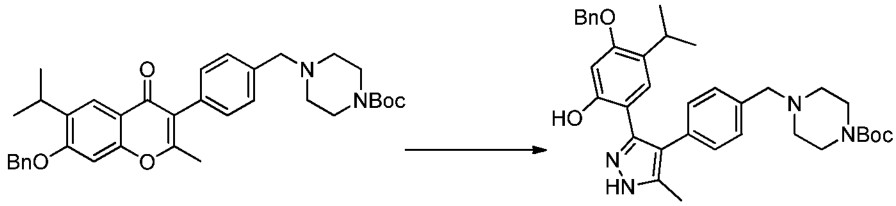
[001743] Step 1: Synthesis of tert-butyl 4-(4-(7-(benzyloxy)-6-isopropyl-2-methyl-4-oxo-4H-chromen-3-yl)benzyl)piperazine-1-carboxylate



[001744] A suspension of 7-(benzyloxy)-3-(4-bromophenyl)-6-isopropyl-2-methyl-4H-chromen-4-one (1.848 g, 4.0 mmol), potassium 1-trifluroboratomethyl-4-(N-Boc)-piperazine (1.356 g, 4.4 mmol), Cs_2CO_3 (3.912 g), $Pd(OAc)_2$ (28 mg), XPhos (116 mg) in THF/H_2O (10 : 1, 8.0 mL) in a pressure bottle was stirred at 80 °C for 19 hrs. The reaction mixture was diluted with water, extracted with DCM and dried with Na_2SO_4. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford tert-butyl 4-(4-(7-(benzyloxy)-6-isopropyl-2-methyl-4-oxo-4H-chromen-3-yl)benzyl)piperazine-1-carb

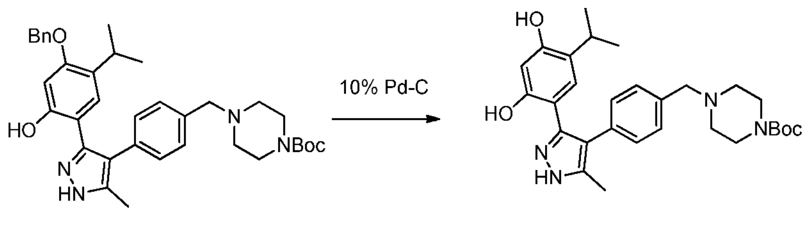
oxylate (2.02 g, 87%) as an yellow solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 0.6 Hz, 1H), 7.51 – 7.33 (m, 7H), 7.27 – 7.19 (m, 2H), 6.86 (s, 1H), 5.19 (s, 2H), 3.54 (s, 2H), 3.48 – 3.35 (m, 5H), 2.43 (t, *J* = 4.9 Hz, 4H), 2.28 (s, 3H), 1.57 (s, 9H), 1.28 (d, *J* = 6.8 Hz, 6H). ESMS calculated for $C_{36}H_{42}N_2O_5$: 582.3; found: 583.7 $(M + H)^+$.

[001745] Step 2: Synthesis of tert-butyl 4-(4-(3-(4-(benzyloxy)-2-hydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



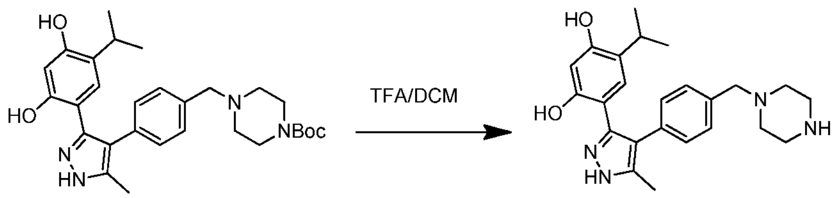
[001746] To a solution of tert-butyl 4-(4-(7-(benzyloxy)-6-isopropyl-2-methyl-4-oxo-4H-chromen-3-yl)benzyl)piperazine-1-carboxylate (2.02 g, 3.47 mmol) in ethanol (30 mL) was added hydrazine hydrate (4.0 mL). The reaction mixture was refluxed for 5 hrs. Solvent was evaporated under a reduced pressure to give a residue. The residue was diluted with DCM and water, adjusted pH to 6-9 using 1 N HCl, extracted with DCM, washed with brine and dried with Na_2SO_4. Solvent was evaporated under reduced pressure to give tert-butyl 4-(4-(3-(4-(benzyloxy)-2-hydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate (2.2143 g) as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 10.79 (s, 1H), 9.74 (s, 1H), 7.46 – 7.21 (m, 9H), 6.91 (s, 1H), 6.58 (s, 1H), 5.05 (s, 2H), 3.56 (s, 2H), 3.45 (t, *J* = 4.8 Hz, 4H), 3.11 (p, *J* = 6.9 Hz, 1H), 2.44 (t, *J* = 5.0 Hz, 4H), 2.25 (s, 3H), 1.47 (s, 9H), 0.79 (d, *J* = 6.9 Hz, 6H).

[001747] Step 3: Synthesis of tert-butyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



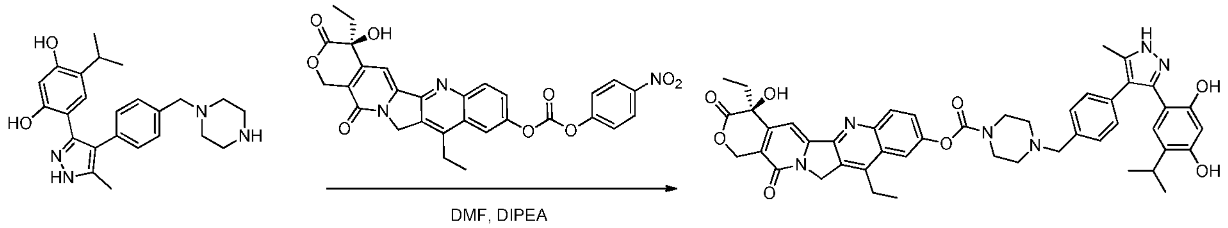
[001748] A suspension of tert-butyl 4-(4-(3-(4-(benzyloxy)-2-hydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)pipe razine-1-carboxylate (2.21 g, 3.708 mmol) and 10% Pd-C (wet) (300 mg) in EtOAc (80 mL) and methanol (40 mL) was stirred at room temperature under hydrogen balloon for 4 hrs. The reaction mixture was filtered through Celite and washed with DCM. Solvents were evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford tert-butyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate (1.59 g, 85%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.91 (s, 1H), 10.87 (s, 1H), 9.26 (s, 1H), 7.35 (d, J = 7.7 Hz, 2H), 7.20 (d, J = 7.6 Hz, 2H), 6.75 (s, 1H), 6.29 (s, 1H), 3.53 (s, 2H), 3.17 (d, J = 5.3 Hz, 4H), 2.93 – 2.85 (m, 1H), 2.38-2.34 (m, 4H), 2.14 (s, 3H), 1.39 (s, 9H), 0.71 (d, J = 6.8 Hz, 6H). ESMS calculated for $C_{29}H_{38}N_4O_4$: 506.3; found: 507.5 $(M + H)^+$.

[001749] Step 4: Synthesis of 4-isopropyl-6-(5-methyl-4-(4-(piperazin-1-ylmethyl)phenyl)-1H-pyrazol-3-yl)benzene-1,3-diol



[001750] A solution of tert-butyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate (1.59 g, 3.14 mmol) in DCM (40 mL) and TFA (4.0 mL) was stirred at room temperature for 1.5 h. Solvents were evaporated under reduced pressure to give a residue, which was triturated with ether and dried under vacuum to afford 4-isopropyl-6-(5-methyl-4-(4-(piperazin-1-ylmethyl)phenyl)-1H-pyrazol-3-yl)benzene-1,3-diol TFA salt (2.41 g) as a white solid. ESMS calculated for $C_{24}H_{30}N_4O_2$: 406.2; found: 407.5 $(M + H)^+$.

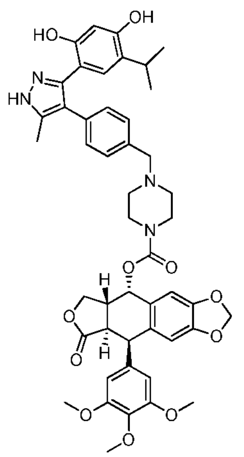
[001751] Step 5: Synthesis of (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



[001752] A solution of 4-isopropyl-6-(5-methyl-4-(4-(piperazin-1-ylmethyl)phenyl)-1H-pyrazol-3-yl)benzene-1,3-diol TFA salt (60 mg), (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (4-nitrophenyl) carbonate (56 mg, 0.10 mmol) and DIPEA (0.10 mL) in DMF (2.0 mL) was stirred at room temperature for 2 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford the desired product (32.1 mg) as an yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 10.88 (s, 1H), 9.29 (s, 1H), 8.19 (d, J = 9.2 Hz, 1H), 8.00 (d, J = 2.5 Hz, 1H), 7.68 (dd, J = 9.1, 2.5 Hz, 1H), 7.40-7.23 (m, 4H), 6.77 (s, 1H), 6.54 (s, 1H), 6.31 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 3.73-3.51 (m, 6H), 3.21-3.15 (m, 1H), 2.98 – 2.86 (m, 1H), 2.60-2.50 (m, 6H), 2.16 (s, 3H), 1.90-1.84 (m, 2H), 1.29 (t, J = 7.3 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H), 0.76 (brs, 6H). ESMS calculated for $C_{47}H_{48}N_6O_8$: 824.4; found: 825.7 $(M + H)^+$.

[001753] SDC-TRAP-0326

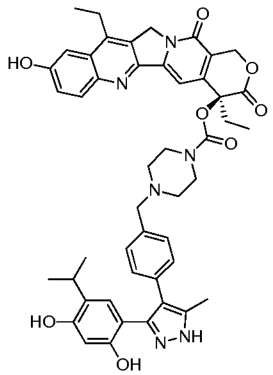
[001754] (5S,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



[001755] Using 4-nitrophenyl ((5S,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl) carbonate as starting material, the title compound was prepared analogously to SDC-TRAP-0325 (step 5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 10.88 (s, 1H), 9.29 (s, 1H), 7.35 (s, 2H), 7.20 (s, 2H), 6.90 (s, 1H), 6.74 (s, 1H), 6.61 (s, 1H), 6.33 (s, 2H), 6.30 (s, 1H), 6.02 (dd, *J* = 7.0, 1.1 Hz, 2H), 5.83 – 5.74 (m, 1H), 4.56 (d, *J* = 4.6 Hz, 1H), 4.42 – 4.33 (m, 1H), 4.18 (dd, *J* = 10.6, 8.6 Hz, 1H), 3.63 (s, 6H), 3.61 (s, 3H), 3.54 (s, 2H), 3.46 – 3.29 (m, 5H), 2.92-2.68 (m, 2H), 2.42 (brs, 4H), 2.15 (s, 3H), 0.71 (brs, 6H). ESMS calculated for $C_{47}H_{50}N_4O_{11}$: 846.4; found: 847.7 $(M + H)^+$.

[001756] SDC-TRAP-0327

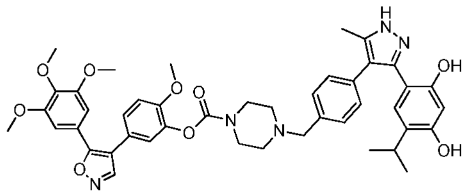
[001757] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



[001758] Using (S)-tert-butyl (4,11-diethyl-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-4,9-diyl) (4-nitrophenyl) dicarbonate as starting material, the title compound was prepared analogously to SDC-TRAP-0325 (step 5) and de-protected of Boc group using TFA/DCM. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 10.87 (s, 1H), 10.34 (s, 1H), 9.28 (s, 1H), 8.04 (d, *J* = 9.8 Hz, 1H), 7.41 (dq, *J* = 5.0, 2.6 Hz, 2H), 7.35 (s, 2H), 7.19 (s, 2H), 6.97 (s, 1H), 6.72 (s, 1H), 6.31 (s, 1H), 5.44 (d, *J* = 4.0 Hz, 2H), 5.29 (s, 2H), 3.78-3.50 (m, 4H), 3.29-3.25 (m, 2H), 3.09 (q, *J* = 7.6 Hz, 2H), 2.89 (p, *J* = 6.9 Hz, 1H), 2.59-2.55 (m, 2H), 2.40-2.10 (m, 7H), 1.30 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H), 0.73 (brs, 6H). ESMS calculated for $C_{47}H_{48}N_6O_8$: 824.4; found: 825.8 $(M + H)^+$.

[001759] SDC-TRAP-0328

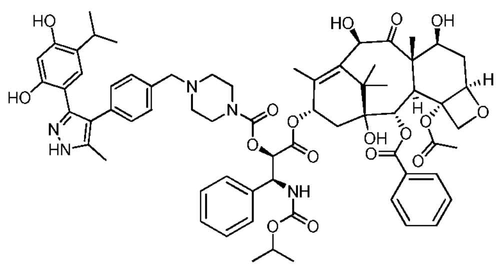
[001760] 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



[001761] Using 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl (4-nitrophenyl) carbonate as starting material, the title compound was prepared analogously to SDC-TRAP-0325 (step 5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 10.87 (s, 1H), 9.29 (s, 1H), 8.87 (s, 1H), 7.42 – 7.29 (m, 3H), 7.26 – 7.16 (m, 4H), 6.88 (s, 2H), 6.75 (s, 1H), 6.30 (s, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.69 (s, 6H), 3.57 (brs, 4H), 3.42 (s, 2H), 2.93 – 2.85 (m, 1H), 2.45 (brs, 4H), 2.16 (s, 3H), 0.72 (d, J = 7.5 Hz, 6H). ESMS calculated for $C_{44}H_{47}N_5O_9$: 789.3; found: 790.7 $(M + H)^+$.

[001762] SDC-TRAP-0329

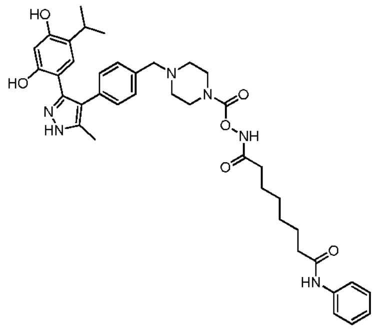
[001763] (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



[001764] Using (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(((4-nitrophenoxy)carbonyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate as starting material, the title compound was prepared analogously to SDC-TRAP-0325 (step 5). ^{1}H NMR (400 MHz, DMSO-d_6) δ12.94 (s, 1H), 10.87 (s, 1H), 9.30 (s, 1H), 8.03 – 7.90 (m, 2H), 7.75-7.63 (m, 3H), 7.42-7.15 (m, 9H), 6.76 (s, 1H), 6.31 (s, 1H), 5.79-5.74 (m, 1H), 5.40 (d, J = 7.2 Hz, 1H), 5.15 – 4.88 (m, 4H), 4.42 (s, 1H), 4.11-4.00 (m, 3H), 3.64 (d, J = 7.1 Hz, 1H), 3.55-3.30 (m, 5H), 2.98-1.23 (m, 34H), 0.98 (d, J = 4.3 Hz, 6H), 0.73 (s, 6H). ESMS calculated for $C_{68}H_{81}N_5O_{17}$: 1239.6; found: 1240.3 $(M + H)^+$.

[001765] SDC-TRAP-0330

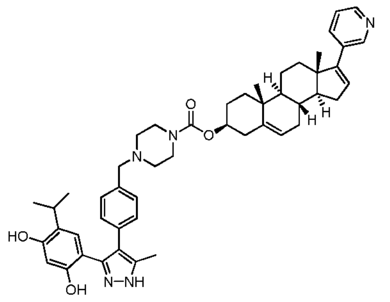
[001766] N1-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carbonyl)oxy)-N8-phenyloctanediamide



[001767] Using N[1]-(((4-nitrophenoxy)carbonyl)oxy)-N[8]-phenyloctanediamide as starting material, the title compound was prepared analogously to SDC-TRAP-0325 (step 5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 11.43 (s, 1H), 10.86 (s, 1H), 9.84 (s, 1H), 9.28 (s, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.32 – 7.17 (m, 4H), 7.01 (tt, J = 7.3, 1.2 Hz, 1H), 6.75 (s, 1H), 6.30 (s, 1H), 3.54 (s, 2H), 3.50-3.35 (m, 4 H), 2.94 – 2.86 (m, 1H), 2.42 (brs, 4H), 2.29 (t, J = 7.4 Hz, 2H), 2.15 (s, 3H), 2.08 (t, J = 7.2 Hz, 2H), 1.60-0.80 (m, 8H), 0.71 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{39}H_{48}N_6O_6$: 696.4; found: 697.8 $(M + H)^+$.

[001768] SDC-TRAP-0331

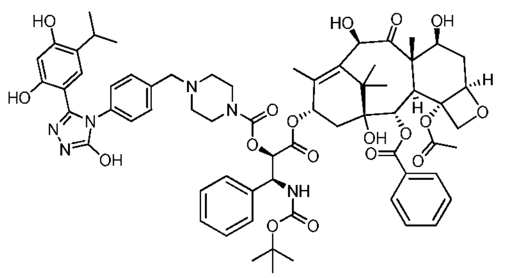
[001769] (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-methyl-1H-pyrazol-4-yl)benzyl)piperazine-1-carboxylate



[001770] Using (3S,8R,9S,10R,13S,14S)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,7,8,9,10,11,12,13,14,15-dodecahydro-1H-cyclopenta[a]phenanthren-3-yl (4-nitrophenyl) carbonate as starting material, the title compound was prepared analogously to SDC-TRAP-0325 (step 5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.92 (s, 1H), 10.87 (s, 1H), 9.28 (s, 1H), 8.59 (dd, J = 2.3, 0.9 Hz, 1H), 8.44 (dd, J = 4.7, 1.6 Hz, 1H), 7.76 (dt, J = 8.1, 1.9 Hz, 1H), 7.39 – 7.30 (m, 3H), 7.20 (d, J = 7.4 Hz, 2H), 6.75 (s, 1H), 6.30 (s, 1H), 6.12 (dd, J = 3.2, 1.8 Hz, 1H), 5.39 (d, J = 4.9 Hz, 1H), 4.40 – 4.30 (m, 1H), 3.54 (s, 2H), 3.36 (brs, 4H), 2.94 – 2.85 (m, 1H), 2.40 – 0.71 (m, 34H). ESMS calculated for $C_{49}H_{59}N_5O_4$: 781.5; found: 782.3 $(M + H)^+$.

[001771] SDC-TRAP-0332

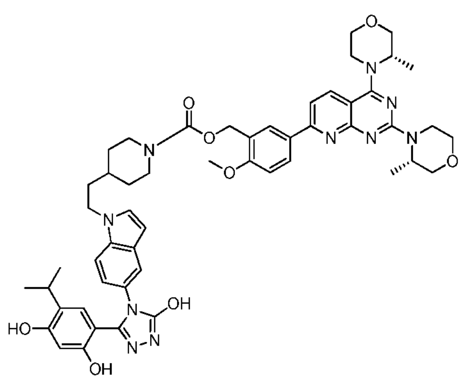
[001772] (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate



[001773] A solution of docetaxel (100 mg, 0.125 mmol), 4-nitrophenylchloroformate (25 mg, 0.125 mmol), TEA (0.10) and DMAP (10 mg) in DCM (6.0 mL) was stirred at room temperature for 1 hr. Solvent was evaporated under reduced pressure to give a residue. A solution of the above residue ((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)a mino)-2-(((4-nitrophenoxy)carbonyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate), 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (60 mg, 0.15 mmol) and TEA (0.03 mL) in DMF (2.0 mL) was stirred at room temperature for 2 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate (17.2 mg) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 9.61 (s, 1H), 9.42 (s, 1H), 8.02 – 7.88 (m, 3H), 7.76 – 7.60 (m, 3H), 7.45 – 7.28 (m, 6H), 7.16 (dd, J = 7.8, 3.0 Hz, 3H), 6.78 (s, 1H), 6.27 (s, 1H), 5.82 – 5.74 (m, 1H), 5.40 (d, J = 7.0 Hz, 1H), 5.14 – 4.87 (m, 4H), 4.42 (s, 1H), 4.05-3.99 (m, 3H), 3.63 (d, J = 7.2 Hz, 1H), 3.49 (s, 2H), 3.32-2.97 (m, 3H), 2.48-1.49 (m, 15H), 1.51 (s, 3H), 1.36 (s, 9H), 1.24 (s, 3H), 0.99-0.94 (m, 12H). ESMS calculated for $C_{66}H_{78}N_6O_{18}$: 1242.6; found: 1243.5 $(M + H)^+$.

[001774] SDC-TRAP-0333

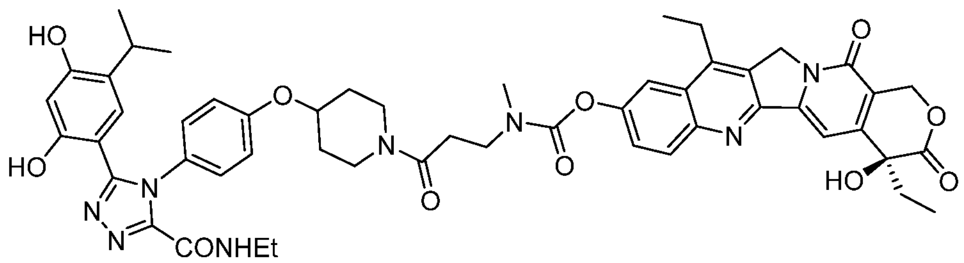
[001775] (5-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-2-methoxybenzyl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate



[001776] A solution of (5-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-2-methoxyphenyl)methanol (68 mg, 0.15 mmol), 4-nitrophenylchloroformate (30 mg, 0.15 mmol) and DIPEA (0.10) in DCM was stirred at room temperature for 1 hr. Solvent was evaporated under reduced pressure to give a residue. A solution of the above residue (4-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-2-(hydroxymethyl)phenyl (4-nitrophenyl) carbonate), 4-(5-hydroxy-4-(1-(2-(piperidin-4-yl)ethyl)-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol (75 mg, 0.15 mmol) and DIPEA (0.30 mL) in DMF (3.0 mL) was stirred at room temperature for overnight. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford (5-(2,4-bis((S)-3-methylmorpholino)pyrido[2,3-d]pyrimidin-7-yl)-2-methoxybenzyl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate (31 mg) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 9.52 (d, J = 17.9 Hz, 2H), 8.16 (dt, J = 6.7, 2.1 Hz, 3H), 7.59 (d, J = 8.5 Hz, 1H), 7.48 – 7.39 (m, 3H), 7.18 (d, J = 9.3 Hz, 1H), 6.91 (dd, J = 8.6, 2.0 Hz, 1H), 6.67 (s, 1H), 6.41 (d, J = 3.1 Hz, 1H), 6.23 (d, J = 2.3 Hz, 1H), 5.13 (s, 2H), 4.41 (d, J = 11.6 Hz, 2H), 4.19 (t, J = 7.4 Hz, 2H), 4.02 – 3.82 (m, 8H), 3.77 – 3.69 (m, 2H), 3.68 – 3.54 (m, 5H), 3.42 (t, J = 11.3 Hz, 1H), 3.23-3.15 (m, 3H), 2.92 – 2.81 (m, 1H), 1.72 – 1.62 (m, 4H), 1.36 (d, J = 6.7 Hz, 3H), 1.27 – 1.05 (m, 6H), 0.77 (d, J = 6.9 Hz, 6H). ESMS calculated for $C_{52}H_{60}N_{10}O_8$: 952.5; found: 953.3 $(M + H)^+$.

[001777] SDC-TRAP-0334

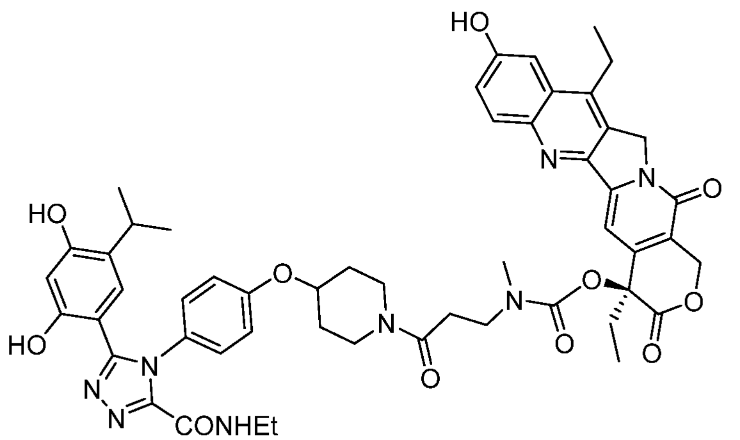
[001778] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidin-1-yl)-3-oxopropyl)(methyl)carbamate



[001779] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 (s, 3H), 8.17 (d, J = 9.2 Hz, 1H), 8.01 – 7.93 (m, 1H), 7.74 – 7.62 (m, 2H), 7.18 – 7.01 (m, 4H), 6.70 (s, 1H), 6.40 (s, 1H), 6.05 (s, 1H), 5.44 (d, J = 4.7 Hz, 1H), 5.25 (s, 2H), 4.92 (dd, J = 11.8, 6.8 Hz, 1H), 4.69 (d, J = 10.6 Hz, 2H), 4.03 (m, 1H), 3.79 (m, 2H), 3.59 (m, 2H), 3.5 (m, 5H), 3.17 (q, J = 7.6 Hz, 2H), 3.03 – 2.87 (m, 2H), 2.5 (m, 2H), 2.21 – 1.96 (m, 5H), 1.73 (m, 2H), 1.30 (t, J = 7.6 Hz, 3H), 1.01 – 0.81 (m, 10H). ppm; ESMS calculated for $C_{52}H_{56}N_8O_{11}$: 968.4; found: 969.6 (M + H$^+$).

[001780] SDC-TRAP-0335

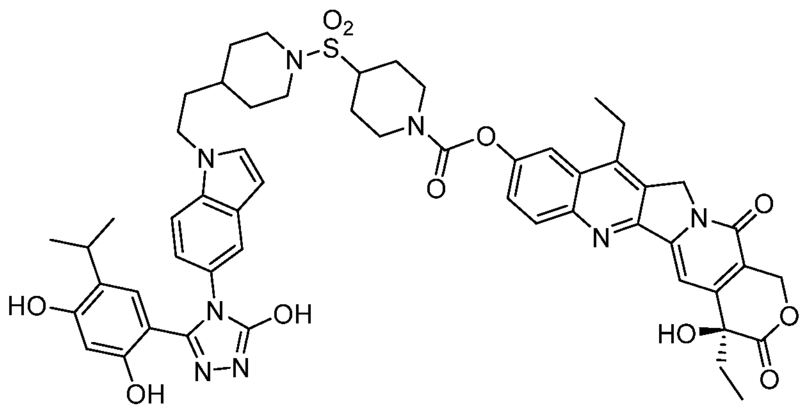
[001781] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidin-1-yl)-3-oxopropyl)(methyl)carbamate



[001782] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.03 (ddd, J = 9.1, 8.0, 5.0 Hz, 2H), 7.40 – 7.18 (m, 6H), 7.18 – 6.77 (m, 4H), 6.63 – 6.30 (m, 4H), 5.84 – 5.54 (m, 2H), 5.41 (ddd, J = 16.9, 9.0, 3.2 Hz, 2H), 5.32 – 5.02 (m, 4H), 4.61 (d, J = 59.2 Hz, 1H), 4.41-4.55 (m, 1H), 3.75 – 2.53 (m, 15H), 2.36 – 0.39 (m, 12H). ppm; ESMS calculated for $C_{52}H_{56}N_8O_{11}$: 968.4; found: 969.6 (M + H$^+$).

[001783] SDC-TRAP-0336

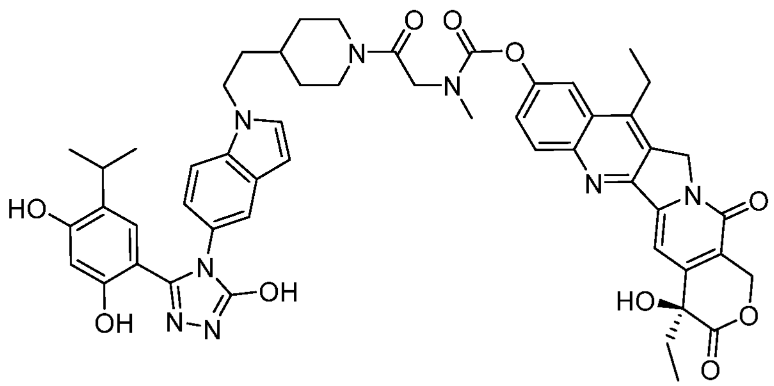
[001784] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)sulfonyl)piperidine-1-carboxylate



[001785] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.22 (qd, *J* = 6.2, 2.9 Hz, 1H), 7.86 (h, *J* = 2.6 Hz, 1H), 7.77 – 6.99 (m, 6H), 6.53 (dq, *J* = 6.3, 3.0 Hz, 1H), 6.37 (td, *J* = 6.6, 3.4 Hz, 2H), 5.86 – 5.55 (m, 1H), 5.47 – 5.10 (m, 3H), 4.73 – 3.98 (m, 4H), 3.86 (d, *J* = 12.7 Hz, 2H), 3.38 (s, 1H), 3.25 – 2.80 (m, 8H), 2.25 – 0.80 (m, 19H), 0.50 (m, 6H). ppm; ESMS calculated for $C_{54}H_{58}N_8O_{11}S$: 1026.4; found: 1027.6 (M + H$^+$).

[001786] SDC-TRAP-0337

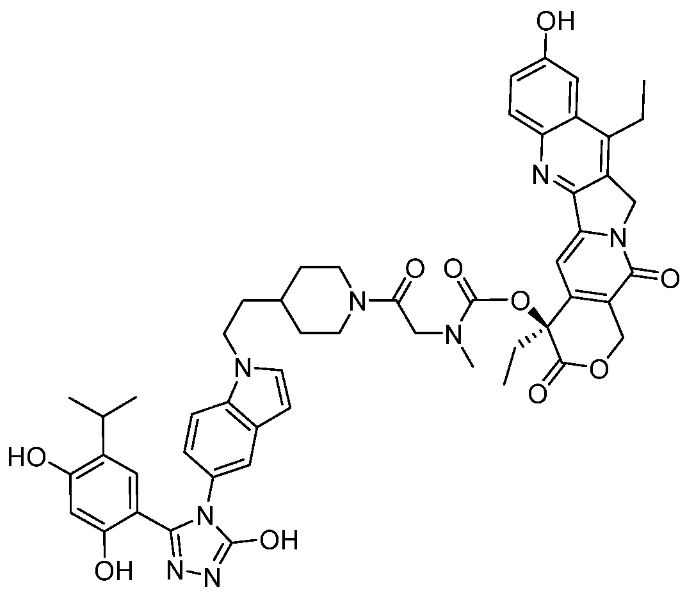
[001787] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-2-oxoethyl)(methyl)carbamate



[001788] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 (ddd, *J* = 9.6, 5.8, 3.6 Hz, 1H), 8.06 – 7.79 (m, 1H), 7.79 – 7.50 (m, 3H), 7.40 (m, 1H), 7.25 – 6.97 (m, 2H), 6.52 (dd, *J* = 7.7, 4.7 Hz, 1H), 6.43 – 6.20 (m, 2H), 5.86 – 5.56 (m, 1H), 5.49 – 5.10 (m, 4H), 4.61 (d, *J* = 13.1 Hz, 1H), 4.48 – 3.95 (m, 4H), 3.80 (d, *J* = 14.3 Hz, 1H), 3.55 – 3.00 (m, 6H), 2.75 (dd, *J* = 69.7, 9.9 Hz, 2H), 2.00 – 1.48 (m, 8H), 1.48 – 0.90 (m, 7H), 0.58 – 0.25 (m, 6H). ppm; ESMS calculated for $C_{52}H_{54}N_8O_{10}$: 950.4; found: 951.5 (M + H$^+$).

[001789] SDC-TRAP-0338

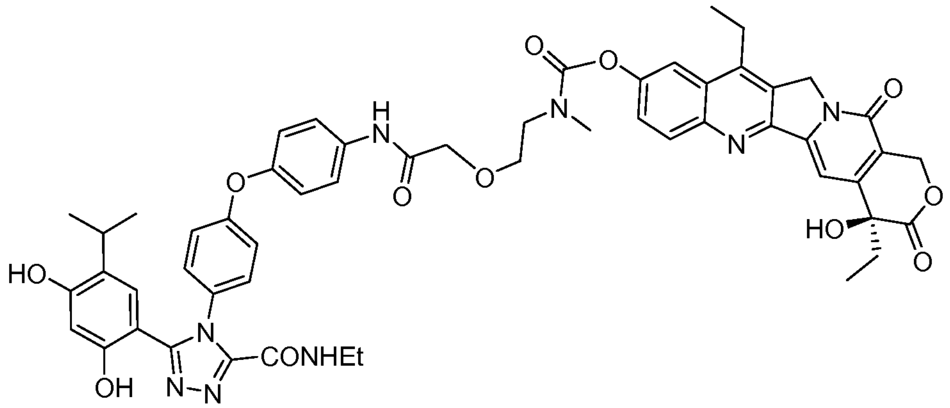
[001790] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (2-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-2-oxoethyl)(methyl)carbamate



[001791] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 9.4 Hz, 1H), 8.00 – 7.72 (m, 1H), 7.56 (d, *J* = 15.7 Hz, 2H), 7.43 (d, *J* = 8.3 Hz, 1H), 7.38 – 6.91 (m, 5H), 6.66 – 6.41 (m, 1H), 6.34 (dd, *J* = 8.0, 4.0 Hz, 2H), 5.67 (d, *J* = 17.0 Hz, 1H), 5.40 (dd, *J* = 16.9, 10.7 Hz, 1H), 5.18 (d, *J* = 10.9 Hz, 2H), 4.63 – 4.31 (m, 1H), 4.31 – 4.10 (m, 1H), 4.10 – 3.50 (m, 2H), 3.39 (dt, *J* = 4.0, 1.9 Hz, 2H), 3.30 – 2.65 (m, 12H), 2.50 (s, 1H), 2.39 – 2.02 (m, 3H), 1.95 (s, 1H), 1.83 (s, 1H), 1.75 – 0.65 (m, 6H), 0.45 (ddd, *J* = 14.7, 12.1, 7.1 Hz, 6H). ppm; ESMS calculated for $C_{52}H_{54}N_8O_{10}$: 950.4; found: 951.6 (M + H^+).

[001792] SDC-TRAP-0339

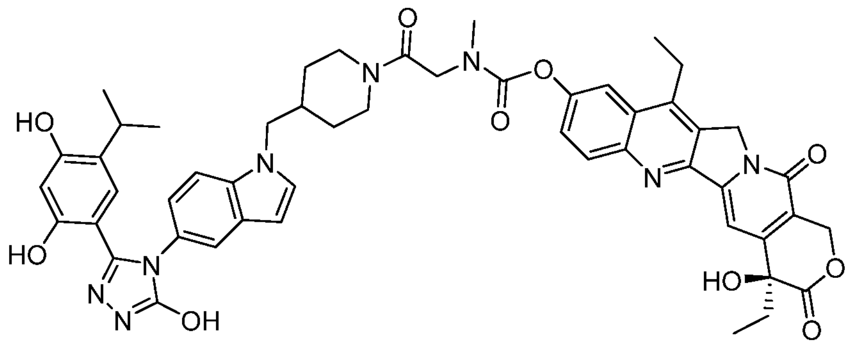
[001793] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(2-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)phenyl)amino)-2-oxoethoxy)ethyl)(methyl)carbamate



[001794] [1]H NMR (400 MHz, Chloroform-*d*) δ 11.44 (s, 1H), 8.84 (s, 1H), 8.15 (dd, *J* = 15.1, 9.1 Hz, 2H), 7.92 – 7.30 (m, 8H), 7.30 - 6.70 (m, 4H), 6.60 -6.20 (m, 4H), 5.78 (dd, *J* = 16.3, 9.7 Hz, 1H), 5.47 – 5.10 (m, 3H), 4.45 – 3.54 (m, 9H), 3.40 (m, 2H), 3.20 (s, 1H), 3.05 – 2.70 (m, 4H), 1.90 (m, 2H), 1.20 (m, 6H), 0.70 – 0.50 (m, 6H). ppm; ESMS calculated for $C_{54}H_{54}N_8O_{12}$: 1006.4; found: 1007.6 ($M + H^+$).

[001795] SDC-TRAP-0340

[001796] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (2-(4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)methyl)piperidin-1-yl)-2-oxoethyl)(methyl)carbamate

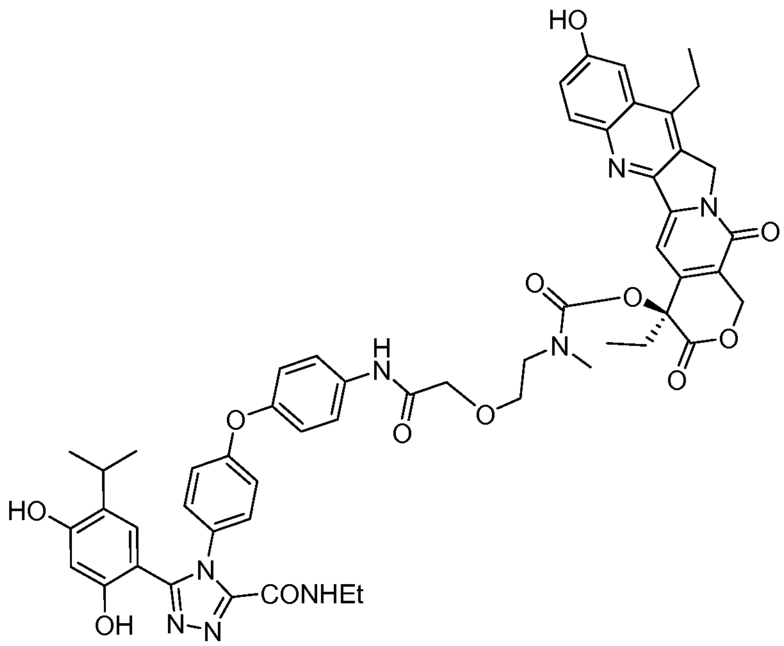


[001797] [1]H NMR (400 MHz, DMSO-d_6) δ 11.91 (s, 1H), 9.58 (d, *J* = 9.1 Hz, 1H), 8.20 (dd, *J* = 9.1, 3.0 Hz, 1H), 8.0 (d, J = 4 Hz, 1H), 7.69 – 7.47 (m, 2H), 7.47 – 7.36 (m, 1H), 7.33 (d, *J* = 1.9 Hz, 1H), 7.07 – 6.80 (m, 1H), 6.66 (d, *J* = 7.0 Hz, 1H), 6.55 (d, *J* = 2.6 Hz, 1H), 6.44 (dd,

J = 8.4, 3.0 Hz, 1H), 6.25 (d, J = 2.9 Hz, 1H), 5.40 (d, J = 38.9 Hz, 3H), 4.45 – 4.05 (m, 5H), 3.80 (m, 1H), 3.32 (s, 3H), 3.25 - 3.15 (m, 2H), 3.18 (s, 1H), 2.93 (s, 1H), 2.90 – 2.80 (m, 2H), 2.56 (s, 3H), 2.1 (m, 2H), 1.88 (dt, J = 14.8, 7.0 Hz, 2H), 1.49 (m, 2H), 1.39 – 1.25 (m, 3H), 1.30 – 1.05 (m, 3H), 0.88 - 0.76 (m, 6H). ppm; ESMS calculated for $C_{51}H_{52}N_8O_{10}$: 936.4; found: 937.6 (M + H^+).

[001798] SDC-TRAP-0341

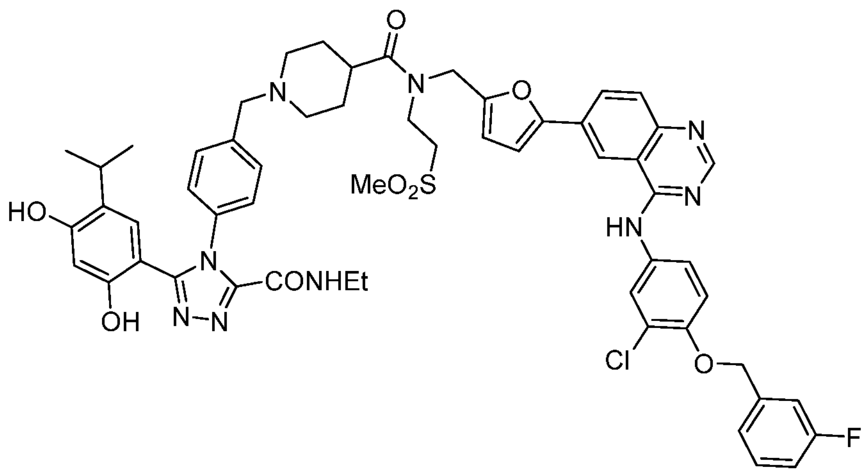
[001799] (S)-4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl (2-(2-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)phenyl)amino)-2-oxoethoxy)ethyl)(methyl)carbamate



[001800] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (dd, J = 15.1, 9.2 Hz, 1H), 7.57 – 6.67 (m, 10H), 6.67 – 6.22 (m, 2H), 5.49 (ddd, J = 118.7, 52.0, 16.8 Hz, 2H), 5.14 – 4.73 (m, 1H), 4.62 (d, J = 18.5 Hz, 1H), 4.25 – 3.37 (m, 8H), 3.36 (s, 3H), 3.25- 2.80 (m, 6H), 2.20 – 2.05 (m, 2H), 1.70 – 1.65 (m, 1H), 1.40 -1.20 (m, 7H), 1.00 – 0.70 (m, 7H). ppm; ESMS calculated for $C_{54}H_{54}N_8O_{12}$: 1006.4; found: 1007.7 (M + H^+).

[001801] SDC-TRAP-0342

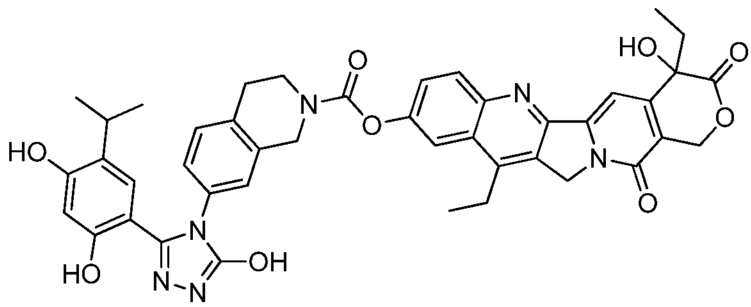
[001802] N-((5-(4-((3-chloro-4-((3-fluorobenzyl)oxy)phenyl)amino)quinazolin-6-yl)furan-2-yl)methyl)-1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)-N-(2-(methylsulfonyl)ethyl)piperidine-4-carboxamide

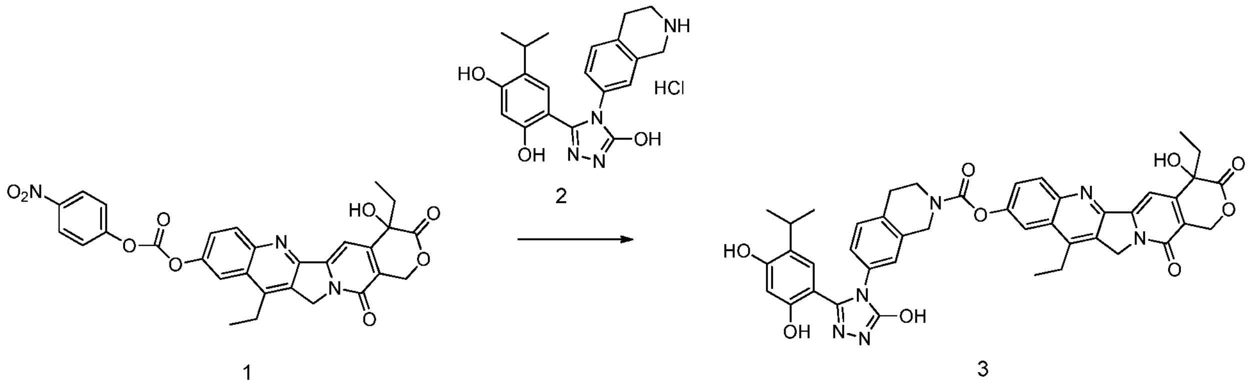


[001803] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 9.05 (s, 1H), 8.50 (s, 1H), 8.60 -8.45 (m, 3H), 8.10- 7.85 (m, 3H), 7.50 – 7.30 (m, 5H), 7.30 – 7.15 (m, 3H), 7.10 -6.85 (m, 3H), 6.52 (s, 1H), 6.43 (s, 1H), 6.30 (m, 2H), 5.16 (s, 2H), 4.76 (s, 2H), 4.00 – 3.61 (m, 4H), 3.50 (m, 2H), 3.30 – 3.15 (m, 4H), 2.92 – 2.80 (m, 4H), 2.10 (m, 2H), 1.85 – 1.60 (m, 4H), 1.20 -0.90 (m, 3H), 0.60 (m, 6H). ppm; ESMS calculated for $C_{56}H_{57}ClFN_9O_8S$: 1069.4; found: 1070.1 (M + H^+).

[001804] SDC-TRAP-0343

[001805] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 7-(3-(5-ethyl-2,4-dihydroxyphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate



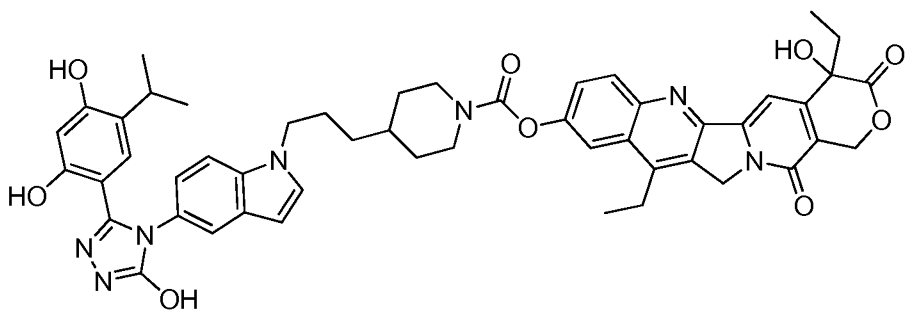


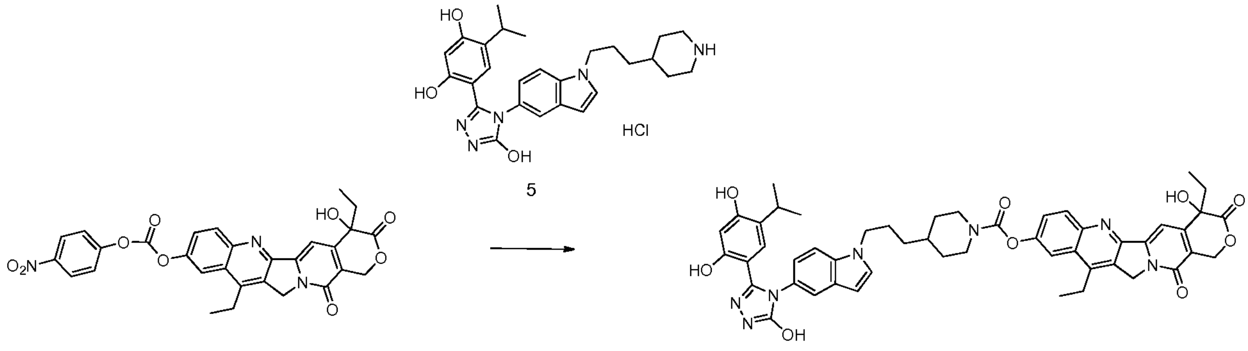
[001806] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 9.60 (d, J = 4.3 Hz, 1H), 9.44 (s, 1H), 8.19 (d, J = 9.1 Hz, 1H), 8.04 (s, 1H), 7.70 (s, 1H), 7.33 (s, 1H), 7.22 (t, J = 13.1 Hz, 2H), 7.00 (d, J = 8.1 Hz, 1H), 6.87 (s, 1H), 6.54 (s, 1H), 6.27 (s, 1H), 5.44 (s, 2H), 5.35 (s, 2H), 4.83 (s, 1H), 4.60 (s, 1H), 3.90 (s, 1H), 3.71 (s, 1H), 3.23 – 3.14 (m, 3H), 3.01 (dt, J = 13.4, 6.4 Hz, 2H), 2.91 (s, 1H), 1.88 (dq, J = 14.9, 7.3 Hz, 2H), 1.29 (t, 3H), 1.01 (d, J = 6.6 Hz, 6H), 0.88 (t, J = 7.3 Hz, 3H).

