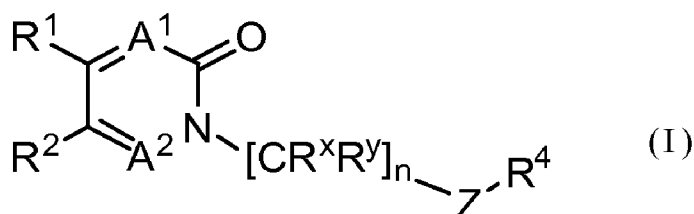




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(54) Title: GLS1 INHIBITORS FOR TREATING DISEASE



(57) Abstract: Disclosed herein are compounds and compositions useful in the treatment of GLS1 mediated diseases, such as cancer, having the structure of Formula I: Methods of inhibition GLS1 activity in a human or animal subject are also provided.

GLS1 INHIBITORS FOR TREATING DISEASE

[001] This application claims the benefit of priority of United States provisional Application No 62/020,519, filed July 3, 2014, the disclosure of which is hereby incorporated by reference as if written herein in its entirety.

[002] The present disclosure relates to new heterocyclic compounds and compositions, and their application as pharmaceuticals for the treatment of disease. Methods of inhibition of GLS1 activity in a human or animal subject are also provided for the treatment of diseases such as cancer.

[003] Metabolic deregulation is a hallmark of cancer as tumors exhibit an increased demand for nutrients and macromolecules to fuel their rapid proliferation. Glutamine (Gln), the most abundant amino acid in circulation, plays an essential role in providing cancer cells with biosynthetic intermediates required to support proliferation and survival. Specifically, glutaminolysis, or the enzymatic conversion of glutamine to glutamate, provides proliferating cancer cells with a source of nitrogen for amino acid and nucleotide synthesis, and a carbon skeleton to fuel ATP and NADPH synthesis through the TCA cycle. In addition to supporting cell growth, glutamine metabolism plays a critical role in maintaining cellular redox homeostasis as glutamate can be converted into glutathione, the major intracellular antioxidant.

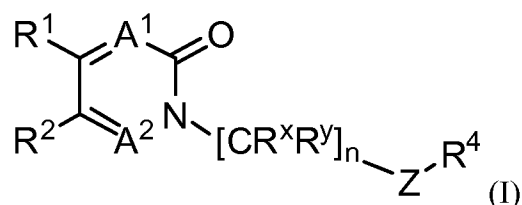
[004] Glutaminolysis is regulated by mitochondrial glutaminase (GLS), the rate limiting enzyme that catalyzes the conversion of Gln to glutamate and ammonia. Mammalian cells contain 2 genes that encode glutaminase: the kidney-type (GLS1) and liver-type (GLS2) enzymes. Each has been detected in multiple tissue types, with GLS1 being widely distributed throughout the body. GLS1 is a phosphate-activated enzyme that exists in humans as two major splice variants, a long form (referred to as KGA) and a short form (GAC), which differ only in their C-terminal sequences. Both forms of GLS1 are thought to bind to the inner membrane of the mitochondrion in mammalian cells, although at least one report suggests that glutaminase may exist in the intramembrane space, dissociated from the membrane. GLS is frequently overexpressed in human tumors and has been shown to be positively regulated by oncogenes such as Myc. Consistent with the observed dependence of cancer cell lines on glutamine metabolism, pharmacological inhibition of GLS offers the potential to target Gln addicted tumors.

[005] Thus, there is a need for glutaminase inhibitors that are specific and capable of being formulated for in vivo use.

SUMMARY

[006] Accordingly, the inventors herein disclose new compositions and methods for inhibiting glutaminase activity.

[007] Provided is compound of structural Formula I



or a salt thereof, wherein: n is chosen from 3, 4, and 5; each R^x and R^y is independently chosen from alkyl, cyano, H, and halo, wherein two R^x groups together with the atoms to which they are attached optionally form a cycloalkyl ring; A^1 and A^2 are independently chosen from C-H, C-F, and N; R^1 and R^4 are independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, hydroxyl, $\text{C}(\text{R}^3)_2\text{C}(\text{O})\text{R}^3$, $\text{C}(\text{R}^3)_2\text{C}(\text{O})\text{N}(\text{R}^3)_2$, $\text{C}(\text{R}^3)_2\text{N}(\text{R}^3)_2$, $\text{C}(\text{R}^3)_2\text{NR}^3\text{C}(\text{O})\text{R}^3$, $\text{C}(\text{R}^3)_2\text{NR}^3\text{C}(\text{O})\text{OR}^3$, $\text{C}(\text{R}^3)_2\text{NR}^3\text{C}(\text{O})\text{N}(\text{R}^3)_2$, $\text{C}(\text{R}^3)_2\text{NR}^3\text{S}(\text{O})\text{R}^3$, $\text{C}(\text{R}^3)_2\text{NR}^3\text{S}(\text{O})_2\text{R}^3$, $\text{N}(\text{R}^3)_2$, $\text{NR}^3\text{C}(\text{O})\text{R}^3$, $\text{NR}^3\text{C}(\text{O})\text{OR}^3$, $\text{NR}^3\text{C}(\text{O})\text{N}(\text{R}^3)_2$, $\text{NR}^3\text{S}(\text{O})\text{R}^3$, $\text{NR}^3\text{S}(\text{O})_2\text{R}^3$, $\text{C}(\text{O})\text{N}(\text{R}^3)_2$, $\text{S}(\text{O})\text{N}(\text{R}^3)_2$, $\text{S}(\text{O})_2\text{N}(\text{R}^3)_2$, $\text{C}(\text{O})\text{R}^3$, SR^3 , $\text{S}(\text{O})\text{R}^3$, and $\text{S}(\text{O})_2\text{R}^3$, wherein each R^1 and R^4 may be optionally substituted with between 0 and 3 R^z groups; R^2 is chosen from alkyl, heterocycloalkyl, cyano, cycloalkyl, H, halo, and haloalkyl, wherein R^1 and R^2 together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^z groups; each R^3 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein each R^3 may be optionally substituted with between 0 and 3 R^z groups, wherein two R^3 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^z groups; each R^z group is independently chosen from alkenyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyarylalkyl, alkoxycycloalkyl, alkoxycycloalkylalkyl, alkoxyhaloalkyl, alkoxyheteroaryl, alkoxyheteroarylalkyl,

alkoxyheterocycloalkyl, alkoxyheterocycloalkylalkyl, alkyl, alkylaryl, alkylarylalkyl, alkylcycloalkyl, alkylcycloalkylalkyl, alkylheteroaryl, alkylheteroarylalkyl, alkylheterocycloalkyl, alkylheterocycloalkylalkyl, aryl, arylalkyl, arylalkyloxy, arylhaloalkyl, aryloxy, cyano, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, cycloalkylhaloalkyl, cycloalkyloxy, H, halo, haloalkoxy, haloalkoxyalkyl, haloalkoxyaryl, haloalkoxyarylalkyl, haloalkoxycycloalkyl, haloalkoxycycloalkylalkyl, haloalkoxyheteroaryl, haloalkoxyheteroarylalkyl, haloalkoxyheterocycloalkyl, haloalkoxyheterocycloalkylalkyl, haloalkyl, haloalkylaryl, haloalkylarylalkyl, haloalkylcycloalkyl, haloalkylcycloalkylalkyl, haloalkylheteroaryl, haloalkylheteroarylalkyl, haloalkylheterocycloalkyl, haloalkylheterocycloalkylalkyl, haloaryl, haloarylalkyl, haloarylalkyloxy, haloaryloxy, halocycloalkyl, halocycloalkylalkyl, halocycloalkylalkyloxy, halocycloalkyloxy, haloheteroaryl, haloheteroarylalkyl, haloheteroarylalkyloxy, haloheteroaryloxy, haloheterocycloalkyl, haloheterocycloalkylalkyl, haloheterocycloalkylalkyloxy, haloheterocycloalkyloxy, heteroaryl, heteroarylalkyl, heteroarylalkyloxy, heteroarylhaloalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkylalkyloxy, heterocycloalkylhaloalkyl, heterocycloalkyloxy, hydroxyl, oxo, $N(R^6)_2$, $NR^6C(O)C(R^6)_3$, $NR^6C(O)OC(R^6)_3$, $NR^6C(O)N(R^6)_2$, $NR^6S(O)C(R^6)_3$, $NR^6S(O)_2C(R^6)_3$, $C(O)N(R^6)_2$, $S(O)N(R^6)_2$, $S(O)_2N(R^6)_2$, $C(O)C(R^6)_3$, $SC(R^6)_3$, $S(O)C(R^6)_3$, and $S(O)_2C(R^6)_3$; each R^6 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein two R^6 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^x groups; and Z is heteroaryl, which may be optionally substituted.

[008] Provided is a composition comprising a compound of Formula I and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[009] Provided is a method of inhibiting GLS1 activity in a biological sample comprising contacting the biological sample with a compound of Formula I.

[010] Provided is a method of treating a GLS1-mediated disorder in a subject in need thereof, comprising the step of administering to the subject a compound of Formula I.

- [011] Provided is a method of treating a GLS1-mediated disorder in a subject in need thereof, comprising the sequential or co-administration of a compound of Formula I or a pharmaceutically acceptable salt thereof, and another therapeutic agent.
- [012] Provided is a compound of any of Formula I for use in human therapy.
- [013] Provided is a compound of any of Formula I for use in treating a GLS1-mediated disease.
- [014] Provided is a use of a compound of Formula I for the manufacture of a medicament to treat a GLS1-mediated disease.