[001807] ESMS calculated for $C_{42}H_{38}N_6O_9$: 784.3; found: 785.6 ($M+H^+$).

[001808] SDC-TRAP-0344

[001809] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(3-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)propyl)piperidine-1-carboxylate





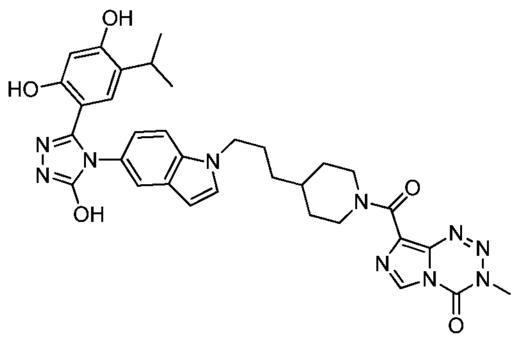
4 5 6

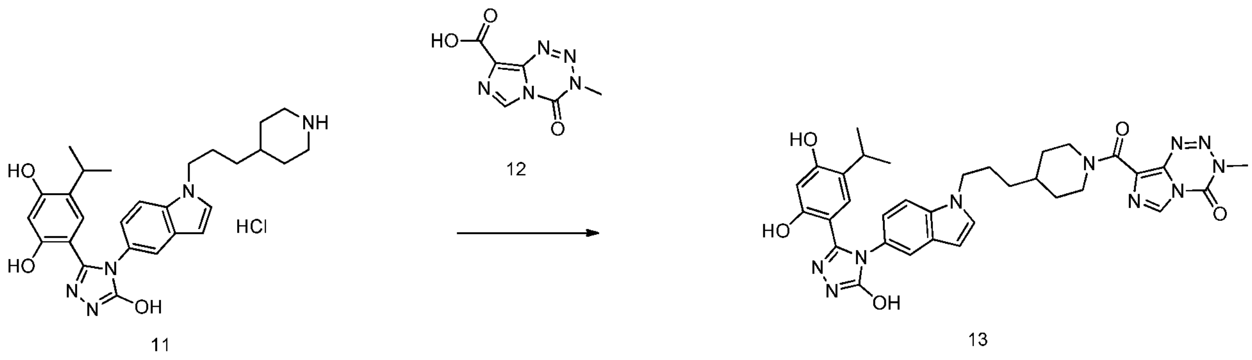
[001810] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 9.55 (d, J = 15.0 Hz, 2H), 8.16 (d, J = 9.1 Hz, 1H), 7.97 (d, J = 2.6 Hz, 1H), 7.65 (dd, J = 9.1, 2.5 Hz, 1H), 7.55 – 7.41 (m, 3H), 7.32 (s, 1H), 6.95 (dd, J = 8.7, 2.0 Hz, 1H), 6.68 (s, 1H), 6.53 (s, 1H), 6.44 (d, J = 3.0 Hz, 1H), 6.24 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.20 (t, J = 6.9 Hz, 3H), 4.02 (s, 1H), 3.43 – 3.29 (m, 1H), 3.24 – 3.14 (m, 2H), 3.04 (s, 1H), 2.89 (p, J = 7.1 Hz, 2H), 1.87 (tt, J = 14.8, 7.1 Hz, 3H), 1.72 (d, J = 12.2 Hz, 2H), 1.52 (s, 1H), 1.33 – 1.03 (m, 11H), 0.88 (t, J = 7.3 Hz, 3H), 0.79 (d, J = 6.9 Hz, 6H).

[001811] ESMS calculated for $C_{50}H_{51}N_7O_9$: 893.4; found: 894.7 ($M+H^+$).

[001812] SDC-TRAP-0345

[001813] 8-(4-(3-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)propyl)piperidine-1-carbonyl)-3-methylimidazo[5,1-d][1,2,3,5]tetrazin-4(3H)-one

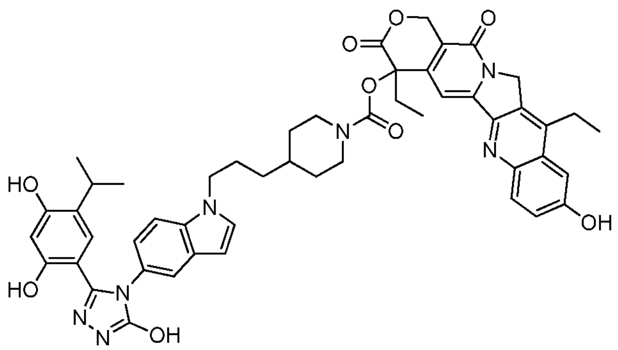


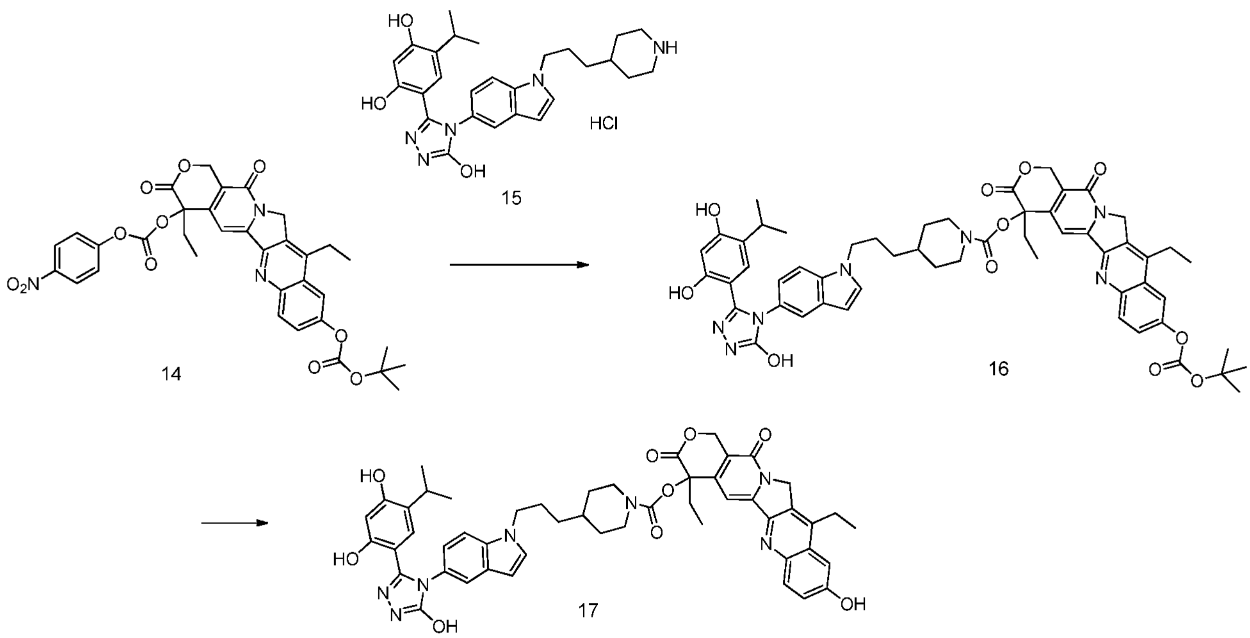


[001814] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 9.55 (d, J = 13.7 Hz, 2H), 8.80 (s, 1H), 8.19 (s, 1H), 7.46 (dd, J = 23.2, 10.2 Hz, 3H), 6.93 (d, J = 8.6 Hz, 1H), 6.67 (d, J = 4.6 Hz, 1H), 6.45 – 6.39 (m, 1H), 6.23 (s, 1H), 4.17 (t, J = 6.7 Hz, 2H), 3.84 (s, 3H), 3.62 (d, J = 9.8 Hz, 2H), 3.41 (m, 1H), 3.15 (q, J = 7.2, 6.3 Hz, 1H), 3.02 (t, J = 12.6 Hz, 1H), 2.54 (s, 3H), 1.76 (d, J = 11.5 Hz, 2H), 1.58 (d, J = 13.2 Hz, 2H), 1.30 – 1.20 (m, 12H).

[001815] ESMS calculated for $C_{33}H_{36}N1_0O_5$: 652.3; found 653.6 (M+H$^+$). SDC-TRAP-0346

[001816] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(3-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)propyl)piperidine-1-carboxylate



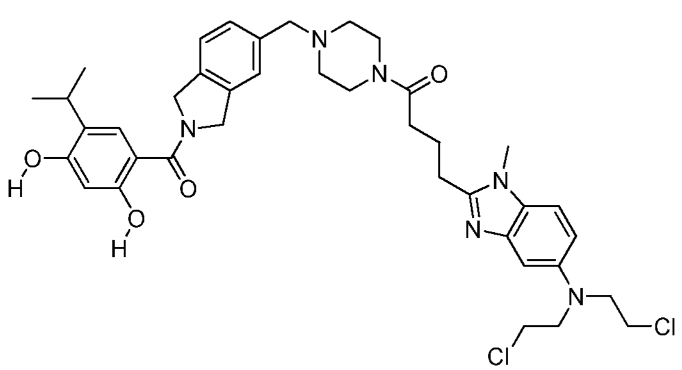


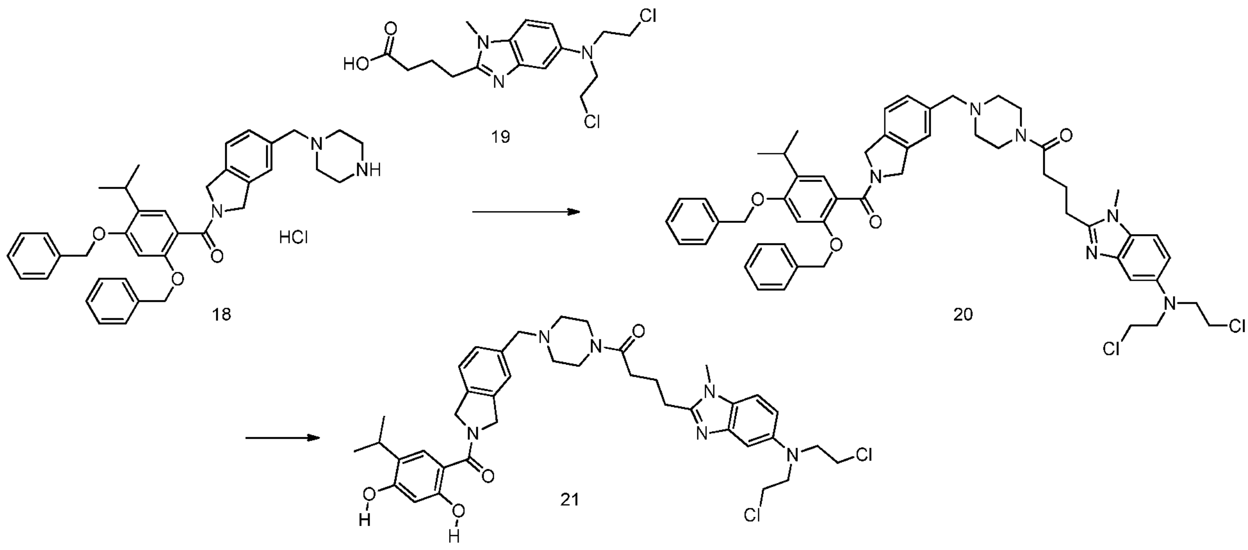
[001817] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 10.31 (s, 1H), 9.54 (d, J = 9.3 Hz, 2H), 7.97 (m, 1H), 7.49 (m, 1H), 7.41 (d, J = 8.0 Hz, 4H), 6.94 (m, 2H), 6.65 (d, J = 13.7 Hz, 1H), 6.42 (s, 1H), 6.23 (s, 1H), 5.43 (d, J = 3.0 Hz, 2H), 5.29 (s, 2H), 4.18 (s, 4H), 3.76 (m, 2H) 3.45 – 3.33 (m, 2H), 3.31 (s, 2H), 3.08 (d, J = 7.6 Hz, 1H), 2.12 (s, 3H), 1.76 (s, 4H), 1.51 (m, 1H), 1.28 (t, J = 8.3, 7.9 Hz, 3H), 1.22 – 1.05 (m, 6H), 0.91 (d, J = 7.3 Hz, 3H).

[001818] ESMS calculated for $C_{50}H_{51}N_7O_9$: 893.4; found: 894.7 ($M+H^+$).

[001819] SDC-TRAP-0347

[001820] 4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)-1-(4-((2-(2,4-dihydroxy-5-isopropylbenzoyl)isoindolin-5-yl)methyl)piperazin-1-yl)butan-1-one



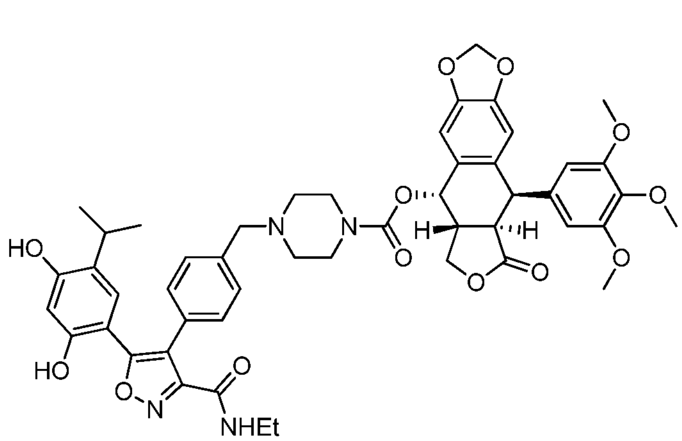


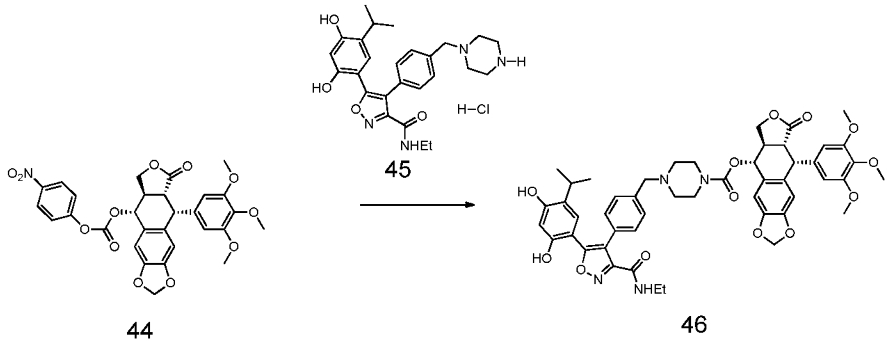
[001821] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 9.63 (s, 1H), 7.42 m, 3H), 7.24 (m, 2H), 7.04 (s, 1H), 6.88 (dd, J = 15.0, 5.8 Hz, 2H), 6.39 (s, 1H), 4.77 (s, 4H), 3.72 (m, 9H), 3.62 (pd, J = 6.6, 3.9 Hz, 6H), 3.34 (m 3.14 (qd, J = 7.4, 4.2 Hz, 5H), 2.87 (d, J = 8.1 Hz, 2H), 2.46 (d, J = 7.1 Hz, 2H), 1.97 (t, J = 7.4 Hz, 2H), 1.17 – 1.08 (m, 6H).

ESMS calculated for $C_{39}H_{48}Cl_2N_6O_4$: 734.3; found 735.6 (M+H$^+$).

[001822] SDC-TRAP-0348

[001823] (5S,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazine-1-carboxylate



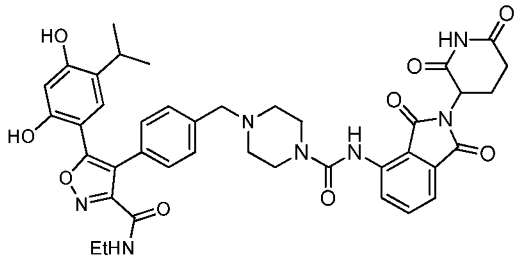


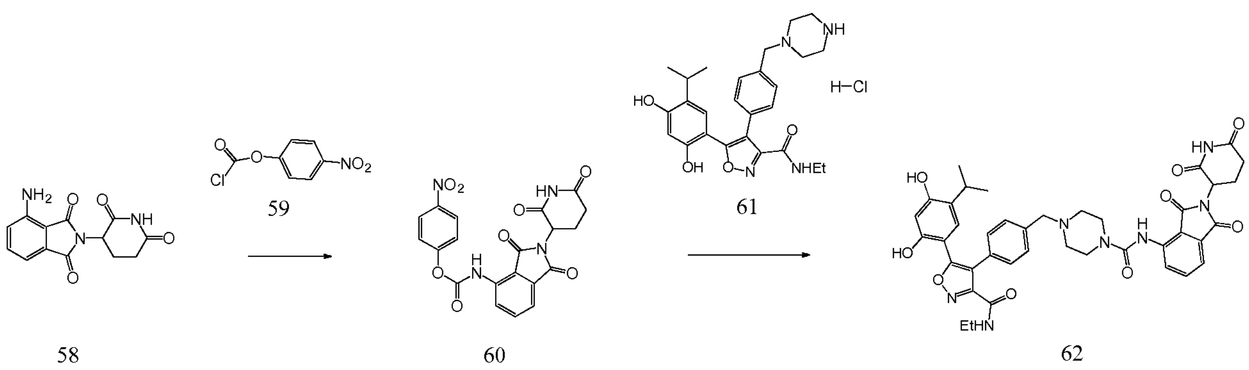
[001824] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.76 (s, 1H), 9.66 (s, 1H), 8.83 (t, J = 5.7 Hz, 1H), 7.28 – 7.16 (m, 4H), 6.89 (s, 1H), 6.71 (s, 1H), 6.60 (s, 1H), 6.44 (s, 1H), 6.33 (s, 2H), 6.02 (d, J = 5.6 Hz, 2H), 5.78 (d, J = 9.3 Hz, 1H), 4.55 (d, J = 4.6 Hz, 1H), 4.37 (t, J = 7.8 Hz, 1H), 4.17 (t, J = 9.7 Hz, 1H), 3.62 (d, J = 4.4 Hz, 9H), 3.50 – 3.33 (m, 5H), 3.22 (p, J = 7.0 Hz, 2H), 2.96 (p, J = 6.9 Hz, 1H), 2.74 (dt, J = 14.6, 8.5 Hz, 1H), 2.36 (s, 4H), 1.08 (q, J = 7.3 Hz, 3H), 0.89 (d, J = 6.9 Hz, 6H).

ESMS calculated for $C_{49}H_{52}N_4O_{13}$: 904.4; found: 905.8 (M+H$^+$).

[001825] SDC-TRAP-0349

[001826] 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-((4-((2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)carbamoyl)piperazin-1-yl)methyl)phenyl)-N-ethylisoxazole-3-carboxamide



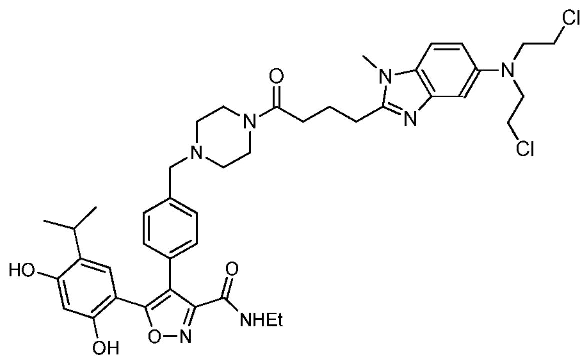


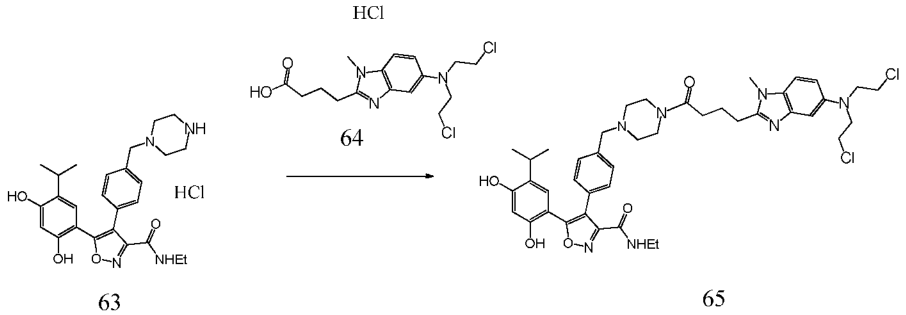
[001827] Pomolidamide 58 (218 mgs, 0.8 mmoles) and 4-nitrophenyl chloroformate (242 mgs, 1.2 mmoles) were combined in anhydrous tetrahydrofuran (20 mls). The reaction was placed under nitrogen atmosphere and heated at 75° C for 30 mins. The tetrahydrofuran was evaporated *in vacuo* and the resulting yellow solid was suspended in ethyl acetate. This was filtered to yield 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)carbamate (224 mgs, 64%).

[001828] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 9.77 (s, 1H), 9.66 (s, 1H), 9.06 (s, 1H), 8.84 (t, J = 5.7 Hz, 1H), 8.43 (d, J = 8.5 Hz, 1H), 7.78 (dd, J = 8.5, 7.3 Hz, 1H), 7.50 (d, J = 7.2 Hz, 1H), 7.29 – 7.16 (m, 4H), 6.73 (s, 1H), 6.44 (s, 1H), 5.14 (dd, J = 12.8, 5.4 Hz, 1H), 3.48 (dd, J = 10.0, 5.2 Hz, 6H), 3.29 – 3.14 (m, 2H), 3.02 – 2.83 (m, 2H), 2.65 – 2.52 (m, 2H), 2.42 (t, J = 5.0 Hz, 4H), 2.09 – 2.01 (m, 1H), 1.07 (t, J = 7.2 Hz, 3H), 0.91 (d, J = 6.8 Hz, 6H). ESMS calculated for $C_{40}H_{41}N_7O_9$: 763.3; found: 764.7(M+H$^+$).

[001829] SDC-TRAP-0350

[001830] 4-(4-((4-(4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)butanoyl)piperazin-1-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethylisoxazole-3-carboxamide





63 65

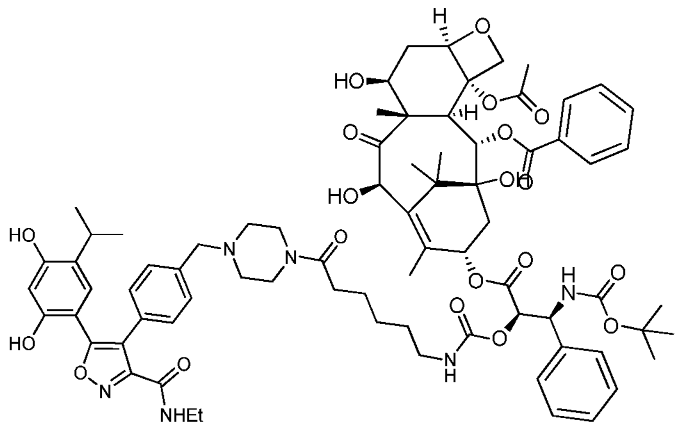
[001831] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 9.66 (s, 1H), 8.84 (t, J = 5.6 Hz, 1H), 7.38 (s, 1H), 7.28 – 7.16 (m, 4H), 6.90 (d, J = 2.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 6.72 (s, 1H), 6.44 (s, 1H), 3.71 (d, J = 8.7 Hz, 11H), 3.45 (m, 4H), 3.22 (p, J = 7.2 Hz, 2H), 3.01 – 2.93 (m, 1H), 2.86 (s, 2H), 2.44 (d, J = 7.3 Hz, 2H), 2.40-2.28 (m, 4H), 1.99 (dt, J = 15.2, 7.5

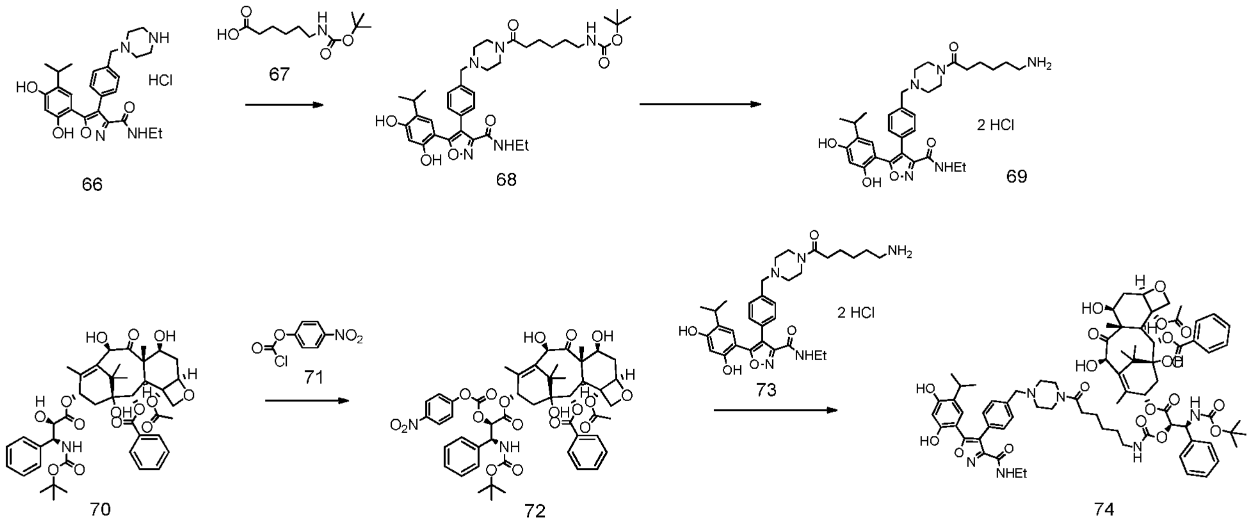
Hz, 2H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 6H).

ESMS calculated for $C_{42}H_{51}Cl_2N_7O_5$: 803.3; found 804.8 ($M+H^+$).

[001832] SDC-TRAP-0351

[001833] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(((6-(4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazin-1-yl)-6-oxohexyl)carbamoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate





[001834] Docetaxel 70 (107 mgs, 0.11 mmoles) was dissolved in anhydrous dichloromethane (10 mls) and cooled with an ice bath. The 4-nitrophenyl chloroformate (23 mgs, 0.115 mmoles) was added, followed by N,N-diisopropylethyl amine (29 µl, 0.16 mmoles). The reaction was allowed to warm to room temperature and was stirred for hours.

Additional 4-nitrophenyl chloroformate (2 mgs, 0.01 mmoles) was added and the reaction was stirred another one hour. The reaction was then cooled in an ice bath and the solution was washed with cold dilute sodium bicarbonate. The organic phase was dried over sodium sulfate and evaporated *in vacuo* to give (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(((4-nitrophenoxy)carbonyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate. Presumed recovery of crude product to carry to the next step 0.11 mmoles.

[001835] 4-(4-((4-(6-aminohexanoyl)piperazin-1-yl)methyl)phenyl)-5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethylisoxazole-3-carboxamide dihydrochloride 69 (81 mgs, 0.11 mmoles), (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(((4-nitrophenoxy)carbonyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate 72 (107 mgs, 0.11 mmoles), and N,N-diisopropylethyl amine were combined in anhydrous N,N-dimethylformamide (2 mls). The solution was stirred at room temperature for three days. The reaction was diluted with 15 mls of dichloromethane and washed with 5 mls of water. After extracting with 5 mls of dichloromethane the combined organic phases were washed with another 5 mls of water and dried over sodium sulfate. After evaporating the solvent *in vacuo* the crude product was purified on a medium pressure high performance silica column, eluting with 0-25% methanol/ dichloromethane. Obtained (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(((6-(4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazin-1-yl)-6-oxohexyl)carbamoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate as a white solid (39 mgs, 25%).

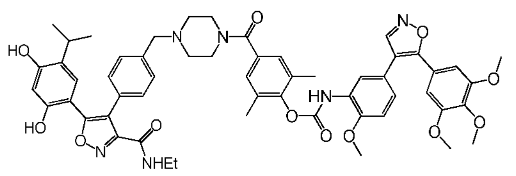
[001836] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.77 (s, 1H), 9.67 (s, 1H), 8.84 (t, J = 5.7 Hz, 1H), 8.01 – 7.94 (m, 2H), 7.72 (m, 2H), 7.66 (m, 2H), 7.48 – 7.36 (m, 3H), 7.32 (d, J = 7.7 Hz, 1H), 7.27 – 7.19(m, 4H), 7.13 (m, 1H), 6.72 (s, 1H), 6.44 (s, 1H), 5.71 (s, 1H), 5.38 (d, J = 7.3 Hz, 1H), 5.09 – 4.97 (m, 3H), 4.94 – 4.85 (m, 3H), 4.38 (d, J = 7.2 Hz, 1H), 4.02 (h, J = 7.6 Hz, 3H), 3.61 (d, J = 7.1 Hz, 1H), 3.43 (d, J = 13.1 Hz, 6H), 3.28 – 3.16 (m, 2H), 2.97 (p, J = 7.0

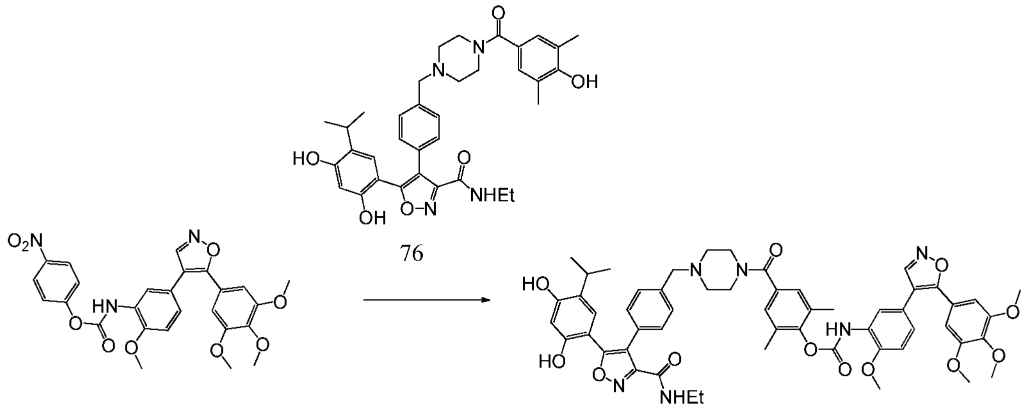
Hz, 3H), 2.35 (s, 2H), 2.30 – 2.21 (m, 8H), 1.74 – 1.58 (m, 4H), 1.43 (d, *J* = 54.7 Hz, 7H), 1.36 (s, 8H), 1.23 (s, 3H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.91 (d, *J*=7.2 Hz 6H).

ESMS calculated for $C_{76}H_{94}N6O_{20}$: 1410.7; found 1411.8 ($M+H^+$).

[001837] SDC-TRAP-0409

[001838] 4-(4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazine-1-carbonyl)-2,6-dimethylphenyl (2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)carbamate





76

75

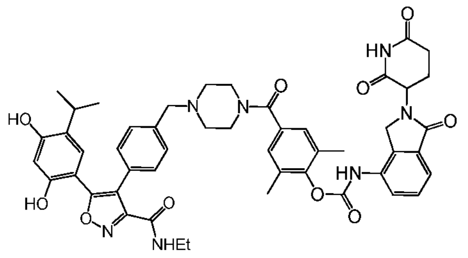
77

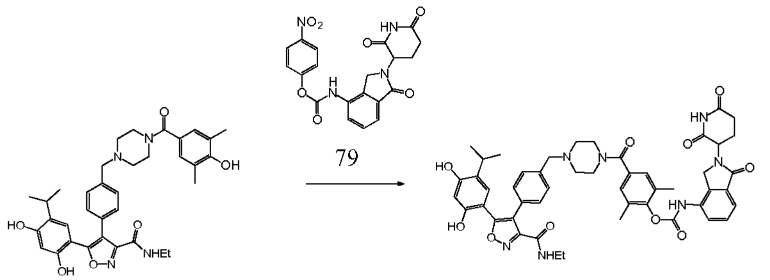
[001839] ^1H NMR (400 MHz, DMSO-d_6) δ 11.43 (s, 1H), 9.76 (s, 1H), 9.66 (s, 1H), 9.43 (s, 1H), 8.84 (d, *J* = 5.6 Hz, 2H), 7.80 (s, 1H), 7.33 – 7.14 (m, 7H), 7.11 (s, 2H), 6.89 (s, 2H), 6.73 (s, 1H), 6.43 (s, 1H), 4.90 (q, *J* = 5.4 Hz, 1H), 3.88 (s, 3H), 3.85 – 3.73 (m, 1H), 3.65 (d, *J* = 5.5 Hz, 9H), 3.48 (s, 2H), 3.38 (q, *J* = 8.2, 7.6 Hz, 2H), 3.22 (p, *J* = 6.8 Hz, 2H), 2.97 (p, *J* = 7.0 Hz, 1H), 2.37 (s, 5H), 2.14 (s, 6H), 1.07 (t, J=7.2 Hz,3H), 0.90 (d, *J* = 6.9 Hz, 6H).

ESMS calculated for $C_{55}H_{58}N_6O_{12}$: 994.4; found 995.9 ($M+H^+$).

[001840] SDC-TRAP-0410

[001841] 4-(4-(4-(5-(2,4-dihydroxy-5-isopropylphenyl)-3-(ethylcarbamoyl)isoxazol-4-yl)benzyl)piperazine-1-carbonyl)-2,6-dimethylphenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate





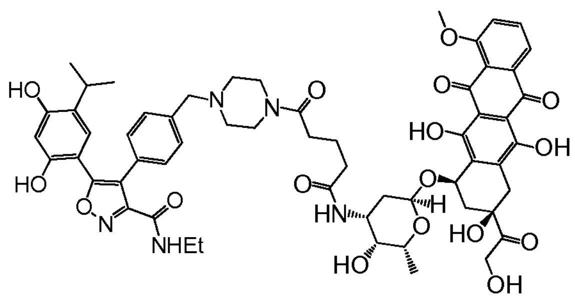
78 79 80

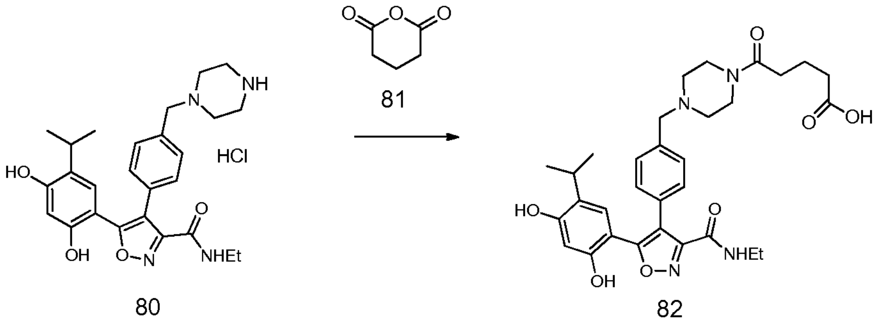
[001842] H NMR (400 MHz, DMSO-d_6) δ 11.01 (d, J = 8.1 Hz, 1H), 10.33 (s, 0H), 9.77 (s, 1H), 9.66 (s, 1H), 8.84 (t, J = 5.7 Hz, 1H), 7.81 (q, J = 4.2 Hz, 1H), 7.54 (d, J = 4.5 Hz, 2H), 7.30 – 7.13 (m, 6H), 6.96 (s, 1H), 6.73 (d, J = 3.0 Hz, 1H), 6.44 (s, 1H), 5.14 (dd, J = 13.4, 5.1 Hz, 1H), 4.45 (dt, J = 37.2, 18.6 Hz, 2H), 3.70 – 3.42 (m, 4H), 3.34 (s, 1H), 3.22 (p, J = 7.1 Hz, 0H), 3.01 – 2.85 (m, 2H), 2.66 – 2.57 (m, 1H), 2.37 (s, 5H), 2.25 – 2.13 (m, 6H), 2.04 (d, J = 13.0 Hz, 1H), 1.23 (s, 0H), 1.12 – 1.01 (m, 3H), 0.90 (dd, J = 6.9, 3.2 Hz, 6H).

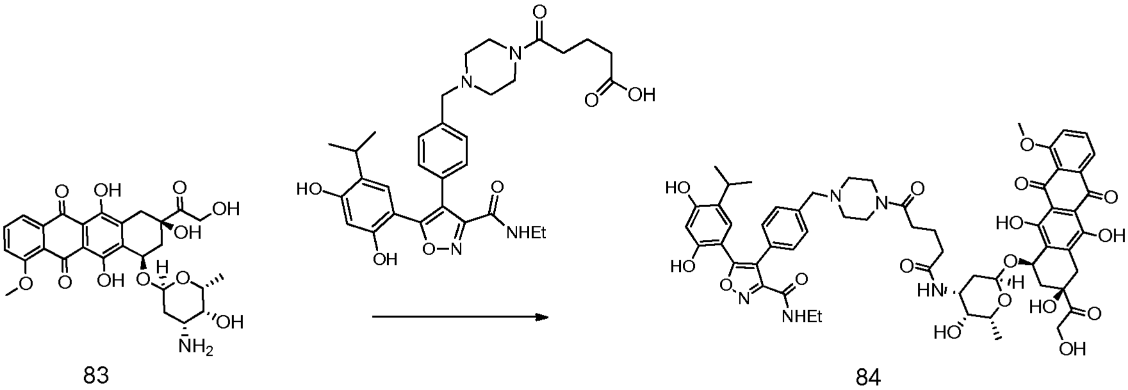
ESMS calculated for $C_{49}H_{51}N_7O_{10}$: 897.4; found 898.8 ($M+H^+$).

[001843] SDC-TRAP-0411

[001844] 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-((4-(5-(((2R,3R,4R,6S)-3-hydroxy-2-methyl-6-(((1R,3R)-3,5,12-trihydroxy-3-(2-hydroxyacetyl)-10-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-1-yl)oxy)tetrahydro-2H-pyran-4-yl)amino)-5-oxopentanoyl)piperazin-1-yl)methyl)phenyl)isoxazole-3-carboxamide



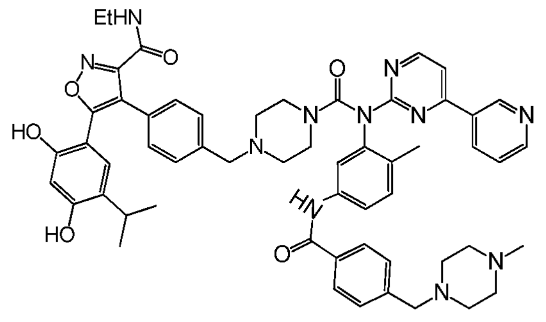


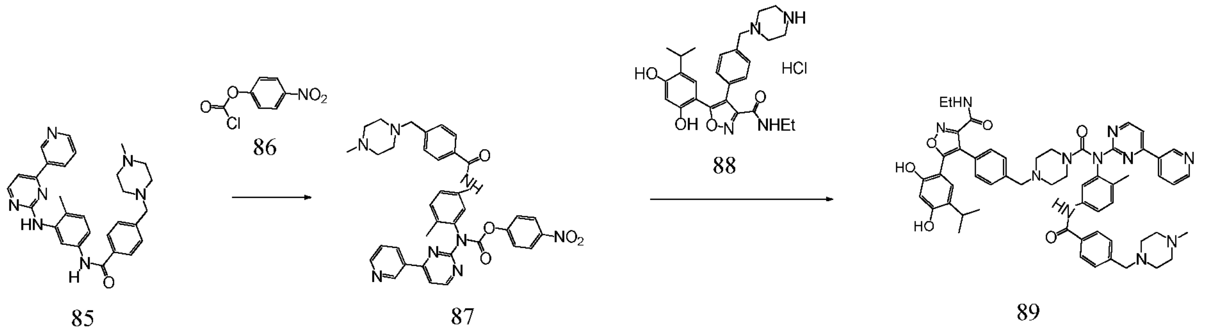


[001845] ^{1}H NMR (400 MHz, DMSO-d_6) δ 14.05 (t, J = 13.1 Hz, 1H), 13.31 – 13.23 (m, 1H), 9.76 (s, 1H), 9.66 (d, J = 3.1 Hz, 1H), 8.83 (t, J = 5.7 Hz, 1H), 7.65 (q, J = 5.6, 4.5 Hz, 2H), 7.49 (dd, J= 16.9, 8.0 Hz, 1H), 7.19 (q, J= 8.4, 7.8 Hz, 4H), 6.72 (s, 1H), 6.43 (s, 1H), 5.46 (d, J = 8.7 Hz, 1H), 5.22 (s, 1H), 4.97 – 4.82 (m, 3H), 4.73 (dd, J = 10.2, 6.0 Hz, 1H), 4.57 (q, J = 5.1, 4.0 Hz, 3H), 4.19 – 4.12 (m, 2H), 4.02 – 3.94 (m, 5H), 3.47 – 3.35 (m, 9H), 3.22 (p, J = 6.9 Hz, 2H), 3.04 – 2.90 (m, 6H), 2.31 (d, J = 9.1 Hz, 3H), 2.21 (dd, J = 15.1, 8.3 Hz, 5H), 2.15 – 2.02 (m, 3H), 1.97 (d, J = 8.3 Hz, 1H), 1.82 (d, J = 12.3 Hz, 1H), 1.62 (dd, J = 14.9, 7.5 Hz, 3H), 1.40 (s, 1H), 1.24 (d, J = 6.2 Hz, 2H), 1.09 (dt, J = 16.9, 7.1 Hz, 7H), 0.93 – 0.86 (m, 6H). ESMS calculated for $C_{58}H_{65}N_5O_{17}$:1103.44; found 1104.4 (M+H^{+})

[001846] SDC-TRAP-0352

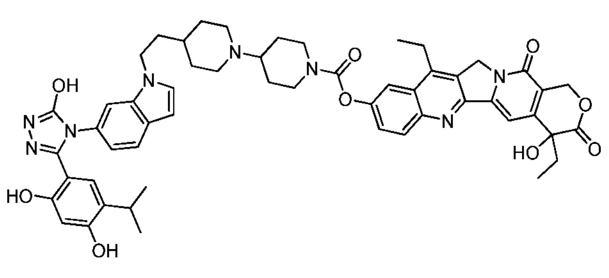
[001847] 5-(2,4-dihydroxy-5-isopropylphenyl)-N-ethyl-4-(4-((4-((2-methyl-5-(4-((4-methyl piperazin-1-yl)methyl)benzamido)phenyl)(4-(pyridin-3-yl)pyrimidin-2-yl)carbamoyl)piperaz in-1-yl)methyl)phenyl)isoxazole-3-carboxamide





[001848] [1]H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 9.76 (s, 1H), 9.65 (s, 1H), 9.23 (d, J = 2.2 Hz, 1H), 8.83 (t, J = 5.7 Hz, 1H), 8.73 (dd, J = 4.8, 1.7 Hz, 1H), 8.67 (d, J = 5.2 Hz, 1H), 8.40 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.79 – 7.69 (m, 2H), 7.68 – 7.55 (m, 2H), 7.44 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 8.4 Hz, 1H), 7.18 (q, J = 8.1 Hz, 4H), 6.67 (s, 1H), 6.43 (s, 1H), 3.58 (s, 2H), 3.55-3.25 (m 6H), 3.27 – 3.15 (m, 2H), 2.91 (p, J = 6.9 Hz, 1H), 2.70 (br m 8), 2.37 (s, 7H), 2.05 (s, 3H), 1.23 (s, 3H), 1.07 (dt, J = 14.1, 7.1 Hz, 3H), 0.83 (d, J = 6.8 Hz, 6H). ESMS calculated for $C_{56}H_{61}N_{11}O_6$: Exact Mass: 983.5; found 1411.8 ($M+H^+$)

[001849] SDC-TRAP-0353:



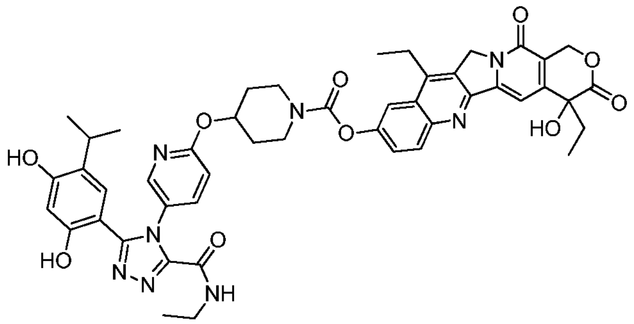
[001850] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indo lizino[1,2-b]quinolin-9-yl 4-(2-(6-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-[1,4'-bipiperidine]-1'-carboxylate.

[001851] [1]H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 9.55 (d, J = 23.3 Hz, 2H), 8.17 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.67 (dd, J = 9.1, 2.5 Hz, 1H), 7.57 – 7.37 (m, 3H), 7.32 (s, 1H), 6.95 (dd, J = 8.6, 2.1 Hz, 1H), 6.68 (s, 1H), 6.59 – 6.33 (m, 2H), 6.26 (s, 1H), 5.39

(d, J = 40.6 Hz, 4H), 4.30-4.08 (m, 4H), 3.20 – 2.85 (m, 10H), 2.13-1.69 (m, 10H), 1.39-1.14 (m, 6H), 0.88 (t, J = 8.0 Hz, 3H), 0.80 (d, J = 4.0 Hz, 6H);

[001852] ESMS calculated ($C_{54}H_{58}N_8O_9$): 962.4; found: 963.6 (M+H).

[001853] SDC-TRAP-0354

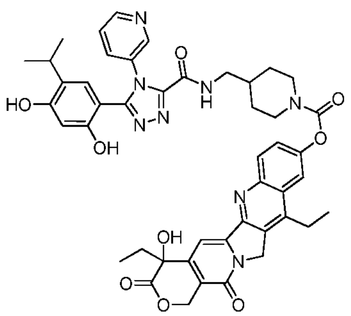


[001854] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)pyridin-2-yl)oxy)piperidine-1-carboxylate.

[001855] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.74 (s, 1H), 9.02 (t, J = 5.9 Hz, 1H), 8.19 (d, J = 9.2 Hz, 1H), 8.09 (d, J = 2.7 Hz, 1H), 8.03 (d, J = 2.5 Hz, 1H), 7.73 (ddd, J = 20.0, 8.9, 2.6 Hz, 1H), 7.33 (s, 1H), 6.90 (d, J = 8.8 Hz, 1H), 6.79 (s, 1H), 6.53 (s, 1H), 6.33 (d, J = 2.2 Hz, 1H), 5.39 (d, J = 37.7 Hz, 3H), 5.28 (s, 1H), 4.02 (s, 1H), 3.83 (s, 1H), 3.58 (s, 1H), 3.42-3.16 (m, 7H), 2.99 (p, J = 6.9 Hz, 1H), 2.11-2.07 (m, 2H), 1.93-1.71 (m, 4H), 1.30 (t, J = 7.6 Hz, 3H), 1.07 (t, J = 7.1 Hz, 3H), 0.96 (d, J = 4.0 Hz, 6H), 0.88 (t, J = 8.0 Hz, 3H);

[001856] ESMS calculated ($C_{47}H_{48}N_8O_{10}$): 884.4; found: 885.4 (M+H).