DETAILED DESCRIPTION

Abbreviations and Definitions

- [015] To facilitate understanding of the disclosure, a number of terms and abbreviations as used herein are defined below as follows:
- [016] When introducing elements of the present disclosure or the preferred embodiment(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.
- [017] The term "and/or" when used in a list of two or more items, means that any one of the listed items can be employed by itself or in combination with any one or more of the listed items. For example, the expression "A and/or B" is intended to mean either or both of A and B, i.e. A alone, B alone or A and B in combination. The expression "A, B and/or C" is intended to mean A alone, B alone, C alone, A and B in combination, A and C in combination, B and C in combination or A, B, and C in combination.
- [018] When ranges of values are disclosed, and the notation "from n_1 ... to n_2 " or "between n_1 ... and n_2 " is used, where n_1 and n_2 are the numbers, then unless otherwise specified, this notation is intended to include the numbers themselves and the range between them. This range may be integral or continuous between and including the end values. By way of example, the range "from 2 to 6 carbons" is intended to include two, three, four, five, and six carbons, since carbons come in integer units. Compare, by way of example, the range "from 1 to 3 μM (micromolar)," which is intended to include 1 μM , 3 μM , and everything in between to any number of significant figures (e.g., 1.255 μM , 2.1 μM , 2.9999 μM , etc.).

[019] The term “about,” as used herein, is intended to qualify the numerical values that it modifies, denoting such a value as variable within a margin of error. When no particular margin of error, such as a standard deviation to a mean value given in a chart or table of data, is recited, the term “about” should be understood to mean that range which would encompass the recited value and the range which would be included by rounding up or down to that figure as well, taking into account significant figures.

[020] The term “acyl,” as used herein, alone or in combination, refers to a carbonyl attached to an alkenyl, alkyl, aryl, cycloalkyl, heteroaryl, heterocycle, or any other moiety where the atom attached to the carbonyl is carbon. An “acetyl” group refers to a -C(O)CH_3 group. An “alkylcarbonyl” or “alkanoyl” group refers to an alkyl group attached to the parent molecular moiety through a carbonyl group. Examples of such groups include methylcarbonyl and ethylcarbonyl. Examples of acyl groups include formyl, alkanoyl and aroyl.

[021] The term “alkenyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain hydrocarbon radical having one or more double bonds and containing from 2 to 20 carbon atoms. In certain embodiments, the alkenyl will comprise from 2 to 6 carbon atoms. The term “alkenylene” refers to a carbon-carbon double bond system attached at two or more positions such as ethenylene $[(-\text{CH}=\text{CH}-), (-\text{C}::\text{C}-)]$. Examples of suitable alkenyl radicals include ethenyl, propenyl, 2-methylpropenyl, 1,4-butadienyl and the like. Unless otherwise specified, the term “alkenyl” may include “alkenylene” groups.

[022] The term “alkoxy,” as used herein, alone or in combination, refers to an alkyl ether radical, wherein the term alkyl is as defined below. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

[023] The term “alkyl,” as used herein, alone or in combination, refers to a straight-chain or branched-chain alkyl radical containing from 1 to 20 carbon atoms. In certain embodiments, the alkyl will comprise from 1 to 10 carbon atoms. In further embodiments, the alkyl will comprise from 1 to 6 carbon atoms. Alkyl groups may be optionally substituted as defined herein. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, nonyl and the like. The term “alkylene,” as used herein, alone or in combination, refers to a saturated aliphatic group derived from a straight or

branched chain saturated hydrocarbon attached at two or more positions, such as methylene ($-\text{CH}_2-$). Unless otherwise specified, the term “alkyl” may include “alkylene” groups.

[024] The term “alkylamino,” as used herein, alone or in combination, refers to an alkyl group attached to the parent molecular moiety through an amino group. Suitable alkylamino groups may be mono- or dialkylated, forming groups such as, for example, N-methylamino, N-ethylamino, N,N-dimethylamino, N,N-ethylmethylamino and the like.

[025] The term “alkylidene,” as used herein, alone or in combination, refers to an alkenyl group in which one carbon atom of the carbon-carbon double bond belongs to the moiety to which the alkenyl group is attached.

[026] The term “alkylthio,” as used herein, alone or in combination, refers to an alkyl thioether ($\text{R}-\text{S}-$) radical wherein the term alkyl is as defined above and wherein the sulfur may be singly or doubly oxidized. Examples of suitable alkyl thioether radicals include methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, iso-butylthio, sec-butylthio, tert-butylthio, methanesulfonyl, ethanesulfinyl, and the like.

[027] The term “alkynyl,” as used herein, alone or in combination, refers to a straight-chain or branched chain hydrocarbon radical having one or more triple bonds and containing from 2 to 20 carbon atoms. In certain embodiments, the alkynyl comprises from 2 to 6 carbon atoms. In further embodiments, the alkynyl comprises from 2 to 4 carbon atoms. The term “alkynylene” refers to a carbon-carbon triple bond attached at two positions such as ethynylene ($-\text{C}:::\text{C}-$, $-\text{C}\equiv\text{C}-$). Examples of alkynyl radicals include ethynyl, propynyl, hydroxypropynyl, butyn-1-yl, butyn-2-yl, pentyn-1-yl, 3-methylbutyn-1-yl, hexyn-2-yl, and the like. Unless otherwise specified, the term “alkynyl” may include “alkynylene” groups.

[028] The terms “amido” and “carbamoyl” as used herein, alone or in combination, refer to an amino group as described below attached to the parent molecular moiety through a carbonyl group, or vice versa. The term “C-amido” as used herein, alone or in combination, refers to a $-\text{C}(\text{O})\text{N}(\text{RR}')$ group with R and R' as defined herein or as defined by the specifically enumerated “R” groups designated. The term “N-amido” as used herein, alone or in combination, refers to a $\text{RC}(\text{O})\text{N}(\text{R}')$ group, with R and R' as defined herein or as defined by the specifically enumerated “R” groups designated. The term “acylamino” as used herein, alone or in combination, embraces an acyl group attached to the parent moiety through an amino group. An example of an “acylamino” group is acetylamino ($\text{CH}_3\text{C}(\text{O})\text{NH}-$).

[029] The term “amino,” as used herein, alone or in combination, refers to $\text{—NRR}'$, wherein R and R' are independently selected from the group consisting of hydrogen, alkyl, acyl, heteroalkyl, aryl, cycloalkyl, heteroaryl, and heterocycloalkyl, any of which may themselves be optionally substituted. Additionally, R and R' may combine to form heterocycloalkyl, either of which may be optionally substituted.

[030] The term “aryl,” as used herein, alone or in combination, means a carbocyclic aromatic system containing one, two or three rings wherein such polycyclic ring systems are fused together. The term “aryl” embraces aromatic groups such as phenyl, naphthyl, anthracenyl, and phenanthryl.

[031] The term “arylalkenyl” or “aralkenyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkenyl group.

[032] The term “arylalkoxy” or “aralkoxy,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkoxy group.

[033] The term “arylalkyl” or “aralkyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkyl group.

[034] The term “arylalkynyl” or “aralkynyl,” as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an alkynyl group.

[035] The term “arylalkanoyl” or “aralkanoyl” or “aroyl,” as used herein, alone or in combination, refers to an acyl radical derived from an aryl-substituted alkanecarboxylic acid such as benzoyl, naphthoyl, phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, and the like.

[036] The term aryloxy as used herein, alone or in combination, refers to an aryl group attached to the parent molecular moiety through an oxy.

[037] The terms “benzo” and “benz,” as used herein, alone or in combination, refer to the divalent radical $\text{C}_6\text{H}_4^{\cdot}$ derived from benzene. Examples include benzothiophene and benzimidazole.

[038] The term “carbamate,” as used herein, alone or in combination, refers to an ester of carbamic acid (—NHCOO—) which may be attached to the parent molecular moiety from either the nitrogen or acid end, and which may be optionally substituted as defined herein.

[039] The term “O-carbamyl” as used herein, alone or in combination, refers to a $\text{—OC(O)NRR}'$, group-with R and R' as defined herein.

[040] The term “N-carbamyl” as used herein, alone or in combination, refers to a $\text{ROC(O)NR}'$ - group, with R and R' as defined herein.

[041] The term “carbonyl,” as used herein, when alone includes formyl [$-\text{C(O)H}$] and in combination is a $-\text{C(O)}-$ group.

[042] The term “carboxyl” or “carboxy,” as used herein, refers to $-\text{C(O)OH}$ or the corresponding “carboxylate” anion, such as is in a carboxylic acid salt. An “O-carboxy” group refers to a $\text{RC(O)O}-$ group, where R is as defined herein. A “C-carboxy” group refers to a $-\text{C(O)OR}$ groups where R is as defined herein.

[043] The term “cyano,” as used herein, alone or in combination, refers to $-\text{CN}$.

[044] The term “cycloalkyl,” or, alternatively, “carbocycle,” as used herein, alone or in combination, refers to a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl group wherein each cyclic moiety contains from 3 to 12 carbon atom ring members and which may optionally be a benzo fused ring system which is optionally substituted as defined herein. In certain embodiments, the cycloalkyl will comprise from 5 to 7 carbon atoms. Examples of such cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, tetrahydronaphthyl, indanyl, octahydronaphthyl, 2,3-dihydro-1H-indenyl, adamantyl and the like. “Bicyclic” and “tricyclic” as used herein are intended to include both fused ring systems, such as decahydronaphthalene, octahydronaphthalene as well as the multicyclic (multicentered) saturated or partially unsaturated type. The latter type of isomer is exemplified in general by, bicyclo[1,1,1]pentane, camphor, adamantane, and bicyclo[3,2,1]octane.

[045] The term “ester,” as used herein, alone or in combination, refers to a carboxy group bridging two moieties linked at carbon atoms.

[046] The term “ether,” as used herein, alone or in combination, refers to an oxy group bridging two moieties linked at carbon atoms.

[047] The term “halo,” or “halogen,” as used herein, alone or in combination, refers to fluorine, chlorine, bromine, or iodine.

[048] The term “haloalkoxy,” as used herein, alone or in combination, refers to a haloalkyl group attached to the parent molecular moiety through an oxygen atom.