[001857] SDC-TRAP-0355

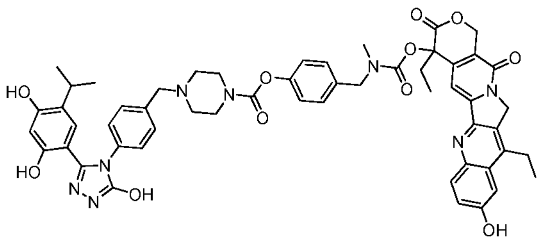


[001858] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((5-(2,4-dihydroxy-5-isopropylphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamido)methyl)piperidine-1-carboxylate.

[001859] [1]H NMR (400 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.67 (s, 1H), 9.17 (t, J = 6.1 Hz, 1H), 8.57 67 (dd, J = 6.1, 4.2 Hz, 1H), 8.49 (d, J = 3.8 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.77 (ddd, J = 8.1, 2.6, 1.5 Hz, 1H), 7.67 (dd, J = 9.1, 2.5 Hz, 1H), 7.46 (ddd, J = 8.1, 4.8, 0.8 Hz, 1H), 7.32 (s, 1H), 6.85 (s, 1H), 6.52 (s, 1H), 6.27 (s, 1H), 5.39 (d, J = 39.9 Hz, 3H), 4.22 (s, 1H), 4.13 – 3.89 (m, 1H), 3.30-3.89 (m, 8H), 1.89 – 1.73 (m, 4H), 1.29 (t, J = 7.8 Hz, 3H), 1.23 – 1.15 (m, 3H), 0.98 (d, J = 7.8 Hz, 6H), 0.88 (t, J = 7.8 Hz, 3H);

[001860] ESMS calculated ($C_{46}H_{46}N_8O_9$): 854.4; found: 855.5 (M+H).

[001861] SDC-TRAP-0356

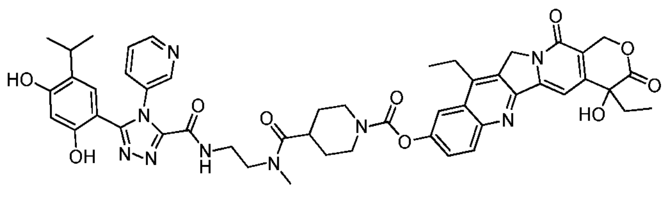


[001862] 4-(((((4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl)oxy)carbonyl)(methyl)amino)methyl)phenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate.

[001863] [1]H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 10.37 (d, J = 6.2 Hz, 1H), 9.62 (s, 1H), 9.42 (s, 1H), 8.04 (dd, J = 9.4, 5.2 Hz, 1H), 7.44 – 7.15 (m, 8H), 7.00 (s, 1H), 6.93-6.91 (m, 2H), 6.79 (s, 1H), 6.27 (s, 1H), 5.49 – 5.42 (m, 2H), 5.32-5.28 (m, 2H), 4.51-4.41 (m, 2H), 3.60-3.44 (m, 4H), 3.16-2.95 (m, 4H), 2.73 (s, 1H), 2.50-2.12 (m, 5H), 1.34 – 1.23 (m, 5H), 0.99 – 0.65 (m, 11H);

[001864] ESMS calculated ($C_{54}H_{54}N_8O_{11}$): 990.4; found: 991.7 (M+H).

[001865] SDC-TRAP-0357

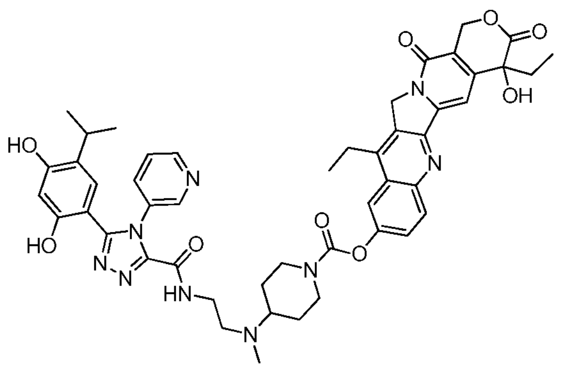


[001866] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl-4-((2-(5-(2,4-dihydroxy-5-isopropylphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamido)ethyl)(methyl)carbamoyl)piperidine-1-carboxylate.

[001867] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.81 (d, J = 12.2 Hz, 1H), 9.68 (s, 1H), 8.60-8.55 (m, 1H), 8.50 – 8.38 (m, 1H), 8.17 (dd, J = 9.1, 3.8 Hz, 1H), 8.01 (d, J = 2.5 Hz, 1H), 7.95 – 7.71 (m, 1H), 7.68 (ddd, J = 9.1, 4.1, 2.4 Hz, 1H), 7.47 – 7.41 (m, 1H), 7.33 (s, 1H), 6.86 (d, J = 11.9 Hz, 1H), 6.54 (s, 1H), 6.25 (d, J = 1.3 Hz, 1H), 5.39 (d, J = 39.9 Hz, 4H), 4.24 (s, 1H), 4.05 (s, 1H), 3.50-3.34 (s, 4H), 3.25-2.80 (m, 8H), 1.89-1.81 (m, 2H), 1.75-1.23 (m, 9H), 1.08 – 0.70 (m, 9H);

[001868] ESMS calculated ($C_{49}H_{51}N_9O_{10}$): 925.4; found: 926.6 (M+H).

[001869] SDC-TRAP-0358

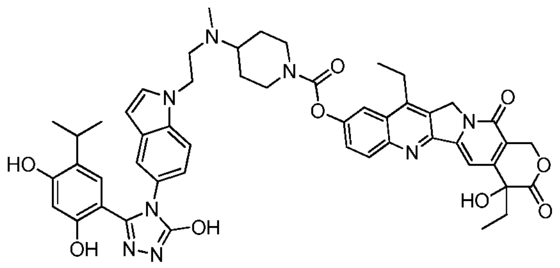


[001870] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((2-(5-(2,4-dihydroxy-5-isopropylphenyl)-4-(pyridin-3-yl)-4H-1,2,4-triazole-3-carboxamido)ethyl)(methyl)amino)piperidine-1-carboxylate.

[001871] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.84 (s, 1H), 9.69 (s, 1H), 8.82 (t, J = 5.8 Hz, 1H), 8.57 (dd, J = 4.8, 1.5 Hz, 1H), 8.49 (d, J = 2.6 Hz, 1H), 8.17 (d, J = 9.1 Hz, 1H), 8.00 (d, J = 2.5 Hz, 1H), 7.76 (ddd, J = 8.2, 2.5, 1.5 Hz, 1H), 7.68 (dd, J = 9.2, 2.5 Hz, 1H), 7.46 (dd, J = 8.1, 4.8 Hz, 1H), 7.32 (s, 1H), 6.84 (s, 1H), 6.54 (s, 1H), 6.26 (s, 1H), 5.39 (d, J = 40.2 Hz, 4H), 4.28 (s, 1H), 4.11 (d, J = 5.3 Hz, 1H), 3.28-2.90 (m, 8H), 2.66-2.57 (m, 3H), 2.25 (s, 3H), 1.89 – 1.71 (m, 4H), 1.35 – 1.11 (m, 4H), 0.97 (d, J = 4.0 Hz, 6H), 0.86 (t, J = 7.8 Hz, 3H);

[001872] ESMS calculated ($C_{48}H_{51}N_9O_9$): 897.4; found: 898.6 (M+H).

[001873] SDC-TRAP-0359

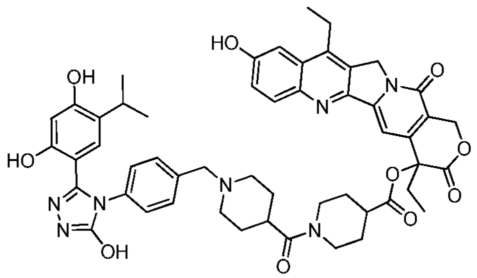


[001874] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)(methyl)amino)piperidine-1-carboxylate.

[001875] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 9.56 (s, 1H), 9.51 (s, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.96 (d, *J* = 4.0 Hz, 1H), 7.65 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.42 (d, *J* = 3.9 Hz, 1H), 7.32 (s, 1H), 6.95 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.71 (s, 1H), 6.54 (s, 1H), 6.43 (d, *J* = 4.0 Hz, 1H), 6.24 (s, 1H), 5.39 (d, *J* = 42.0 Hz, 4H), 4.44 – 3.89 (m, 4H), 3.30 – 2.60 (m, 9H), 2.30 (s, 2H), 1.92-1.82 (m, 2H), 1.71-1.60 (m, 2H), 1.55-1.35 (m, 2H), 1.28 (t, *J* = 7.6 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.81 (d, *J* = 4.0 Hz, 6H);

[001876] ESMS calculated ($C_{50}H_{52}N_8O_9$): 908.4; found: 909.7 (M+H).

[001877] SDC-TRAP-0360

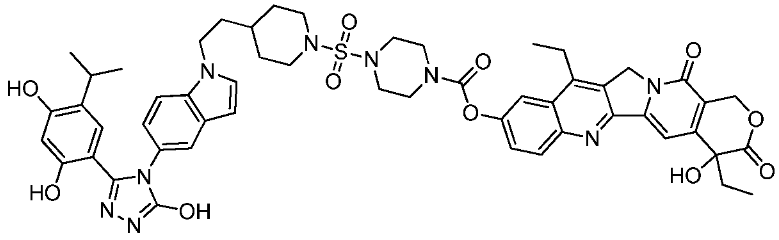


[001878] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 1-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)piperidine-4-carboxylate.

[001879] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.60 (s, 1H), 9.41 (s, 1H), 8.01 (d, *J* = 9.8 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 6.92 (s, 2H), 6.75 (s, 1H), 6.25 (s, 1H), 5.48 (s, 2H), 5.29 (s, 2H), 4.15 – 4.06 (m, 2H), 3.86 (s, 2H), 3.13-2.73 (m, 11H), 2.15 (d, J = 7.4 Hz, 2H), 1.94 (brs, 4H), 1.54 (brs, 4H), 1.28 (t, J = 7.6 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.2 Hz, 6H).

[001880] ESMS calculated ($C_{52}H_{55}N_7O_{10}$): 937.4; found: 938.6 (M+H).

[001881] SDC-TRAP-0361

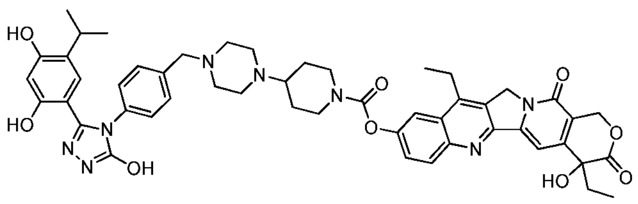


[001882] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)sulfonyl)piperazine-1-carboxylate

[001883] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.95 (s, 1H), 9.63 (s, 1H), 9.57 (s, 1H), 8.25 (d, J = 9.1 Hz, 1H), 8.07 (d, J = 2.5 Hz, 1H), 7.75 (dd, J = 9.2, 2.5 Hz, 1H), 7.59 – 7.46 (m, 3H), 7.39 (s, 1H), 7.01 (dd, J = 8.7, 2.0 Hz, 1H), 6.75 (s, 1H), 6.59 (s, 1H), 6.50 (d, J = 3.0 Hz, 1H), 6.30 (s, 1H), 5.50 (s, 2H), 5.41 (s, 2H), 4.29 (t, J = 7.1 Hz, 2H), 3.80 (s, 2H), 3.69 – 3.58 (m, 4H), 3.38 – 3.28 (m, 5H), 3.23 (d, J = 5.2 Hz, 2H), 3.01 – 2.86 (m, 3H), 2.01 – 1.82 (m, 4H), 1.78 (d, J = 6.5 Hz, 2H), 1.40 – 1.19 (m, 5H), 0.94 (t, J = 7.3 Hz, 3H), 0.86 (d, J = 6.9 Hz, 6H).

[001884] ESMS calculated ($C_{53}H_{57}N_9O_{11}S$): 1027.4; found: 1028.7 (M+H).

[001885] SDC-TRAP-0362

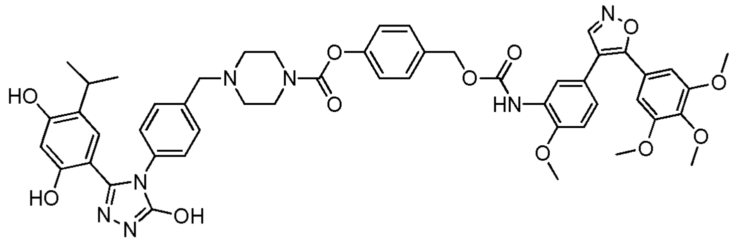


[001886] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)piperidine-1-carboxylate.

[001887] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 9.61 (s, 1H), 9.42 (s, 1H), 8.18 (d, J = 9.1 Hz, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.67 (dd, J = 9.1, 2.5 Hz, 1H), 7.33 (s, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 6.77 (s, 1H), 6.53 (s, 1H), 6.27 (s, 1H), 5.44 (s, 2H), 5.35 (s, 2H), 4.28 (brs, 2H), 4.14 – 4.06 (m, 2H), 3.44 (s, 3H), 3.21 – 3.14 (m, 6H), 2.99-2.94 (m, 4H), 2.39 (brs, 3H), 1.91-1.82 (m, 4H), 1.30 (t, J = 7.2 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 6H), 0.89 (t, *J* = 7.1 Hz, 3H).

[001888] ESMS calculated ($C_{50}H_{54}N_8O_9$): 910.4; found: 911.9 (M+H).

[001889] SDC-TRAP-0363



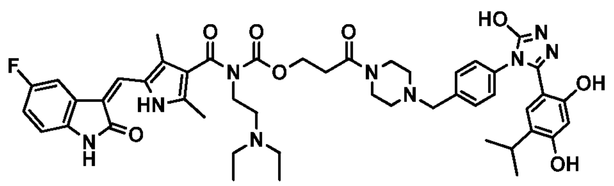
[001890] 4-((((2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)carbamoyl)oxy)methyl)phenyl 4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate.

[001891] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.72 (s, 1H), 9.76 (s, 1H), 9.56 (s, 1H), 8.86 (s, 1H), 8.34 (d, *J* = 2.1 Hz, 1H), 7.39-7.23 (m, 9H), 7.05 (d, *J* = 7.9 Hz, 2H), 6.94 (s, 2H), 6.91 (s, 1H), 6.28 (s, 1H), 5.19 (t, *J* = 8.0 Hz, 1H), 4.48 (d, *J* = 5.7 Hz, 2H), 3.91 (s, 3H), 3.72 (s, 3H), 3.69 (s, 6H), 3.65 – 3.39 (m, 5H), 3.02-2.95 (m, 1H), 2.42 (brs, 5H), 0.98 (d, *J* = 6.9 Hz, 6H).

[001892] ESMS calculated ($C_{50}H_{51}N_7O_{12}$): 941.4; found: 943.0 (M+H).

[001893] SDC-TRAP-0364

[001894] (Z)-3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-3-oxopropyl (2-(diethylamino)ethyl)(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamate



[001895] (Z)-tert-butyl 3-(((2-(diethylamino)ethyl)(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamoyl)oxy)propanoate was prepared according using the procedure similar to the one outline in patent application WO2012/088529 A1, using tert-butyl 3-hydroxypropionate as the alcohol substrate.

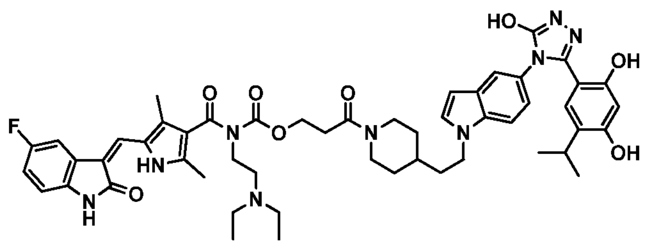
[001896] A round-bottom flask was charged with (Z)-tert-butyl 3-(((2-(diethylamino)ethyl)(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamoyl)oxy)propanoate (0.074 mmol), CH_2Cl_2 (1 mL) and HCl (4M in dioxane, 1 mL) at 22 ^{0}C. The mixture was stirred for 3.5 h, then concentrated under reduced pressure to yield (Z)-3-(((2-(diethylamino)ethyl)(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamoyl)oxy)propanoic acid.

[001897] SDC-TRAP-0364 was synthesized from (Z)-3-(((2-(diethylamino)ethyl)(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamoyl)oxy)propanoic acid in a similar manner as described for SDC-TRAP-0252.

[001898] ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.81 (s, 1H), 11.97 (s, 1H), 10.96 (s, 1H), 9.62 (s, 1H), 9.39 (s, 1H), 7.82 – 7.71 (m, 2H), 7.24 – 7.19 (m, 5H), 6.94 (t, *J* = 8.9 Hz, 1H), 6.85 (dd, *J* = 8.6, 4.8 Hz, 1H), 6.26 (s, 1H), 4.31 – 4.23 (m, 6H), 4.06 – 3.97 (m, 4H), 3.28 – 3.17 (m, 10H), 3.05 – 2.93 (m, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 6H), 0.97 (d, *J* = 6.7 Hz, 6H) ppm; ESMS calculated for $C_{48}H_{56}FN_9O_8$: 905.4; found: 906.8 (M + H$^+$).

[001899] SDC-TRAP-0365

[001900] (Z)-3-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-3-oxopropyl (2-(diethylamino)ethyl)(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamates

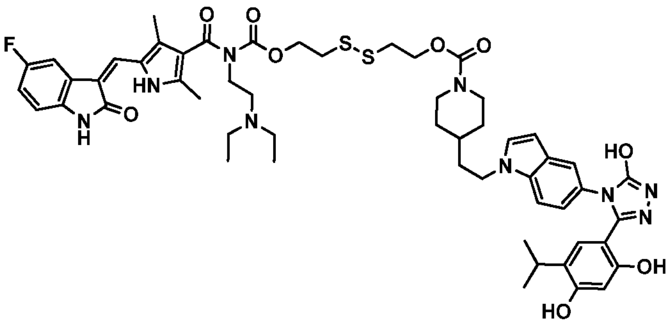


[001901] SDC-TRAP-0365 was synthesized in a similar manner as described for SDC-TRAP-0364, using 4-(5-hydroxy-4-(1-(2-(piperidin-4-yl)ethyl)-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol as the amine partner.

[001902] ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.82 (s, 1H), 11.89 (s, 1H), 10.99 (s, 1H), 9.55 (s, 1H), 9.50 (s, 1H), 9.32 (s, 1H), 7.83 – 7.72 (m, 2H), 7.45 – 7.33 (m, 2H), 6.98 – 6.80 (m, 2H), 6.68 (s, 1H), 6.42 (d, J = 3.1 Hz, 1H), 6.24 (s, 1H), 4.29 – 4.22 (m, 2H), 4.13 – 3.97 (m, 4H), 3.55 – 3.50 (m, 4H), 3.27 – 3.14 (m, 8H), 2.88 (p, J = 7.0 Hz, 1H), 2.35 (s, 3H), 2.31 (s, 3H), 1.63 – 1.58 (m, 2H), 1.55 – 1.50 (m, 3H), 1.26 (t, J = 7.2 Hz, 6H), 0.91 – 0.86 (m, 2H), 0.78 (d, J = 6.9 Hz, 6H).ppm; ESMS calculated for $C_{52}H_{60}FN_9O_8$: 957.5; found: 958.9 (M + H^+).

[001903] SDC-TRAP-0366

[001904] (Z)-12-ethyl-9-(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)-8-oxo-7-oxa-3,4-dithia-9,12-diazatetradecyl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate



[001905] (Z)-2-((2-hydroxyethyl)disulfanyl)ethyl (2-(diethylamino)ethyl)(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamate was prepared according using the procedure similar to the one outline in patent application WO2012/088529 A1, using 2,2'-disulfanediyldiethanol as the alcohol substrate.

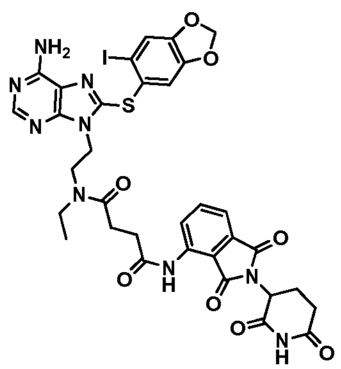
[001906] SDC-TRAP-0366 was synthesized in a similar manner as described for SDC-TRAP-0249, using (Z)-2-((2-hydroxyethyl)disulfanyl)ethyl (2-(diethylamino)ethyl)(5-((5-fluoro-2-oxoindolin-3-ylidene)methyl)-2,4-dimethyl-1H-pyrrole-3-carbonyl)carbamate as the alcohol partner, and 4-(5-hydroxy-4-(1-(2-(piperidin-4-yl)ethyl)-1H-indol-5-yl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol as the amine partner.

[001907] ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.86 (s, 1H), 11.88 (s, 1H), 10.97 (s, 1H), 9.53 (s, 1H), 9.32 (s, 1H), 7.77 (dd, J = 8.0, 4.0 Hz, 1H), 7.74 (s, 1H), 7.49 – 7.39 (m, 3H), 7.00 – 6.88 (m, 2H), 6.91 – 6.81 (m, 1H), 6.68 (s, 1H), 6.42 (d, J = 3.1 Hz, 1H), 6.23 (s, 1H), 4.32 (t,

J = 5.9 Hz, 2H), 4.17 (dt, J = 17.6, 6.7 Hz, 4H), 4.04 (t, J = 7.6 Hz, 2H), 3.89 (s, 1H), 3.49 (s, 3H), 3.29 – 3.18 (m, 4H), 2.87 (dt, J = 17.1, 6.1 Hz, 6H), 2.37 (s, 3H), 2.33 (s, 3H), 1.65 (q, J = 8.1, 6.9 Hz, 4H), 1.24 (t, J = 7.2 Hz, 6H), 1.09 – 0.98 (m, 3H), 0.78 (d, J = 6.9 Hz, 6H) ppm; ESMS calculated for $C_{54}H_{64}FN_9O_9S_2$: 1066.3; found: 1067.0 ($M + H^+$).

[001908] SDC-TRAP-0367

[001909] N1-(2-(6-amino-8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)-N 4-(2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)-N1-ethylsuccinamide



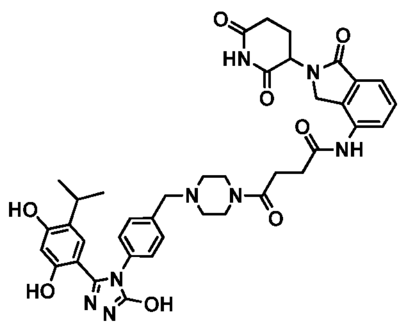
[001910] 9-(3-(ethylamino)propyl)-8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-a mine was prepared according to a similar procedure described in *J. Med. Chem.* 2006, *49*, 381 – 390.

[001911] SDC-TRAP-0367 was synthesized in a similar manner as described for SDC-TRAP-0246, using 9-(3-(ethylamino)propyl)-8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-6-amine as the amine partner.

[001912] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 9.73 – 9.64 (m, 1H), 8.47 (dt, J = 8.9, 4.7 Hz, 1H), 8.21 – 8.12 (m, 3H), 7.88 – 7.79 (m, 1H), 7.65 – 7.55 (m, 1H), 7.50 – 7.40 (m, 2H), 6.09 – 6.00 (m, 2H), 5.14 (dd, J = 12.7, 5.4 Hz, 1H), 4.52 – 4.28 (m, 2H), 3.73 – 3.65 (m, 2H), 2.96 – 2.81 (m, 2H), 2.66 – 2.52 (m, 8H), 0.97 (t, J = 7.1 Hz, 0H).ppm; ESMS calculated for $C_{33}H_{30}IN_9O_8S$: 839.1; found: 840.5 ($M + H^+$).

[001913] SDC-TRAP-0368

[001914] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)be nzyl)piperazin-1-yl)-N-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)-4-oxobutanamide

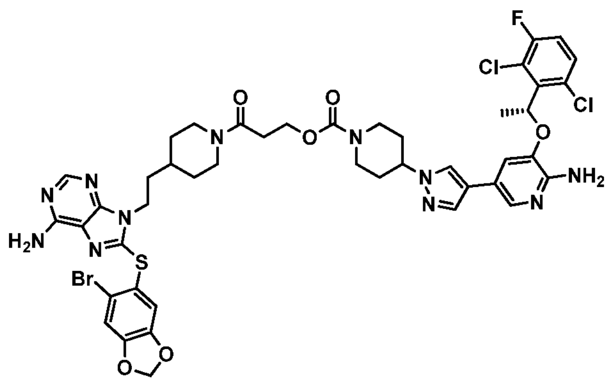


[001915] SDC-TRAP-0368 was synthesized in a similar manner as described for SDC-TRAP-0246, using 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol as the amine partner.

[001916] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (d, J = 1.5 Hz, 1H), 11.05 (s, 1H), 9.95 (s, 1H), 9.71 (d, J = 3.8 Hz, 1H), 9.45 (d, J = 2.2 Hz, 1H), 7.83 (ddd, J = 7.4, 3.7 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.19 – 7.12 (m, 2H), 6.80 (s, 1H), 6.33 (d, J = 2.9 Hz, 1H), 5.15 (dd, J = 13.3, 5.1 Hz, 1H), 4.37 (t, J = 17.6 Hz, 0H), 3.67 – 3.53 (m, 6H), 3.19 – 3.05 (m, 1H), 3.05 – 2.86 (m, 2H), 2.70 – 2.52 (m, 6H), 2.39 – 2.25 (m, 2H), 2.09 – 1.98 (m, 2H), 0.96 (d, J = 6.8 Hz, 6H).ppm; ESMS calculated for $C_{39}H_{42}N_8O_8$: 750.3; found: 751.3 ($M + H^+$).

[001917] SDC-TRAP-0369

[001918] (R)-3-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)-3-oxopropyl 4-(4-(6-amino-5-(1-(2,6-dichloro-3-fluorophenyl)ethoxy)pyridin-3-yl)-1H-pyrazol-1-yl)piperidine-1-carboxylate

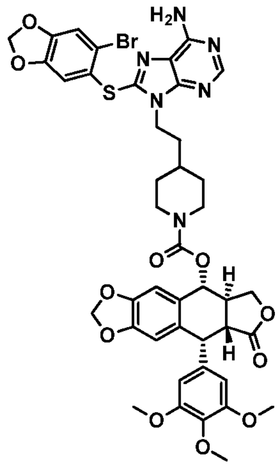


[001919] SDC-TRAP-0369 was synthesized in a similar manner as described for SDC-TRAP-0253, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner.

[001920] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.20 (s, 3H), 8.30 (s, 1H), 7.64 – 7.59 (m, 1H), 7.57 – 7.46 (m, 2H), 7.33 (dt, *J* = 9.5, 4.8 Hz, 1H), 7.14 – 7.05 (m, 2H), 6.93 (d, *J* = 1.5 Hz, 1H), 6.85 (s, 1H), 6.11 (q, *J* = 6.7 Hz, 1H), 6.01 (s, 2H), 5.95 – 5.90 (m, 2H), 4.60 (d, *J* = 13.4 Hz, 1H), 4.43 (td, *J* = 6.8, 1.4 Hz, 2H), 4.33 – 4.20 (m, 3H), 3.87 (d, *J* = 13.5 Hz, 1H), 3.66 (dq, *J* = 13.4, 6.7 Hz, 4H), 3.10 (q, *J* = 7.4 Hz, 4H), 3.04 – 2.93 (m, 2H), 2.71 (t, *J* = 6.8 Hz, 2H), 1.66 – 1.35 (m, 7H), 1.28 – 1.14 (m, 6H).ppm; ESMS calculated for $C_{44}H_{45}BrCl_2FN_{11}O_6S$: 1025.2; found: 1026.1 (M + H^+).

[001921] SDC-TRAP-0370

[001922] (5R,5aR,8aR,9R)-8-oxo-9-(3,4,5-trimethoxyphenyl)-5,5a,6,8,8a,9-hexahydrofuro[3',4':6,7]naphtho[2,3-d][1,3]dioxol-5-yl 4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidine-1-carboxylate

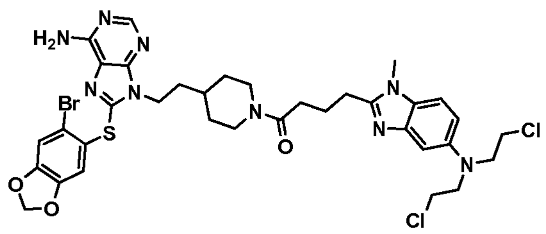


[001923] SDC-TRAP-0370 was synthesized in a similar manner as described for SDC-TRAP-0249, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner, and Podophyllotoxin as the alcohol partner.

[001924] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 3.9 Hz, 1H), 7.14 – 7.07 (m, 1H), 6.99 – 6.90 (m, 1H), 6.83 (s, 1H), 6.54 (d, *J* = 1.9 Hz, 1H), 6.39 (s, 2H), 6.07 – 5.95 (m, 4H), 5.80 (d, *J* = 9.1 Hz, 1H), 4.60 (d, *J* = 4.3 Hz, 1H), 4.45 (t, *J* = 8.2 Hz, 1H), 4.35 – 4.16 (m, 3H), 3.81 (s, 3H), 3.75 (s, 6H), 2.93 (d, *J* = 4.4 Hz, 1H), 2.88 – 2.77 (m, 5H), 1.89 – 1.79 (m, 2H), 1.77 – 1.66 (m, 5H) ppm; ESMS calculated for $C_{42}H_{41}BrN_6O_{11}S$: 918.2; found: 919.6 (M + H^+).

[001925] SDC-TRAP-0371

[001926] 1-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)-4-(5-(bis(2-chloroethyl)amino)-1-methyl-1H-benzo[d]imidazol-2-yl)butan-1-one

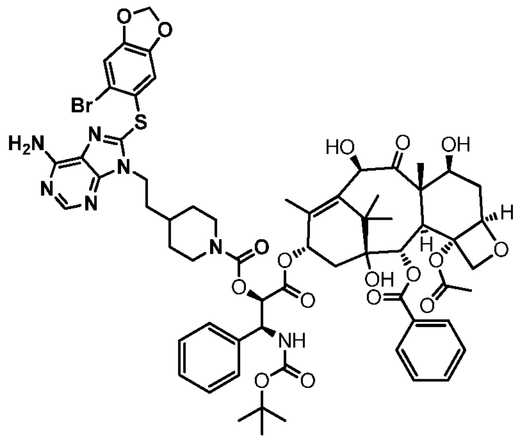


[001927] SDC-TRAP-0371 was synthesized in a similar manner as described for SDC-TRAP-0252, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner.

[001928] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.32 (s, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 2H), 6.83 (s, 1H), 6.79 (dd, *J* = 8.0, 4.0 Hz, 1H), 5.99 (s, 2H), 5.78 (s, 2H), 4.29 – 4.20 (m, 2H), 3.76 – 3.59 (m, 11H), 2.99 – 2.86 (m, 4H), 2.53 – 2.42 (m, 2H), 2.17 (p, *J* = 7.1 Hz, 2H), 1.87 – 1.66 (m, 7H), 1.49 (dqd, *J* = 10.6, 7.3, 6.8, 3.0 Hz, 1H), 1.34 – 1.23 (m, 1H) ppm; ESMS calculated for $C_{35}H_{40}BrCl_2N_9O_3S$: 817.2; found: 818.6 (M + H$^+$).

[001929] SDC-TRAP-0372

[001930] (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidine-1-carboxylate

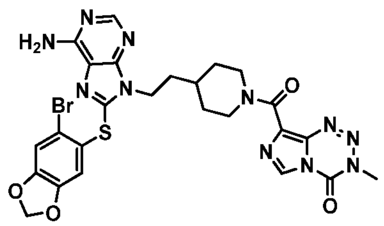


[001931] SDC-TRAP-0372 was synthesized in a similar manner as described for SDC-TRAP-0244, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner and Docetaxel as the alcohol partner.

[001932] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (s, 1H), 8.13 – 8.05 (m, 2H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.42 – 7.33 (m, 2H), 7.34 – 7.25 (m, 4H), 7.10 (s, 1H), 6.84 (s, 1H), 6.19 (s, 1H), 6.05 – 5.98 (m, 3H), 5.67 (d, *J* = 7.1 Hz, 1H), 5.57 (d, *J* = 9.6 Hz, 1H), 5.22 (s, 1H), 4.98 – 4.90 (m, 1H), 4.34 – 4.14 (m, 6H), 3.90 (d, *J* = 7.0 Hz, 4H), 2.68 (t, *J* = 11.8 Hz, 2H), 2.52 (d, *J* = 14.9 Hz, 1H), 2.38 (s, 3H), 2.26 – 2.21 (m, 1H), 2.16 – 2.07 (m, 1H), 1.96 – 1.81 (m, 5H), 1.77 – 1.62 (m, 7H), 1.38 – 1.09 (m, 16H).ppm; ESMS calculated for $C_{63}H_{72}BrN_7O_{17}S$: 1311.4; found: 1312.5 ($M + H^+$).

[001933] SDC-TRAP-0373

[001934] 8-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl) piperidine-1-carbonyl)-3-methylimidazo[5,1-d][1,2,3,5]tetrazin-4(3H)-one

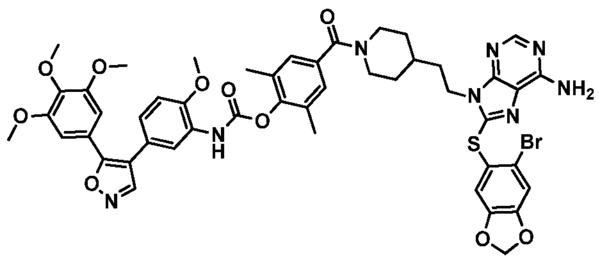


[001935] SDC-TRAP-0373 was synthesized in a similar manner as described for SDC-TRAP-0368, using 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine as the amine partner.

[001936] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.63 (s, 1H), 8.17 (s, 1H), 7.23 (s, 1H), 7.05 (s, 1H), 6.08 (s, 2H), 4.32 (t, J = 7.4 Hz, 2H), 3.97 (s, 3H), 3.39 – 3.34 (m, 4H), 1.90 – 1.73 (m, 3H), 1.73 – 1.52 (m, 3H).ppm; ESMS calculated for $C_{25}H_{24}BrN_{11}O_4S$: 655.1; found: 656.4 (M + H^+).

[001937] SDC-TRAP-0374

[001938] 4-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl) piperidine-1-carbonyl)-2,6-dimethylphenyl (2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)carbamate



[001939] Synthesis of 4-nitrophenyl (2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)carbamate: A round-bottomed flask was charged with 2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)aniline (SDC-TRAP-0412, 0.56 mmol), THF (10 mL), 4-nitrophenyl chloroformate, and refluxed for 23 h. The solution was diluted with hexanes (20 mL) and concentrated under reduced pressure to yield the crude product. This product was used in the next step without further purification.

[001940] Synthesis of (4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)(4-hydroxy-3,5-dimethylphenyl)methanone: A round-bottomed flask was charged with 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine (0.14 mmol), 4-hydorxy-3,5-dimethylbenzoic acid (0.17 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.14 mmol), HOBt (0.28 mmol), DMF (1 mL) and diisopropyl ethylamine (0.42 mmol) at 21 ^{o}C. The solution was stirred at the same temperature for 9 h, then concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (CH_2Cl_2/MeOH) to afford the desired product as a white solid.

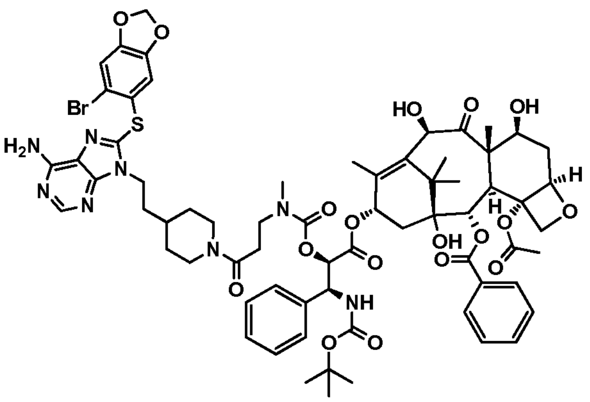
[001941] SDC-TRAP-0374 was synthesized in a similar manner as described for SDC-TRAP-0244, using 4-nitrophenyl

(2-methoxy-5-(5-(3,4,5-trimethoxyphenyl)isoxazol-4-yl)phenyl)carbamate and (4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)(4-hydroxy-3,5-dimethylphenyl)methanone as the two coupling partners.

[001942] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.43 – 8.20 (m, 3H), 7.75 (s, 1H), 7.19 – 7.02 (m, 4H), 7.01 – 6.87 (m, 3H), 6.83 (s, 1H), 6.00 (s, 2H), 5.60 (s, 2H), 4.26 (t, *J* = 7.5 Hz, 2H), 3.98 (s, 3H), 3.85 (s, 4H), 3.74 (s, 6H), 2.24 (s, 6H), 2.00 – 1.43 (m, 7H).ppm; ESMS calculated for $C_{48}H_{47}BrN_8O_{10}S$: 1008.2; found: 1009.6 ($M + H^+$).

[001943] SDC-TRAP-0375

[001944] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-2-(((3-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)-3-oxopropyl)(methyl)carbamoyl)oxy)-3-((tert-butoxycarbonyl)amino)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate



[001945] Tert-butyl (3-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)-3-oxopropyl)(methyl)carbamate was prepared from 8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9-(2-(piperidin-4-yl)ethyl)-9H-purin-6-amine and 3-((tert-butoxycarbonyl)(methyl)amino)propanoic acid using a similar procedure as described for the synthesis of SDC-TRAP-0252. The product was then deprotected with HCl (4M in dioxane) to yield the amine 1-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)-3-(methylamino)propan-1-one.

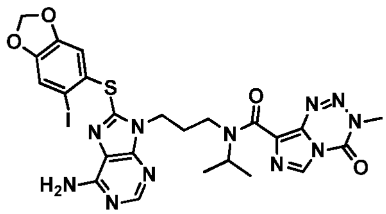
[001946] SDC-TRAP-0375 was synthesized in a similar manner as described for SDC-TRAP-0244, using

1-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)-3-(methylamino)propan-1-one as the amine coupling partner.

[001947] ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.37 – 8.21 (m, 1H), 8.12 (t, *J* = 7.4 Hz, 2H), 7.72 – 7.56 (m, 1H), 7.56 – 7.44 (m, 2H), 7.38 (dd, *J* = 10.0, 4.3 Hz, 2H), 7.35 – 7.26 (m, 4H), 7.08 (d, *J* = 1.4 Hz, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 6.31 – 6.12 (m, 1H), 5.99 (q, *J* = 1.4 Hz, 2H), 5.92 – 5.58 (m, 2H), 5.58 – 5.34 (m, 1H), 5.34 – 5.04 (m, 1H), 5.04 – 4.87 (m, 1H), 4.37 – 4.12 (m, 6H), 4.00 – 3.62 (m, 4H), 3.01 – 2.94 (m, 1H), 2.87 (s, 3H), 2.76 – 2.24 (m, 12H), 2.09 – 1.63 (m, 15H), 1.44 – 0.86 (m, 16H).ppm; ESMS calculated for $C_{67}H_{79}BrN_8O_{18}S$: 1396.4; found: 1397.9 (M + H$^+$).

[001948] SDC-TRAP-0376

[001949] N-(3-(6-amino-8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)propyl)-N-isopropyl-3-methyl-4-oxo-3,4-dihydroimidazo[5,1-d][1,2,3,5]tetrazine-8-carboxamide

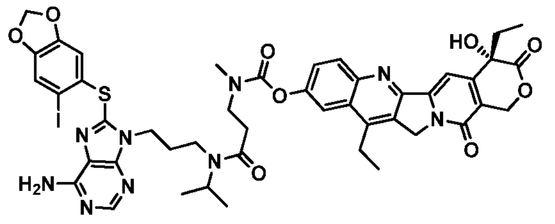


[001950] SDC-TRAP-0376 was synthesized in a similar manner as described for SDC-TRAP-0248, using 8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine as the amine partner.

[001951] ^{1}H NMR (400 MHz, Methanol-*d*$_4$) δ 8.67 – 8.45 (m, 1H), 8.39 – 8.19 (m, 1H), 7.33 – 7.23 (m, 1H), 7.13 – 6.96 (m, 1H), 5.95 (s, 2H), 4.42 – 4.13 (m, 2H), 4.04 (t, *J* = 6.1 Hz, 1H), 3.83 (s, 3H), 3.50 – 3.38 (m, 2H), 2.31 – 2.12 (m, 1H), 2.03 (dt, *J* = 12.8, 4.6 Hz, 1H), 1.31 – 1.20 (m, 3H), 1.09 (d, *J* = 8.3, 6.6 Hz, 3H).ppm; ESMS calculated for $C_{24}H_{24}IN_{11}O_4S$: 689.5; found: 690.5 (M + H$^+$).

[001952] SDC-TRAP-0377

[001953] (S)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (3-((3-(6-amino-8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)propyl)(isopropyl)amino)-3-oxopropyl)(methyl)carbamate

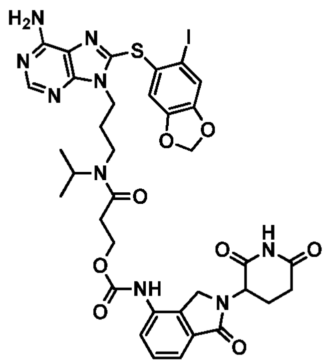


[001954] (R)-4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl (4-nitrophenyl) carbonate (0.1 mmol) was dissolved in DMF (1 mL), followed by the addition of N-(3-(6-amino-8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)propyl)-N-isopropyl-3-(methylamino)propanamide (0.1 mmol) (prepared in similar manner as described for 1-(4-(2-(6-amino-8-((6-bromobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)ethyl)piperidin-1-yl)-3-(methylamino)propan-1-one in the example of SDC-TRAP-0375) and Et_3N (0.2 mmol). The solution was stirred at room temperature for 4 h. Removal of solvents followed by silica gel chromatography purification (CH_2Cl_2/MeOH) afforded the desired product as a white solid.

[001955] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.17 (dd, J = 13.1, 8.6 Hz, 1H), 7.96 (dt, J = 9.4, 7.2 Hz, 1H), 7.84 (td, J = 11.1, 10.3, 2.5 Hz, 1H), 7.57 – 7.42 (m, 2H), 7.23 – 7.11 (m, 1H), 7.02 – 6.82 (m, 1H), 5.95 – 5.82 (m, 2H), 5.48 (d, J = 16.3 Hz, 1H), 5.29 (d, J = 16.2 Hz, 1H), 5.13 (t, J = 8.4 Hz, 2H), 4.28 – 4.08 (m, 3H), 3.83 – 3.71 (m, 1H), 3.64 – 3.51 (m, 1H), 3.21 – 3.05 (m, 7H), 2.70 (tt, J = 29.5, 7.0 Hz, 2H), 2.05 – 1.80 (m, 4H), 1.35 – 1.23 (m, 3H), 1.21 – 1.04 (m, 6H), 0.91 (dd, J = 7.6, 1.5 Hz, 3H).ppm; ESMS calculated for $C_{45}H_{46}IN_9O_9S$: 1015.2; found: 1016.2 (M + H^+).

[001956] SDC-TRAP-0378

[001957] 3-((3-(6-amino-8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)propyl)(isopropyl)amino)-3-oxopropyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate



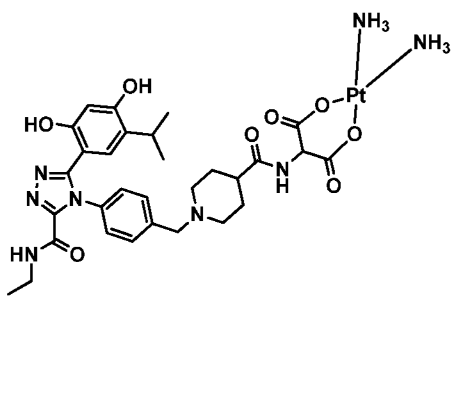
[001958] Preparation of 3-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)oxy)propanoic acid: 4-nitrophenyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate (prepared as illustrated in the example for SDC-TRAP-0245) (1.2 mmol) was added to a round-bottomed flask containing tert-butyl 3-hydroxypropanoate (1.4 mmol), DMF (6 mL) and Et_3N (3.6 mmol) at 22 ^{0}C. The solution was stirred for 3 h, then concentrated under reduced pressure. The resulting crude oil was subjected to silica gel chromatography purification (CH_2Cl_2/MeOH) to afford the desired product as a white solid. The product was then deprotected with HCl (4M in dioxane) to yield the acid 3-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)oxy)propanoic acid.

[001959] SDC-TRAP-0378 was synthesized in a similar manner as described for SDC-TRAP-0252, using 3-(((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamoyl)oxy)propanoic acid as the acid partner and 8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine as the amine partner.

[001960] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.61 (d, J = 4.0 Hz, 1H), 8.30 (dd, J = 8.4, 1.2 Hz, 1H), 8.06 (s, 1H), 7.50 (7.2, 1.2 Hz, 1H), 7.42 – 7.29 (m, 3H), 7.02 (s, 1H), 5.94 (s, 2H), 5.01 (dd, J = 13.2, 5.2 Hz, 1H), 4.37 (s, 2H), 4.29 – 4.17 (m, 3H), 3.66 – 3.59 (m, 2H), 3.31 – 3.23 (m, 2H), 3.13 (q, J = 7.2 Hz, 2H), 2.82 – 2.73 (m, 2H), 2.65 – 2.59 (m, 1H), 2.37 – 2.30 (m, 1H), 2.12 – 2.01 (m, 2H), 1.09 (d, J = 6.4 Hz, 6H) ppm; ESMS calculated for $C_{35}H_{36}IN_9O_8S$: 869.7; found: 870.0 (M + H$^+$).

[001961] SDC-TRAP-0379

[001962] 2-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carboxamido)carboxylate diammineplatinum (II)



[001963] A round-bottomed flask was charged with diethyl 2-((tert-butoxycarbonyl)amino)malonate (0.90 mmol) and TFA (10% in CH_2Cl_2, 10 mL) at 21 ^{0}C, and stirred at the same temperature for 2 h. The solution was concentrated under reduced pressure, then charged with DMF (4 mL), 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl) piperidine-4-carboxylic acid (0.75 mmol), HATU (1.13 mmol), and diisopropyl amine (2.25 mmol) at 21 ^{0}C. The solution was stirred for 2 h, then concentrated under reduced pressure. The resulting crude oil was subjected to silica gel chromatography purification (CH_2Cl_2/MeOH) to afford the desired product diethyl 2-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carboxamido)malonate as a white solid.

[001964] A round-bottomed flask was charged with cisplatin (0.36 mmol), silver sulfate (0.72 mmol) and H_2O (1 mL). The mixture was stirred for 1 h at 21 ^{0}C, then filtered via filter paper.

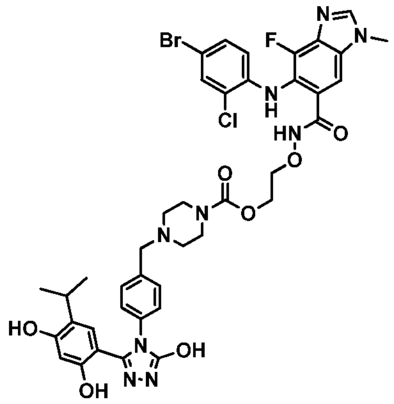
[001965] diethyl 2-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carboxamido)malonate (0.3 mmol) was stirred in a round-bottomed flask containing EtOH (1 mL), H_2O (1 mL) and barium hydroxide (0.78 mmol). The solution was stirred for 30 min in a 70 ^{0}C oil bath, then cooled to 21 ^{0}C, then added to the platinum solution prepared above. The solution was stirred for 16 h at 21 ^{0}C in the dark, then filtered via filter paper. The filtrate was treated with DMF (10 mL), and the resulting precipitate was isolated via vacuum filtration. The precipitate was purified by reverse-phase C18 chromatography (0.1% formic acid in H_2O/0.1% formic acid in MeCN), followed by lyophilizing the desired fractions to yield SDC-TRAP-0379 as a beige solid.

[001966] ^{1}H NMR (400 MHz, Deuterium Oxide) δ 7.27 – 7.24 (m, 3H), 7.12 – 7.10 (m, 3H), 6.84 (s, 1H), 3.19 – 3.16 (m, 1H), 2.98 (q, J = 7.2 Hz, 2H), 2.78 – 2.67 (m, 4H), 2.38 – 2.30 (m, 1H), 1.91 – 1.83 (m, 2H), 1.52 – 1.43 (m, 2H), 0.80 (t, J = 7.2 Hz, 3H), 0.56 (d, J = 0.56 Hz, 3H), 0.07 (d, J = 6.8 Hz, 3H) ppm; ESMS calculated for $C_{30}H_{40}N_8O_8Pt$: 835.8; found: 858.8 ($M + Na^+$).

[001967] SDC-TRAP-0380

[001968] 2-((5-((4-bromo-2-chlorophenyl)amino)-4-fluoro-1-methyl-1H-benzo[d]imidazole-6-carboxamido)oxy)ethyl

4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carboxylate

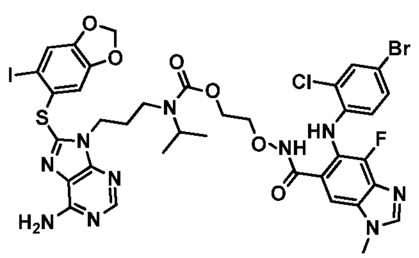


[001969] Compound SDC-TRAP-0380 was synthesized in a similar manner as described for compound SDC-TRAP-0249, using Selumetinib as the alcohol partner and 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol as the amine partner.

[001970] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.41 (d, J = 8.3 Hz, 2H), 7.92 (d, J = 2.2 Hz, 1H), 7.71 (dd, J = 8.5, 2.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.44 – 7.36 (m, 2H), 7.32 – 7.24 (m, 2H), 6.77 (d, J = 10.7 Hz, 1H), 6.29 (d, J = 3.6 Hz, 1H), 4.54 – 4.42 (m, 4H), 4.00 (s, 3H), 3.61 (d, J = 8.3 Hz, 2H), 3.52 – 3.40 (m, 4H), 3.10 – 2.99 (m, 1H), 2.43 (s, 2H), 2.15 (s, 2H), 0.93 (d, J = 6.8 Hz, 6H) ppm; ESMS calculated for $C_{40}H_{40}BrClFN_9O_7$: 893.2; found: 919.9 (M + HCN).

[001971] SDC-TRAP-0381

[001972] 2-((5-((4-bromo-2-chlorophenyl)amino)-4-fluoro-1-methyl-1H-benzo[d]imidazole-6-carboxamido)oxy)ethyl (3-(6-amino-8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9H-purin-9-yl)propyl)(isopropyl)carbamate



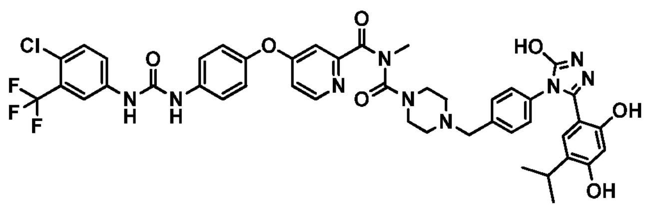
[001973] Compound SDC-TRAP-0381 was synthesized in a similar manner as described for compound SDC-TRAP-0249, using Selumetinib as the alcohol partner and

8-((6-iodobenzo[d][1,3]dioxol-5-yl)thio)-9-(3-(isopropylamino)propyl)-9H-purin-6-amine as the amine partner.

[001974] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.28 – 8.22 (m, 1H), 8.08 (d, J = 4.0 Hz, 1H), 8.02 – 7.96 (m, 1H), 7.71 (d, J = 2.7 Hz, 1H), 7.53 (dt, J = 8.7, 2.2 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.25 – 7.19 (m, 1H), 6.89 (s, 1H), 5.86 (s, 2H), 4.34 (s, 4H), 4.25 – 4.08 (m, 3H), 3.87 (s, 3H), 3.29 – 3.22 (m, 2H), 2.10 – 2.05 (m, 2H), 1.02 (d, J = 7.0 Hz, 6H) ppm; ESMS calculated for $C_{36}H_{34}BrClFIN_{10}O_6S$: 996.0; found: 1022.7 (M + HCN).

[001975] SDC-TRAP-0382

[001976] N-(4-(4-(3-(4-chloro-3-(trifluoromethyl)phenyl)ureido)phenoxy)picolinoyl)-4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)-N-methylpiperazine-1-carboxamide

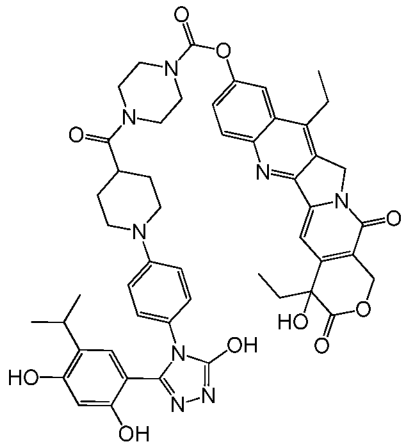


[001977] A round-bottomed flask was charged with Sorafenib (0.63 mmol), Et_3N (22 mmol) and THF (20 mL). The mixture was stirred in a 60 ^{0}C oil bath for 8 min, the a solution of triphosgene (0.67 mmol) in THF (10 mL) was added to it. The solution was then stirred at 21 ^{0}C for 1 h, then concentrated under reduced pressure. To the crude solid was added THF (1.5 mL), MeCN (1.5 mL), Et_3N (0.82 mmol) and stirred in a 50 ^{0}C oil bath for 16 h. MeOH (10 mL) and phosphate-buffered saline (pH 7.4) (100 mL) were added to the mixture, and the solution was extracted with EtOAc (20 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude solid was subjected to silica gel chromatography purification (CH_2Cl_2/MeOH) to afford the desired product as a pale-yellow solid.

[001978] ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.44 (d, J = 8.0 Hz, 1H), 7.66 – 7.54 (m, 1H), 7.48 (d, J = 8.0 Hz, 3H), 7.37 – 7.26 (m, 3H), 7.21 (d, J = 2.6 Hz, 1H), 7.12 – 6.99 (m, 2H), 6.99 – 6.81 (m, 2H), 6.75 (d, J = 1.4 Hz, 1H), 6.65 (dd, J = 5.6, 2.6 Hz, 1H), 6.30 (s, 1H), 3.71 – 3.48 (m, 6H), 3.37 (s, 3H), 3.04 (pd, J = 6.9, 4.3 Hz, 1H), 2.69 – 2.45 (m, 4H), 0.91 (d, J = 8.0 Hz, 6H) pm; ESMS calculated for $C_{44}H_{41}ClF_3N_9O_7$: 899.3; found: 856.0 (M – C_3H_7).

[001979] SDC-TRAP-0413

[001980] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperidine-4-carbonyl)piperazine-1-carboxylate

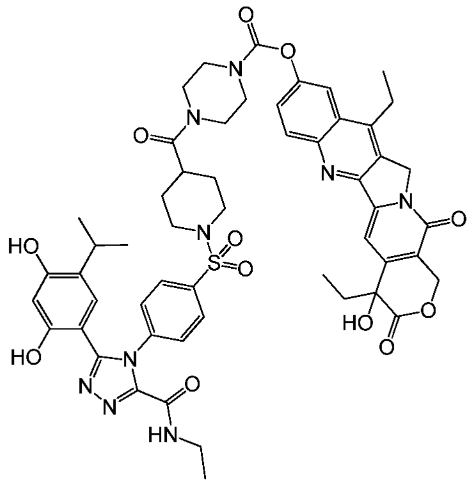


[001981] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 9.59 (s, 1H), 9.47 (s, 1H), 8.19 (d, J = 9.1 Hz, 1H), 8.02 (d, J = 2.5 Hz, 1H), 7.69 (dd, J = 9.2, 2.5 Hz, 1H), 7.33 (s, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.93 (d, J = 8.7 Hz, 2H), 6.78 (s, 1H), 6.53 (s, 1H), 6.28 (s, 1H), 5.44 (s, 2H), 5.33 (s, 2H), 3.80 – 3.50(m, 10H), 3.19 (q, J = 7.6 Hz, 2H), 2.98 (p, J = 6.9 Hz, 1H), 2.92 – 2.72 (m, 3H), 1.88 (hept, J = 7.2 Hz, 2H), 1.71 (q, J = 11.9, 10.3 Hz, 4H), 1.30 (t, J = 7.6 Hz, 3H), 0.93 (dd, J = 26.1, 7.1 Hz, 9H).

[001982] ESMS calculated for $C_{50}H_{52}N_8O_{10}$: 924.38; Found 925.2 $(M+H)^+$.

[001983] SDC-TRAP-0383

[001984] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(1-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperidine-4-carbonyl)piperazine-1-carboxylate

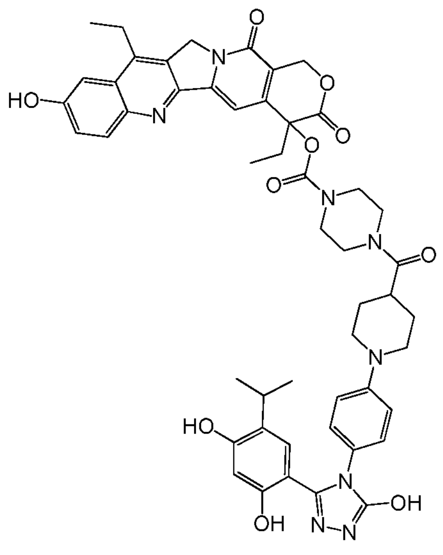


[001985] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (d, J = 2.0 Hz, 1H), 9.71 (s, 1H), 9.07 (t, J = 5.6 Hz, 1H), 8.18 (dd, J = 9.1, 1.6 Hz, 1H), 8.01 (s, 1H), 7.78 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 9.3 Hz, 1H), 7.60 – 7.53 (m, 2H), 7.32 (d, J = 2.2 Hz, 1H), 6.74 (s, 1H), 6.53 (d, J = 1.9 Hz, 1H), 6.28 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 3.71 - 3.59 (m, 4H), 3.27 – 3.15 (m, 4H), 3.03 – 2.93 (m, 1H), 2.69-2.52 (m, 2H), 2.53 – 2.47 (m, 4H), 2.39 (t, J = 12.0 Hz, 2H), 1.87 (p, J = 7.2 Hz, 2H), 1.78 (d, J = 13.3 Hz, 3H), 1.62 (q, J = 11.7, 11.3 Hz, 2H), 1.37 – 1.24 (m, 3H), 1.22 – 1.03 (m, 3H), 1.02 – 0.84 (m, 9H).

[001986] ESMS calculated for $C_{53}H_{57}N_9O_{12}S$: 1043.38; Found 1044.2 $(M+H)^+$

[001987] SDC-TRAP-0384

[001988] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperidine-4-carbonyl)piperazine-1-carboxylate

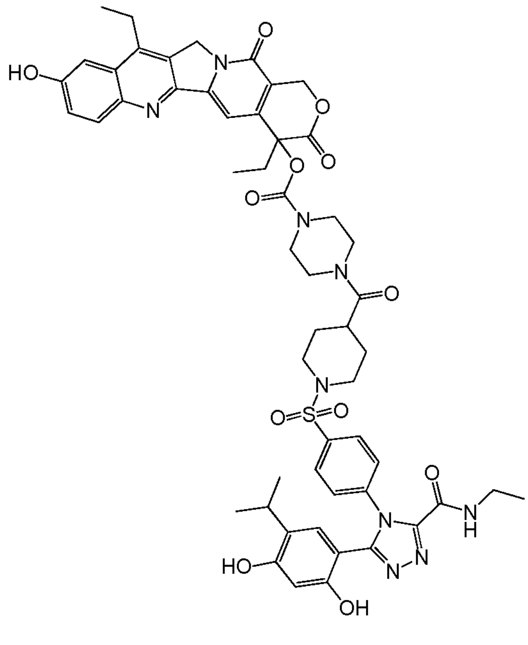


[001989] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 10.39 (s, 1H), 9.79 (s, 1H), 9.55 (s, 1H), 8.09 (s, 1H), 7.99 (d, J = 9.7 Hz, 1H), 7.45 (d, J = 5.7 Hz, 2H), 7.27 (s, 1H), 7.06 – 6.85 (m, 5H), 6.76 (s, 1H), 6.35 (s, 1H), 5.45 (d, J = 3.6 Hz, 2H), 5.29 (s, 2H), 3.72 - 3.35 (m, 6H), 3.08 (q, J = 7.6 Hz, 2H), 2.98 – 2.75 (m, 5H), 2.16 (q, J = 7.3 Hz, 2H), 1.75-1.55 (m, 4H), 1.29 (t, J = 7.6 Hz, 4H), 0.93 (dd, J = 15.4, 7.6 Hz, 9H).

[001990] ESMS calculated for $C_{50}H_{52}N_8O_{10}$: 924.38; Found 925.2 $(M+H)^+$.

[001991] SDC-TRAP-0385

[001992] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(1-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperidine-4-carbonyl)piperazine-1-carboxylate

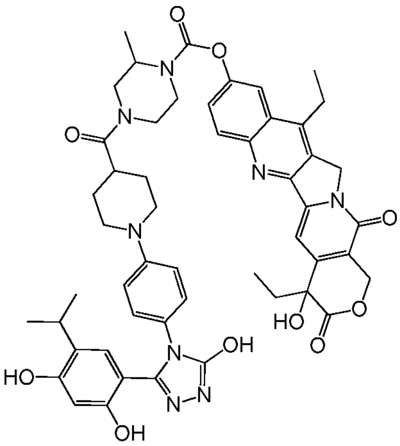


[001993] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H), 9.89 (d, J = 17.1 Hz, 1H), 9.71 (d, J = 17.3 Hz, 1H), 9.05 (s, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.82 – 7.70 (m, 2H), 7.61 – 7.49 (m, 2H), 7.40 (d, J = 7.3 Hz, 2H), 6.97 (s, 1H), 6.74 (d, J = 12.9 Hz, 1H), 6.27 (d, J = 15.2 Hz, 1H), 5.45 (s, 2H), 5.28 (s, 2H), 3.70 – 3.62 (m, 6H), 3.42 (s, 2H), 3.24 – 3.08(m, 5H), 2.96 (s, 1H), 2.44 – 2.31 (m, 3H), 2.15 (q, J = 7.5 Hz, 2H), 1.74– 1.55 (m, 4H), 1.29 (d, J = 7.7 Hz, 3H), 1.12 – 0.86 (m, 12H).

[001994] ESMS calculated for $C_{53}H_{57}N_9O_{12}S$: 1043.38; Found 1044.2 $(M+H)^+$.

[001995] SDC-TRAP-0386

[001996] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperidine-4-carbonyl)-2-methylpiperazine-1-carboxylate

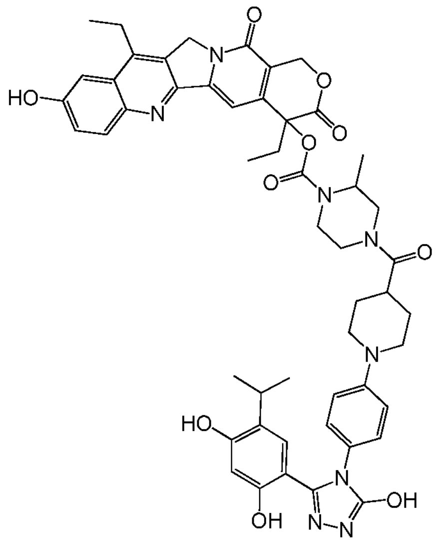


[001997] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.85 (s, 1H), 9.59 (s, 1H), 9.47 (s, 1H), 8.19 (d, J = 9.1 Hz, 1H), 8.02 (s, 1H), 7.69 (dd, J = 9.1, 2.5 Hz, 1H), 7.33 (s, 1H), 7.02 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.78 (s, 1H), 6.53 (s, 1H), 6.28 (s, 1H), 5.44 (s, 2H), 5.34 (s, 2H), 4.49 (s, 1H), 4.31 (t, J = 14.7 Hz, 2H), 4.11 - 3.89 (m, 3H), 3.77 (d, J = 11.3 Hz, 2H), 3.20 (q, J = 7.8 Hz, 2H), 2.96 -2.80 (m, 6H), 1.86 (tt, J = 18.1, 9.2 Hz, 3H), 1.71 (s, 4H), 1.30 (t, J = 7.5 Hz, 3H), 0.93-0.87 (m, 9H).

[001998] ESMS calculated for $C_{51}H_{54}N_8O_{10}$: 938.40; Found 939.2 $(M+H)^+$.

[001999] SDC-TRAP-0387

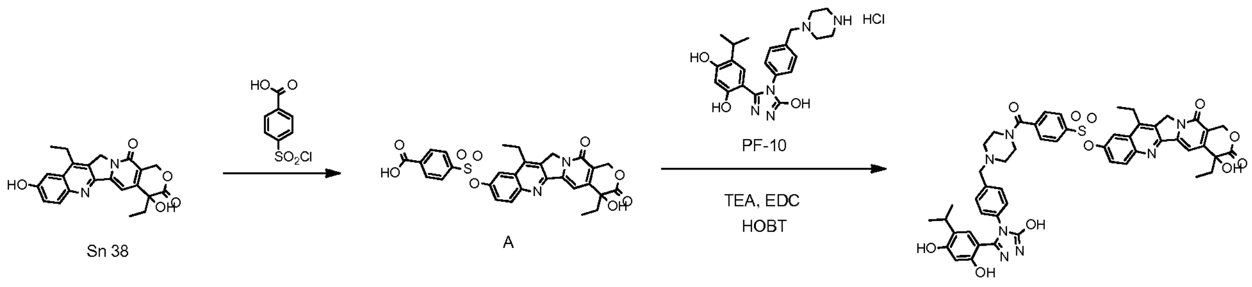
[002000] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperidine-4-carbonyl)-2-methylpiperazine-1-carboxylate



[002001] ESMS calculated for $C_{51}H_{54}N_8O_{10}$: 938.40; Found 939.2 $(M+H)^+$.

[002002] SDC-TRAP-0388

[002003] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carbonyl)benzenesulfonate



[002004] To a stirred suspension of SN 38 (200 mg, 0.5mmol) in THF (15mL) was dropped 1N NaOH to pH 9. A solution of 4-chlorosulfonylbenzoic acid (220mg, 1.0mmol) in THF 5mL was added slowly to the above solution. The pH value of the mixture was kept at 8-9 by the addition of 1N NaOH. The reaction mixture was stirring at room temperature for 1h.Then the solution was brought to pH 7 by the addition 1.0 N HCl and the THF was removed in vacuo. The product precipitated when the aqueous solution was acidified with 1N HCl to pH 1. The formed product A was collected, washed small amount water and dried under vacuum overnight. Yield: 205mg, (72%)

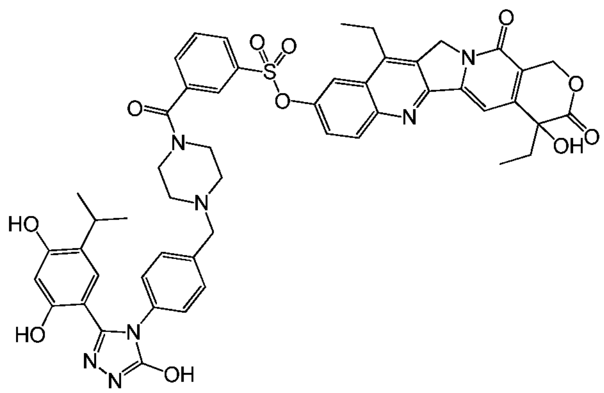
[002005] To a solution of PF-10 (120 mg, 0.24 mmol) and acid A (140 mg, 0.24) in DMF (4mL), was added TEA (100ul, 0.8mmol), EDC (80mg, 0.4mmol) and 20 mg HOBT. The mixture was stirred for 5h at RT. The resulting reaction mixture was poured into ice- water (35 mL) and precipitated product was collected and washed with water. The filtered material was purified by flash chromatography (hexane-EtOAc 1:1 and EtOAc-MeOH 95:5) gave SDC-TRAP-0388 (yield: 125mg, 54%).

[002006] ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.92 (s, 1H), 9.58 (s, 1H), 9.38 (s, 1H), 8.20 (d, *J* = 9.2 Hz, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 7.77 (dd, *J* = 9.1, 2.5 Hz, 1H), 7.66 – 7.64 (m, 3H), 7.32-7.30 (m, 3H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.78 (s, 1H), 6.53 (s, 1H), 6.25 (s, 1H), 5.43 (s, 2H), 5.31(s, 2H), 3.62 - 3.46 (m, 4H), 3.25 (q, *J* = 7.7 Hz, 2H), 3.02-2.94 (m, 3H), 2.42-2.32(m, 4H), 1.86 (hept, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.5 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 6H), 0.86 (t, *J* = 7.3 Hz, 3H).

[002007] ESMS calculated for $C_{51}H_{49}N_7O_{11}S$: 967.32; Found: 968.0 $(M+H)^+$.

[002008] SDC-TRAP-0389

[002009] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 3-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carbonyl)benzenesulfonate

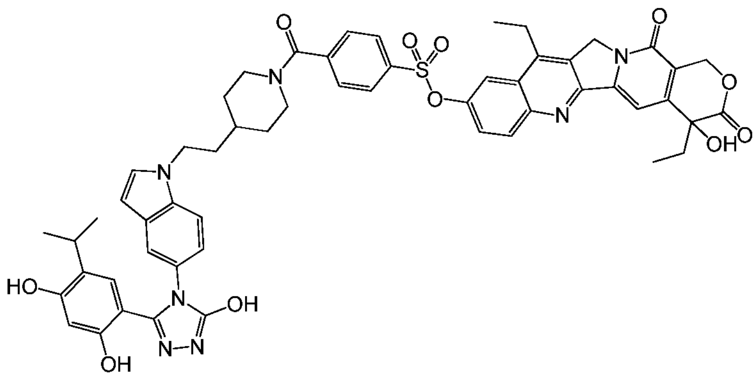


[002010] ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 11.92 (s, 1H), 9.58 (s, 1H), 9.39 (s, 1H), 8.20 (d, *J* = 9.2 Hz, 1H), 8.00 (d, *J* = 2.4 Hz, 1H), 7.84-7.73 (m, 3H),7.60-7.58(m, 1H), 7.32(s,1H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.76 (s, 1H), 6.50 (s, 1H), 6.25 (s, 1H), 5.41 (s, 2H), 5.31 (s, 2H), 3.54-3.39 (m, 4H), 3.06-2.94 (m, 4H), 2.36-2.12(m, 4H), 1.81 (hept, *J* = 7.1 Hz, 2H), 1.10 (t, *J* = 7.5 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 6H), 0.82 (t, *J* = 7.3 Hz, 3H).

[002011] ESMS calculated for $C_{51}H_{49}N_7O_{11}S$: 967.32; Found: 968.0 $(M+H)^+$.

[002012] SDC-TRAP-0390

[002013] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carbonyl)benzenesulfonate

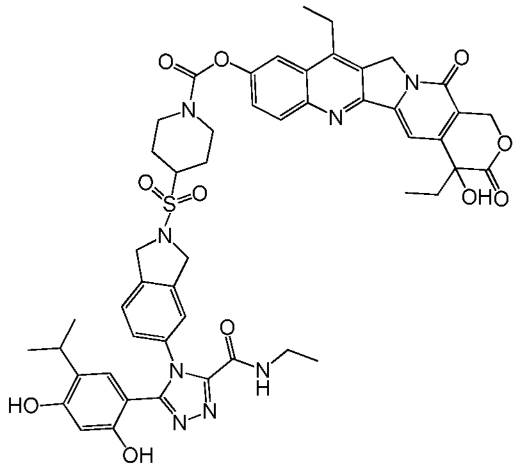


[002014] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.88 (s, 1H), 9.54 (s, 1H), 9.50 (s, 1H), 8.20 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 2.4 Hz, 2H), 7.78 (dd, J = 9.1, 2.5 Hz, 1H), 7.65 – 7.60 (m, 3H), 7.48-7.43(m, 3H), 7.32(s, 1H), 6.95-6.92(m, 1H), 6.68(s, 1H), 6.53 (s, 1H), 6.43 (s, 1H), 6.23 (s, 1H), 5.43 (s, 2H), 5.31 (s, 2H), 4.22-4.20 (m, 2H), 3.04-2.75 (m, 4H), 1.89-1.82 (m, 3H), 1.73-1.62(m, 3H), 1.10 (t, J = 7.5 Hz, 3H),), 0.83 (t, J = 7.3 Hz, 3H). 0.78 (d, J = 6.9 Hz, 6H),

[002015] ESMS calculated for $C_{55}H_{53}N_7O_{11}S$: 1019.35; Found: 1020.0 $(M+H)^+$.

[002016] SDC-TRAP-0391

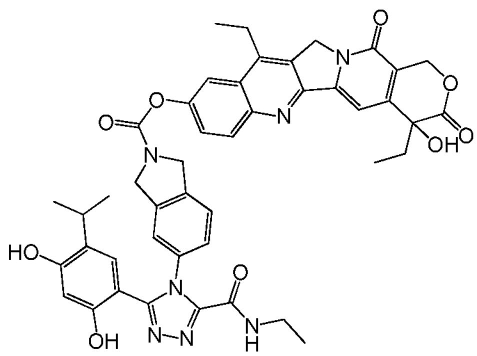
[002017] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)isoindolin-2-yl)sulfonyl)piperidine-1-carboxylate



[002018] ESMS calculated for $C_{50}H_{52}N_8O_{11}S$: 972.35; Found 973.2 $(M+H)^+$.

[002019] SDC-TRAP-0392

[002020] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)isoindoline-2-carboxylate

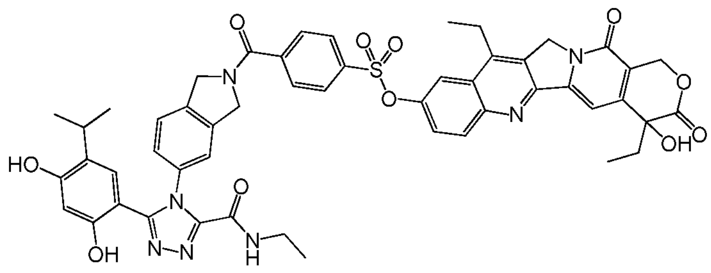


[002021] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (t, J = 5.4 Hz, 1H), 9.72 (d, J = 6.9 Hz, 1H), 9.01 (q, J = 5.5 Hz, 1H), 8.21 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 5.7 Hz, 1H), 7.75 (q, J = 8.5, 6.8 Hz, 1H), 7.52 – 7.38 (m, 2H), 7.36 – 7.28 (m, 2H), 6.68 (d, J = 7.1 Hz, 1H), 6.52 (dd, J = 7.0, 3.5 Hz, 1H), 6.33 (t, J = 5.1 Hz, 1H), 5.43 (d, J = 7.7 Hz, 2H), 5.34 (t, J = 5.2 Hz, 2H), 5.06 – 4.92 (m, 2H), 4.80 - 4.73 (m, 2H), 3.24 – 3.11 (m, 4H), 2.97 (d, J = 7.7 Hz, 1H), 1.88 (p, J = 8.6, 7.6 Hz, 2H), 1.30 (dd, J = 10.8, 5.8 Hz, 3H), 1.06 (dt, J = 10.9, 7.3 Hz, 3H), 0.89 (td, J = 10.7, 10.1, 5.2 Hz, 9H).

[002022] ESMS calculated for $C_{45}H_{43}N_7O_9$: 825.31; Found 826.2 $(M+H)^+$.

[002023] SDC-TRAP-0393

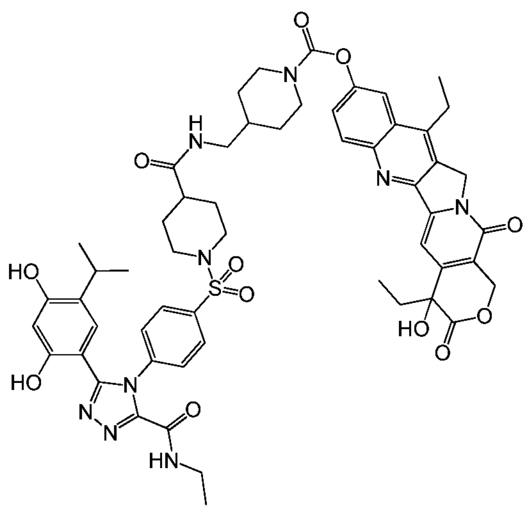
[002024] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)isoindoline-2-carbonyl)benzenesulfonate



[002025] ESMS calculated for $C_{51}H_{47}N_7O_{11}S$: 965.31; Found 966.2 $(M+H)^+$.

[002026] SDC-TRAP-0394

[002027] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((1-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperidine-4-carboxamido)methyl)piperidine-1-carboxylate



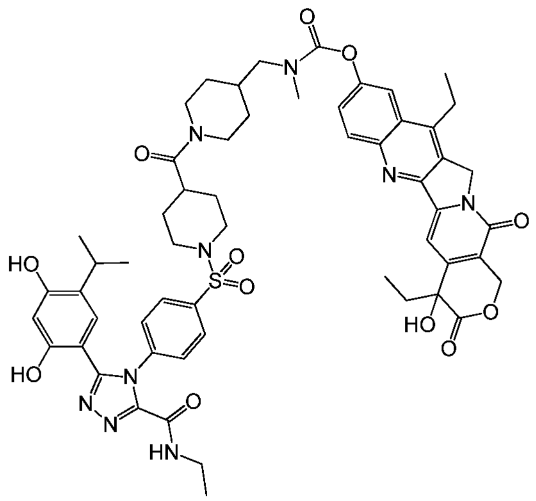
[002028] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.99 (s, 1H), 9.73 (s, 1H), 9.06 (t, J = 5.9 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.97 (d, J = 2.5 Hz, 1H), 7.90 (t, J = 5.8 Hz, 1H), 7.82 – 7.74 (m, 2H), 7.65 (dd, J = 9.1, 2.5 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.32 (s, 1H), 6.75 (s, 1H), 6.54 (s, 1H), 6.29 (s, 1H), 5.44 (s, 2H), 5.33 (s, 2H), 4.24 (d, J = 13.0 Hz, 1H), 3.71 (d, J = 11.8 Hz, 2H), 3.25 – 3.13 (m, 4H), 3.08 – 2.86 (m, 5H), 2.36 – 2.25 (m, 2H), 2.15 (t, J = 11.6 Hz, 1H), 1.84–

1.53 (m, 8H), 1.30 (dd, J = 10.8, 5.8 Hz, 3H), 1.06 (dt, J = 10.9, 7.3 Hz, 3H), 0.97 – 0.84 (m, 9H).

[002029] ESMS calculated for $C_{55}H_{61}N_9O_{12}S$: 1071.42; Found 1072.2 $(M+H)^+$.

[002030] SDC-TRAP-0395

[002031] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ((1-(1-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperidine-4-carbonyl)piperidin-4-yl)methyl)(methyl)carbamate

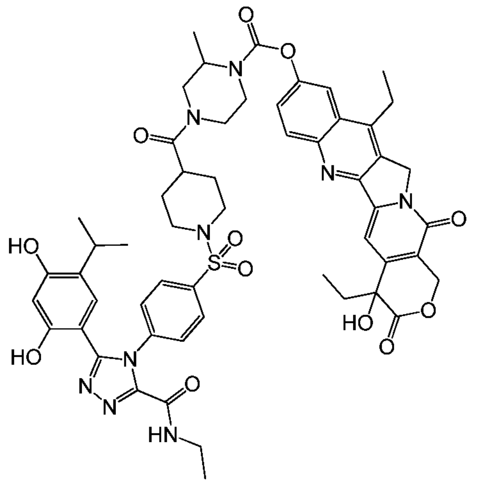


[002032] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.90 (d, J = 2.2 Hz, 1H), 9.71 (s, 1H), 9.11 – 9.03 (m, 1H), 8.17 (d, J = 9.1 Hz, 1H), 7.96 (dd, J = 13.5, 2.4 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.64 (ddd, J = 8.6, 5.8, 2.5 Hz, 1H), 7.55 (d, J = 8.1 Hz, 2H), 7.32 (s, 1H), 6.75 (d, J = 4.4 Hz, 1H), 6.54 (s, 1H), 6.27 (s, 1H), 5.44 (s, 2H), 5.33 (s, 2H), 4.40 (d, J = 15.1 Hz, 1H), 3.95 (s, 1H), 3.68 (d, J = 10.3 Hz, 2H), 3.40– 3.11 (m, 7H), 2.99 (d, J = 11.2 Hz, 4H), 2.66 – 2.53 (m, 2H), 2.34 (d, J = 12.3 Hz, 2H), 1.87 (hept, J = 7.2 Hz, 2H), 1.70 (d, J = 13.7 Hz, 4H), 1.58 (d, J = 12.6 Hz, 2H), 1.33 – 1.24 (m, 3H), 1.22 – 1.01 (m, 3H), 0.98 – 0.84 (m, 9H).

[002033] ESMS calculated for $C_{56}H_{63}N_9O_{12}S$: 1085.43; Found 1086.2 $(M+H)^+$.

[002034] SDC-TRAP-0396

[002035] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(1-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperidine-4-carbonyl)-2-methylpiperazine-1-carboxylate

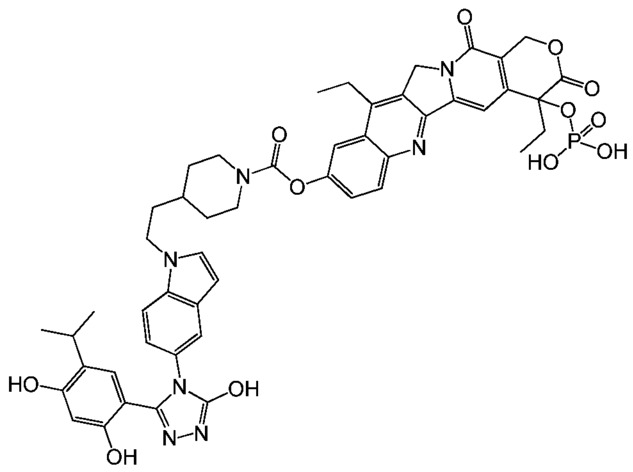


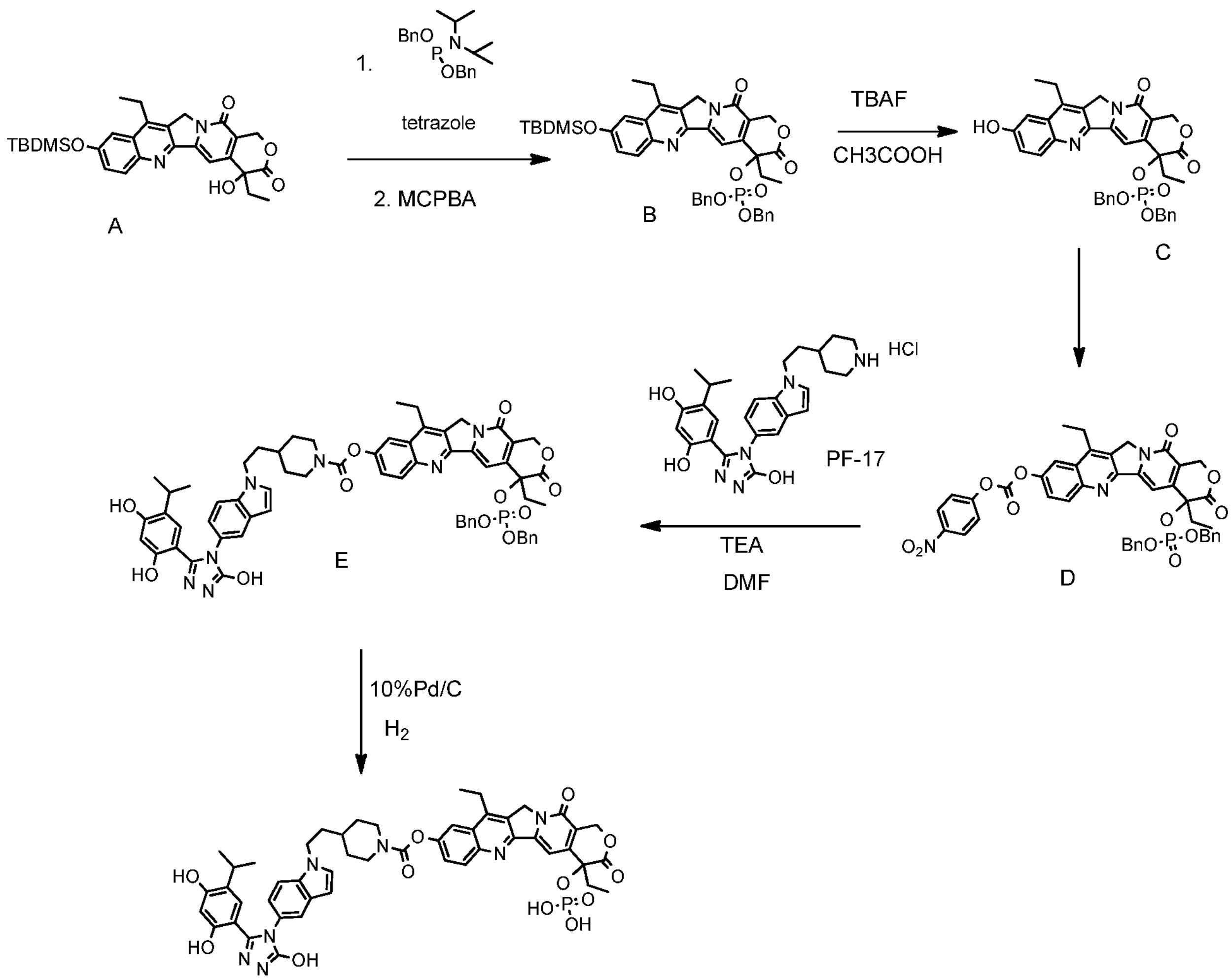
[002036] ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (s, 1H), 9.49 (s1H), 8.84 (s1H), 7.94 (d, J = 7.1 Hz, 1H), 7.76 (s, 1H), 7.54 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 9.1 Hz, 1H), 7.33 (d, J = 8.3 Hz, 2H), 7.08 (s, 1H), 6.50 (s, 1H), 6.30 (s, 1H), 6.05 (s, 1H), 5.20 (s, 2H), 5.09 (s, 2H), 4.06 (s, 1H), 3.80- 3.06 (m, 4H), 2.96 (s, 3H), 2.81 - 2.73 (m, 4H), 1.62 - 1.05 (m, 7H), 0.99 (s, 3H), 0.93 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H), 0.71 -0.64 (m, 9H).

[002037] ESMS calculated for $C_{54}H_{59}N_9O_{12}S$: 1057.40; Found 1058.2 $(M+H)^+$.

[002038] SDC-TRAP-0397

[002039] 4,11-diethyl-3,14-dioxo-4-(phosphonooxy)-3,4,12,14-tetrahydro-1H-pyrano[3',4': 6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate





SDC-TRAP-0397

[002040] A solution of 10-O-tert-butyldimethylsilyl-SN-38 A (510mg, 1.0mmol), 1-*H*-tetrazole (140mg, 2.0mmol), dibenzyl diisopropyl phosphoramidite (625mg, 1.8mmol) in CH_2Cl_2 (10 mL) was stirred at RT under nitrogen for 1h. The mixture was then cooled to 0 °C and a solution of m-chloroperoxybenzoic acid (350 mg, 77-77%w/w) in CH2C12 (3mL) was added, maintaining the temperature at 0°C. The resulting mixture was allowed to warm to RT, diluted with CH_2Cl_2 (20 mL) and the organic layer was washed with aqueous sodium metabisulfite and sodium bicarbonate and dried over $MgSO_4$ .The solvent was evaporated and crude product was purified by flash chromatography (Hexane/EtOAc gradient elution 3:1 – 1:1), to obtain compound B (yield: 720mg, 93.8%)

[002041] Compound B (720 mg, 0.93mmol) was dissolved in CH_2Cl_2 (30mL) and treated with and acetic acid (0.3mL, 5mmol) and 1M solution of tetrabutylammonium fluoride in THF (2.5mL, 2.5mmol). The reaction mixture was stirred for 1h, diluted with CH_2Cl_2 (50mL), washed with brine and water and dried over $MgSO_4$ The solvent was evaporated and crude product was purified by flash chromatography (Hexane/EtOAc gradient elution) to obtain compound C, (yield: 570mg, 94.0%)

[002042] To a solution of compound C (560mg, 0.85mmol) in CH_2Cl_2 (35mL) was added p-nitrophenyl chloroformate (205mg, 1.0mmol) and DIPEA (130mg, 1.0mmol). The reaction mixture was stirred at RT for 1h, diluted with CH_2Cl_2 (50mL), washed with water and brine and dried over $MgSO_4$ .The product was purified by flash chromatography, eluting with EtOAc to afford compound D as a yellow solid (yield: 570mg, 94.0%)

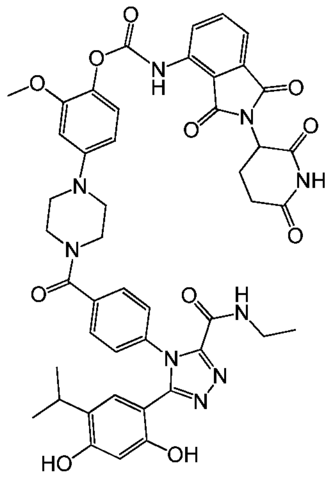
[002043] To a stirred solution of amine FP-17.HCl (350mg, 0.7mmol) and carbamate D (560mg, 0.69mmol) in anhydrous DMF (10 mL) was added TEA (200mg, 2.0mmol). The reaction mixture was stirring at room temperature for 1h.The resulting reaction mixture was poured into ice- water (50 mL) and precipitated product was collected and washed with water. The filtered material was purified by flash chromatography (hexane-EtOAC 1:1 and EtOAc) gave compound E (yield: 450mg, 58%).

[002044] Compound E (400mg,0.35mmol) was hydrogenated in MeOH-EtOAc (50mL, 1:1) using Pd/C (10%, dry, 20mg) and H_2 balloon at 1 atm at room temperature for 2hr. 10%Pd/C was filtered off through a pad of celite and the mother liquid was concentrated to give SDC-TRAP-0397 as yellow solid (yield: 320mg,, 95%).

[002045] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.90 (s, 1H), 11.47 (s, 2H), 9.53 (s, 2H), 8.19 (d, J = 9.1 Hz, 1H), 7.98 (d, J = 2.6 Hz, 1H), 7.65 (dd, J = 9.2, 2.5 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.33 (s, 1H), 6.95 (dd, J = 8.7, 2.1 Hz, 1H), 6.70 (s, 1H), 6.45 (d, J = 3.1 Hz, 1H), 6.24 (s, 1H), 5.36 (d, J = 9.9 Hz, 4H), 4.26 (q, J = 13.2, 10.2 Hz, 3H), 4.03 (q, J = 7.2 Hz, 2H), 3.19 (q, J = 7.6 Hz, 2H), 3.02 (d, J = 13.3 Hz, 1H), 2.89 (dq, J = 17.8, 11.1, 9.0 Hz, 2H), 2.13 (d, J = 8.1 Hz, 2H), 1.87 – 1.71 (m, 4H), 1.49 (s, 1H), 1.23 (dt, J = 43.8, 7.3 Hz, 7H), 0.79 (dd, J = 15.0, 7.1 Hz, 9H): ESMS calculated for $C_{49}H_{50}N_7O_{12}P$: 959.33; Found 960.2 $(M+H)^+$.

[002046] SDC-TRAP-0398

[002047] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperazin-1-yl)-2-methoxyphenyl (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)carbamate

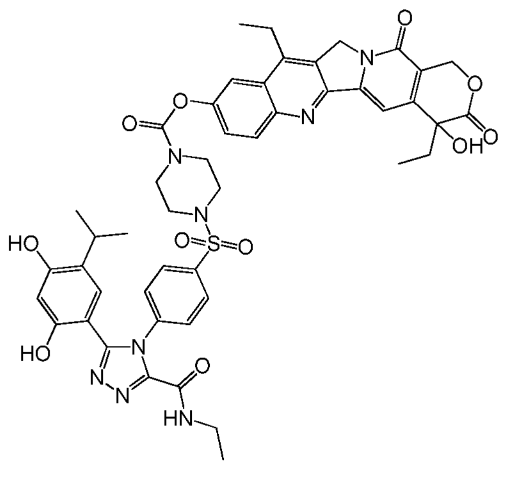


[002048] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 10.23 (s, 1H), 9.74 (s, 1H), 9.48 (s, 1H), 9.08 – 8.99 (m, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.88 (t, J = 8.0 Hz, 1H), 7.65 (d, J = 7.4 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 13.6 Hz, 2H), 6.55 (dd, J = 9.3, 2.7 Hz, 1H), 6.33 (s, 1H), 5.18 (dd, J = 12.7, 5.5 Hz, 1H), 3.80 (s, 3H), 3.37 – 3.11 (m, 6H), 2.94 (dt, J = 25.2, 9.4 Hz, 2H), 2.65-2.51 (m, 1H), 2.08 (d, J = 12.4 Hz, 1H), 1.12 (dt, J = 44.2, 7.1 Hz, 3H), 0.92 (d, J = 6.8 Hz, 6H).

[002049] ESMS calculated for $C_{46}H_{46}N_9O_{11}$: 899.32; Found 900.2 $(M+H)^+$.

[002050] SDC-TRAP-0399

[002051] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperazine-1-carboxylate

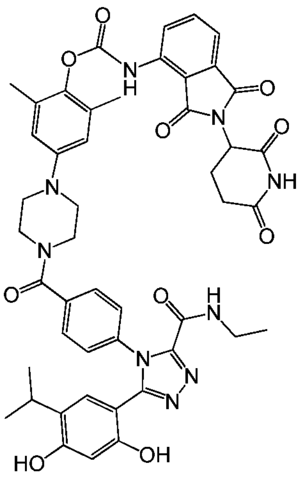


[002052] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.10 (s, 1H), 9.76 (s, 1H), 9.08 (t, J = 5.9 Hz, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 2.6 Hz, 1H), 7.88 – 7.80 (m, 2H), 7.64 (dd, J = 8.8, 2.3 Hz, 3H), 7.31 (s, 1H), 6.69 (s, 1H), 6.53 (s, 1H), 6.32 (s, 1H), 5.43 (s, 2H), 5.32 (s, 2H), 3.78 (s, 2H), 3.59 (s, 2H), 3.17 - 3.07 (m, 6H), 2.95 (p, J = 6.8 Hz, 1H), 1.86 (hept, J = 7.1 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H), 1.05 (t, J = 7.1 Hz, 3H), 0.94 – 0.78 (m, 9H).

[002053] ESMS calculated for $C_{47}H_{48}N_8O_{11}S$: 932.32; Found 933.2 $(M+H)^+$.

[002054] SDC-TRAP-0400

[002055] 4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperazin-1-yl)-2,6-dimethylphenyl (2-(2,6-dioxopiperidin-3-yl)-1,3-dioxoisoindolin-4-yl)carbamate

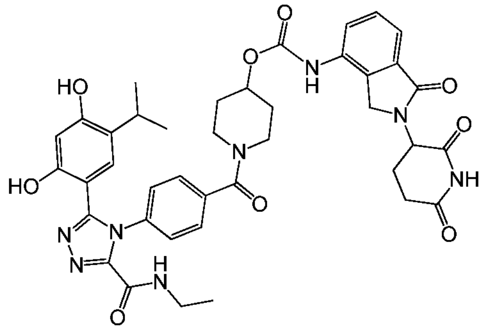


[002056] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.18 (s, 1H), 10.22 (s, 1H), 9.74 (s, 1H), 9.69 (s, 1H), 9.03 (t, J = 5.9 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 8.4, 7.3 Hz, 1H), 7.67 (d, J = 7.3 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.46 – 7.38 (m, 2H), 6.74 (d, J = 14.6 Hz, 3H), 6.33 (s, 1H), 5.17 (dd, J = 12.8, 5.4 Hz, 1H), 3.48 (s, 2H), 3.26 – 3.14 (m, 6H), 3.02 – 2.84 (m, 2H), 2.67 – 2.51 (m, 2H), 2.15 (s, 6H), 1.07 (t, J = 7.2 Hz, 3H), 0.97 – 0.80 (m, 6H).