[049] The term “haloalkyl,” as used herein, alone or in combination, refers to an alkyl radical having the meaning as defined above wherein one or more hydrogens are replaced with a halogen. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A

monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Haloalkylene" refers to a haloalkyl group attached at two or more positions. Examples include fluoromethylene ($-\text{CFH}-$), difluoromethylene ($-\text{CF}_2-$), chloromethylene ($-\text{CHCl}-$) and the like.

[050] The term "heteroalkyl," as used herein, alone or in combination, refers to a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, fully saturated or containing from 1 to 3 degrees of unsaturation, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. Up to two heteroatoms may be consecutive, such as, for example, $-\text{CH}_2\text{-NH-OCH}_3$.

[051] The term "heteroaryl," as used herein, alone or in combination, refers to a 3 to 15 membered unsaturated heteromonocyclic ring, or a fused monocyclic, bicyclic, or tricyclic ring system in which at least one of the fused rings is aromatic, which contains at least one atom selected from the group consisting of O, S, and N. In certain embodiments, the heteroaryl will comprise from 5 to 7 carbon atoms. The term also embraces fused polycyclic groups wherein heterocyclic rings are fused with aryl rings, wherein heteroaryl rings are fused with other heteroaryl rings, wherein heteroaryl rings are fused with heterocycloalkyl rings, or wherein heteroaryl rings are fused with cycloalkyl rings. Examples of heteroaryl groups include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl, pyranlyl, furyl, thienyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, isothiazolyl, indolyl, isoindolyl, indolizinyll, benzimidazolyl, quinolyl, isoquinolyl, quinoxalinyll, quinazolinyl, indazolyl, benzotriazolyl, benzodioxolyl, benzopyranlyl, benzoxazolyl, benzoxadiazolyl, benzothiazolyl, benzothiadiazolyl, benzofuryl, benzothienyl, chromonyl, coumarinyl, benzopyranlyl, tetrahydroquinolinyl, tetrazolopyridazinyl, tetrahydroisoquinolinyl, thienopyridinyl, furopyridinyl, pyrrolopyridinyl and the like. Exemplary tricyclic heterocyclic

groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[052] The terms “heterocycloalkyl” and, interchangeably, “heterocycle,” as used herein, alone or in combination, each refer to a saturated, partially unsaturated, or fully unsaturated monocyclic, bicyclic, or tricyclic heterocyclic group containing at least one heteroatom as a ring member, wherein each the heteroatom may be independently selected from the group consisting of nitrogen, oxygen, and sulfur. In certain embodiments, the heterocycloalkyl will comprise from 1 to 4 heteroatoms as ring members. In further embodiments, the heterocycloalkyl will comprise from 1 to 2 heteroatoms as ring members. In certain embodiments, the heterocycloalkyl will comprise from 3 to 8 ring members in each ring. In further embodiments, the heterocycloalkyl will comprise from 3 to 7 ring members in each ring. In yet further embodiments, the heterocycloalkyl will comprise from 5 to 6 ring members in each ring. “Heterocycloalkyl” and “heterocycle” are intended to include sulfones, sulfoxides, N-oxides of tertiary nitrogen ring members, and carbocyclic fused and benzo fused ring systems; additionally, both terms also include systems where a heterocycle ring is fused to an aryl group, as defined herein, or an additional heterocycle group. Examples of heterocycle groups include aziridinyl, azetidiny, 1,3-benzodioxolyl, dihydroisoindolyl, dihydroisoquinolinyl, dihydrocinnolyl, dihydrobenzodioxinyl, dihydro[1,3]oxazolo[4,5-b]pyridinyl, benzothiazolyl, dihydroindolyl, dihydropyridinyl, 1,3-dioxanyl, 1,4-dioxanyl, 1,3-dioxolanyl, isoindolinyl, morpholinyl, piperazinyl, pyrrolidinyl, tetrahydropyridinyl, piperidinyl, thiomorpholinyl, and the like. The heterocycle groups may be optionally substituted unless specifically prohibited.

[053] The term “hydrazinyl” as used herein, alone or in combination, refers to two amino groups joined by a single bond, i.e., --N--N-- .

[054] The term “hydroxy,” as used herein, alone or in combination, refers to --OH .

[055] The term “hydroxyalkyl,” as used herein, alone or in combination, refers to a hydroxy group attached to the parent molecular moiety through an alkyl group.

[056] The term “imino,” as used herein, alone or in combination, refers to =N-- .

[057] The term “iminohydroxy,” as used herein, alone or in combination, refers to =N(OH) and =N--O-- .

[058] The phrase “in the main chain” refers to the longest contiguous or adjacent chain of carbon atoms starting at the point of attachment of a group to the compounds of any one of the formulas disclosed herein.

[059] The term “isocyanato” refers to a –NCO group.

[060] The term “isothiocyanato” refers to a –NCS group.

[061] The phrase “linear chain of atoms” refers to the longest straight chain of atoms independently selected from carbon, nitrogen, oxygen and sulfur.

[062] The term “lower,” as used herein, alone or in a combination, where not otherwise specifically defined, means containing from 1 to and including 6 carbon atoms.

[063] The term “lower aryl,” as used herein, alone or in combination, means phenyl or naphthyl, either of which may be optionally substituted as provided.