[002057] ESMS calculated for $C_{47}H_{47}N_9O_{11}$: 897.34; Found 898.2 $(M+H)^+$.

[002058] SDC-TRAP-0401

[002059] 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzoyl)piperidin-4-yl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate

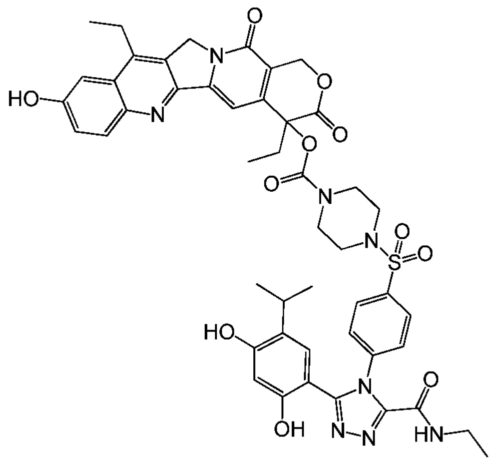


[002060] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.02 (s, 1H), 10.27 (s, 1H), 9.74 (s, 1H), 9.60 (s, 1H), 9.02 (t, J = 5.9 Hz, 1H), 7.76 (dd, J = 6.2, 2.8 Hz, 1H), 7.48 (t, J = 6.7 Hz, 4H), 7.41 (d, J = 8.2 Hz, 2H), 6.69 (s, 1H), 6.32 (s, 1H), 5.14 (dd, J = 13.2, 5.2 Hz, 1H), 4.94 (p, J = 4.8 Hz, 1H), 4.40 (q, J = 17.6 Hz, 2H), 3.18 (p, J = 6.9 Hz, 3H), 2.92 (ddd, J = 17.9, 12.7, 6.1 Hz, 2H), 2.65-2.52 (m, 1H), 2.43 – 2.27 (m, 1H), 2.01 (d, J = 17.2 Hz, 2H), 1.63 (s, 2H), 1.05 (t, J = 7.1 Hz, 3H), 0.88 (d, J = 6.7 Hz, 6H).

[002061] ESMS calculated for $C_{40}H_{42}N_8O_9$ 778.31; Found 779.2 $(M+H)^+$.

[002062] SDC-TRAP-0402

[002063] 4,11-diethyl-9-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-4-yl 4-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperazine-1-carboxylate



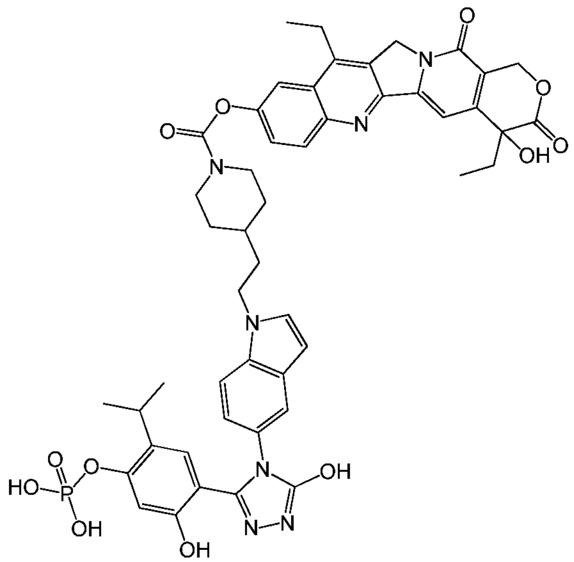
[002064] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (s, 1H), 10.26 (s, 1H), 9.75 (s, 1H), 9.00 (t, J = 5.8 Hz, 1H), 7.97 (d, J = 8.9 Hz, 1H), 7.91 – 7.79 (m, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.40 –

7.31 (m, 2H), 6.96 (s, 1H), 6.62 (s, 1H), 6.31 (s, 1H), 5.42 (d, $J = 3.8$ Hz, 2H), 5.25 (s, 2H), 3.82 (s, 2H), 3.73 (s, 2H), 3.25 - 3.09 (m, 6H), 2.87 (dd, $J = 14.0, 7.1$ Hz, 1H), 2.19 – 2.09 (m, 2H), 1.58 – 1.44 (m, 1H), 1.27 (t, $J = 7.5$ Hz, 3H), 1.05 (t, $J = 7.1$ Hz, 3H), 0.94 – 0.78 (m, 9H).

[002065] ESMS calculated for $C_{47}H_{48}N_8O_{11}S$: 932.32; Found 933.2 $(M+H)^+$.

[002066] SDC-TRAP-0403

[002067] 4,11-diethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl 4-(2-(5-(3-hydroxy-5-(2-hydroxy-5-isopropyl-4-(phosphonooxy)phenyl)-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidine-1-carboxylate

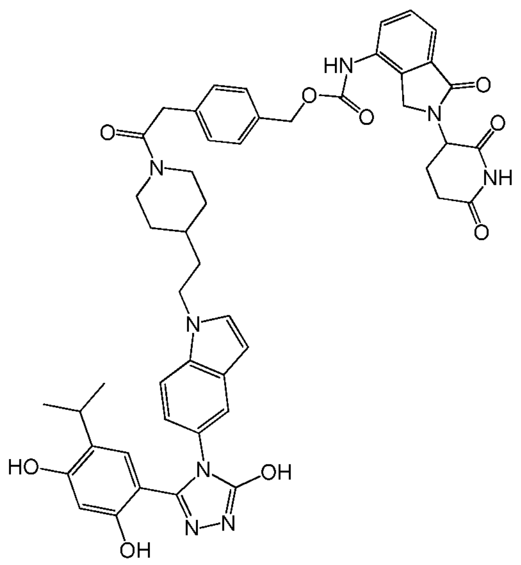


[002068] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 9.85 (s, 1H), 8.15 (d, $J = 9.1$ Hz, 1H), 7.97 (d, $J = 2.5$ Hz, 1H), 7.65 (dd, $J = 9.2, 2.5$ Hz, 1H), 7.54 – 7.42 (m, 3H), 7.32 (s, 1H), 7.00 – 6.88 (m, 2H), 6.84 (s, 1H), 6.51 (s, 1H), 6.45 (d, $J = 3.1$ Hz, 1H), 5.43 (s, 2H), 5.32 (s, 2H), 4.24 (q, $J = 11.1, 9.2$ Hz, 3H), 3.18 (q, $J = 7.6$ Hz, 2H), 3.02 (h, $J = 7.6$ Hz, 2H), 2.87 (s, 1H), 1.95 – 1.70 (m, 6H), 1.50 (d, $J = 11.9$ Hz, 1H), 1.23 (dt, $J = 43.8, 7.3$ Hz, 3H), 0.92 – 0.78 (m, 9H).

[002069] ESMS calculated for $C_{49}H_{50}N_7O_{12}P$: 959.33; Found 960.2 $(M+H)^+$.

[002070] SDC-TRAP-0404

[002071] 4-(2-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-2-oxoethyl)benzyl (2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-4-yl)carbamate

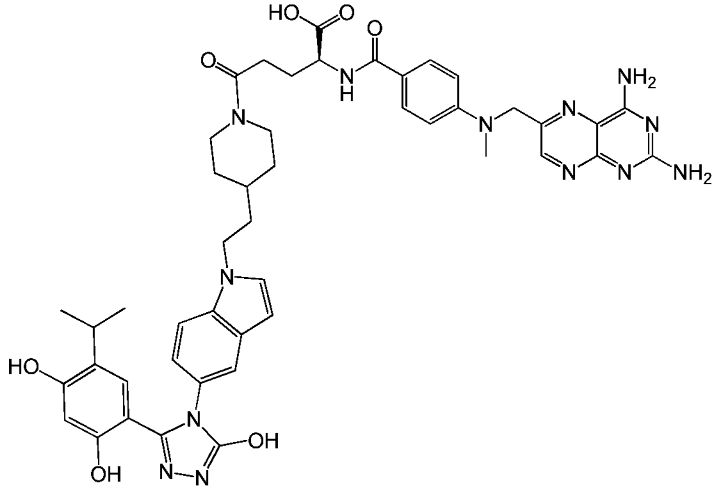


[002072] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 11.02 (s, 1H), 9.66 (s, 1H), 9.57 (s, 1H), 9.51 (s, 1H), 7.87 – 7.75 (m, 1H), 7.55 – 7.33 (m, 7H), 7.23 (d, J = 8.1 Hz, 2H), 6.93 (dd, J = 8.7, 2.0 Hz, 1H), 6.68 (s, 1H), 6.42 (dd, J = 3.1, 0.8 Hz, 1H), 6.23 (s, 1H), 5.14 (s, 2H), 4.39 (q, J = 17.4 Hz, 3H), 4.19 (t, J = 7.2 Hz, 2H), 3.90 (d, J = 13.3 Hz, 1H), 3.76 – 3.63 (m, 2H), 2.89 (dq, J = 13.4, 6.7 Hz, 3H), 2.65 – 2.56 (m, 1H), 2.39 – 2.24 (m, 1H), 2.05 – 1.96 (m, 1H), 1.76 – 1.59 (m, 4H), 1.40 (s, 1H), 0.98 (d, J = 13.8 Hz, 2H), 0.79 (d, J = 6.8 Hz, 6H).

[002073] ESMS calculated for $C_{49}H_{50}N_8O_9$ 894.37; Found 895.2 $(M+H)^+$.

[002074] SDC-TRAP-0405

[002075] (S)-2-(4-(((2,4-diaminopteridin-6-yl)methyl)(methyl)amino)benzamido)-5-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)piperidin-1-yl)-5-oxopentanoic acid

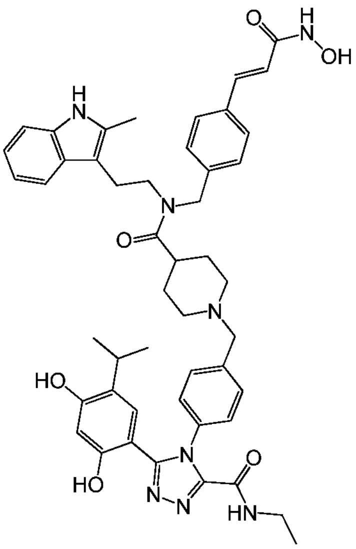


[002076] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 9.69 (s, 1H), 9.51 (s, 1H), 8.56 (s, 1H), 8.14 – 8.07 (m, 1H), 7.70 (d, *J* = 8.6 Hz, 3H), 7.49 – 7.39 (m, 4H), 6.93 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.69 (s, 1H), 6.62 (s, 2H), 6.42 (d, *J* = 3.1 Hz, 1H), 6.24 (s, 1H), 4.77 (s, 2H), 4.37 – 4.22 (m, 1H), 4.17 (d, *J* = 7.4 Hz, 2H), 3.74 (d, *J* = 12.8 Hz, 1H), 3.53 (s, 1H), 3.19 (s, 3H), 2.87 (tt, *J* = 16.1, 9.2 Hz, 2H), 2.42 (t, *J* = 8.2 Hz, 1H), 2.36 (s, 2H), 2.02 (dt, *J* = 13.3, 6.5 Hz, 1H), 1.64 (p, *J* = 8.7, 7.0 Hz, 4H), 1.38 (s, 1H), 1.13 – 0.87 (m, 2H), 0.80 (d, *J* = 6.9 Hz, 6H).

[002077] ESMS calculated for $C_{49}H_{50}N_8O_9$ 897.40; Found 898.3 $(M+H)^+$.

[002078] SDC-TRAP-0406

[002079] (E)-1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)benzyl)-N-(4-(3-(hydroxyamino)-3-oxoprop-1-en-1-yl)benzyl)-N-(2-(2-methyl-1H-indol-3-yl)ethyl)piperidine-4-carboxamide

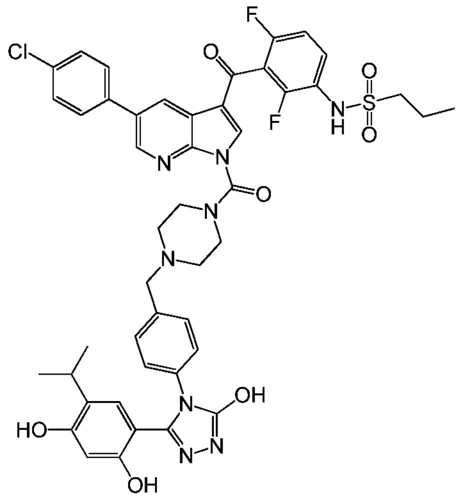


[002080] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (s, 1H), 10.64 (s, 1H), 9.91 (s, 1H), 8.98 (t, *J* = 6.0 Hz, 1H), 7.80 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.64 – 7.45 (m, 3H), 7.43 – 7.19 (m, 7H), 7.03 – 6.87 (m, 2H), 6.67 – 6.55 (m, 1H), 6.37 (q, *J* = 1.3 Hz, 1H), 4.12 (s, 2H), 3.50 (d, *J* = 10.7 Hz, 2H), 3.17 (p, *J* = 7.0 Hz, 2H), 3.01 – 2.78 (m, 7H), 2.60 (d, *J* = 12.0 Hz, 1H), 2.30 (s, 3H), 2.11 (t, *J* = 11.2 Hz, 2H), 1.90 (d, *J* = 12.0 Hz, 2H), 1.68 (q, *J* = 11.1 Hz, 2H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 6H).

[002081] ESMS calculated for $C_{48}H_{54}N_8O_6$ 838.42; Found 839.3 $(M+H)^+$.

[002082] SDC-TRAP-0407

[002083] N-(3-(5-(4-chlorophenyl)-1-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazine-1-carbonyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide

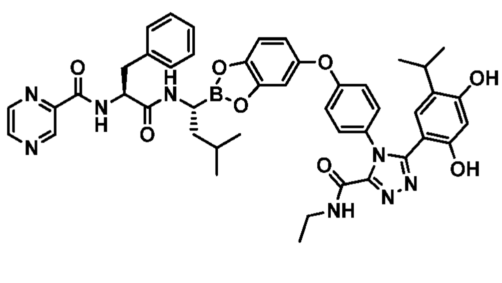


[002084] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H),9.83 (s, 1H), 9.60 (d, J = 9.0 Hz, 1H), 9.39 (d, J = 13.6 Hz, 1H), 8.81 (d, J = 2.2 Hz, 1H), 8.73 (d, J = 2.3 Hz, 1H), 8.53 (s, 1H), 7.89 – 7.79 (m, 2H), 7.68 – 7.56 (m, 3H), 7.37 – 7.27 (m, 3H), 7.14 (t, J = 8.4 Hz, 2H), 6.79 (d, J = 2.7 Hz, 1H), 6.25 (d, J = 9.3 Hz, 1H), 3.68– 3.42 (m, 6H), 3.18 – 3.09 (m, 2H), 3.03 – 2.87 (m, 1H), 1.81 – 1.67 (m, 2H),,), 0.95 - 0.85 (m, 9H).

[002085] ESMS calculated for $C_{46}H_{43}ClF_2N_8O_7S$: 924.26; Found 925.1 $(M+H)^+$.

[002086] SDC-TRAP-0408

[002087] N-((S)-1-(((R)-1-(5-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)benzo[d][1,3,2]dioxaborol-2-yl)-3-methylbutyl)amino)-1-oxo-3-phenylpropan-2-yl)pyrazine-2-carboxamide

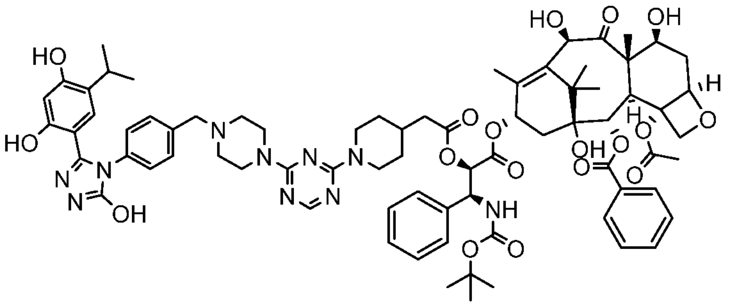


[002088] A round-bottomed flask was purged with N_2, then charged with Velcade (0.06 mmol), toluene/THF (3:1 v/v; 2 mL), 5-(2,4-dihydroxy-5-isopropylphenyl)-4-(4-(3,4-dihydroxyphenoxy)phenyl)-N-ethyl-4H-1,2,4-triazole-3-carboxamide (0.06 mmol), and activated 3Å molecular sieves (200 mg). The mixture was stirred in a 50 ^{0}C oil bath, under N_2 atmosphere, for 20 h, then filtered and concentrated under reduced pressure to yield the desired crude product as a white solid. The solid was purified by reverse-phase C18 chromatography (0.1% formic acid in H_2O/0.1% formic acid in MeCN), followed by lyophilizing the desired fractions to yield SDC-TRAP-0408.

[002089] ESMS calculated for $C_{45}H_{47}BN_8O_8$: 838.4; found: 839.1 (M + H^+).

[002090] SDC-TRAP-0422

[002091] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxy carbonyl)amino)-2-(2-(1-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-1,3,5-triazin-2-yl)piperidin-4-yl)acetoxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate

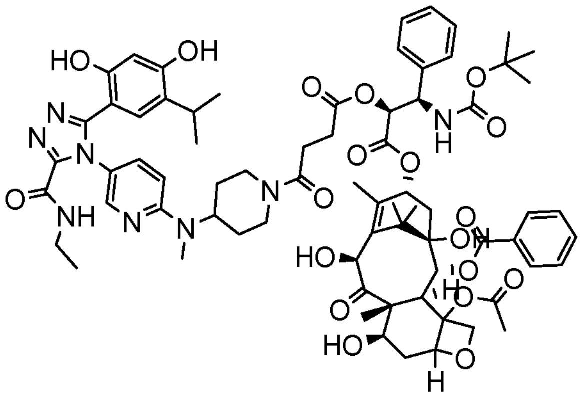


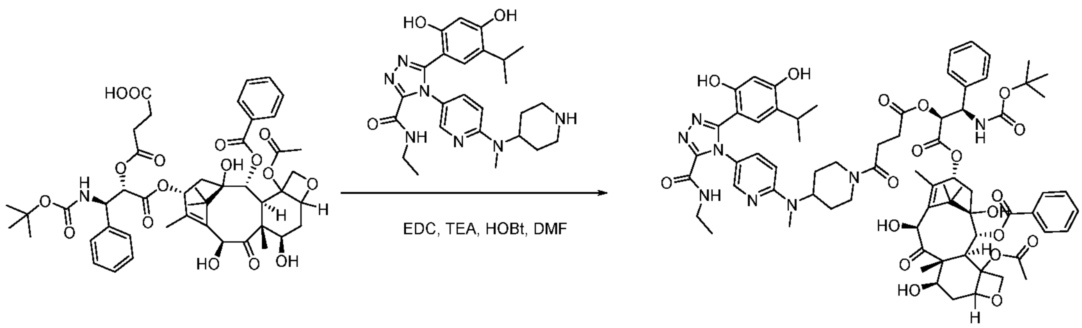
[002092] The title compound was prepared analogously using a similar procedure to that for **SDC-TRAP-0424**.

[002093] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 9.61 (s, 1H), 9.41 (s, 1H), 8.10 (s, 1H), 7.98 (d, J = 7.6 Hz, 2H), 7.89 (d, J = 9.1 Hz, 1H), 7.73 (t, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 2H), 7.47 – 7.29 (m, 6H), 7.14 (d, J = 8.0 Hz, 2H), 6.77 (s, 1H), 6.27 (s, 1H), 5.39 (d, J = 7.2 Hz, 1H), 5.12 -– 4.86 (m, 5H), 4.58 – 0.91 (m, 64H). ESMS calcd for $C_{75}H_{90}N_{10}O_{18}$: 1418.6; found: 1419.4 $(M + H)^+$.

[002094] SDC-TRAP-0423

[002095] (4R,4aR,6S,9R,11R,12R,12aS)-12b-acetoxy-9-(((2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((4-(4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)pyridin-2-yl)(methyl)amino)piperidin-1-yl)-4-oxobutanoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate

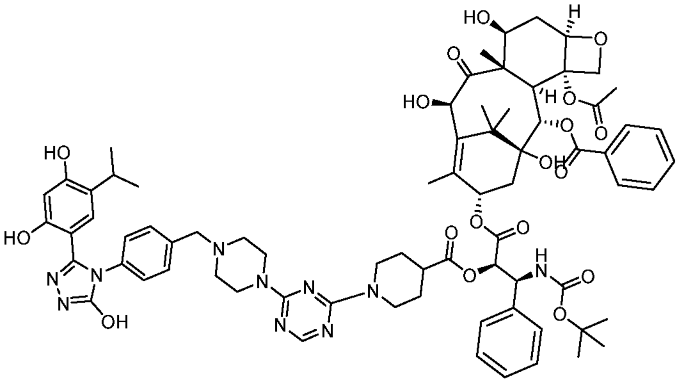




[002096] To a solution of Docetaxel 2'-succinic ester (0.3 g, 0.33 mmol) in DMF (4 mL) was added amine (0.16 g, 0.33 mmol), EDC (0.19 g, 0.99 mmol), TEA (0.14 mL, 1.0 mmol), and HOBt (15 mg, 0.1 mmol). The resulting solution was stirred at room temperature for 120 min before it was quenched with H_2O (10 mL) and extracted with EtOAc (40 mL). The organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave SDC-TRAP-0423 (0.29 g, 64%) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (d, J = 4.9 Hz, 1H), 9.74 (s, 1H), 8.97 (t, J = 5.9 Hz, 1H), 8.06 – 7.92 (m, 3H), 7.89 (s, 1H), 7.75-7.63 (m, 3H), 7.53 – 7.32 (m, 5H), 7.18 (s, 1H), 6.77 (s, 1H), 6.68 (d, J = 9.1 Hz, 1H), 6.33 (s, 1H), 5.79 (d, J = 9.0 Hz, 1H), 5.40 (d, J = 7.1 Hz, 1H), 5.15 – 4.87 (m, 6H), 4.74 (s, 1H), 4.56 – 4.40 (m, 2H), 4.10 – 3.91 (m, 4H), 3.63 (s, 1H), 3.23-3.09 (m, 3H), 3.04 – 2.91 (m, 1H), 2.83 (d, J = 7.0 Hz, 3H), 2.68-2.58 (m, 4H), 2.24 (d, J = 5.9 Hz, 3H), 1.99 (s, 1H), 1.75 – 1.45 (m, 12H), 1.38 (d, J = 2.3 Hz, 9H), 1.17 (t, J = 7.1 Hz, 2H), 1.06 (t, J = 7.2 Hz, 3H), 0.98 (s, 6H), 0.93 (d, J = 6.8 Hz, 6H); ESMS calculated ($C_{72}H_{88}N_8O_{19}$): 1368.6; found: 1369.2 (M+H).

[002097] SDC-TRAP-0424

[002098] (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 1-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-1,3,5-triazin-2-yl)piperidine-4-carboxylate

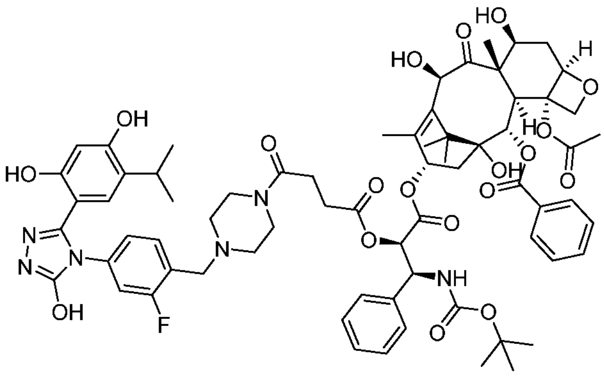


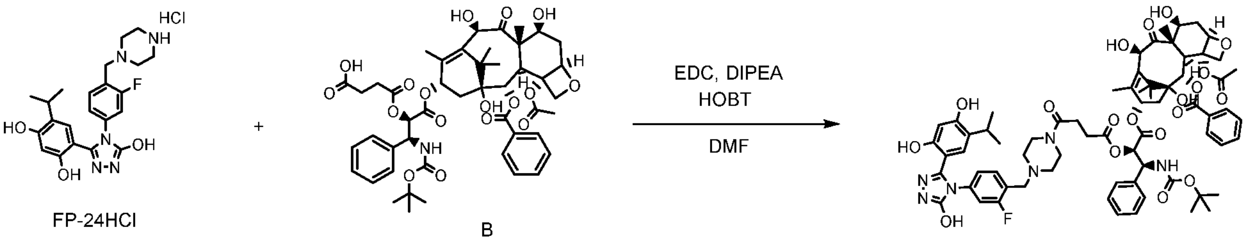
[002099] To a solution of (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl piperidine-4-carboxylate (91.9 mg, 0.1 mmol) and 2,4-dichloro-1,3,5-triazine (15 mg, 0.10 mmol) in DCM (4.0 mL) at 0 °C was added DIPEA (0.05 mL). The reaction mixture was stirred at 0 °C for 1 hrs. Solvent was evaporated to give residue. To a solution of the above residue in DMF (3.0 mL) was added 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol HCl salt (67 mg, 0.14 mmol) and DIPEA (0.10 mL). The reaction mixture was stirred at room temperature for 1.5 hrs. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford the product (110 mg, 78%) as a white solid.

[002100] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 9.63 (s, 1H), 9.42 (s, 1H), 8.46 (brs, 1H), 8.11 (s, 1H), 7.98 - 7.89 (m, 3H), 7.76 – 7.64 (m, 3H), 7.47 – 7.32 (m, 6H), 7.18-7.14 (m, 3H), 6.77 (s, 1H), 6.27 (s, 1H), 5.39 (d, J = 7.1 Hz, 1H), 5.14 – 4.86 (m, 4H), 4.43 (s, 1H), 4.03-3.98 (m, 2H), 3.71-0.93 (m, 55H). ESMS calcd for $C_{74}H_{85}N_{10}O_{18}$: 1404.6; found: 1405.5 $(M + H)^+$.

[002101] SDC-TRAP-0425

[002102] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxy carbonyl)amino)-2-((4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazin-1-yl)-4-oxobutanoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate





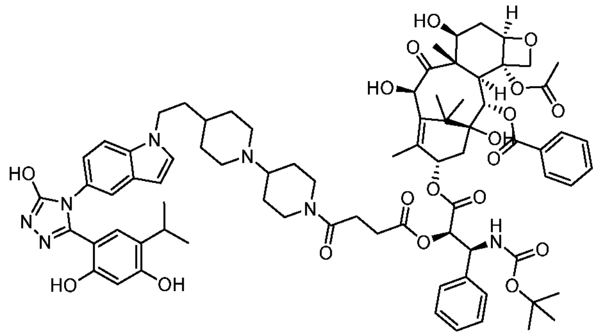
[002103] To a solution of amine **FP-24 HCl** (530 mg1.1 mmol) and acid **B** (910 mg, 1.0mmol) in DMF (8mL), was added DIPEA (300ul, 2.4mmol), EDC (280mg, 1.4mmol) and 50 mg HOBT. The mixture was stirred for 8h at RT. The resulting reaction mixture was poured into ice- water (100 mL) and precipitated product was collected and washed with water. The filtered material was purified by flash chromatography (hexane-EtOAc 1:1 and CH_2Cl_2-MeOH 9:1) gave SDC-TRAP-0425 (yield: 850mg, 64.5%).

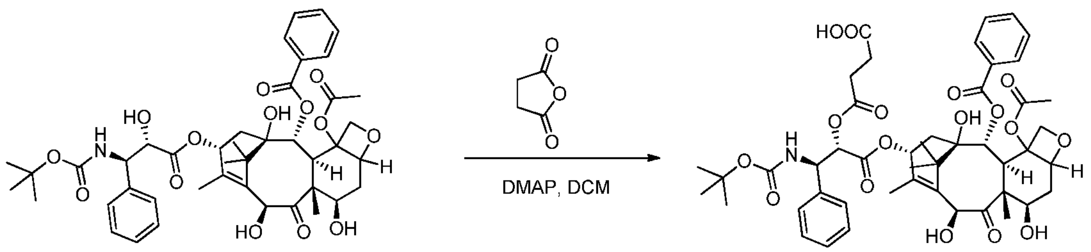
^{1}H NMR (400 MHz, DMSO-d_6) δ 11.97 (s, 1H), 9.61 (s, 1H), 9.38 (s, 1H), 8.02 – 7.95 (m, 2H), 7.84 (d, J = 8.1 Hz, 1H), 7.76 – 7.60 (m, 3H), 7.44 – 7.33 (m, 5H), 7.18 (t, J = 6.8 Hz, 1H), 7.07 (dd, J = 10.8, 2.0 Hz, 1H), 6.98 (dd, J = 8.1, 2.0 Hz, 1H), 6.87 (s, 1H), 6.27 (s, 1H), 5.84 – 5.73 (m, 1H), 5.40 (d, J = 7.1 Hz, 1H), 5.14 – 5.04 (m, 3H), 5.00 (d, J = 7.1 Hz, 1H), 4.94 – 4.86 (m, 2H), 4.43 (s, 1H), 4.03 (d, J = 9.3 Hz, 3H), 3.64 (d, J = 7.0 Hz, 1H), 3.52 (s, 1H), 3.42 (q, J =

12.9, 11.4 Hz, 4H), 3.01 (p, *J* = 6.9 Hz, 1H), 2.60 (s, 3H), 2.40 (s, 2H), 2.34 – 2.22 (m, 6H), 1.87 (dd, *J* = 15.5, 9.2 Hz, 1H), 1.71 – 1.54 (m, 5H), 1.51 (s, 3H), 1.37 (s, 9H), 1.24 (s, 1H), 1.03 – 0.95 (m, 12H). ESMS calculated for $C_{69}H_{81}FN_6O_{19}$: 1316.55; Found 1317.2 $(M+H)^+$.

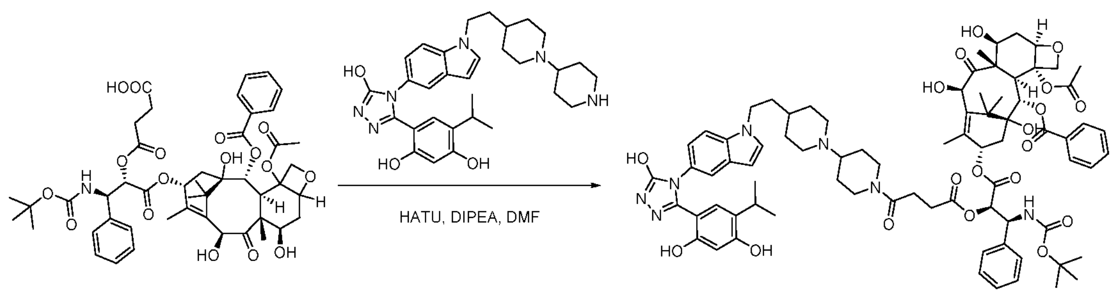
[002104] SDC-TRAP-0426

[002105] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-((4-(4-(2-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-1H-indol-1-yl)ethyl)-[1,4'-bipiperidin]-1'-yl)-4-oxobutanoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate





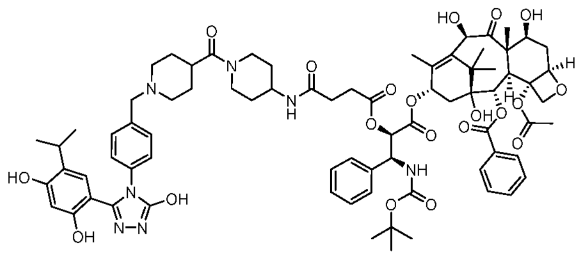
[002106] To a solution of Docetaxel (2 g, 2.48 mmol) in DMF (10 mL) was added succinic anhydride (0.3 g, 3.0 mmol) and DMAP (0.38 mmol, 3.1 mmol). The reaction solution was stirred at room temperature for 1 hr. before 2N HCl solution was added until the white solid crashed out. The suspension was extracted with EtOAc (100 mL). The organic phase was dried over Na2SO4 and concentrated. Column chromatography gave a product (2.1 g, 94%) as off-white solid.

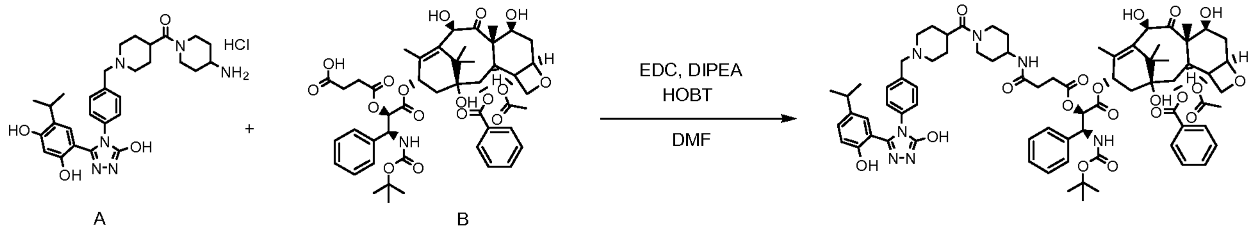


[002107] To a solution of Docetaxel 2'-succinic ester (0.53 g, 0.58 mmol) in DMF (10 mL) was added amine (0.41 g, 0.71 mmol), HATU (0.33 g, 0.87 mmol) and DIPEA (0.3 mL, 1.72 mmol). The resulting solution was stirred at room temperature for 60 min before it was quenched with H_2O (15 mL) and extracted with EtOAc (50 mL). The organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave SDC-TRAP-0426 (0.52 g, 62%) as off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H), 9.56 (s, 1H), 9.52 (s, 1H), 7.99 (d, J = 7.5 Hz, 2H), 7.87 (s, 1H), 7.77 – 7.61 (m, 3H), 7.48 – 7.32 (m, 7H), 7.18 (s, 1H), 6.93 (d, J = 8.5 Hz, 1H), 6.67 (s, 1H), 6.42 (d, J = 3.0 Hz, 1H), 6.23 (s, 1H), 5.77 (d, J = 10.2 Hz, 1H), 5.40 (d, J = 7.1 Hz, 1H), 5.13 – 4.87 (m, 6H), 4.45 (d, J = 4.6 Hz, 1H), 4.34 (s, 1H), 4.19 (s, 2H), 4.01 (s, 3H), 3.84 (s, 1H), 3.63 (s, 1H), 2.99 – 2.57 (m, 8H), 2.24 (d, J = 6.7 Hz, 4H), 2.05 (s, 2H), 1.75-1.61 (m, 11H), 1.51 (s, 3H), 1.37 (s, 9H), 1.29-1.11 (m, 5H), 0.98 (s, 6H), 0.78 (d, J = 6.9 Hz, 6H); ESMS calculated ($C_{78}H_{95}N_7O_{19}$): 1433.6; found: 1434.6 (M+H).

[002108] SDC-TRAP-0427

[002109] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxy carbonyl)amino)-2-((4-((1-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-t riazol-4-yl)benzyl)piperidine-4-carbonyl)piperidin-4-yl)amino)-4-oxobutanoyl)oxy)-3-pheny lpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12 a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate

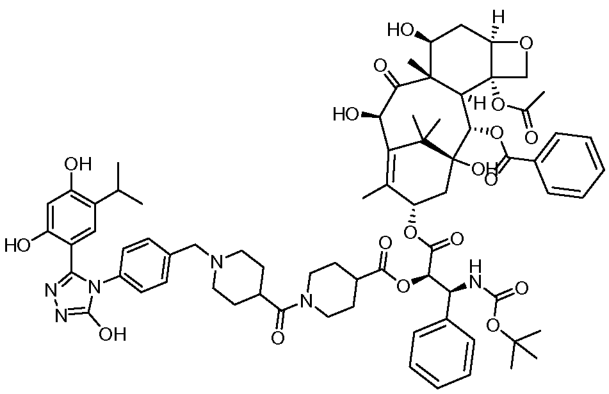




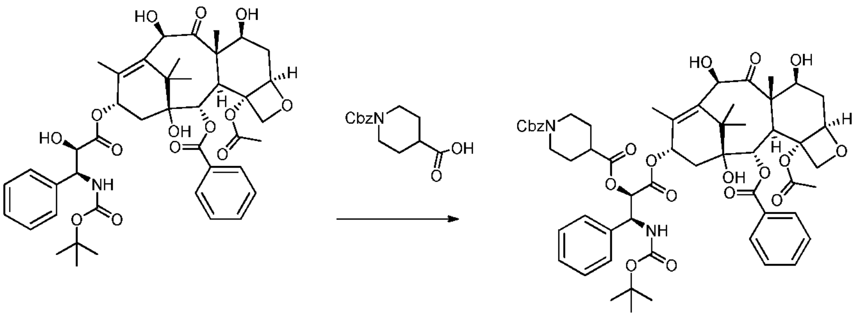
[002110] To a solution of amine **A** (315 mg, 0.55mmol) and acid **B** (460 mg, 0.50mmol) in DMF (7mL), was added DIPEA (200ul, 1.6mmol), EDC (140mg, 0.70mmol) and 50 mg HOBT. The mixture was stirred for 8h at RT. The resulting reaction mixture was poured into ice- water (100 mL) and precipitated product was collected and washed with water. The filtered material was purified by flash chromatography (hexane-EtOAc 1:1 and EtOAc-MeoH 9:1) gave SDC-TRAP-0427 (yield: 485mg, 68%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.58 (s, 1H), 9.41 (s, 1H), 8.02 – 7.95 (m, 2H), 7.84 (t, J = 7.3 Hz, 2H), 7.77 – 7.60 (m, 3H), 7.39 (dt, J = 16.0, 7.7 Hz, 4H), 7.29 (d, J = 8.0 Hz, 2H), 7.22 – 7.09 (m, 3H), 6.75 (s, 1H), 6.27 (s, 1H), 5.83 – 5.73 (m, 1H), 5.40 (d, J = 7.1 Hz, 1H), 5.12 – 5.02 (m, 3H), 5.02 – 4.97 (m, 1H), 4.90 (dd, J = 12.1, 2.6 Hz, 2H), 4.43 (s, 1H), 4.19 (d, J = 12.7 Hz, 1H), 4.11 – 3.96 (m, 3H), 3.63 (d, J = 7.1 Hz, 1H), 3.43 (s, 2H), 3.32 (s, 2H), 3.20 – 3.04 (m, 2H), 2.96 (p, J = 6.8 Hz, 1H), 2.78 (s, 2H), 2.71 (s, 1H), 2.60 (q, J = 15.9, 11.5 Hz, 3H), 2.38 (t, J = 7.2 Hz, 2H), 2.23 (s, 3H), 1.97 (d, J = 10.6 Hz, 2H), 1.84 (dd, J = 15.2, 9.5 Hz, 1H), 1.75 (s, 1H), 1.68 (s, 4H), 1.53 (d, J = 13.3 Hz, 7H), 1.38 (s, 9H), 1.24 (s, 1H), 1.16 (d, J = 11.9 Hz, 1H), 1.00 – 0.90 (m, 12H). ESMS calculated for $C_{76}H_{93}N_7O_{20}$: 1423.65; Found 1425.4 $(M+H)^+$.

[002111] SDC-TRAP-0428

[002112] (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 1-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)piperidine-4-carboxylate

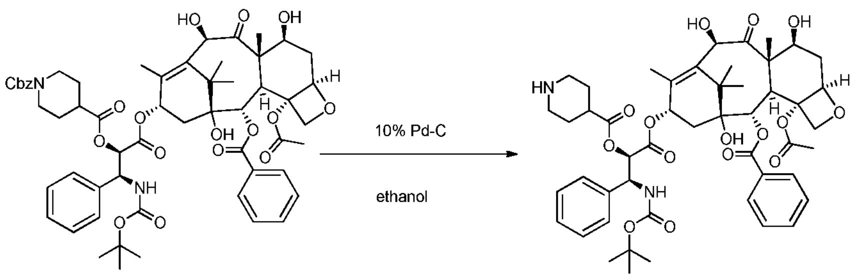


[002113] Step 1: Synthesis of 4-((2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl) 1-benzyl piperidine-1,4-dicarboxylate



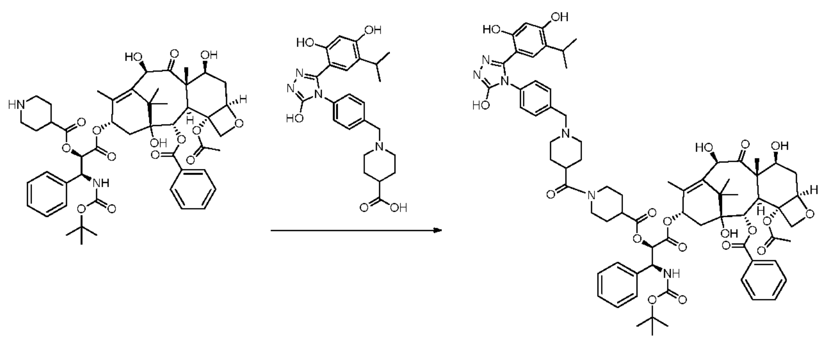
[002114] A solution of docetaxel (400 mg, 0.5 mmol), 1-((benzyloxy)carbonyl)piperidine-4-carboxylic acid (132 mg, 0.5 mmol), EDC HCl salt (105 mg, 0.55 mmol) and DMAP (122 mg, 0.55 mmol) in DCM (20 mL) was stirred at room temperature for overnight. Solvent was evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford 4-((2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl) 1-benzyl piperidine-1,4-dicarboxylate (396 mg, 75%) as a white solid. ESMS calcd for $C_{57}H_{68}N_2O_{17}$: 1052.4; found: 1053.3 $(M + H)^+$.

[002115] Step 2: Synthesis of (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl piperidine-4-carboxylate



[002116] A solution of 4-((2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl) 1-benzyl piperidine-1,4-dicarboxylat (396 mg) and 10% Pd on carbon (100 mg) in ethanol (20 mL) and DCM (5.0 mL) under hydrogen balloon was stirred at room temperature for 3 hrs. The reaction mixture was filtered through celite and washed with MeOH/DCM. Solvent was evaporated under a reduced pressure to give (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl piperidine-4-carboxylate (374 mg). ESMS calcd for $C_{49}H_{62}N_2O_{15}$: 918.4; found: 919.4 $(M + H)^+$.

[002117] Step 3: Synthesis of ((2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 1-(1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carbonyl)piperidine-4-carboxylate

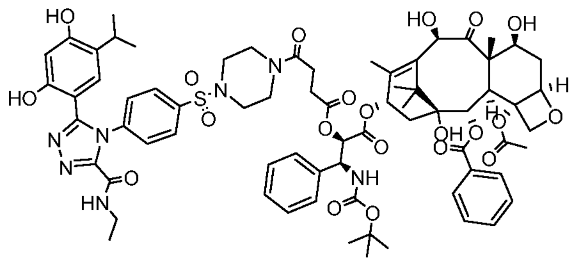


[002118] A solution of (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl piperidine-4-carboxylate (91.9 mg, 0.10 mmol), 1-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperidine-4-carboxylic acid (50 mg, 0.11 mmol) and HATU (42 mg, 0.11 mmol) in DMF (3.0 mL) and

DIPEA (0.10 mL) was stirred at room temperature for overnight. Solvents were evaporated under reduced pressure to give a residue, which was purified by ISCO over silica gel to afford the product (54.7 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.94 (s, 1H), 9.61 (s, 1H), 9.42 (s, 1H), 8.01 – 7.87 (m, 3H), 7.75-7.64 (m, 3H), 7.46 – 7.32 (m, 4H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.21 – 7.09 (m, 3H), 6.76 (s, 1 H), 6.27 (s, 1H), 5.39 (d, *J* = 7.1 Hz, 1H), 5.14 – 4.98 (m, 4H), 4.97 – 4.86 (m, 2H), 4.43 (s, 1H), 4.03-3.98 (m, 2H), 3.79 (s, 1H), 3.62 (d, *J* = 7.2 Hz, 2H), 3.43 (s, 2H), 3.16-0.90 (m, 53H). ESMS calcd for $C_{73}H_{88}N_6O_{19}$: 1352.6; found: 1353.5 $(M + H)^+$.

[002119] SDC-TRAP-0430

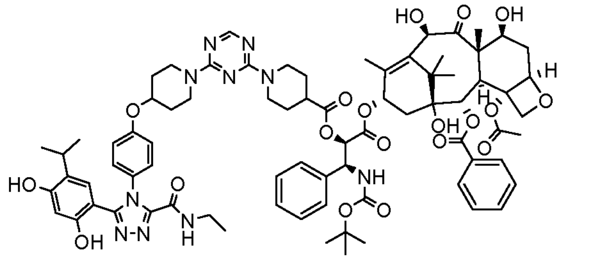
[002120] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxy carbonyl)amino)-2-((4-(4-((4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenyl)sulfonyl)piperazin-1-yl)-4-oxobutanoyl)oxy)-3-phenylpropanoyl)ox y)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecah ydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate



[002121] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.06 (s, 1H), 9.72 (s, 1H), 9.05 (t, *J* = 5.9 Hz, 1H), 7.99 (d, *J* = 7.4 Hz, 2H), 7.91 – 7.50 (m, 7H), 7.50 – 7.25 (m, 4H), 7.17 (t, *J* = 7.0 Hz, 1H), 6.69 (s, 1H), 6.29 (d, *J* = 2.5 Hz, 1H), 5.76 (d, *J* = 0.9 Hz, 2H), 5.40 (d, *J* = 7.1 Hz, 1H), 5.19 – 4.79 (m, 6H), 4.44 (s, 1H), 4.03 (d, *J* = 9.2 Hz, 3H), 3.75-3.42 (m, 4H), 3.27 – 3.08 (m, 2H), 3.09 – 2.70 (m, 6H), 2.59 (s, 3H), 2.25 (s, 3H), 1.96 – 1.78 (m, 1H), 1.64 (d, *J* = 25.4 Hz, 5H), 1.51 (s, 4H), 1.36 (s, 9H), 1.04 (t, *J* = 7.1 Hz, 3H), 0.98 (s, 6H), 0.88 (d, *J* = 6.9 Hz, 6H). ESMS calculated for $C_{71}H_{85}N_7O_{21}S$: 1403.55; Found 1404.2 $(M+H)^+$.

[002122] SDC-TRAP-0431

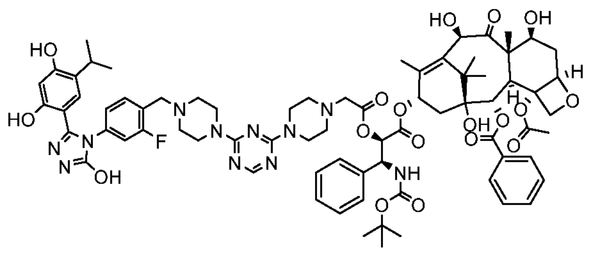
[002123] (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoylox y)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecah ydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)am ino)-1-oxo-3-phenylpropan-2-yl 1-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)phenoxy)piperidin-1-yl)-1,3,5-triazin-2-yl)piperidine-4-carboxylate



[002124] The title compound was prepared analogously using a similar procedure to that for **SDC-TRAP-0424**. [1]H NMR (400 MHz, DMSO-d_6) δ 10.70 (s, 1H), 9.77 (s, 1H), 8.94 (s, 1H), 8.15 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 8.0 Hz, 1H), 7.76 – 7.61 (m, 3H), 7.46 – 7.33 (m, 4H), 7.29 (d, J = 8.8 Hz, 2H), 7.17 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 8.7 Hz, 2H), 6.59 (s, 1H), 6.35 (s, 1H), 5.77 (s, 1H), 5.39 (d, J = 7.4 Hz, 1H), 5.10 -4.86 (m, 6H), 4.71 - 0.84 (m, 63H). ESMS calcd for $C_{77}H_{92}N_{10}O_{19}$: 1460.6; found: 1461.3 $(M + H)^+$.