[064] The term “lower heteroaryl,” as used herein, alone or in combination, means either 1) monocyclic heteroaryl comprising five or six ring members, of which between one and four the members may be heteroatoms selected from the group consisting of O, S, and N, or 2) bicyclic heteroaryl, wherein each of the fused rings comprises five or six ring members, comprising between them one to four heteroatoms selected from the group consisting of O, S, and N.

[065] The term “lower cycloalkyl,” as used herein, alone or in combination, means a monocyclic cycloalkyl having between three and six ring members. Lower cycloalkyls may be unsaturated. Examples of lower cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[066] The term “lower heterocycloalkyl,” as used herein, alone or in combination, means a monocyclic heterocycloalkyl having between three and six ring members, of which between one and four may be heteroatoms selected from the group consisting of O, S, and N. Examples of lower heterocycloalkyls include pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, and morpholinyl. Lower heterocycloalkyls may be unsaturated.

[067] The term “lower amino,” as used herein, alone or in combination, refers to —NRR’, wherein R and R’ are independently selected from the group consisting of hydrogen, lower alkyl, and lower heteroalkyl, any of which may be optionally substituted. Additionally, the R and R’ of a lower amino group may combine to form a five- or six-membered heterocycloalkyl, either of which may be optionally substituted.

- [068] The term “mercaptyl” as used herein, alone or in combination, refers to an RS– group, where R is as defined herein.
- [069] The term “nitro,” as used herein, alone or in combination, refers to –NO₂.
- [070] The terms “oxy” or “oxa,” as used herein, alone or in combination, refer to –O–.
- [071] The term “oxo,” as used herein, alone or in combination, refers to =O.
- [072] The term “perhaloalkoxy” refers to an alkoxy group where all of the hydrogen atoms are replaced by halogen atoms.
- [073] The term “perhaloalkyl” as used herein, alone or in combination, refers to an alkyl group where all of the hydrogen atoms are replaced by halogen atoms.
- [074] The terms “sulfonate,” “sulfonic acid,” and “sulfonic,” as used herein, alone or in combination, refer the –SO₃H group and its anion as the sulfonic acid is used in salt formation.
- [075] The term “sulfanyl,” as used herein, alone or in combination, refers to –S–.
- [076] The term “sulfinyl,” as used herein, alone or in combination, refers to –S(O)–.
- [077] The term “sulfonyl,” as used herein, alone or in combination, refers to –S(O)₂–.
- [078] The term “N-sulfonamido” refers to a RS(=O)₂NR’- group with R and R’ as defined herein.
- [079] The term “S-sulfonamido” refers to a -S(=O)₂NRR’, group, with R and R’ as defined herein.
- [080] The terms “thia” and “thio,” as used herein, alone or in combination, refer to a –S– group or an ether wherein the oxygen is replaced with sulfur. The oxidized derivatives of the thio group, namely sulfinyl and sulfonyl, are included in the definition of thia and thio.
- [081] The term “thiol,” as used herein, alone or in combination, refers to an –SH group.
- [082] The term “thiocarbonyl,” as used herein, when alone includes thioformyl –C(S)H and in combination is a –C(S)– group.
- [083] The term “N-thiocarbamyl” refers to an ROC(S)NR’– group, with R and R’ as defined herein.
- [084] The term “O-thiocarbamyl” refers to a –OC(S)NRR’, group with R and R’ as defined herein.
- [085] The term “thiocyanato” refers to a –CNS group.

[086] The term “trihalomethanesulfonamido” refers to a $X_3CS(O)_2NR-$ group with X is a halogen and R as defined herein.

[087] The term “trihalomethanesulfonyl” refers to a $X_3CS(O)_2-$ group where X is a halogen.

[088] The term “trihalomethoxy” refers to a X_3CO- group where X is a halogen.

[089] The term “trisubstituted silyl,” as used herein, alone or in combination, refers to a silicone group substituted at its three free valences with groups as listed herein under the definition of substituted amino. Examples include trimethylsilyl, tert-butyldimethylsilyl, triphenylsilyl and the like.

[090] Any definition herein may be used in combination with any other definition to describe a composite structural group. By convention, the trailing element of any such definition is that which attaches to the parent moiety. For example, the composite group alkylamido would represent an alkyl group attached to the parent molecule through an amido group, and the term alkoxyalkyl would represent an alkoxy group attached to the parent molecule through an alkyl group.

[091] When a group is defined to be “null,” what is meant is that the group is absent.