[002125] SDC-TRAP-0432

[002126] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(2-(4-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)-2-fluorobenzyl)piperazin-1-yl)-1,3,5-triazin-2-yl)piperazin-1-yl)acetoxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate

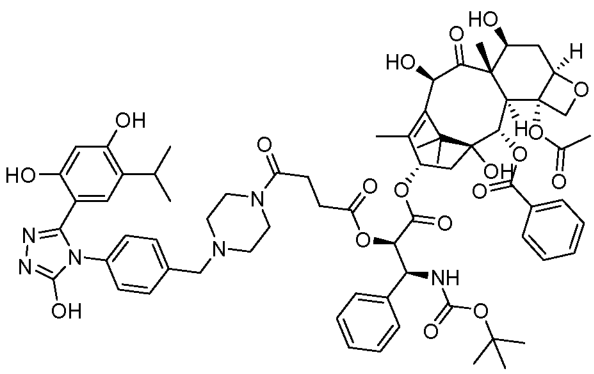


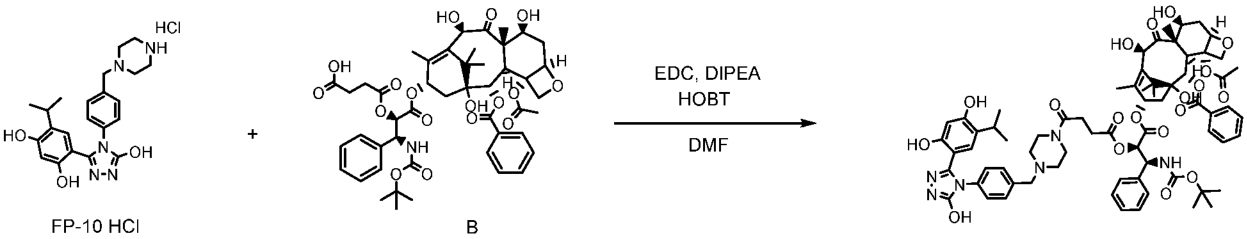
[002127] The title compound was prepared analogously using a similar procedure to that for **SDC-TRAP-0424**.

[002128] ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 9.63 (s, 1H), 9.40 (s, 1H), 8.11 (s, 1H), 7.98 (d, J = 7.5 Hz, 2H), 7.89 (d, J = 9.0 Hz, 1H), 7.75 – 7.61 (m, 3H), 7.46 – 7.31 (m, 5H), 7.16 (d, J = 7.4 Hz, 1H), 7.07 (dd, J = 10.7, 2.0 Hz, 1H), 7.01 – 6.94 (m, 1H), 6.86 (s, 1H), 6.27 (s, 1H), 5.39 (d, J = 7.1 Hz, 1H), 5.14 – 4.86 (m, 6H), 4.42 (s, 1H), 4.01 – 0.94 (m, 60H). ESMS calcd for $C_{74}H_{88}FN_{11}O_{18}$: 1437.6; found: 1439.3 $(M + H)^+$.

[002129] SDC-TRAP-0433

[002130] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxy carbonyl)amino)-2-((4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triaz ol-4-yl)benzyl)piperazin-1-yl)-4-oxobutanoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydrox y-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-meth anocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate



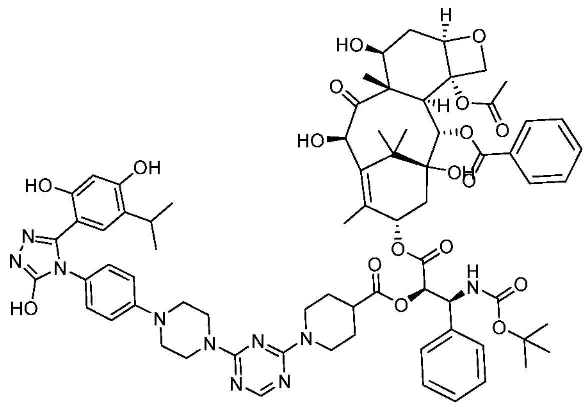


[002131] To a solution of amine **FP-10 HCl** (100 mg, 0.22 mmol) and acid **B** (185 mg, 0.2mmol) in DMF (3mL), was added DIPEA (100ul, 0.8mmol), EDC (60mg, 0.30mmol) and 20 mg HOBT. The mixture was stirred for 8h at RT. The resulting reaction mixture was poured into ice- water (50 mL) and precipitated product was collected and washed with water. The filtered material was purified by flash chromatography (hexane-EtOAc 1:1 and EtOAc-MeOH 9:1) gave SDC-TRAP-0433 (yield: 130mg, 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.58 (s, 1H), 9.40 (s, 1H), 7.99 (d, J = 7.6 Hz, 2H), 7.88 – 7.79 (m, 1H), 7.76 – 7.60 (m, 3H), 7.44 – 7.28 (m, 6H), 7.22 – 7.10 (m, 3H), 6.77 (s, 1H), 6.26 (d, J = 1.3 Hz, 1H), 5.84 –

5.73 (m, 1H), 5.40 (d, J = 7.1 Hz, 1H), 5.08 (s, 2H), 5.00 (d, J = 7.2 Hz, 1H), 4.94 – 4.87 (m, 2H), 4.43 (s, 1H), 4.13 – 3.97 (m, 4H), 3.64 (d, J = 7.1 Hz, 1H),3.47- 3.32 (m, 4H), 3.17 (dd, J = 5.3, 1.3 Hz, 2H), 2.97 (p, J = 6.9 Hz, 1H), 2.61 (d, J = 2.7 Hz, 3H), 2.37 (d, J = 8.2 Hz, 2H), 2.26 (d, J = 14.1 Hz, 6H), 1.86 (dd, J = 15.5, 9.2 Hz, 1H), 1.71 – 1.49 (m, 5H), 1.37 (s, 9H), 1.30 (s, 1H), 1.00 – 0.91 (m, 12H). ESMS calculated for $C_{69}H_{82}N_6O_{19}$: 1298.56; Found 1299.2 $(M+H)^+$.

[002132] SDC-TRAP-0434

[002133] (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 1-(4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)phenyl)piperazin-1-yl)-1,3,5-triazin-2-yl)piperidine-4-carboxylate

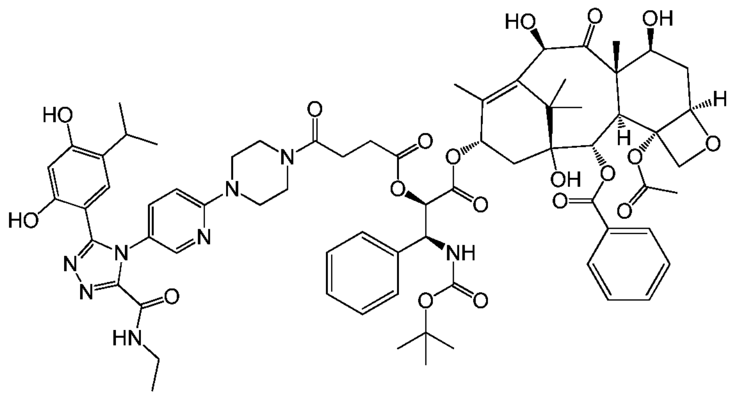


[002134] The title compound was prepared analogously using a similar procedure to that for **SDC-TRAP-0424**. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.84 (s, 1H), 9.57 (s, 1H), 9.43 (s, 1H), 8.16 (s, 1H), 7.97 (d, J = 7.6 Hz, 2H), 7.88 (d, J = 7.6 Hz, 1H), 7.76 – 7.61 (m, 3H), 7.46 – 7.33 (m, 4H), 7.17 (t, J = 7.0 Hz, 1H), 7.05 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 6.79 (s, 1H), 6.26 (s, 1H), 5.39 (d, J = 7.0 Hz, 1H), 5.12 – 4.86 (m, 6H), 4.42 - 0.95 (m, 58H). ESMS calcd for $C_{73}H_{86}N_{10}O_{18}$: 1390.6; found: 1391.3 $(M + H)^+$.

[002135] SDC-TRAP-0435

[002136] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-((4-(4-(5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1

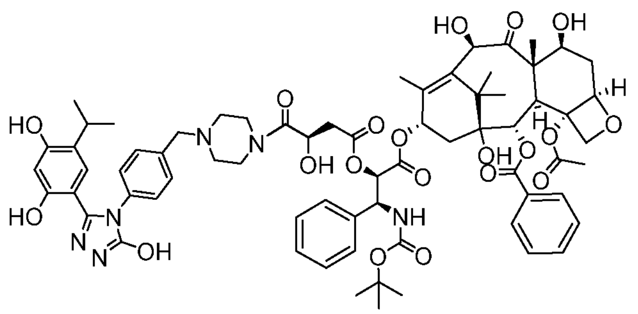
,2,4-triazol-4-yl)pyridin-2-yl)piperazin-1-yl)-4-oxobutanoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate



[002137] ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.08 (s, 1H), 9.69 (s, 1H), 8.97 (s, 1H), 8.00 – 7.97 (m, 3H),7.81-7.84(m, 1H), 7.64 – 7.36 (m, 7H), 7.18 (s, 1H), 6.87– 6.84(m, 1H), 6.81 (s, 1H), 6.31 (s, 1H), 5.76 (s, 1H), 5.39 (s, 1H), 5.15 – 4.82 (m, 5H), 4.45 (s, 1H), 4.02 (s, 2H), 3.75-3.43 (m, 6H), 3.26 – 3.08 (m, 2H), 2.98 (s, 1H), 2.70-2.51 (m, 3H), 2.25 (s, 3H), 1.70 (s, 2H), 1.51 (s, 2H), 1.37 (s, 9H), 1.06 (t, J = 7.2 Hz, 3H), 1.01 – 0.92 (m, 9H). ESMS calculated for $C_{70}H_{84}N_8O_{19}$: 1340.59; Found 1342.6 $(M+H)^+$.

[002138] SDC-TRAP-0436

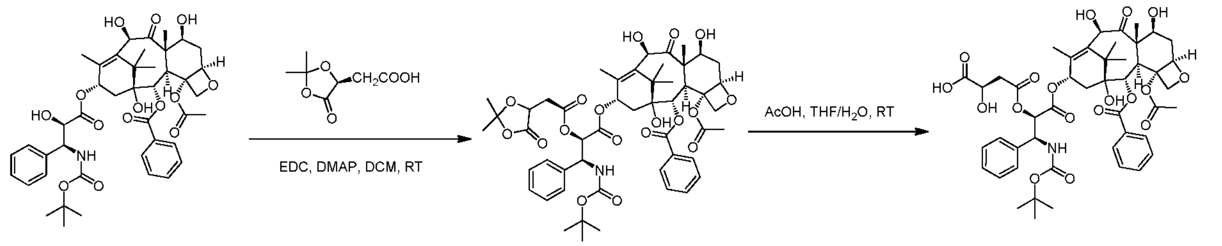
[002139] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(((R)-4-(4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)-3-hydroxy-4-oxobutanoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate



[002140] **Step 1 and 2:**

(R)-4-(((2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-

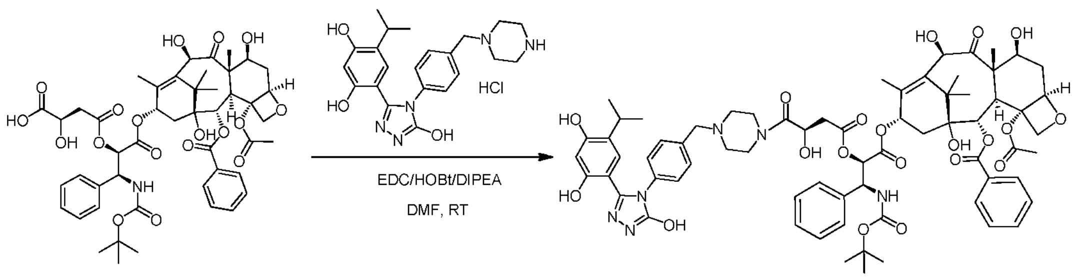
4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)oxy)-2-hydroxy-4-oxobutanoic acid



[002141] To a solution of docetaxel (808 mg, 1 mmol) and (*S*)-2-(2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl)acetic acid (175 mg, 1 mmol) in CH_2Cl_2 (16 mL) was added EDC (210 mg, 1.1 mmol) and DMAP (153 mg, 1.25 mmol). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with DCM and washed with 1N aq. HCl and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was purified via column chromatography (Hexane/EtOAc, 0-100%) yielding 540 mg (56%) of product.

[002142] The above product (540 mg, 0.56 mmol) was dissolved in a mixture of AcOH-THF-H_2O (1:1:1, 80 mL). The mixture was stirred at room temperature for 20 h then 45 ^oC for 5 h. The organic solvents were removed by evaporation in vacuo. The residue was diluted by water and freeze-dried, yielding product (490 mg, 94.7%) as a white solid. ESMS calculated for $C_{47}H_{57}NO_{18}$: 923.6; found: 924 (M + H^+).

[002143] Step 3:

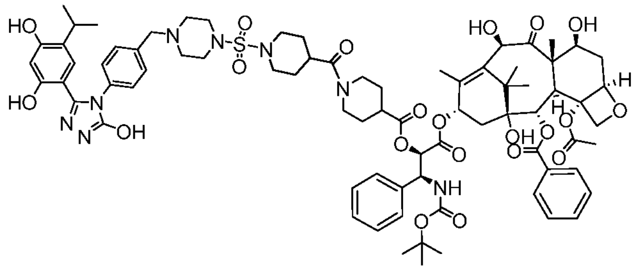


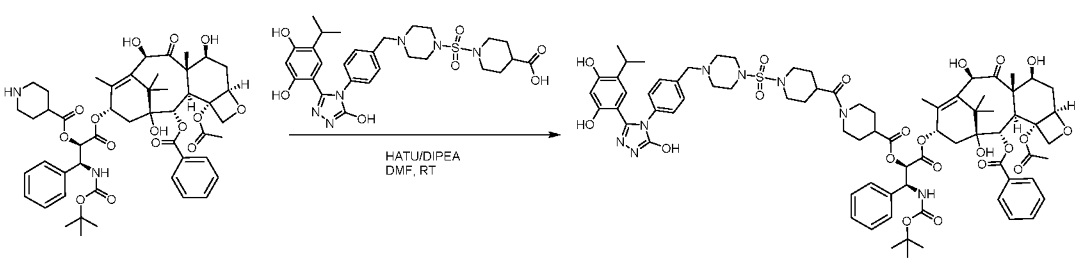
[002144] To a mixture of (R)-4-(((2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)oxy)-2-hydroxy-4-oxobutanoic acid (280 mg, 0.3 mmol) and 4-(5-hydroxy-4-(4-(piperazin-1-ylmethyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-

1,3-diol hydrochloride (135 mg, 0.3 mmol) in DMF (5 mL) was added EDC (118 mg, 0.61 mmol), HOBt (41 mg, 0.3 mmol) followed by DIPEA (0.22 mL, 1.21 mmol). The reaction mixture was stirred at room temperature overnight then concentrated. The crude residue was treated with water, the resulting solid was filtered, dried, purified by ISCO using DCM/MeOH as eluent to afford 186 mg (47.2%) of title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.93 (s, 1H), 9.60 (s, 1H), 9.40 (s, 1H), 7.99-7.98 (m, 2H), 7.84-7.83 (m, 1H), 7.74-7.71 (m, 1H), 7.67-7.63 (m, 2H), 7.42-7.39 (m, 4H), 7.34-7.31 (m, 2H), 7.19-7.14 (m, 3H), 6.78 (s, 1H), 6.26 (s, 1H), 5.81-5.77 (m, 1H), 5.55-5.53 (m, 1H), 5.41-5.39 (m, 1H), 5.11-5.00 (m, 4H), 4.94-4.89 (m, 2H), 4.66-4.61 (m, 1H), 4.44 (s, 1H), 4.11-3.99 (m, 3H), 3.64-3.48 (m, 6H), 2.97-2.84 (m, 3H), 2.60-2.54 (m, 1H), 2.41-2.23 (m, 8H), 1.87-1.81 (m, 1H), 2.86 (s, 3H), 1.64-1.56 (m, 2H), 1.51 (s, 3H), 1.37 (s, 9H), 0.98-0.94 (m, 12H) ppm; ESMS calculated for $C_{69}H_{82}N_6O_{20}$: 1314.56; found: 1315 (M + H$^+$).

[002145] SDC-TRAP-0437

[002146] (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl 1-(1-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)sulfonyl)piperidine-4-carbonyl)piperidine-4-carboxylate

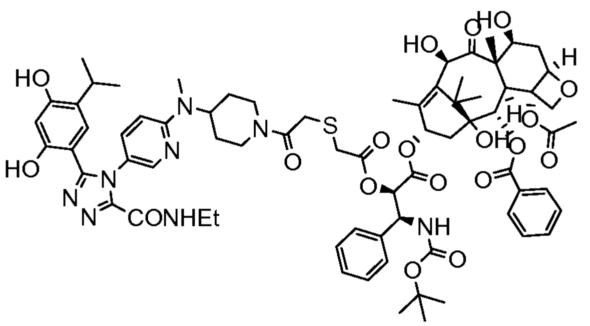


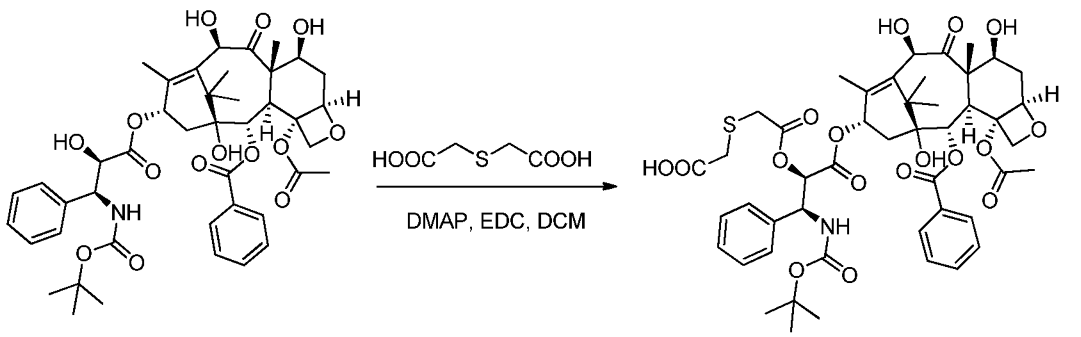


[002147] To a mixture of (2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-tr ihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl piperidine-4-carboxylate (187 mg, 0.2 mmol) and 1-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)sulfonyl)piperidine-4-carboxylic acid (134 mg, 0.22 mmol) in DMF (4 mL) was added HATU (76 mg, 0.2 mmol) and DIPEA (0.15 mL, 0.86 mmol). The reaction mixture was stirred at room temperature overnight then concentrated. The crude residue was treated with water, the resulting solid was filtered, dried, purified by ISCO using DCM/MeOH as eluent to afford 78 mg (26%) of title compound. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.61 (s, 1H), 9.40 (s, 1H), 7.99-7.90 (m, 3H), 7.75-7.72 (m, 1H), 7.68-7.64 (m, 2H), 7.44-7.29 (m, 6H), 7.19-7.12 (m, 3H), 6.79 (s, 1H), 6.26 (s, 1H), 5.77 (broad s, 1H), 5.40-5.38 (m, 1H), 5.10-5.07 (m, 3H), 5.02-5.00 (m, 1H), 4.95-4.88 (m, 2H), 4.43 (s, 1H), 4.11-3.98 (m, 4H), 3.83 (broad s, 1H), 3.63-3.54 (m, 3H), 3.49 (broad s, 2H), 3.23-3.19 (m, 1H), 3.13 (broad s, 4H), 3.01-2.67 (m, 8H), 2.41 (broad s, 4H), 2.30-2.17 (m, 4H), 1.89-1.75 (m, 3H), 1.68-1.60 (m, 5H), 1.55-1.50 (broad s, 7H), 1.37 (broad s, 9H), 0.97-0.94 (m, 12H) ppm; ESMS calculated for $C_{77}H_{96}N_8O_{21}S$: 1500.64; found: 1501 (M + H$^+$).

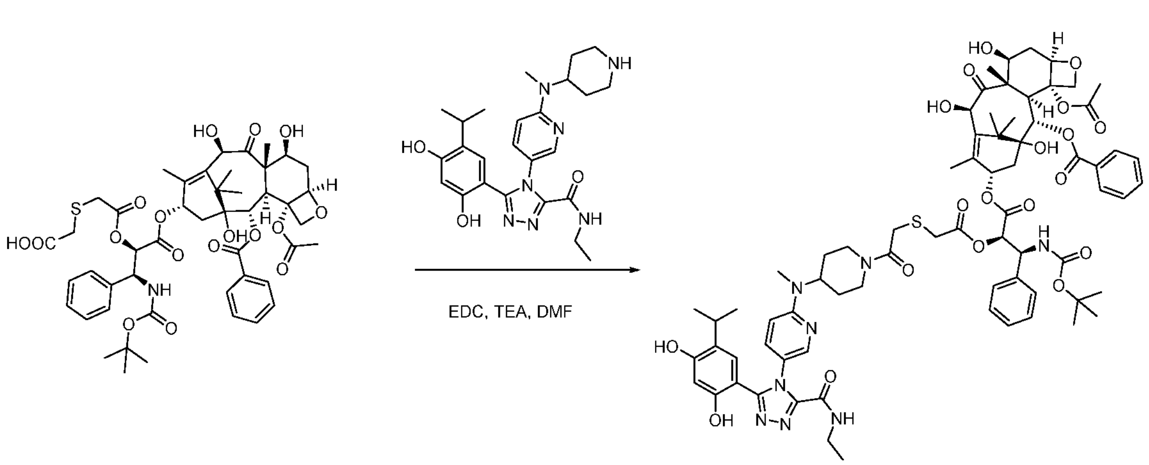
[002148] SDC-TRAP-0438

[002149] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(2-((2-(4-((5-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-(ethylcarbamoyl)-4H-1,2,4-triazol-4-yl)pyridin-2-yl)(methyl)amino)piperidin-1-yl)-2-oxoethyl)thio)acetoxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate





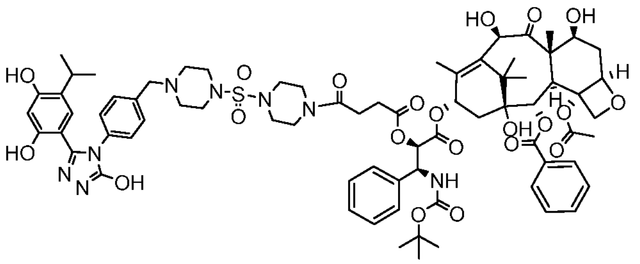
[002150] To a solution of Docetaxel (0.4 g, 0.5 mmol) in DCM (100 mL) was added 2,2'-thiodiacetic acid (0.075 g, 0.5 mmol), DMAP (0.075 g, 0.6 mmol), and EDC (0.19 g, 1.0 mmol). The reaction was stirred at room temperature for 16 hrs. The solution was concentrated and column chromatography gave Docetaxel 2'-carboxylic acid (0.26 g, 54%).

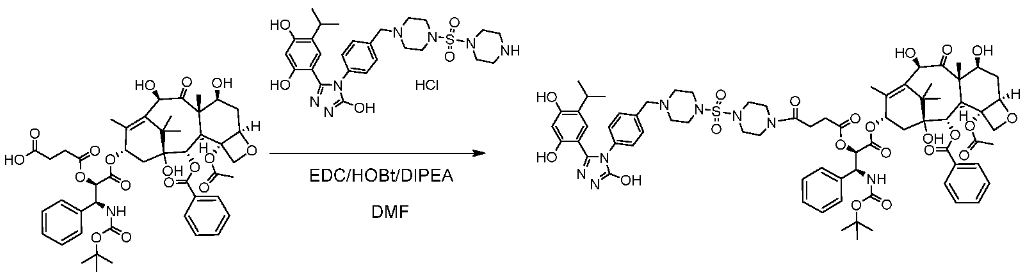


[002151] To the solution of Docetaxel 2'-carboxylic acid (0.1 g, 0.11 mmol) in DMF (5 mL) was added amine (0.05 g, 0.11 mmol), EDC (0.04 g, 0.22 mmol), and TEA (0.03 mL, 0.22 mmol). The reaction was stirred at room temperature for 16 hr. The reaction was quenched with H_2O (10 mL) and extracted with EtOAc (40 mL). The organic phase was dried over Na_2SO_4 and concentrated. Column chromatography gave SDC-TRAP-0438 (0.12 g, 74%). ^1H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 9.73 (s, 1H), 8.97 (t, J = 5.8 Hz, 1H), 8.03 – 7.93 (m, 3H), 7.90 (d, J = 9.6 Hz, 1H), 7.73 (t, J = 7.4 Hz, 1H), 7.66 (t, J = 7.5 Hz, 2H), 7.53 – 7.32 (m, 5H), 7.17 (t, J = 7.3 Hz, 1H), 6.76 (s, 1H), 6.69 (d, J = 9.0 Hz, 1H), 6.33 (s, 1H), 5.78 (d, J = 13.1 Hz, 1H), 5.40 (d, J = 7.3 Hz, 1H), 5.15 (dd, J = 7.6, 4.6 Hz, 1H), 5.12 – 4.99 (m, 3H), 4.94 (d, J = 2.3 Hz, 1H), 4.90 (d, J = 9.7 Hz, 1H), 4.75 (s, 1H), 4.50-4.45 (m, 2H), 4.02-3.95 (m, 4H), 3.70 – 3.52 (m, 5H), 3.24 – 3.13 (m, 4H), 2.96 (q, J = 6.9 Hz, 1H), 2.83 (s, 3H), 2.24 (s, 4H), 1.86 – 1.47 (m, 13H), 1.37 (d, J = 3.0 Hz, 9H), 1.06 (t, J = 7.2 Hz, 3H), 0.97 (s, 6H), 0.92 (d, J = 6.9 Hz, 6H); ESMS calculated ($C_{72}H_{88}N_8O_{19}S$): 1400.6; found: 1401.4 (M+H).

[002152] SDC-TRAP-0440

[002153] (2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-9-(((2R,3S)-3-((tert-butoxycarbonyl)amino)-2-((4-(4-((4-(4-(3-(2,4-dihydroxy-5-isopropylphenyl)-5-hydroxy-4H-1,2,4-triazol-4-yl)benzyl)piperazin-1-yl)sulfonyl)piperazin-1-yl)-4-oxobutanoyl)oxy)-3-phenylpropanoyl)oxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-12-yl benzoate





[002154] To a mixture of 4-(((2R,3S)-1-(((2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-12b-acetoxy-12-(benzoyloxy)-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-1H-7,11-methanocyclodeca[3,4]benzo[1,2-b]oxet-9-yl)oxy)-3-((tert-butoxycarbonyl)amino)-1-oxo-3-phenylpropan-2-yl)oxy)-4-oxobutanoic acid (91 mg, 0.1 mmol) and 4-(5-hydroxy-4-(4-((4-(piperazin-1-ylsulfonyl)piperazin-1-yl)methyl)phenyl)-4H-1,2,4-triazol-3-yl)-6-isopropylbenzene-1,3-diol hydrochloride (60 mg, 0.1 mmol) in DMF (2 mL) was added EDCI (29 mg, 0.15 mmol), HOBt (14 mg, 0.1 mmol) followed by DIPEA (0.07 mL, 0.4 mmol). The reaction mixture was stirred at room temperature overnight then concentrated. The crude residue was dissolved in 10% isopropanol in dichloromethane, washed with water, brine. The organic layer was dried over Na_2SO_4, filtered, the crude residue was purified by ISCO using DCM/MeOH as eluent to afford 63 mg (43.7%) of title compound. ESMS calculated for $C_{73}H_{90}N_8O_{21}S$: 1446.59; found: 1447 ($M + H^+$).

[002155] Example 53: Retention of particular SDC-TRAPs in mouse tumor tissue

[002156] The following example is presented to demonstrate two advantageous properties of SDC-TRAP molecules of the invention, their selective retention in target cells, and, relatedly, systemic stability of SDC-TRAP molecules, *e.g.*, in plasma.

[002157] Comparison of Docetaxel SDC-TRAPs in Female SCID Mouse (H1975)

[002158] Blood samples (~300 µL) were collected by cardiac puncture and immediately centrifuged at 6000 rpm for 8 minutes at approximately 4 °C. Resulting plasma samples (~150 µL) were stored at -80 °C until analysis.

[002159] Following sacrifice, tumors were immediately dissected on ice, flash frozen in liquid N_2, and stored at -80 °C until analysis.

[002160] To 55 µL of plasma samples, 200 µL of methanol containing 150 – 250 ng/mL internal standard(s) was added. Samples were vortex mixed for approximately 1.5 minutes at ambient temperature and then centrifuged at 4400 rpm for 10 min at approximately 4 °C. The resulting supernatants (175 µL) were transferred to a 96-well plate and dried under nitrogen at 40 °C. Dried samples were reconstituted with 100 µL 50/50 (v/v) water/methanol, vortex mixed and 10 µL were injected into LC-MS/MS.

[002161] Tumor samples were weighed and homogenized in 5 volume of ice-cold phosphate buffered saline on ice using a hand-held homogenizer. To 55 µL of tumor homogenate samples, 200 µL of methanol containing 150 – 250 ng/mL internal standard(s) was added. Samples were vortex mixed for approximately 1.5 minutes at ambient temperature and then centrifuged at 4400 rpm for 10 min at approximately 4 °C. The resulting supernatants (175 µL) were transferred to a 96-well plate and dried under nitrogen at 40 °C. Dried samples were reconstituted with 100 µL 50/50 (v/v) water/methanol, vortex mixed and 10 µL were injected into LC-MS/MS.

[002162] Plasma and tumor samples were analyzed by LC-MS/MS using an Agilent 1100 HPLC (Agilent Technologies, Santa Clara, CA) interfaced to an API 4000 tandem mass spectrometer (Applied Biosystems, Foster City, CA). The separation was performed on a Kinetex 2.6µm C18 (30 x 2.1 mm; 100 Å) column (Phenomenex, Torrance, CA) with a run time of 3.5 min per sample using the mobile phase consisted of 0.1% formic acid (A) and acetonitrile including 0.1% formic acid (B). The conditions for elution were as follows: 5 to 95% B (0 –1.7 min), 95% B (1.7 – 2.0 min), 95 to 5% B (2.0 – 2.1 min), and 5% B (2.1 – 3.5 min). The flow rate was 0.5 mL/min. Detection was accomplished in the positive electrospray ionization mode by selected reaction monitoring of the mass transitions m/z 1434.70 → 790.50 for **SDC-TRAP-0426**, m/z 1353.80 → 727.70 for **SDC-TRAP-0428**, m/z 1424.80 → 798.90 for **SDC-TRAP-0427**, and m/z 808.50 → 527.20 for docetaxel. For the internal standards, a deuterium-labeled form of ganetespib, an Hsp90 inhibitor (m/z 369.20 → 327.30) was used for **SDC-TRAP-0428**, **SDC-TRAP-0427** and **SDC-TRAP-0426**, and deuterium-labeled docetaxel (docetaxel-d9; m/z 817.50 → 527.20) was used for docetaxel. Quantitation for each analyte was done by extrapolation from a standard curve ranging from 2.50 to 50000 nM with $1/x^2$ weighting. As can be seen in Table 4, the sustained concentration of docetaxel delivered by these SDC-TRAP molecules is desirably higher than free docetaxel.

Table 4

Compound ID	**Docetaxel (D)**	**SDC-TRAP-0426**		**SDC-TRAP-0428**		**SDC-TRAP-0427**	
Dose	14mg/10mL/kg	25mg/10mL/kg		25mg/10mL/kg		25mg/10mL/kg	
Route	IV	IV		IV		IV	
Formulation	DRD	DRD		DRD		DRD	
Analyte Target	**(D)**	**SDC-TRAP-0426**	**(D)**	**SDC-TRAP-0428**	**(D)**	**SDC-TRAP-0427**	**(D)**
Time (h)	**Plasma Conc. (μM)**						
0.083	35.2	194	152	72.1	221	91.6	193
6	0.541	0.0311	2.71	1.94	17.1	20.9	18.7
24	0.0159	0.0111	0.126	0.00677	4.60	BQL	0.320
48	0.00262	BQL	0.0377	BQL	1.65	BQL	0.0988
72	--	--	--	0.00449	0.680	BQL	0.0929
Time (h)	**Tumor Conc. (nmol/g of tissue)**						
0.083	3.07	2.07	0.150	8.77	0.405	5.37	1.33
6	4.57	0.375	2.27	5.27	1.13	13.6	3.74
24	3.23	0.256	2.00	3.89	1.82	14.6	4.34
48	1.08	0.337	2.09	3.40	1.78	8.02	3.35
72	--	--	--	1.20	1.46	7.18	2.29

[002163] A second, optimized procedure detailed below was used to generate the data in Table 5, below.

[002164] Blood samples (~300 μL) were collected by cardiac puncture and immediately centrifuged at 6000 rpm for 8 minutes at approximately 4 °C. Resulting plasma samples (~150 μL) were transferred to Eppendorf tubes containing approximately 5- 10 mg of NaF, vortex mixed, and stored at -80 °C until analysis.

[002165] Following sacrifice tumors were immediately dissected on ice, flash frozen in liquid N_2, and stored at -80 °C until analysis.

[002166] To 60 μL of plasma samples, 25 μL of 75/25 (v/v) water/acetonitrile containing 100 ng/mL internal standard(s) and 200 μL of acetonitrile were added. Samples were vortex mixed for approximately 2 minutes at ambient temperature and then centrifuged at 4400 rpm for 10 min at approximately 4 °C. The resulting supernatants (300 μL) were transferred to a 96-well plate and dried under nitrogen at 40 °C. Dried samples were reconstituted with 50μL 60/40 (v/v) water/acetonitrile, vortex mixed and 10 μL were injected into LC-MS/MS.

[002167] Tumor samples were weighed and homogenized in 3 volume of ice-cold phosphate buffered saline on ice using a hand-held homogenizer. To 60 μL of tumor homogenate samples, 25 μL of 75/25 (v/v) water/acetonitrile containing 100 ng/mL internal standard(s) and 200 μL of acetonitrile were added. Samples were vortex mixed for approximately 2 minutes at ambient temperature and then centrifuged at 8000 rpm for 8 min at approximately 4 °C. The resulting supernatants (200 μL) were transferred to a 96-well plate and dried under nitrogen at 40 °C. Dried samples were reconstituted with 60μL 60/40 (v/v) water/acetonitrile, vortex mixed and 10 μL were injected into LC-MS/MS.

[002168] Plasma and tumor samples were analyzed by LC-MS/MS using an Agilent 1100 HPLC (Agilent Technologies, Santa Clara, CA) interfaced to an API 4000 tandem mass spectrometer (Applied Biosystems, Foster City, CA). The separation of analytes were performed on a Symmetry Shield 5μm C18 (2.1x100mm; 100Å) column (Waters, Milford, MA) with a run time of 5.0 min per sample using the mobile phase consisted of 0.1% formic acid (A) and acetonitrile containing 0.1% formic acid (B). The conditions for elution were as follows: 10% B (0 –0.5 min), 10 to 25% B (0.5 – 1.5 min), 25 to 95% B (1.5 – 3.0 min), 95% B (3.0 – 3.5 min), 95 – 10% B (3.5 – 4.0 min) and 10% B (4.0 – 5.0 min). The flow rate was 0.6 mL/min. Detection was accomplished in the positive electrospray ionization mode by selected reaction monitoring of the mass transitions m/z 1424.74 → 324.30 for **SDC-TRAP-0427**, m/z 635.37 → 324.30 for [NDP], m/z 1369.60 → 725.40 for SDC-TRAP-0423, and m/z 808.50 → 527.20 for docetaxel. For the internal standards, the following compounds were used: **SDC-TRAP-0428** (m/z 1353.69 → 324.37) for **SDC-TRAP-0427**, the Hsp90 inhibitor moiety (m/z 645.40 → 462.30) of [NDP], the Hsp90 inhibitor moiety (m/z 731.38 → 312.23) of SDC-TRAP-0423 and deuterium-labeled docetaxel (docetaxel-d9; m/z 817.50 → 527.20) for docetaxel. Quantitation for each analyte was done by extrapolation from a standard curve ranging from 1.00 to 25000 ng/mL with $1/x^2$ weighting. As can be seen in Table 5, the sustained concentration of docetaxel delivered by these SDC-TRAP molecules is desirably higher than free docetaxel.

Table 5

Compound ID	SDC-TRAP-0427			SDC-TRAP-0423		Docetaxel
Lot	N/A			N/A		N/A
Dose	7mg/10mL/kg			7mg/10mL/kg		4mg/10mL/kg
Species	Female SCID Mouse (H1975)			Female SCID Mouse (H1975)		F SCID MO (H1975)
Route	IV			IV		IV
Formulation	DRD			DRD		DRD
Appearance	N/A			N/A		N/A
Accuracy	N/A			N/A		N/A
Analyte Target	SDC-TRAP-0427	Non-docetaxel portion [NDP] of SDC-TRAP-0427	(D)	SDC-TRAP-0423	(D)	(D)
Time (h)	Plasma Conc. (µM)					
6	8.39	0.185	0.0795	2.21	0.0838	0.0424
48	0.0118	0.00180	0.00446	BQL	0.00138	BQL
72	0.0101	0.00190	0.00238	BQL	BQL	BQL
Time (h)	Tumor Conc. (nmol/g of tissue)					
6	1.19	0.149	1.11	0.730	0.921	0.818
48	0.458	0.0438	0.753	0.0538	0.857	0.377
72	0.372	0.0475	0.815	0.0186	0.587	0.275

[002169] All publications, patent applications, patents, and other documents cited herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control.

[002170] The specification should be understood as disclosing and encompassing all possible permutations and combinations of the described aspects, embodiments, and examples unless the context indicates otherwise. One of ordinary skill in the art will appreciate that the invention can be practiced by other than the summarized and described aspect, embodiments, and examples, which are presented for purposes of illustration, and that the invention is limited only by the following claims.

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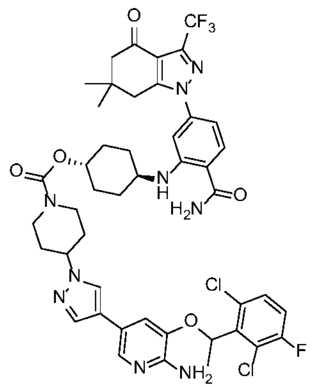
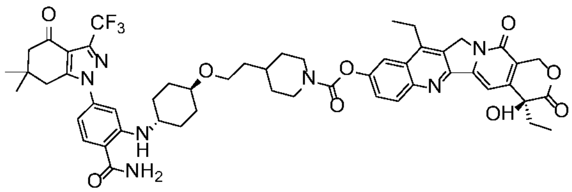
WHAT IS CLAIMED IS:

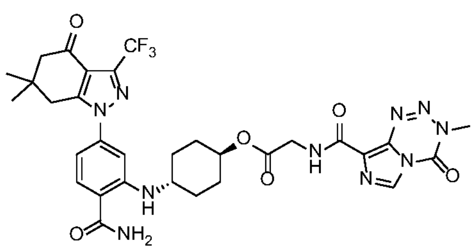
1. A binding moiety-drug conjugate (SDC-TRAP) comprising a binding moiety and an effector moiety, wherein the binding moiety is SNX-5422, and wherein the SDC-TRAP is a compound selected from the group consisting of



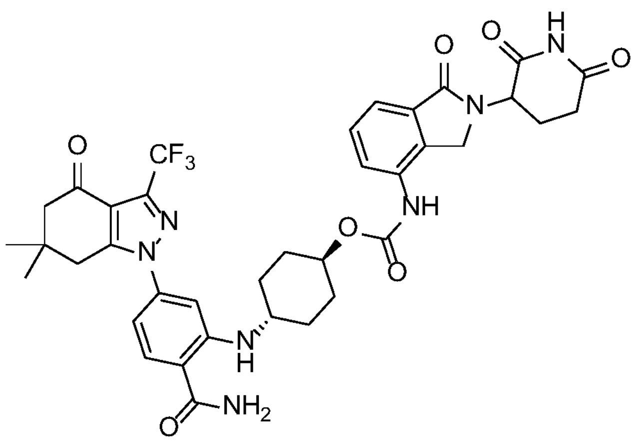
(SDC-TRAP-0276),



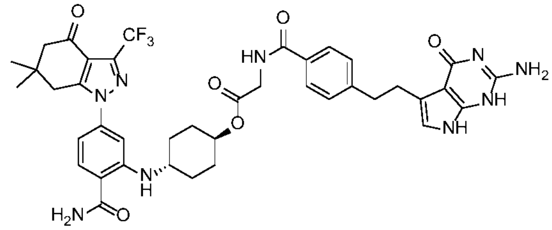
(SDC-TRAP-0277),



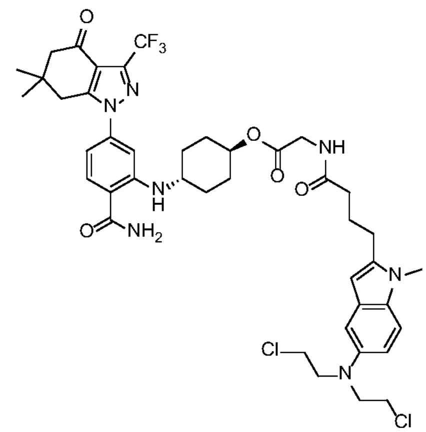
(SDC-TRAP-0278),

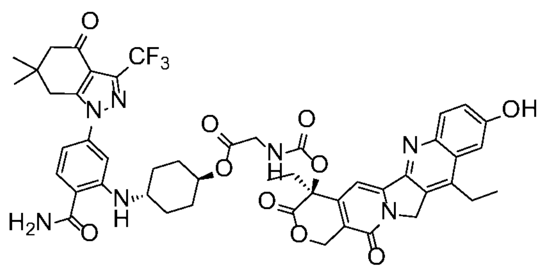


(SDC-TRAP-0279),

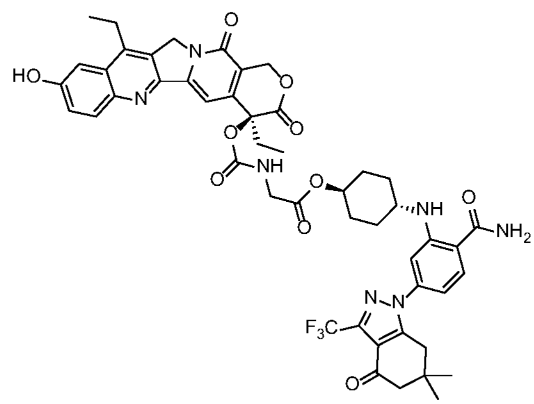


(SDC-TRAP-0280),

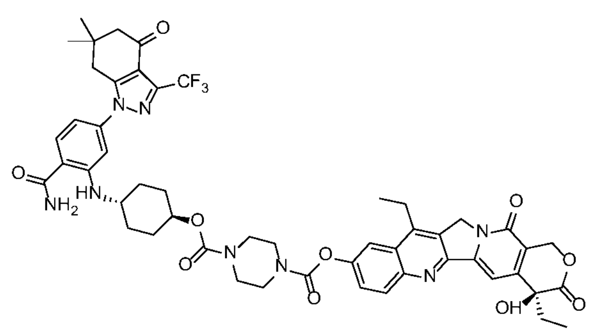




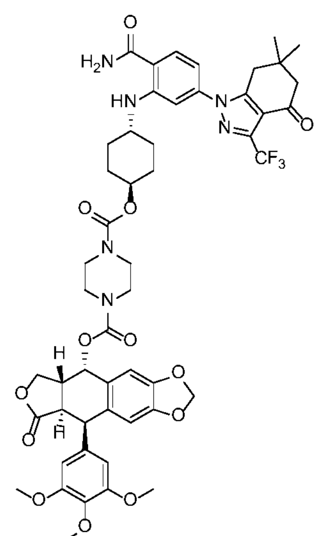
(SDC-TRAP-0281),



(SDC-TRAP-0282), (SDC-TRAP-0283),



(SDC-TRAP-0284),



(SDC-

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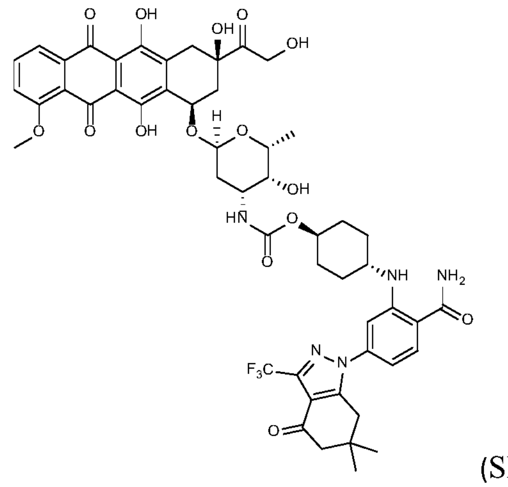
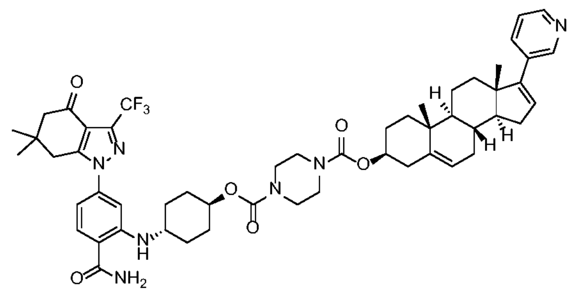
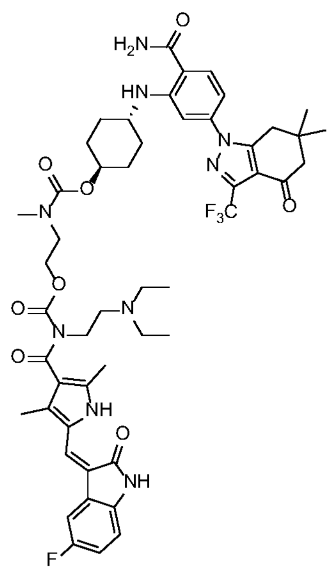
TRAP-0285),



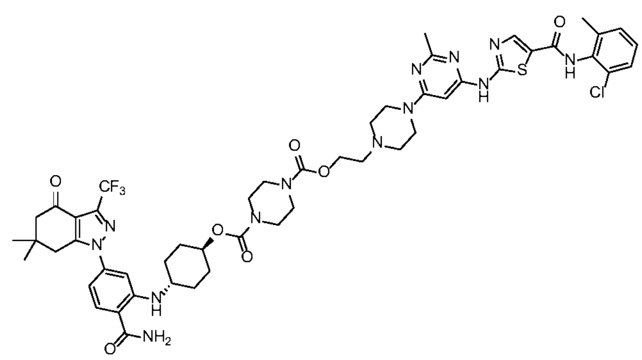
(SDC-TRAP-0286),



(SDC-TRAP-0287),



(SDC-TRAP-0288),



(SDC-TRAP-0289),

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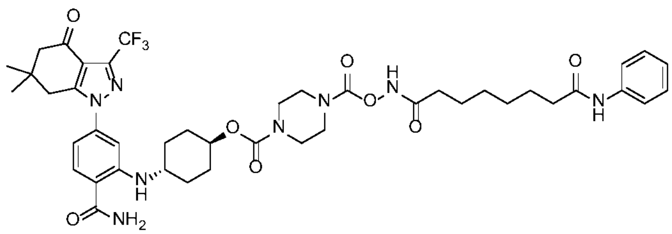
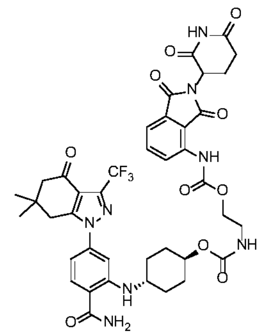
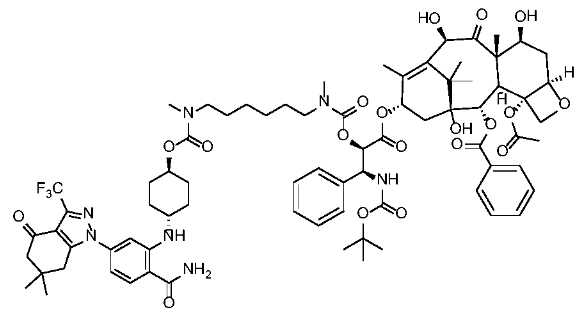


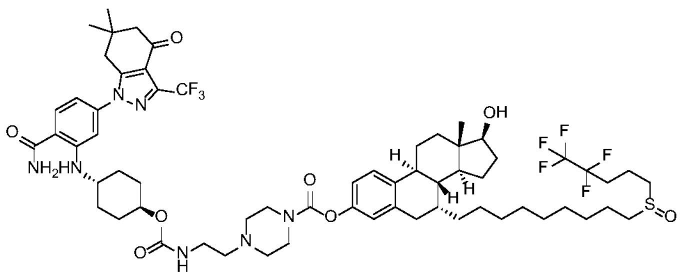
(SDC-TRAP-0290),



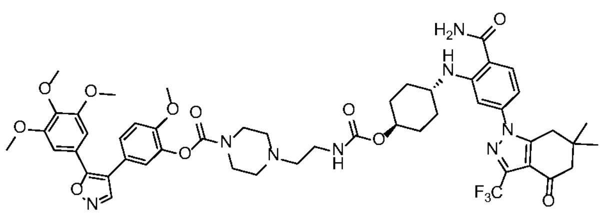
(SDC-TRAP-0291),



(SDC-TRAP-0292),



(SDC-TRAP-0293), and



(SDC-TRAP-0294), or a pharmaceutically acceptable salt thereof.

2. A pharmaceutical composition comprising a therapeutically effective amount of at least one SDC-TRAP of claim 1, and at least one pharmaceutical excipient.

3. A method for treating cancer a subject in need thereof comprising administering a therapeutically effective amount of at least one SDC-TRAP of claim 1 to the subject, thereby treating the subject.

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4. The method of claim 3, wherein the subject has a colon cancer, a breast cancer, an ovarian cancer, a lung cancer, or a skin cancer.

5. The method of claim 4, wherein the lung cancer comprises small cell lung cancer.

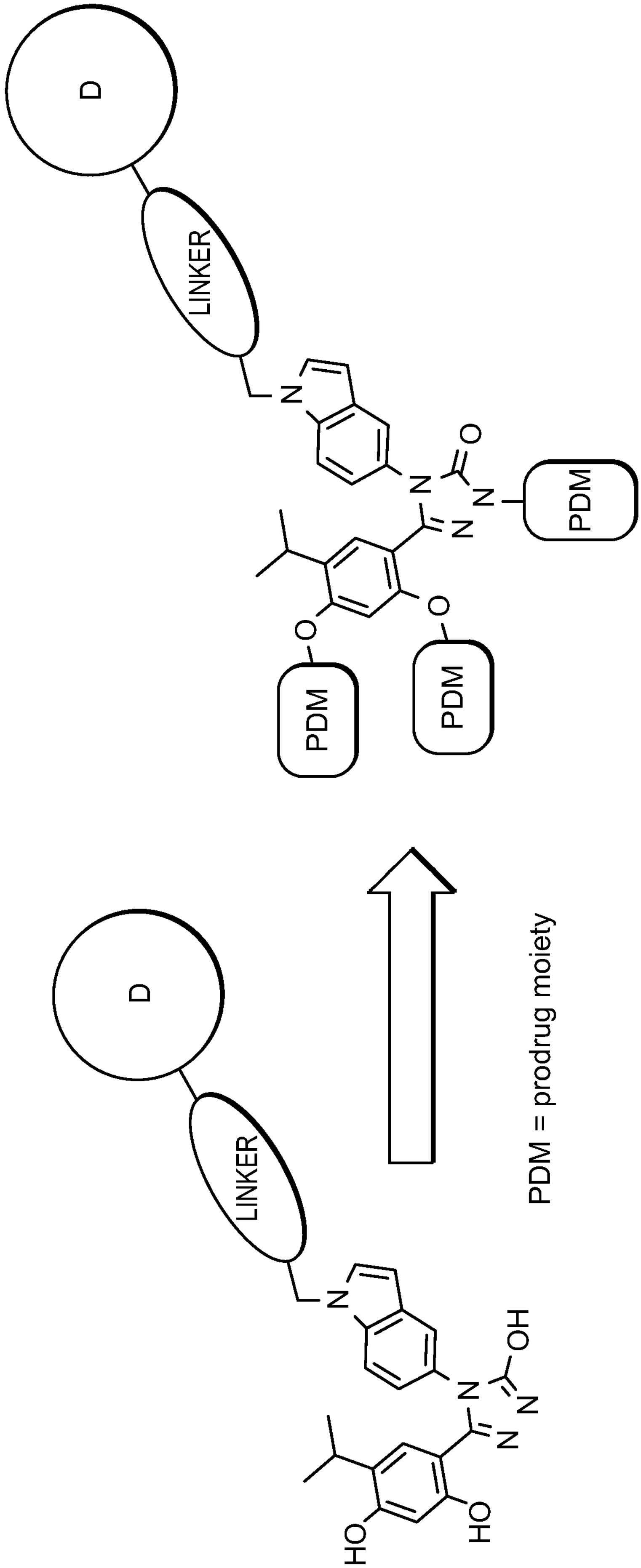


FIG. 1

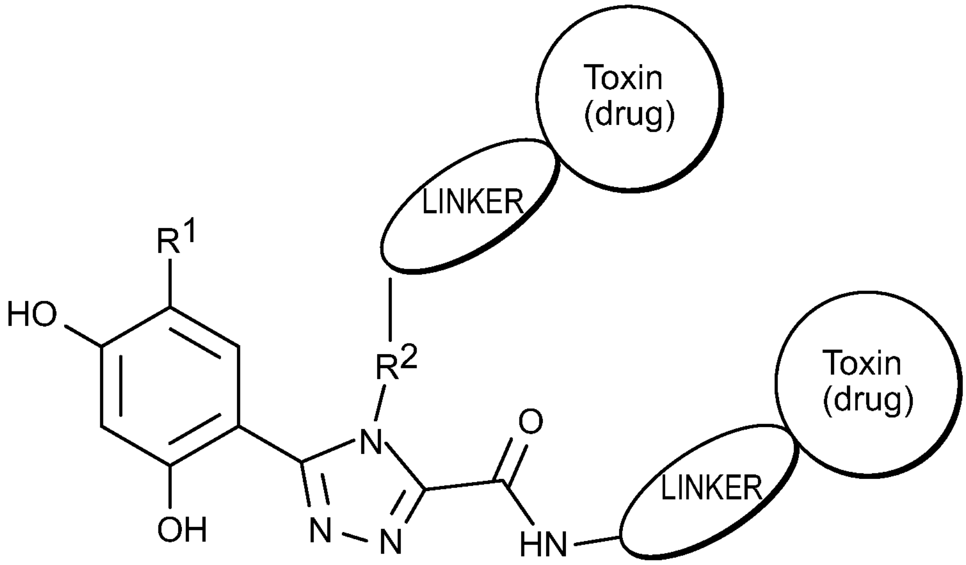


FIG. 2

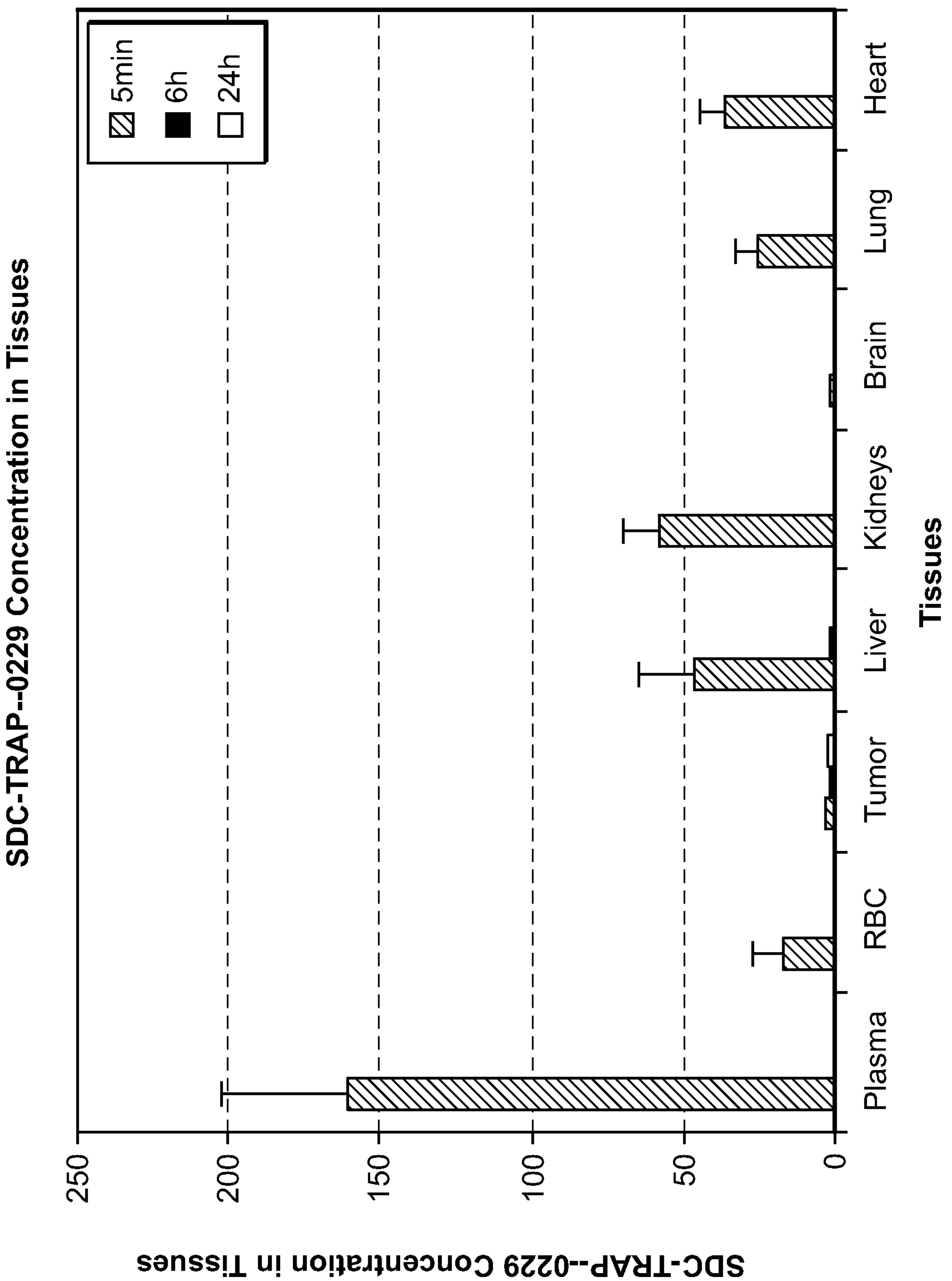
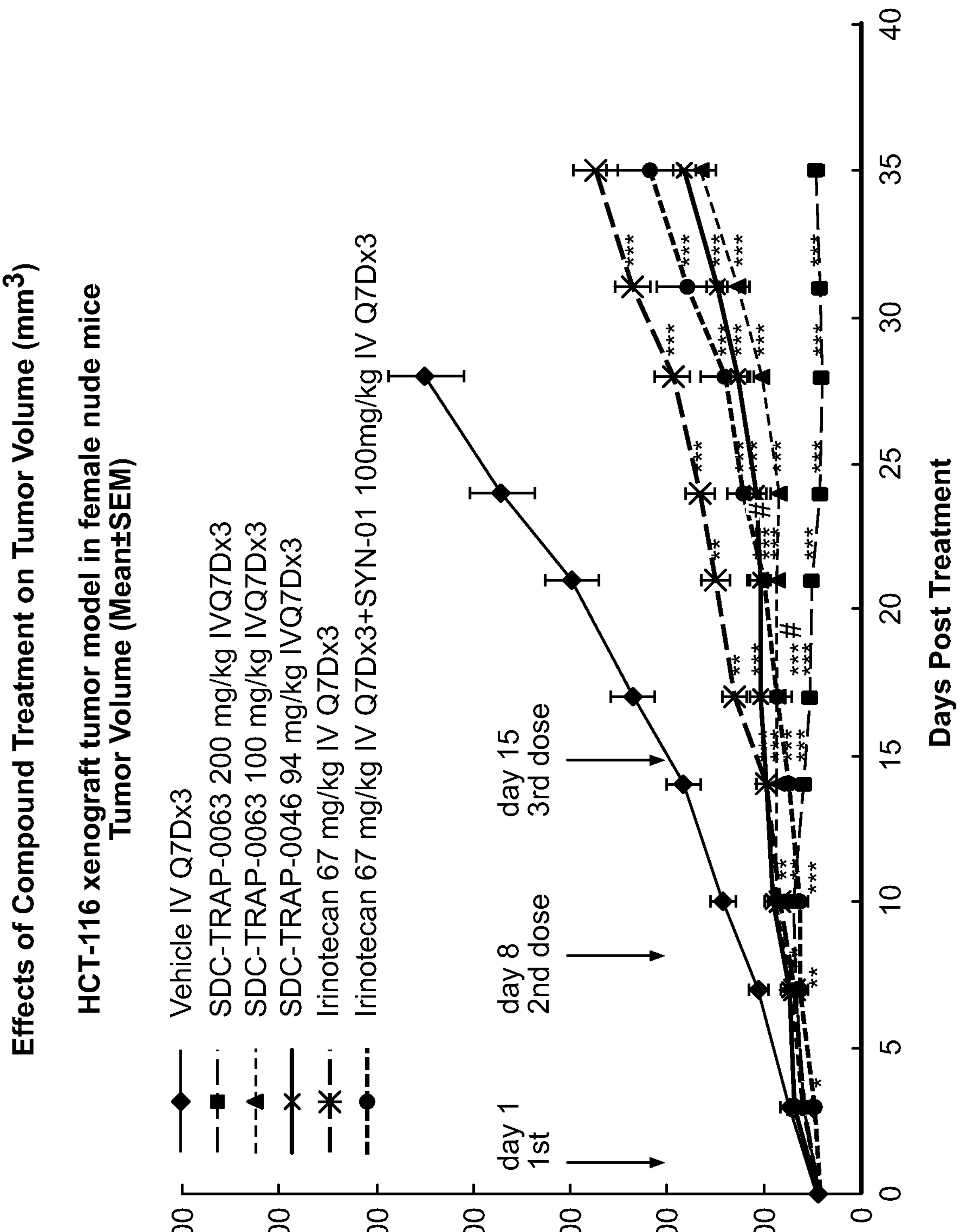

SDC-TRAP--0229 Concentration in Tissues
SDC-TRAP--0229 Concentration in Tissues
250
200
150
100
50
0
5min
6h
24h
Plasma
RBC
Tumor
Liver
Kidneys
Brain
Lung
Heart
Tissues

FIG. 3

FIG. 4



*Data expressed as Mean ± SEM, * P < 0.05, ** P < 0.01 and *** P < 0.001 compared to vehicle group # P < 0.05 compared to irinotecan single agent group*

FIG. 5

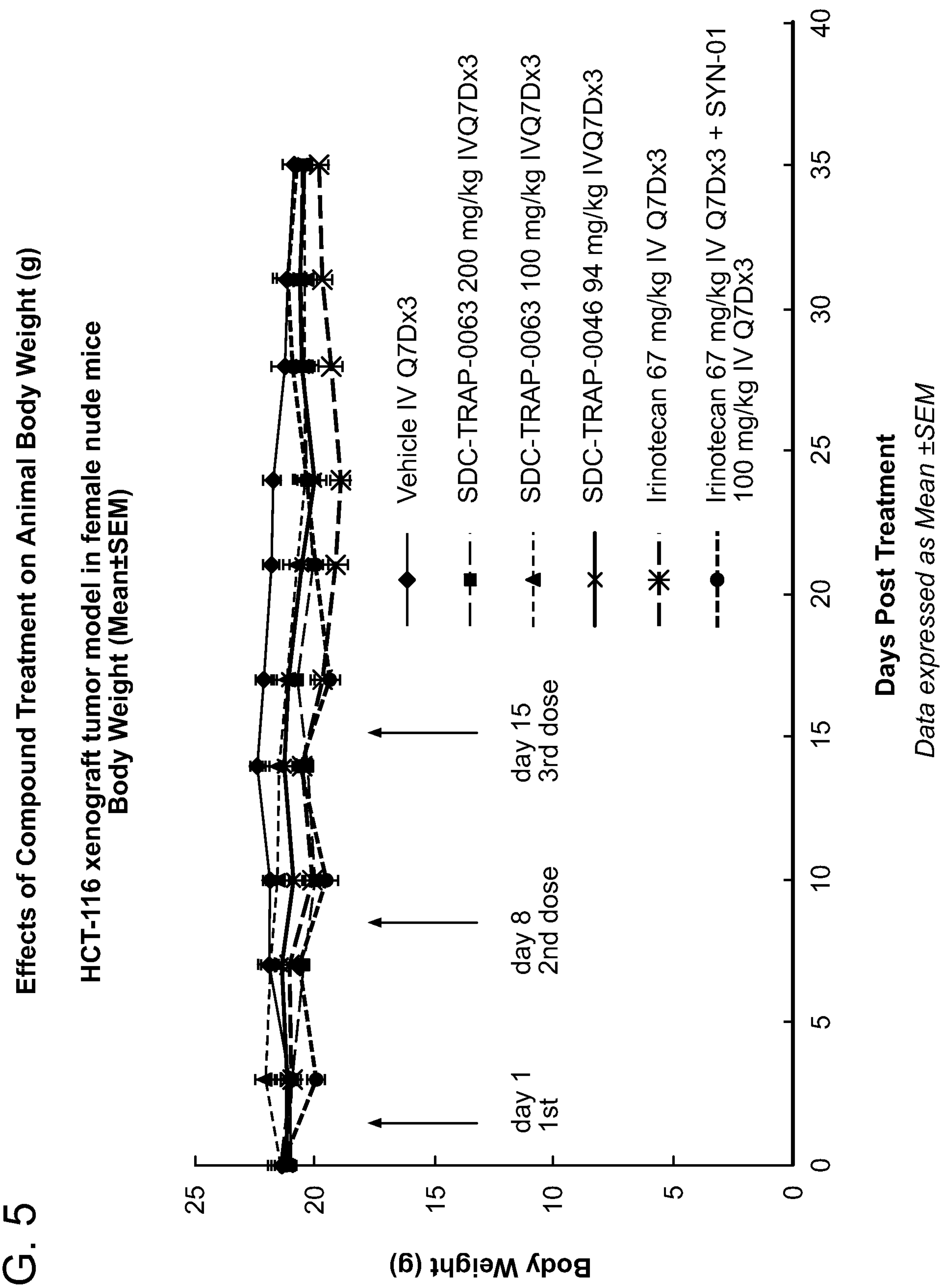

Effects of Compound Treatment on Animal Body Weight (g)
HCT-116 xenograft tumor model in female nude mice
Body Weight (Mean±SEM)
Body Weight (g)
0
5
10
15
20
25
0
5
10
15
20
25
30
35
40
day 1
1st
day 8
2nd dose
day 15
3rd dose
Vehicle IV Q7Dx3
SDC-TRAP-0063 200 mg/kg IVQ7Dx3
SDC-TRAP-0063 100 mg/kg IVQ7Dx3
SDC-TRAP-0046 94 mg/kg IVQ7Dx3
Irinotecan 67 mg/kg IV Q7Dx3
Irinotecan 67 mg/kg IV Q7Dx3 + SYN-01
100 mg/kg IV Q7Dx3
Days Post Treatment
Data expressed as Mean ±SEM

FIG. 6

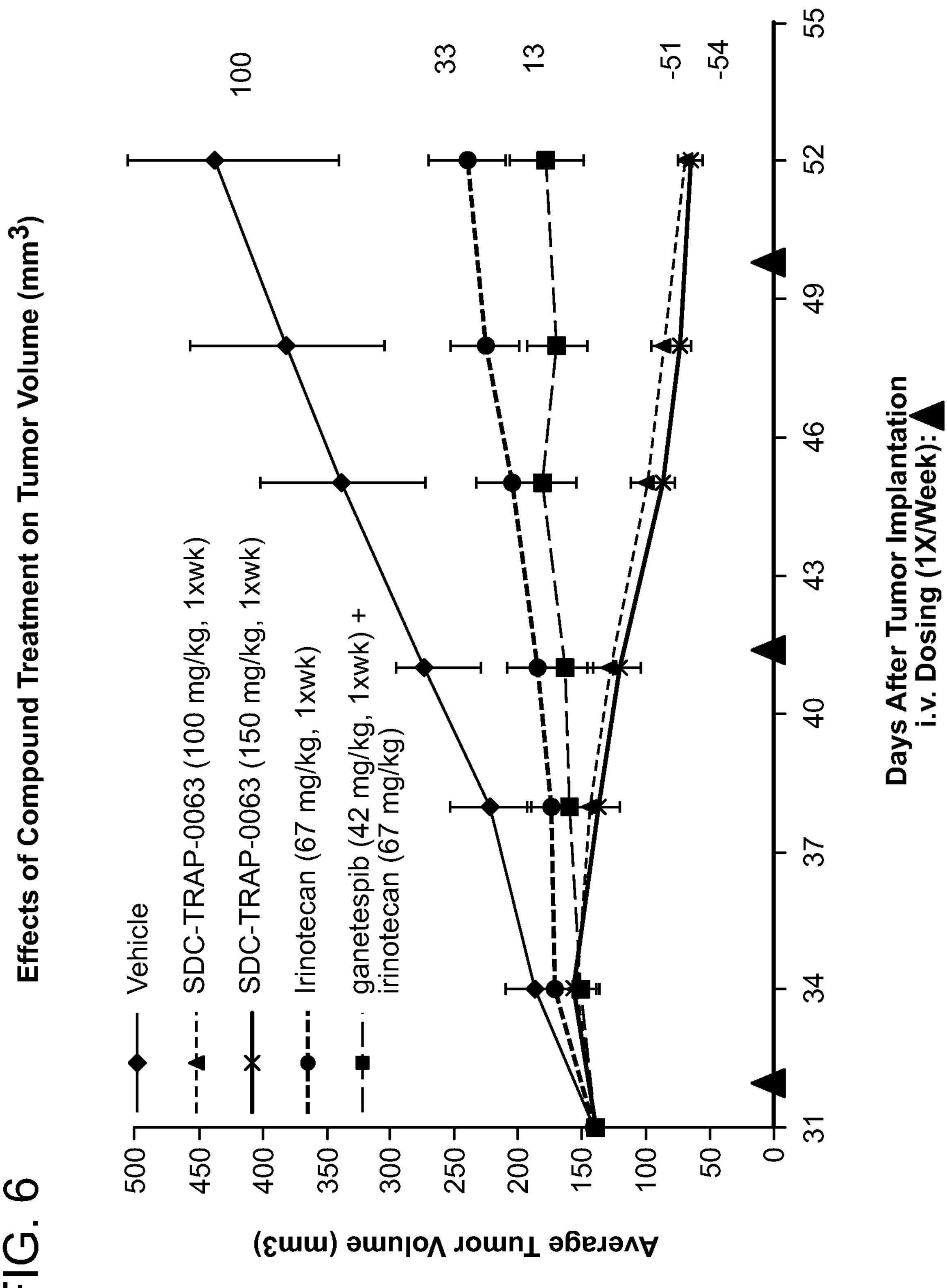

Effects of Compound Treatment on Tumor Volume (mm3)
Vehicle
SDC-TRAP-0063 (100 mg/kg, 1xwk)
SDC-TRAP-0063 (150 mg/kg, 1xwk)
Irinotecan (67 mg/kg, 1xwk)
ganetespib (42 mg/kg, 1xwk) + irinotecan (67 mg/kg)
Average Tumor Volume (mm3)
500
450
400
350
300
250
200
150
100
50
0
31
34
37
40
43
46
49
52
55
100
33
13
-51
-54
Days After Tumor Implantation
i.v. Dosing (1X/Week):

FIG. 7

Effects of Compound Treatment on Animal Body Weight (g)

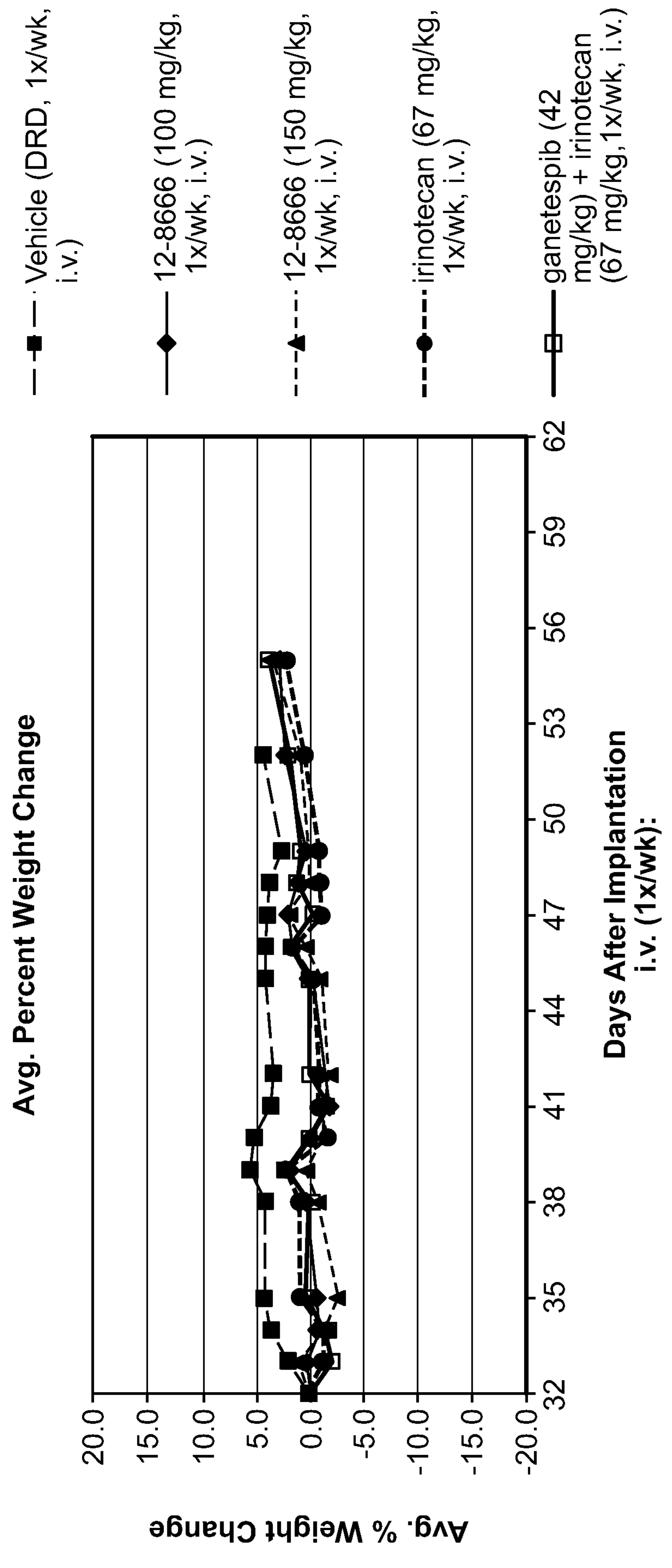


FIG. 8

Effects of Compound Treatment on Tumor Volume (mm^3)

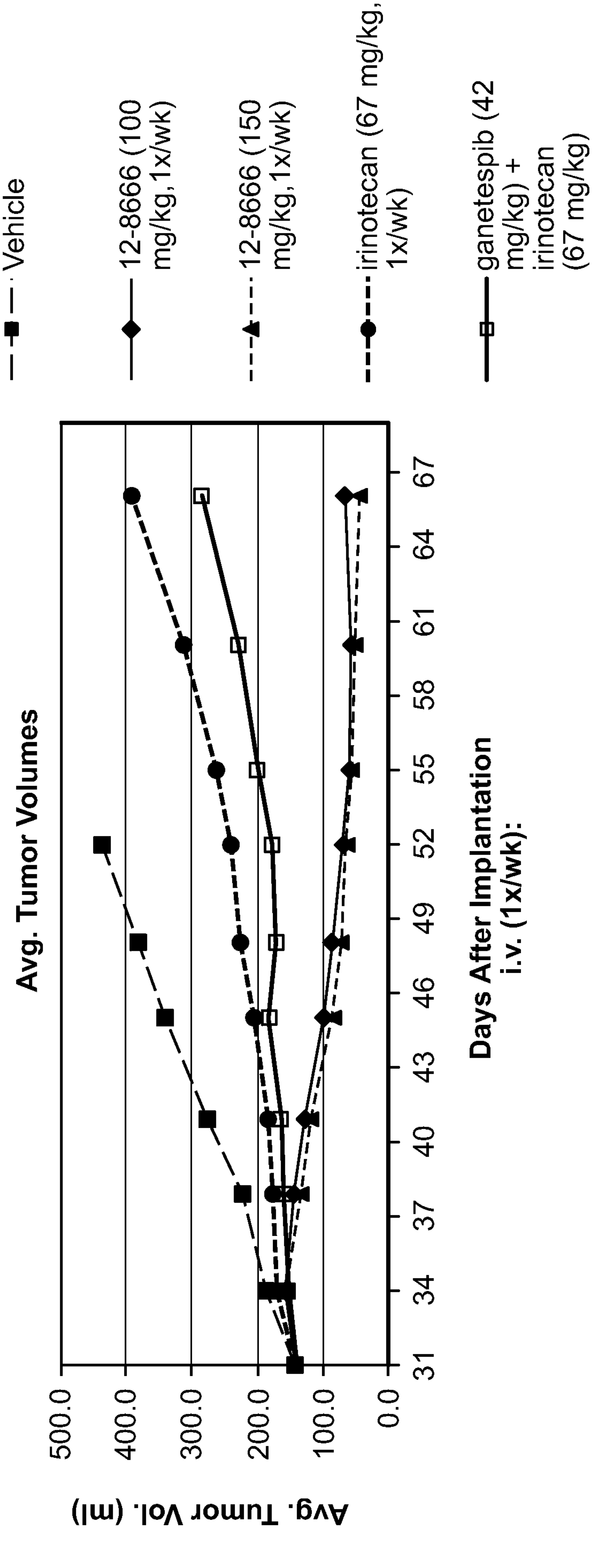


FIG. 9 **SDC-TRAP-0063 Tissue Distribution Study in Female SCID Mice**

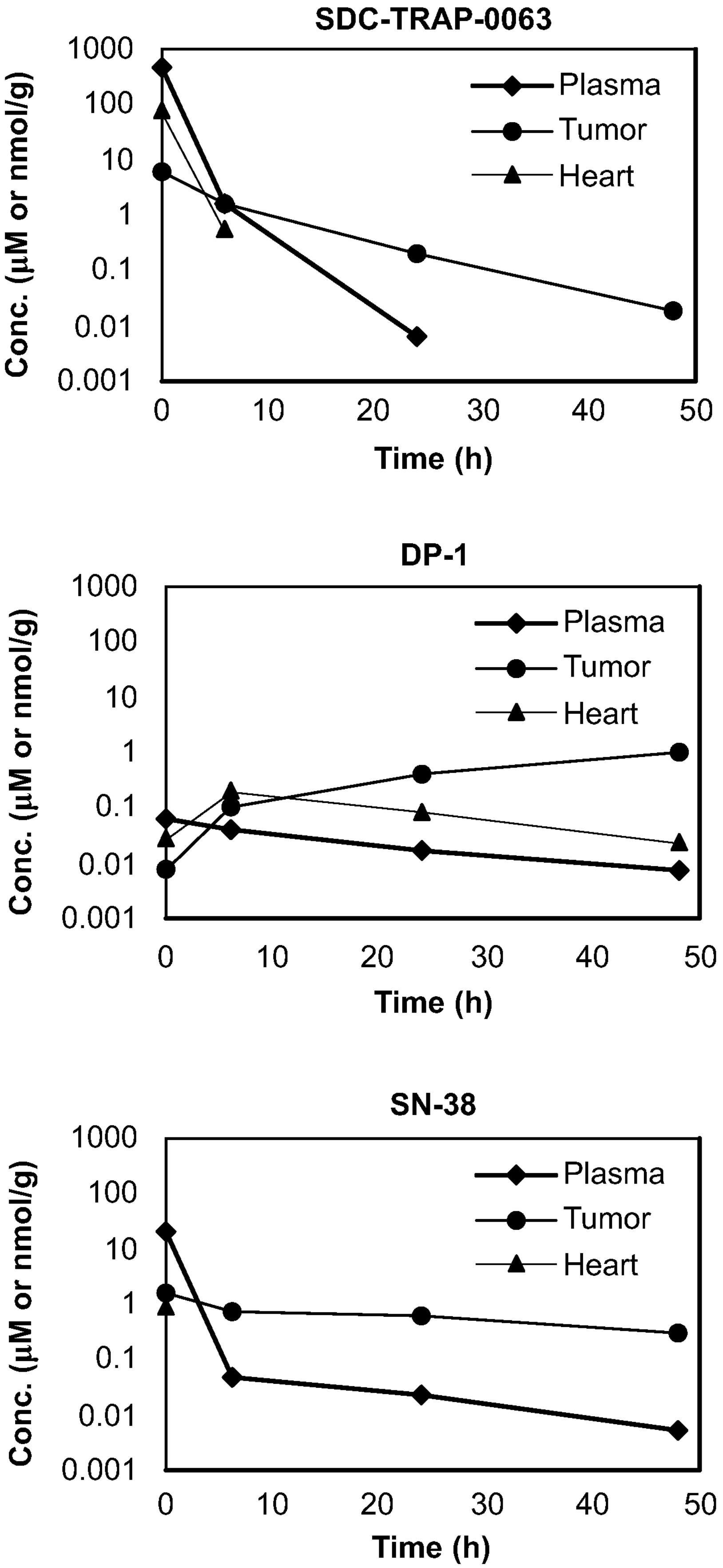


FIG. 10 SDC-TRAP-0063 Tissue Distribution Study in Male SD Mice

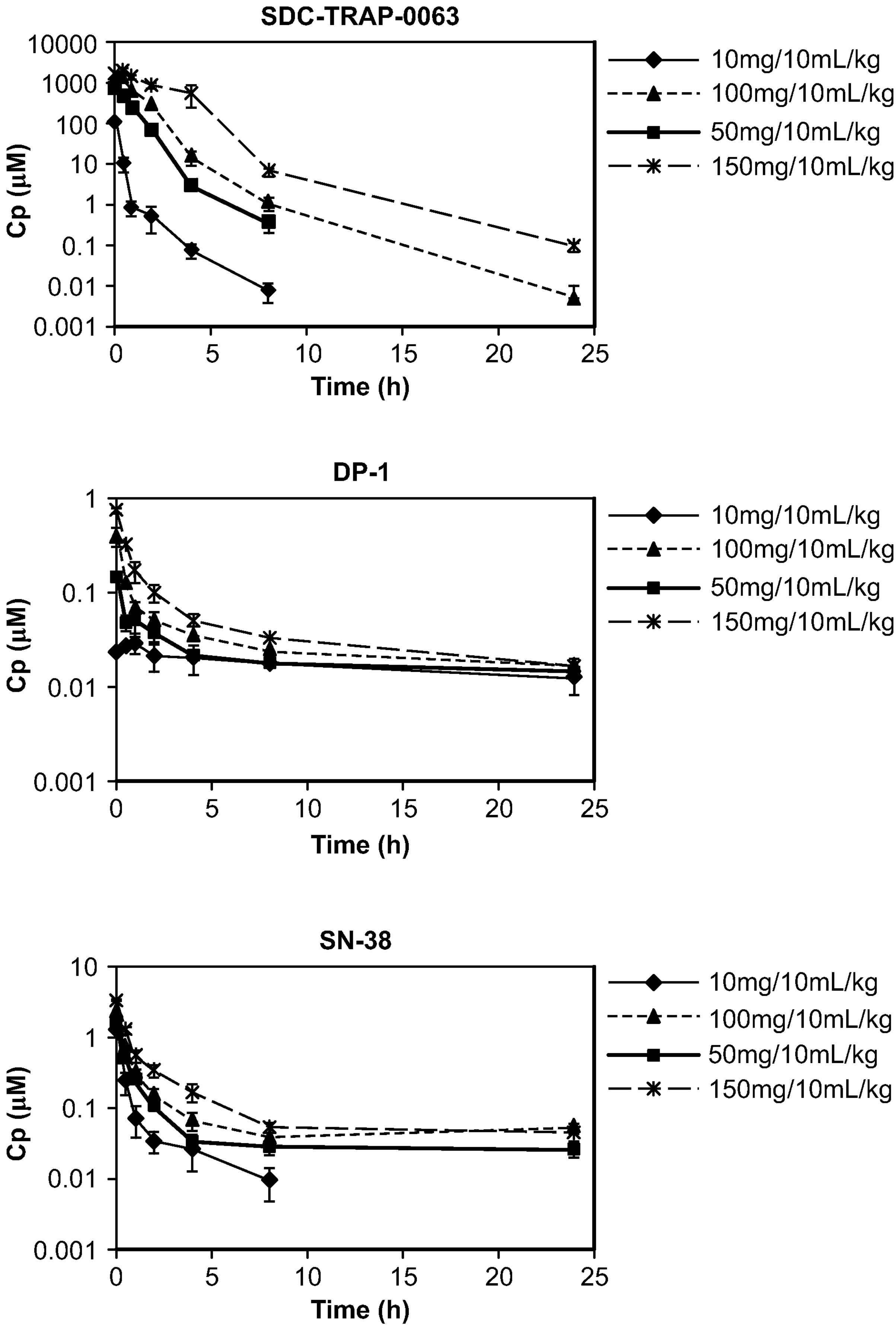


FIG. 11 **SDC-TRAP-0063 Tissue Distribution Study in Male CD-1 Mice**

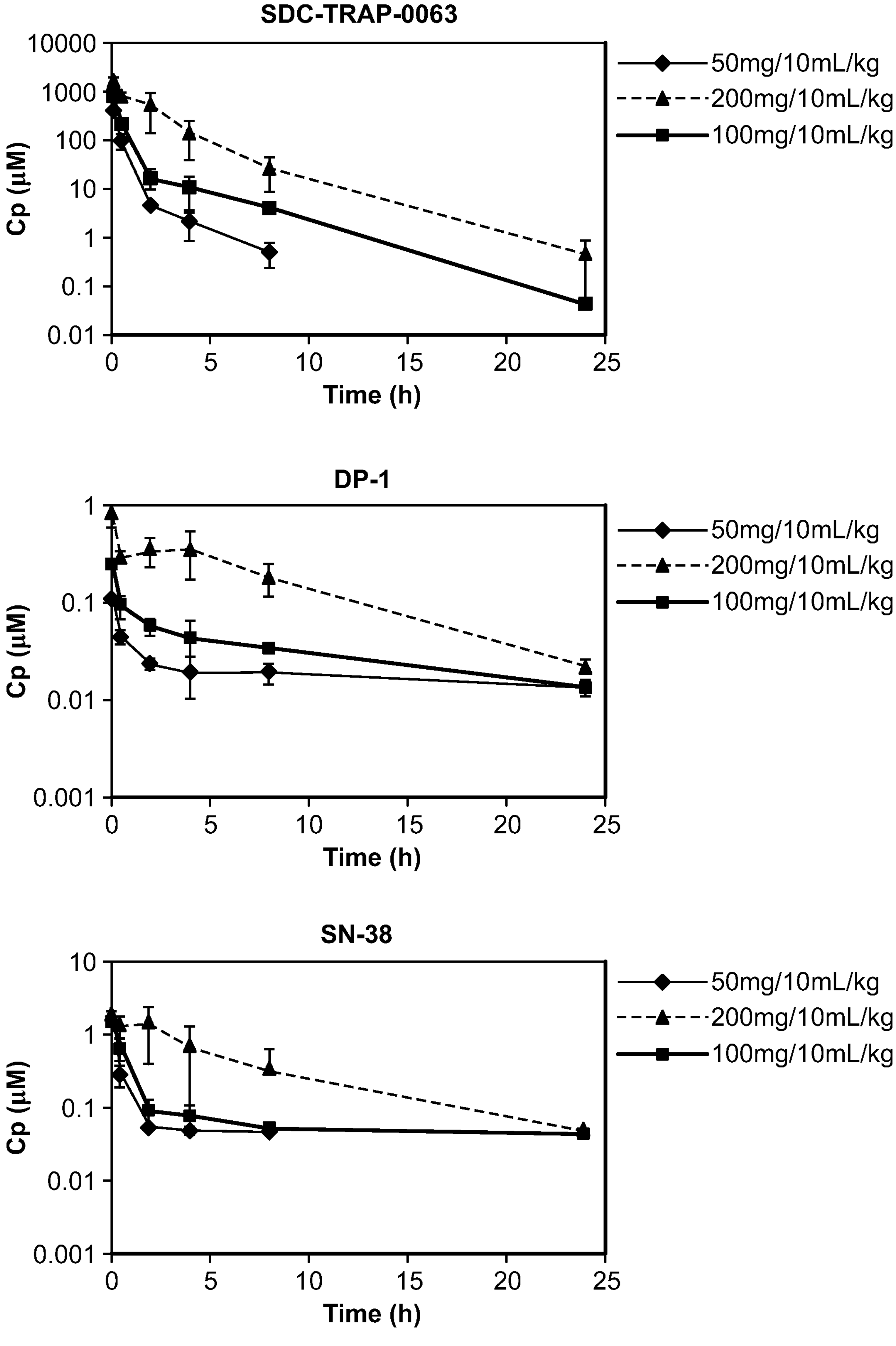


FIG. 12

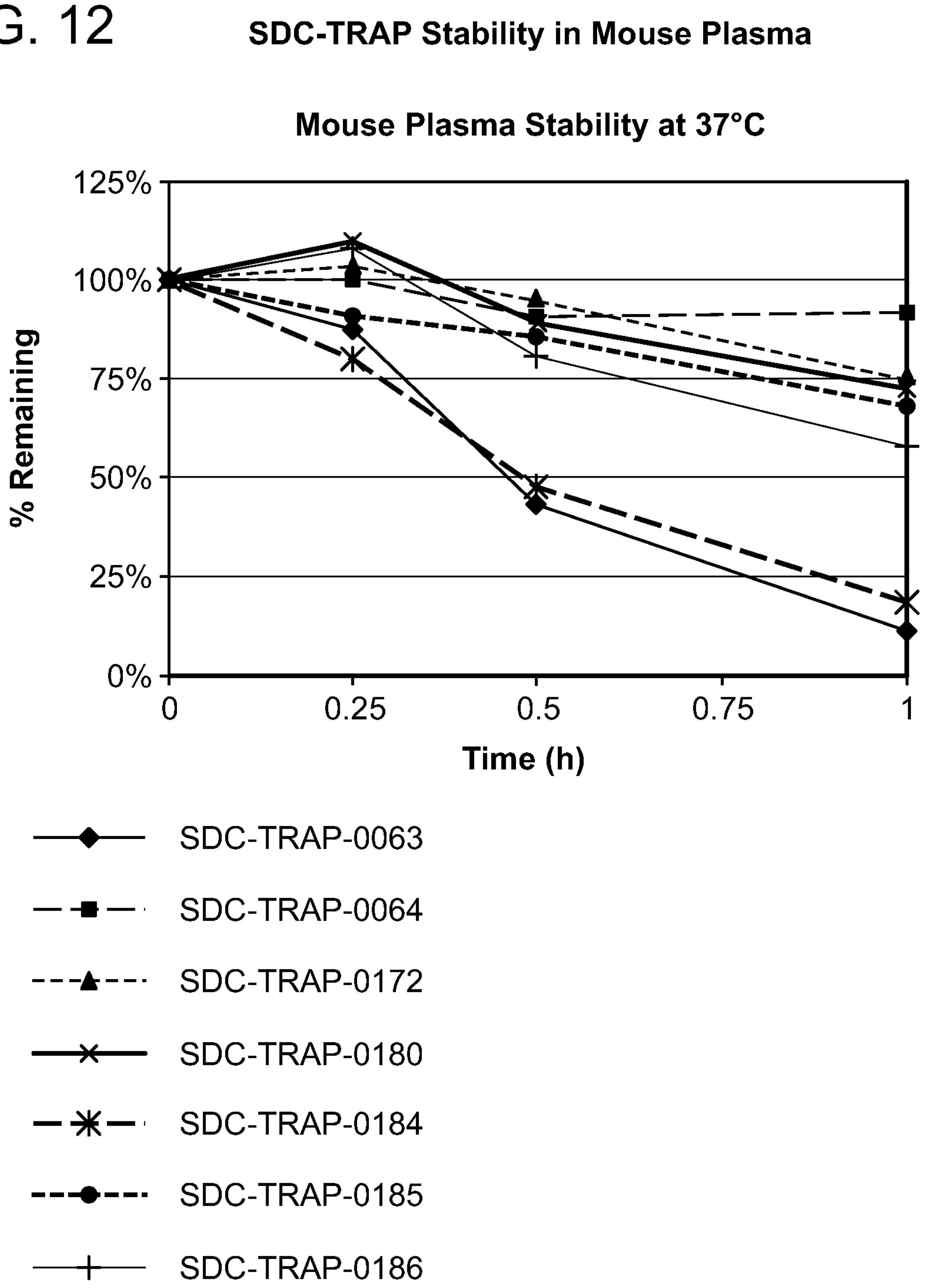
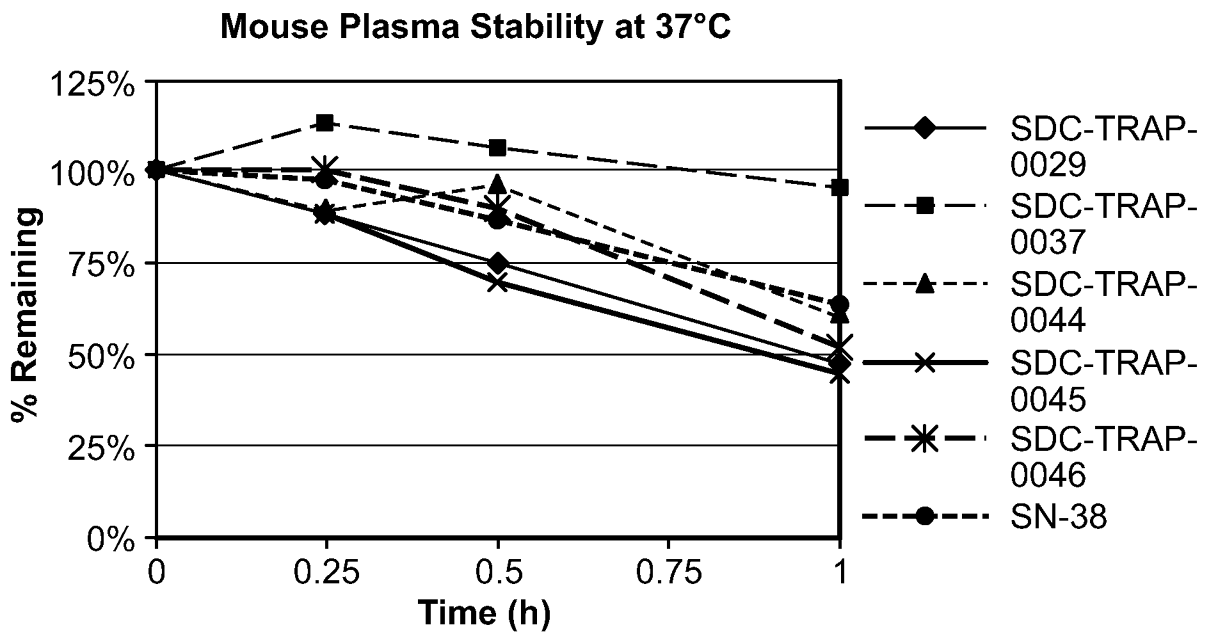
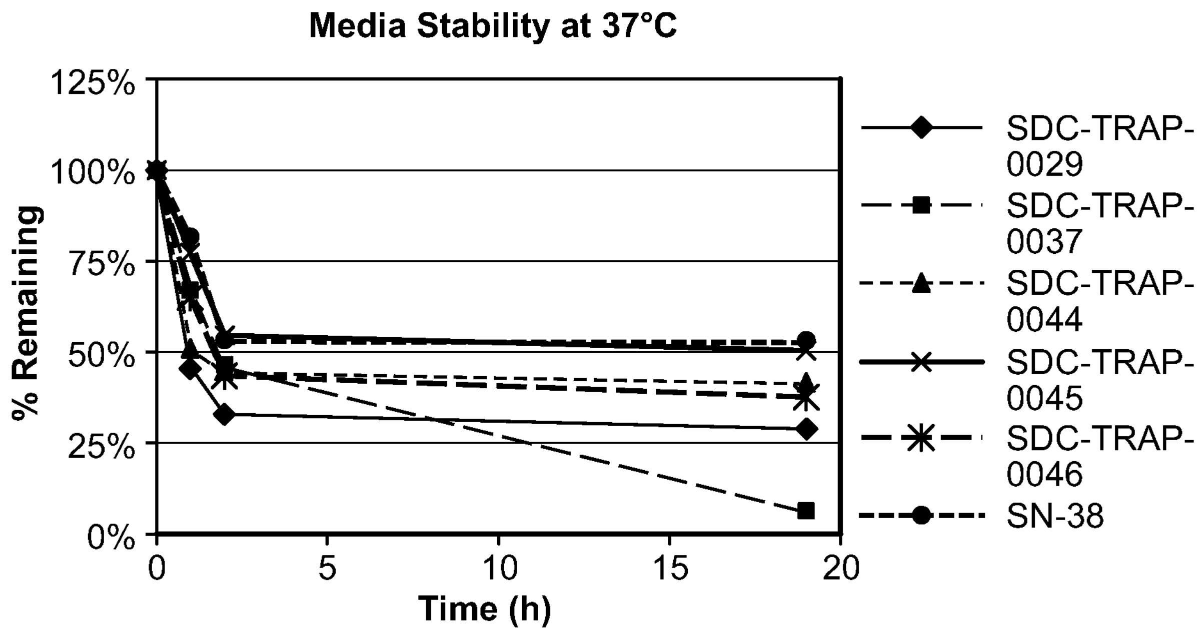