[092] The term “optionally substituted” means the anteceding group may be substituted or unsubstituted. When substituted, the substituents of an “optionally substituted” group may include, without limitation, one or more substituents independently selected from the following groups or a particular designated set of groups, alone or in combination: lower alkyl, lower alkenyl, lower alkynyl, lower alkanoyl, lower heteroalkyl, lower heterocycloalkyl, lower haloalkyl, lower haloalkenyl, lower haloalkynyl, lower perhaloalkyl, lower perhaloalkoxy, lower cycloalkyl, phenyl, aryl, aryloxy, lower alkoxy, lower haloalkoxy, oxo, lower acyloxy, carbonyl, carboxyl, lower alkylcarbonyl, lower carboxyester, lower carboxamido, cyano, hydrogen, halogen, hydroxy, amino, lower alkylamino, arylamino, amido, nitro, thiol, lower alkylthio, lower haloalkylthio, lower perhaloalkylthio, arylthio, sulfonate, sulfonic acid, trisubstituted silyl, N_3 , SH, SCH_3 , $C(O)CH_3$, CO_2CH_3 , CO_2H , pyridinyl, thiophene, furanyl, lower carbamate, and lower urea. Two substituents may be joined together to form a fused five-, six-, or seven-membered carbocyclic or heterocyclic ring consisting of zero to three heteroatoms, for example forming methylenedioxy or ethylenedioxy. An optionally substituted group may be unsubstituted (e.g., $-CH_2CH_3$), fully substituted (e.g., $-CF_2CF_3$), monosubstituted (e.g., -

CH₂CH₂F) or substituted at a level anywhere in-between fully substituted and monosubstituted (e.g., -CH₂CF₃). Where substituents are recited without qualification as to substitution, both substituted and unsubstituted forms are encompassed. Where a substituent is qualified as “substituted,” the substituted form is specifically intended. Additionally, different sets of optional substituents to a particular moiety may be defined as needed; in these cases, the optional substitution will be as defined, often immediately following the phrase, “optionally substituted with.”

[093] The term R or the term R', appearing by itself and without a number designation, unless otherwise defined, refers to a moiety selected from the group consisting of hydrogen, alkyl, cycloalkyl, heteroalkyl, aryl, heteroaryl and heterocycloalkyl, any of which may be optionally substituted. Such R and R' groups should be understood to be optionally substituted as defined herein. Whether an R group has a number designation or not, every R group, including R, R' and R_n where n=(1, 2, 3, ...n), every substituent, and every term should be understood to be independent of every other in terms of selection from a group. Should any variable, substituent, or term (e.g. aryl, heterocycle, R, etc.) occur more than one time in a formula or generic structure, its definition at each occurrence is independent of the definition at every other occurrence. Those of skill in the art will further recognize that certain groups may be attached to a parent molecule or may occupy a position in a chain of elements from either end as written. Thus, by way of example only, an unsymmetrical group such as -C(O)N(R)- may be attached to the parent moiety at either the carbon or the nitrogen.

[094] Asymmetric centers exist in the compounds disclosed herein. These centers are designated by the symbols “R” or “S,” depending on the configuration of substituents around the chiral carbon atom. It should be understood that the disclosure encompasses all stereochemical isomeric forms, including diastereomeric, enantiomeric, and epimeric forms, as well as d-isomers and l-isomers, and mixtures thereof. Individual stereoisomers of compounds can be prepared synthetically from commercially available starting materials which contain chiral centers or by preparation of mixtures of enantiomeric products followed by separation such as conversion to a mixture of diastereomers followed by separation or recrystallization, chromatographic techniques, direct separation of enantiomers on chiral chromatographic columns, or any other appropriate method known in the art. Starting compounds of particular stereochemistry are either commercially available or can be made and resolved by techniques

known in the art. Additionally, the compounds disclosed herein may exist as geometric isomers. The present disclosure includes all *cis*, *trans*, *syn*, *anti*, *entgegen* (*E*), and *zusammen* (*Z*) isomers as well as the appropriate mixtures thereof. Additionally, compounds may exist as tautomers; all tautomeric isomers are provided by this disclosure. Additionally, the compounds disclosed herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms.

[095] The term “bond” refers to a covalent linkage between two atoms, or two moieties when the atoms joined by the bond are considered part of larger substructure. A bond may be single, double, or triple unless otherwise specified. A dashed line between two atoms in a drawing of a molecule indicates that an additional bond may be present or absent at that position.

[096] The term “disease” as used herein is intended to be generally synonymous, and is used interchangeably with, the terms “disorder,” “syndrome,” and “condition” (as in medical condition), in that all reflect an abnormal condition of the human or animal body or of one of its parts that impairs normal functioning, is typically manifested by distinguishing signs and symptoms, and causes the human or animal to have a reduced duration or quality of life.

[097] The term “combination therapy” means the administration of two or more therapeutic agents to treat a therapeutic condition or disorder described in the present disclosure. Such administration encompasses co-administration of these therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each active ingredient. In addition, such administration also encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein.

[098] GLS1 inhibitor is used herein to refer to a compound that exhibits an IC₅₀ with respect to GLS1 activity of no more than about 100 μ M and more typically not more than about 50 μ M, as measured in the GLS1 enzyme assay described generally herein below. IC₅₀ is that concentration of inhibitor that reduces the activity of an enzyme (e.g., GLS1) to half-maximal level. Certain compounds disclosed herein have been discovered to exhibit inhibition against GLS1. In certain embodiments, compounds will exhibit an IC₅₀ with respect to GLS1 of no more than about 10 μ M; in further embodiments, compounds will exhibit an IC₅₀ with respect to

GLS1 of no more than about 5 μ M; in yet further embodiments, compounds will exhibit an IC50 with respect to GLS1 of not more than about 1 μ M; in yet further embodiments, compounds will exhibit an IC50 with respect to GLS1 of not more than about 200 nM, as measured in the GLS1 binding assay described herein.