SDC-TRAP Stability in Mouse Plasma
Mouse Plasma Stability at 37°C
125%
100%
75%
50%
25%
0%
% Remaining
0
0.25
0.5
0.75
1
Time (h)
SDC-TRAP-0063
SDC-TRAP-0064
SDC-TRAP-0172
SDC-TRAP-0180
SDC-TRAP-0184
SDC-TRAP-0185
SDC-TRAP-0186

FIG. 13 **SDC-TRAP Stability in Mouse Plasma and Cell Culture Media**





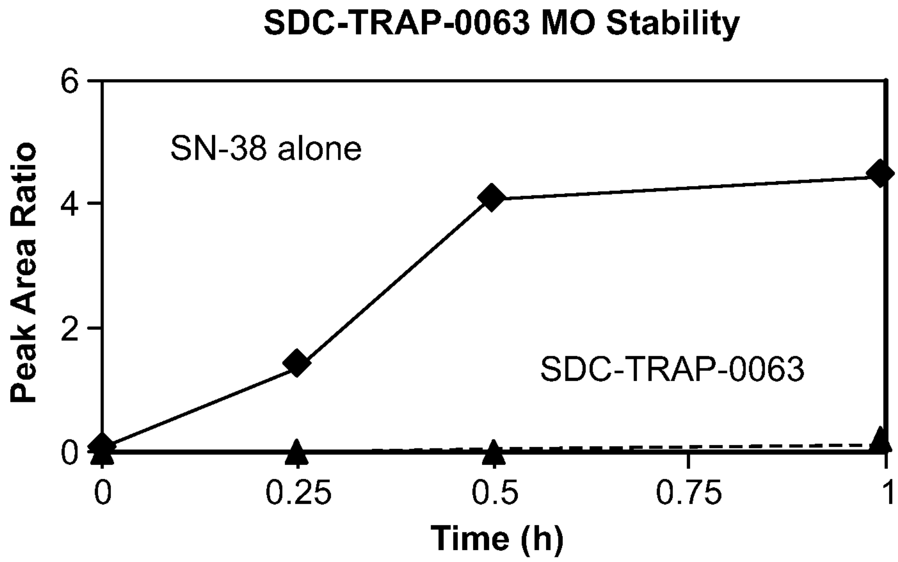


FIG. 14

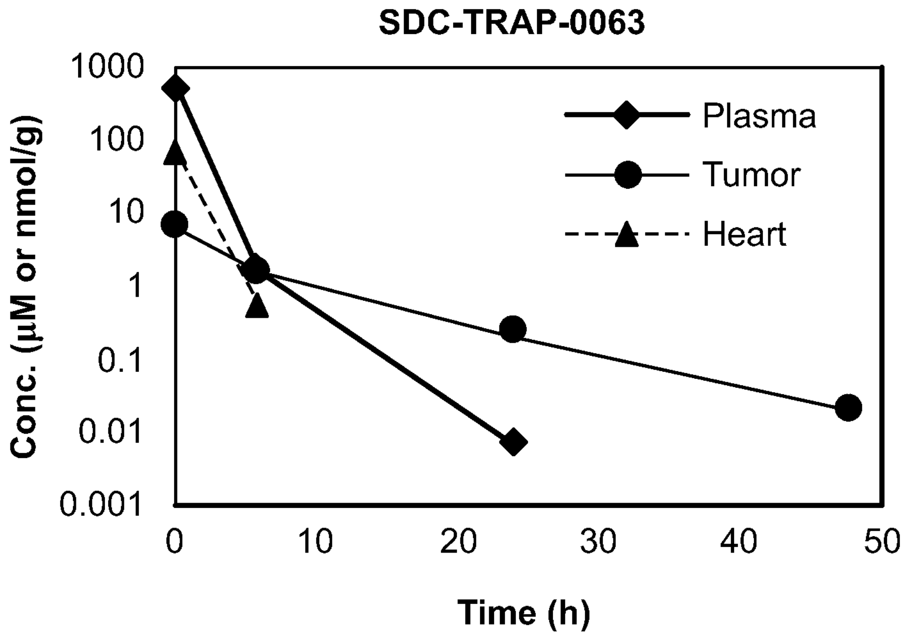


FIG. 15A

FIG. 15B

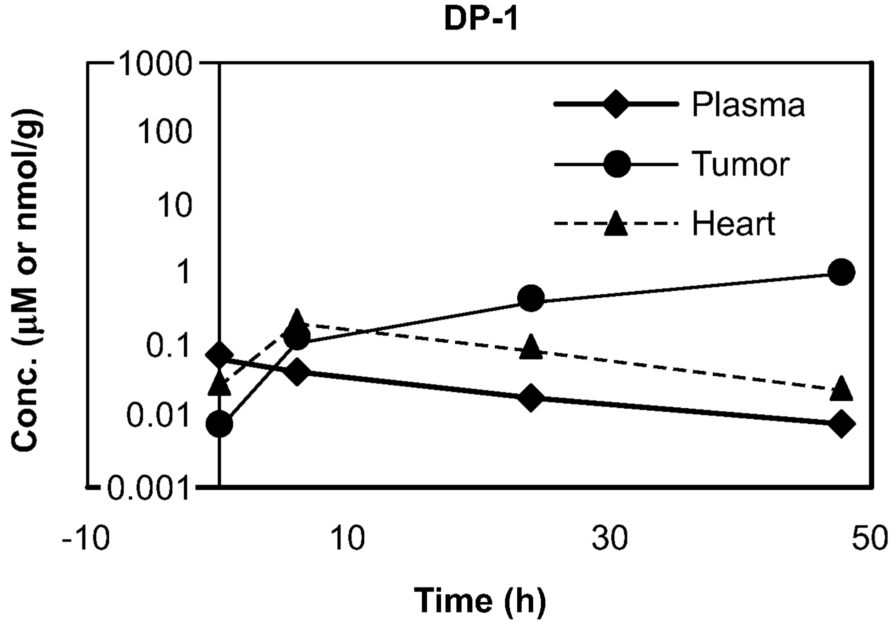


FIG. 15C

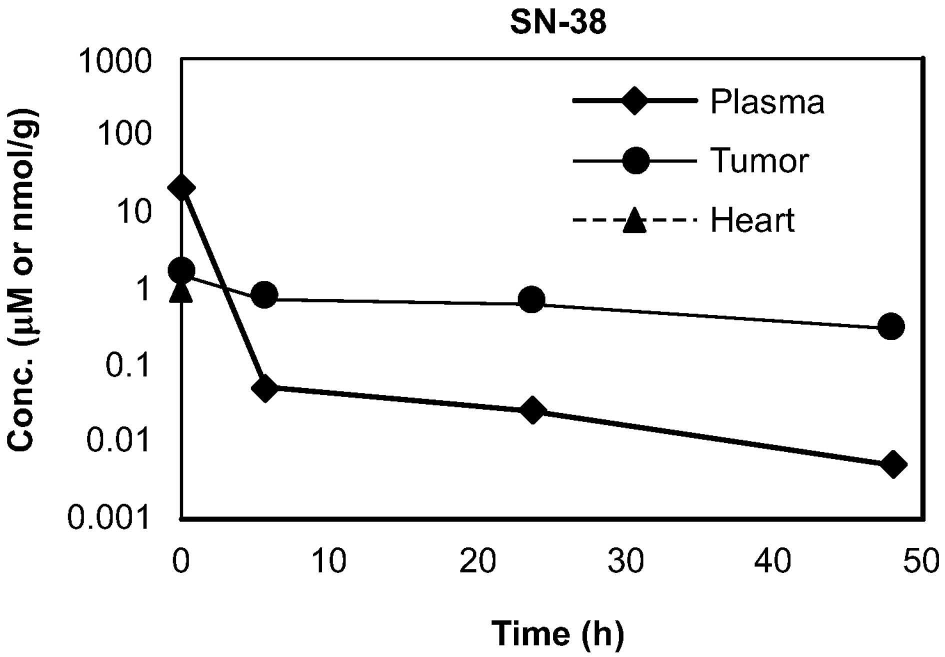


FIG. 16 **Kinetic solubility of SDC-TRAP-0063 lot 6 and lot 8 in ganetespib placebo formulation (35% v/v tween 80, 40% v/v PEG-300, 25% v/v dehydrated alcohol)**

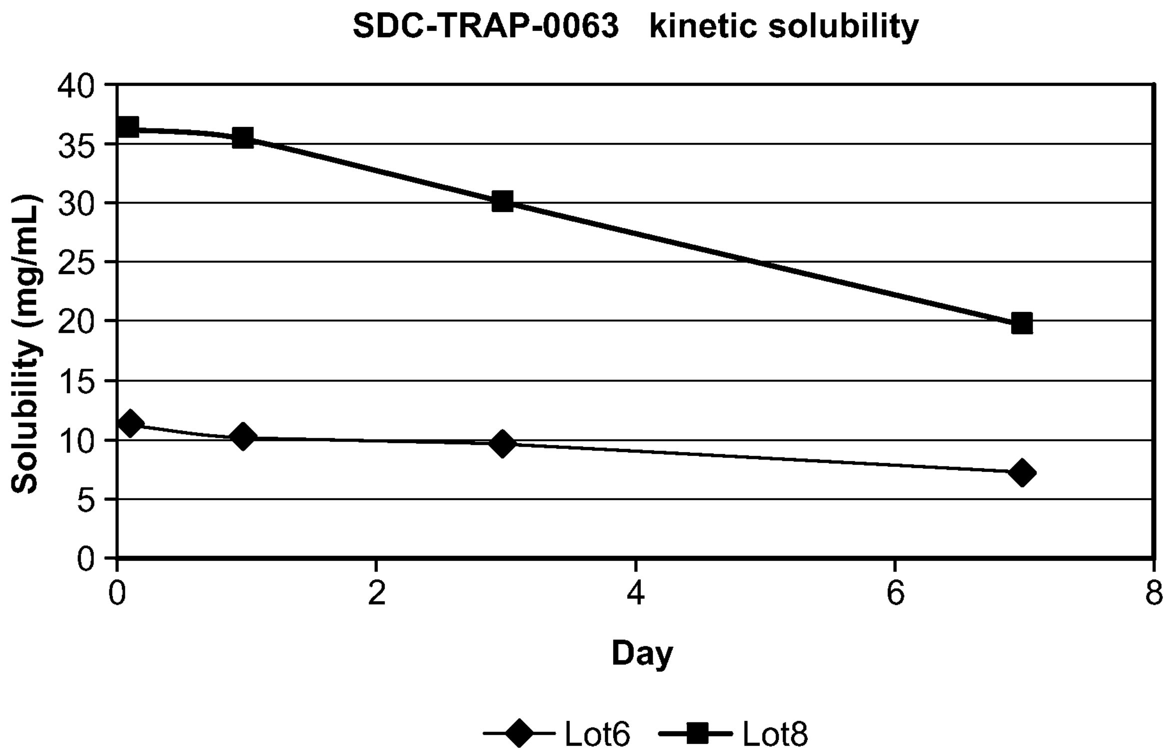


FIG. 17

Physical appearance of SDC-TRAP-0063 stock solution prepared in DMSO and after addition of Tween 80.

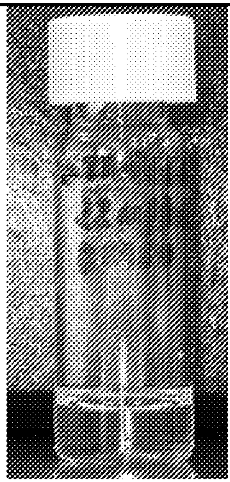
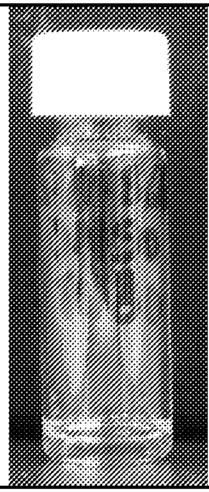
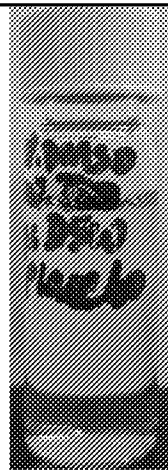
(a) SDC-TRAP-0063 dissolved in DMSO (drug concentration - 22 mg/mL)	(b) After addition of tween 80 to the stock solution of SDC-TRAP-0063 in DMSO	(c) Placebo (without addition of drug) formulation (5% DMSO, 1.8% v/v tween 80)
		
Note that the DMSO-drug stock (a) and DMSO/tween 80 formulation (b) are clear and homogenous solutions. The placebo (without drug) formulation (prepared by dilution with Carbonate buffer, pH 10) is also a clear solution (c).		

FIG. 18

Physical observations of infusion solution prepared using different diluents.

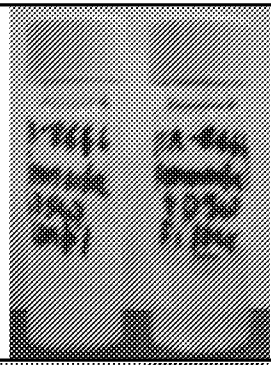
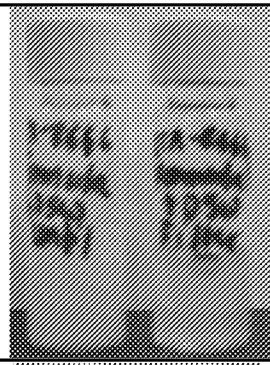
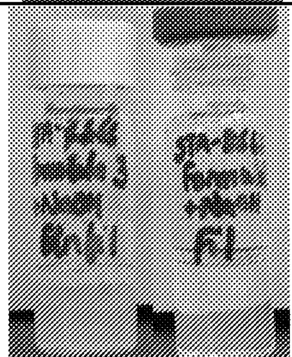
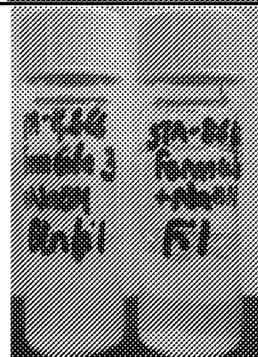
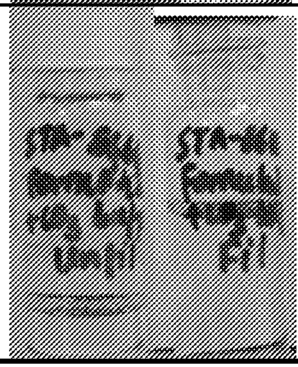
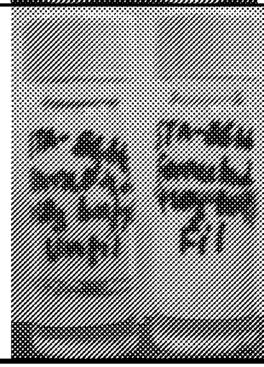
Contents of infusion solution / diluent	Initial	3 hrs
1.8% v/v Tween 80 + 5% v/v DMSO, qs D5W (1 mg/mL SDC-TRAP-0063) <u>Observations:</u> Cloudy solutions at initial and at 3 h period; filtration through 0.22μ filter reduces the cloudy appearance		
1.8% v/v Tween 80 + 5% v/v DMSO, qs D5W, pH 10.5 adjusted with 4.55 mM NaOH (1 mg/mL SDC-TRAP-0063) <u>Observations:</u> Cloudy solution at initial and at 3 h period. Filtration through 0.22μ filter reduces the cloudy appearance		
1.8% v/v Tween 80 + 5% v/v DMSO, qs carbonate buffer, pH 10 (1 mg/mL SDC-TRAP-0063) <u>Observations:</u> Clear yellowish colored solutions; No change in the appearance for at least 3 h for both - filtered and unfiltered solutions.		

FIG. 19

Antitumor activity of SDC-TRAP-0063, irinotecan and ganetespib + irinotecan in human SCLC tumor xenografts. %T/C values for day 60 are used. 1/8 mice in irinotecan group was found dead on day 46.

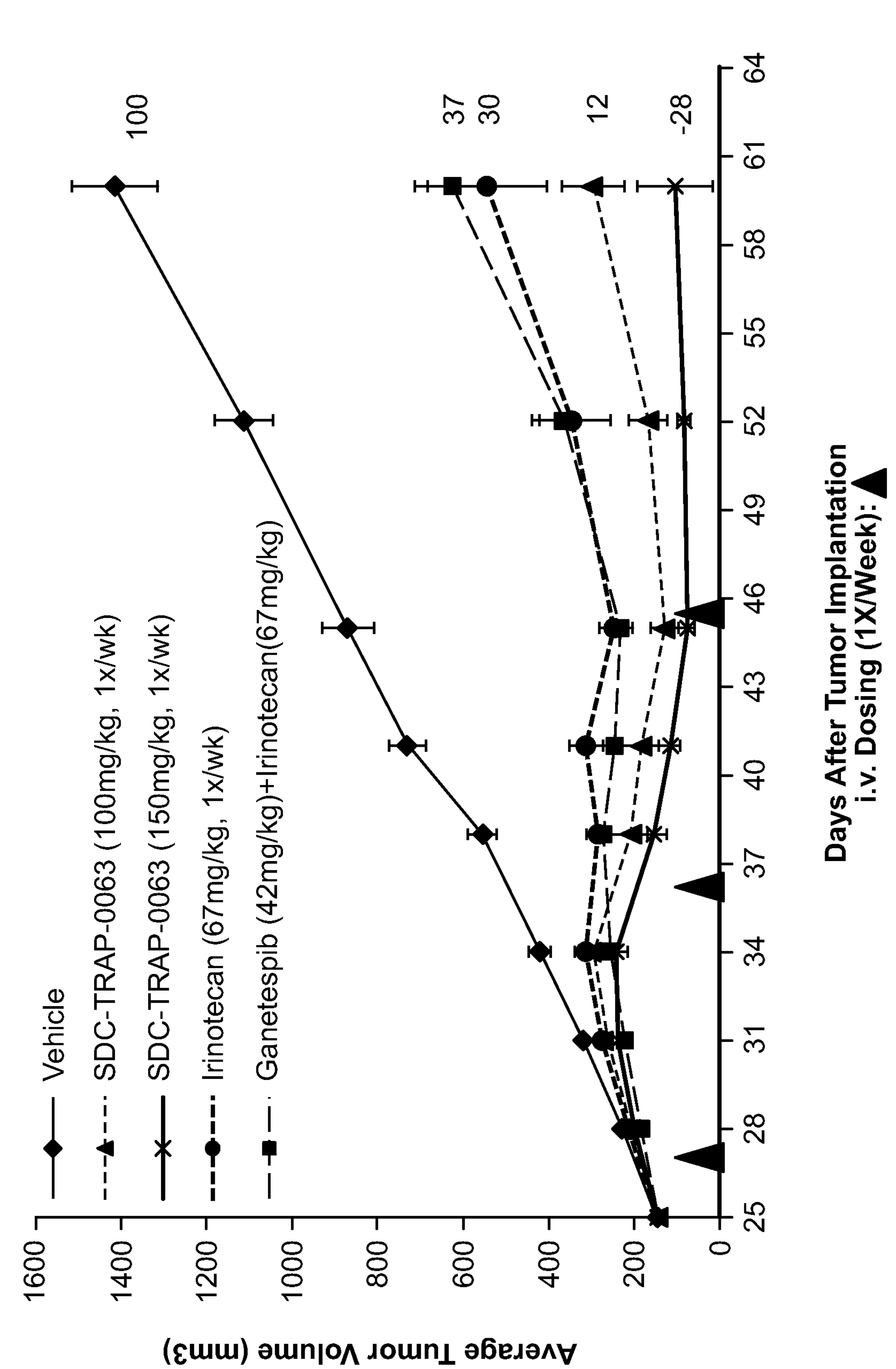


FIG. 20A

Expression of indicated analytes from HCT-116 xenografts treated as indicated.

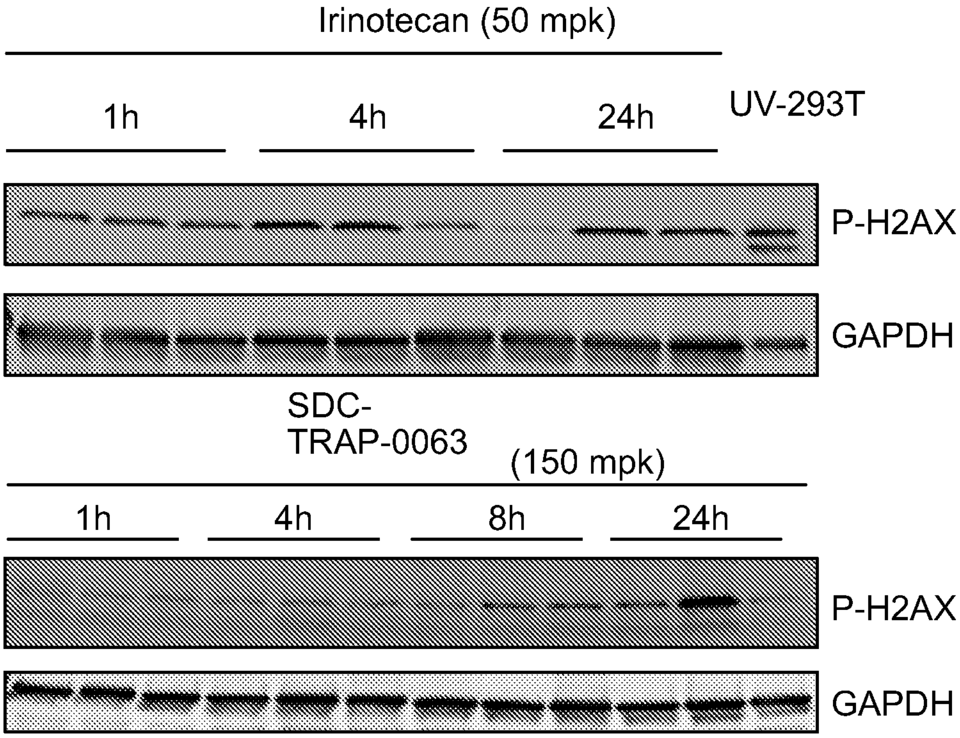


FIG. 20B

Expression of indicated analytes from HCT-116 tumor bearing animals 24 hr post drug exposure.

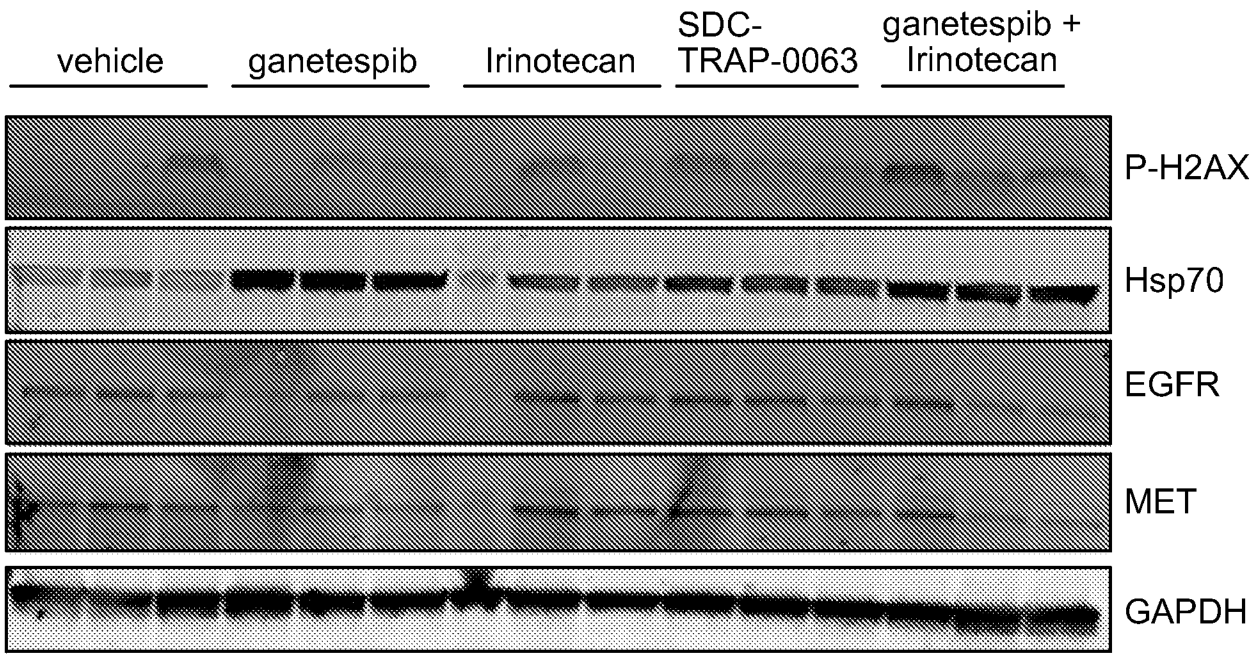


FIG. 21

Expression of the indicated analytes in SCLC xenograft tumors 24 hrs after drug exposure.

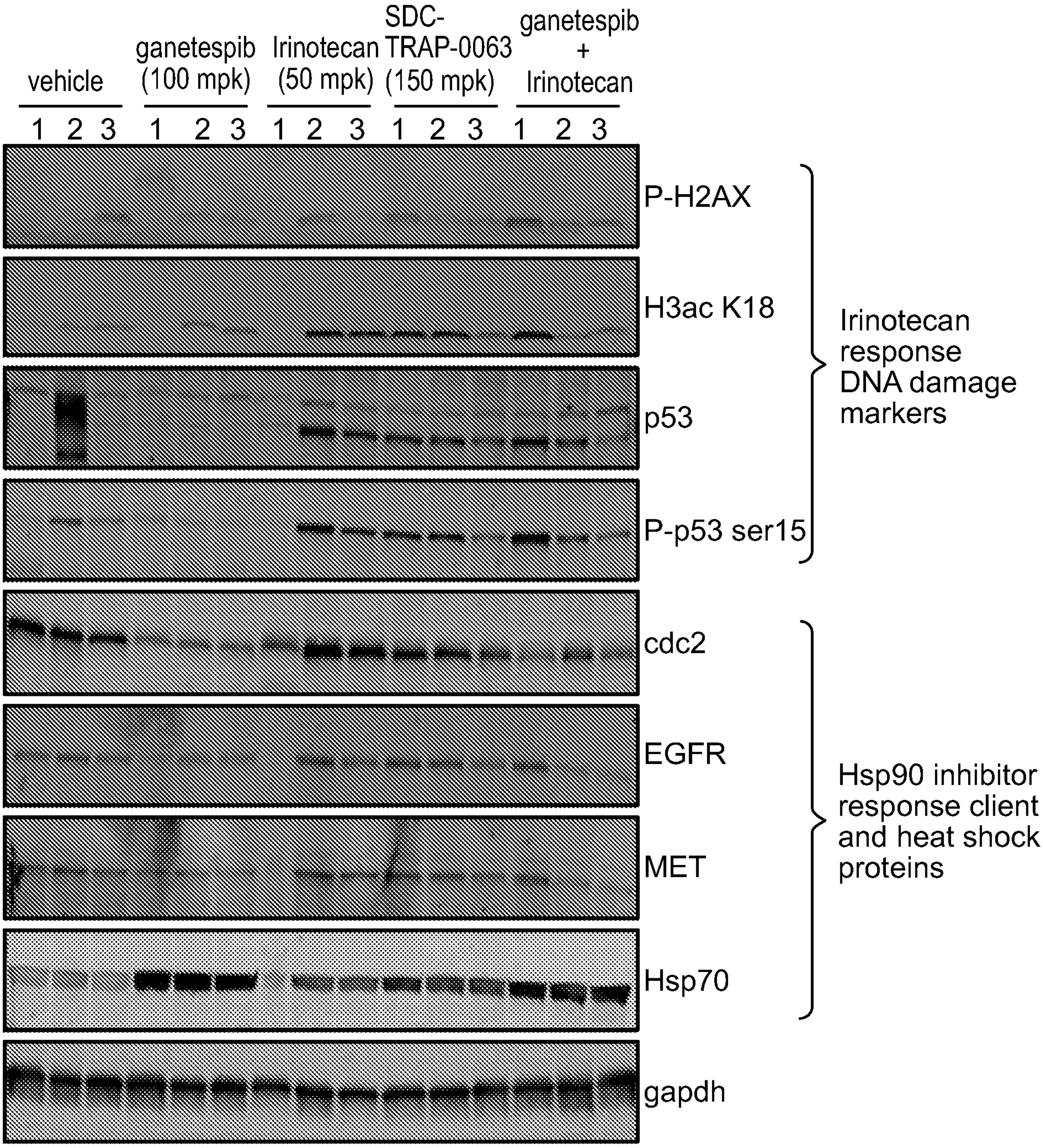


FIG. 22 **Expression of the indicated analytes in SCLC xenograft tumors 24, 72, and 96 hrs after drug exposure.**

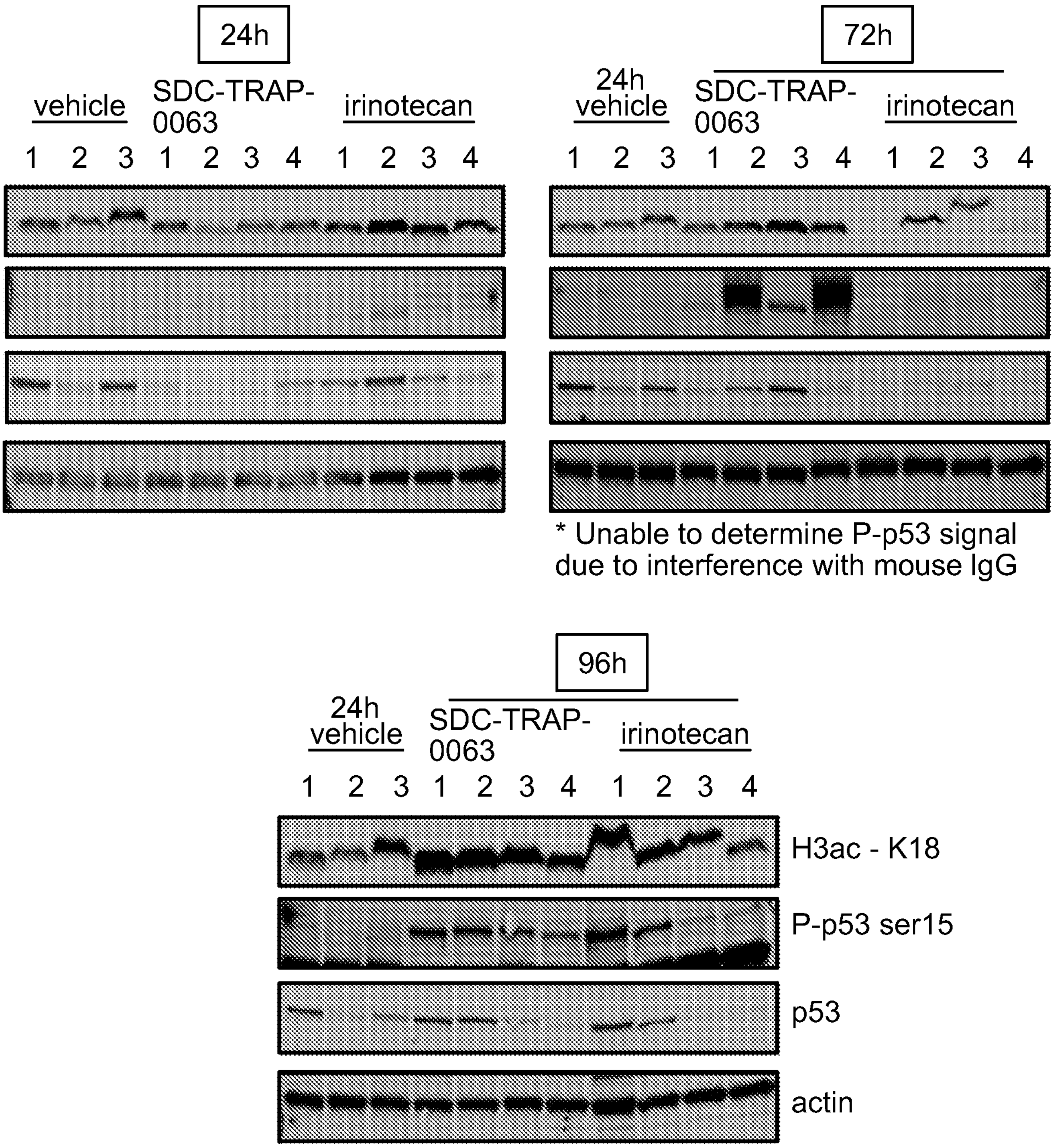


FIG. 23

Antitumor activity of SDC-TRAP-0063, irinotecan and ganetespib + irinotecan in HCT-116 human colorectal xenografts. %T/C values for day 35 are used.

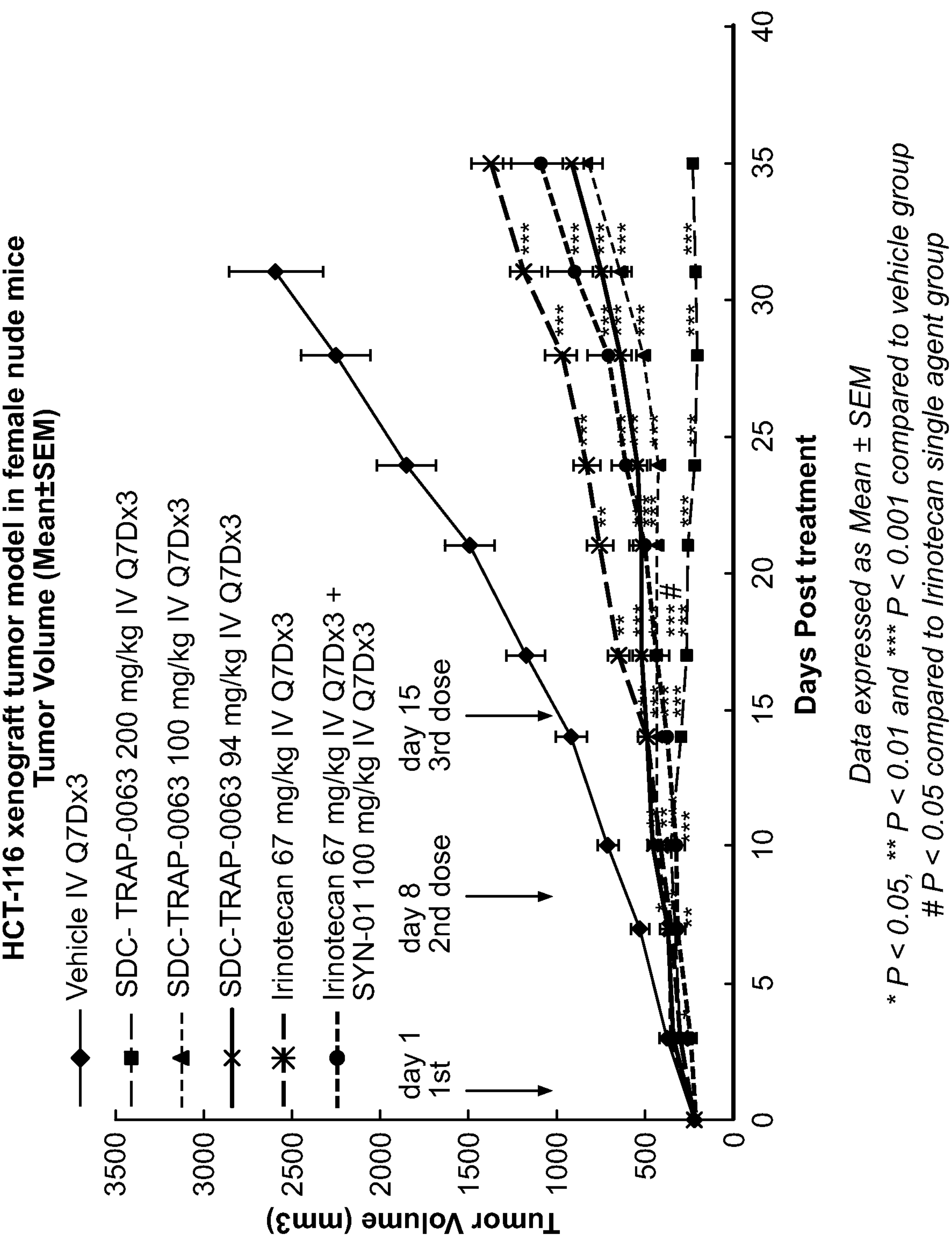


FIG. 24

Antitumor activity of SDC-TRAP-0063, irinotecan and ganetespib + irinotecan in MCF-7 human xenografts. %T/C values for day 66 are used.

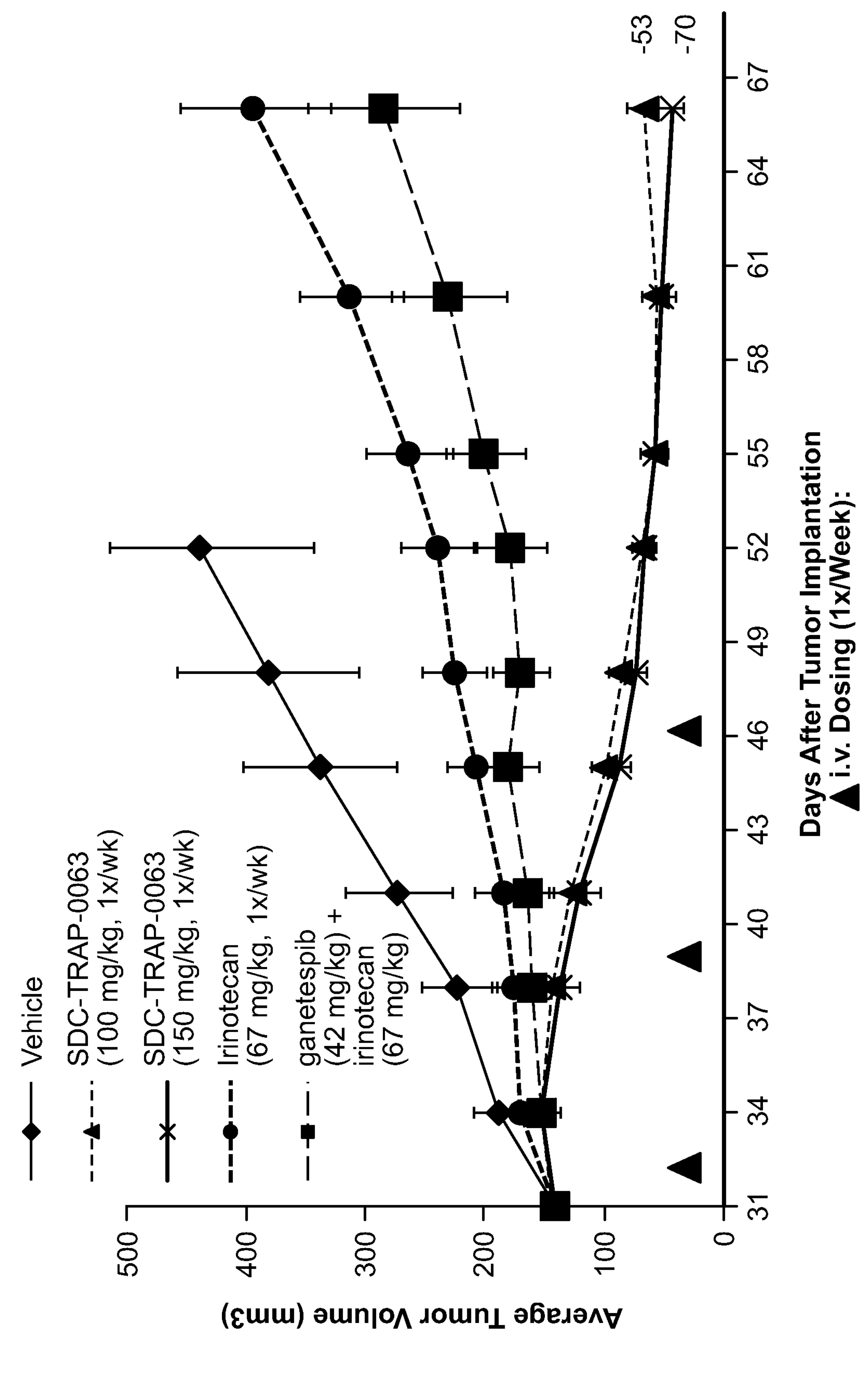
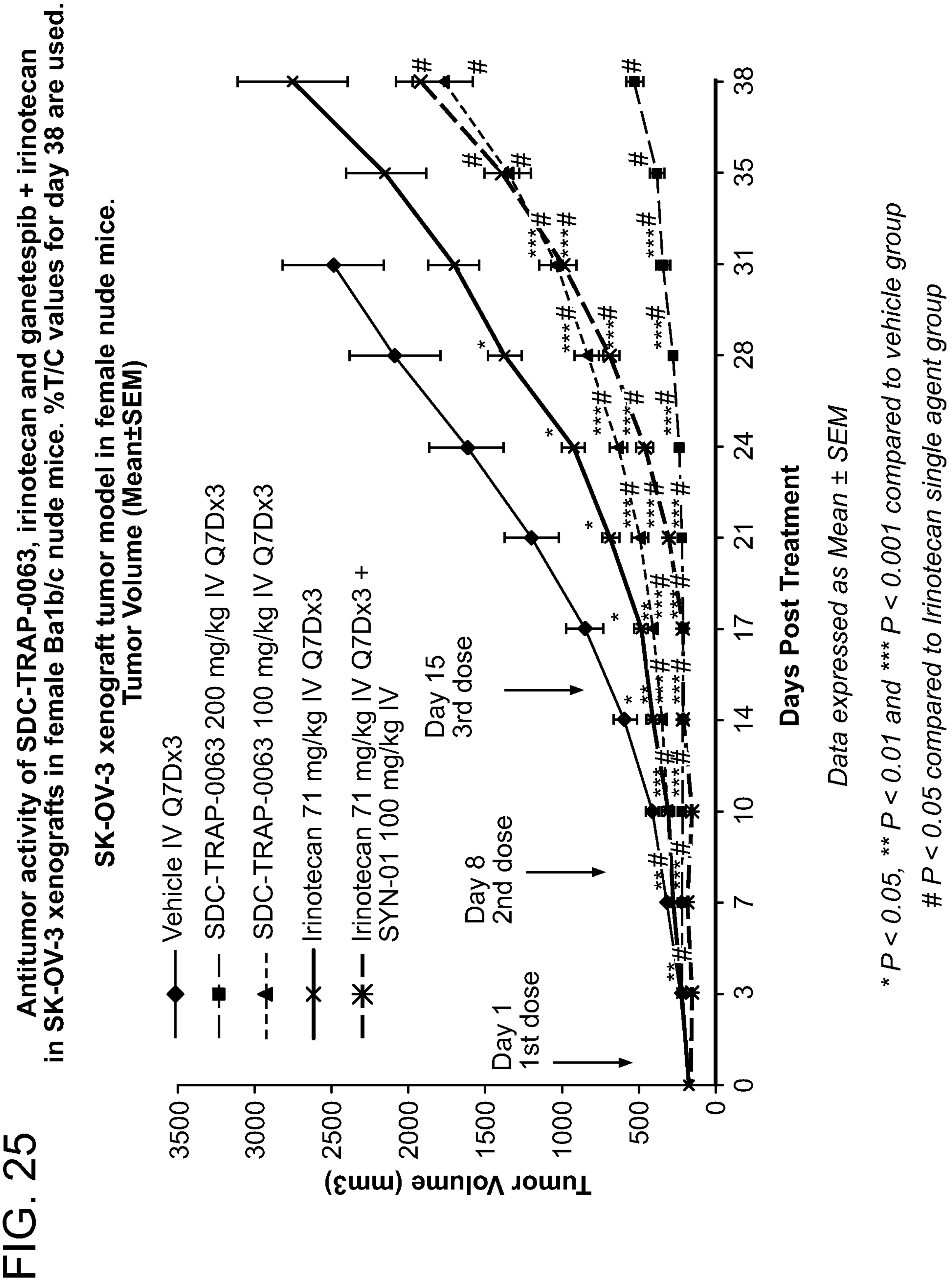


FIG. 25


Antitumor activity of SDC-TRAP-0063, irinotecan and ganetespib + irinotecan in SK-OV-3 xenografts in female Ba1b/c nude mice. %T/C values for day 38 are used.
SK-OV-3 xenograft tumor model in female nude mice.
Tumor Volume (Mean±SEM)
Vehicle IV Q7Dx3
SDC-TRAP-0063 200 mg/kg IV Q7Dx3
SDC-TRAP-0063 100 mg/kg IV Q7Dx3
Irinotecan 71 mg/kg IV Q7Dx3
Irinotecan 71 mg/kg IV Q7Dx3 + SYN-01 100 mg/kg IV
Day 1 1st dose
Day 8 2nd dose
Day 15 3rd dose
Tumor Volume (mm3)
Days Post Treatment
Data expressed as Mean ± SEM
* P < 0.05, ** P < 0.01 and *** P < 0.001 compared to vehicle group
# P < 0.05 compared to Irinotecan single agent group