[0099] The phrase "therapeutically effective" is intended to qualify the amount of active ingredients used in the treatment of a disease or disorder or on the effecting of a clinical endpoint.

[0100] The term "therapeutically acceptable" refers to those compounds (or salts, prodrugs, tautomers, zwitterionic forms, etc.) which are suitable for use in contact with the tissues of patients without undue toxicity, irritation, and allergic response, are commensurate with a reasonable benefit/risk ratio, and are effective for their intended use.

[0101] As used herein, reference to "treatment" of a patient is intended to include prophylaxis. Treatment may also be preemptive in nature, i.e., it may include prevention of disease. Prevention of a disease may involve complete protection from disease, for example as in the case of prevention of infection with a pathogen, or may involve prevention of disease progression. For example, prevention of a disease may not mean complete foreclosure of any effect related to the diseases at any level, but instead may mean prevention of the symptoms of a disease to a clinically significant or detectable level. Prevention of diseases may also mean prevention of progression of a disease to a later stage of the disease.

[0102] The term "patient" is generally synonymous with the term "subject" and includes all mammals including humans. Examples of patients include humans, livestock such as cows, goats, sheep, pigs, and rabbits, and companion animals such as dogs, cats, rabbits, and horses. Preferably, the patient is a human.

[0103] The term "prodrug" refers to a compound that is made more active in vivo. Certain compounds disclosed herein may also exist as prodrugs, as described in Hydrolysis in Drug and Prodrug Metabolism : Chemistry, Biochemistry, and Enzymology (Testa, Bernard and Mayer, Joachim M. Wiley-VHCA, Zurich, Switzerland 2003). Prodrugs of the compounds described herein are structurally modified forms of the compound that readily undergo chemical changes under physiological conditions to provide the compound. Additionally, prodrugs can be converted to the compound by chemical or biochemical methods in an ex vivo environment. For example, prodrugs can be slowly converted to a compound when placed in a transdermal patch

reservoir with a suitable enzyme or chemical reagent. Prodrugs are often useful because, in some situations, they may be easier to administer than the compound, or parent drug. They may, for instance, be bioavailable by oral administration whereas the parent drug is not. The prodrug may also have improved solubility in pharmaceutical compositions over the parent drug. A wide variety of prodrug derivatives are known in the art, such as those that rely on hydrolytic cleavage or oxidative activation of the prodrug. An example, without limitation, of a prodrug would be a compound which is administered as an ester (the "prodrug"), but then is metabolically hydrolyzed to the carboxylic acid, the active entity. Additional examples include peptidyl derivatives of a compound.

[0104] The compounds disclosed herein can exist as therapeutically acceptable salts. The present disclosure includes compounds listed above in the form of salts, including acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable. However, salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Basic addition salts may also be formed and be pharmaceutically acceptable. For a more complete discussion of the preparation and selection of salts, refer to *Pharmaceutical Salts: Properties, Selection, and Use* (Stahl, P. Heinrich. Wiley-VCHA, Zurich, Switzerland, 2002).

[0105] The term "therapeutically acceptable salt," as used herein, represents salts or zwitterionic forms of the compounds disclosed herein which are water or oil-soluble or dispersible and therapeutically acceptable as defined herein. The salts can be prepared during the final isolation and purification of the compounds or separately by reacting the appropriate compound in the form of the free base with a suitable acid. Representative acid addition salts include acetate, adipate, alginate, L-ascorbate, aspartate, benzoate, benzenesulfonate (besylate), bisulfate, butyrate, camphorate, camphorsulfonate, citrate, digluconate, formate, fumarate, gentisate, glutarate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hippurate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isethionate), lactate, maleate, malonate, DL-mandelate, mesitylenesulfonate, methanesulfonate, naphthylsulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphonate, picrate, pivalate, propionate, pyroglutamate, succinate, sulfonate, tartrate, L-tartrate, trichloroacetate, trifluoroacetate, phosphate, glutamate, bicarbonate, para-

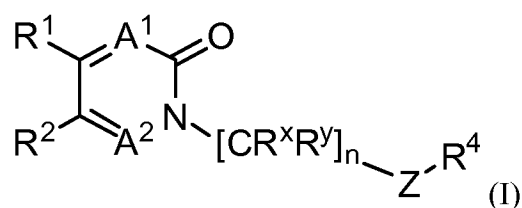
toluenesulfonate (p-tosylate), and undecanoate. Also, basic groups in the compounds disclosed herein can be quaternized with methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides; dimethyl, diethyl, dibutyl, and diamyl sulfates; decyl, lauryl, myristyl, and steryl chlorides, bromides, and iodides; and benzyl and phenethyl bromides. Examples of acids which can be employed to form therapeutically acceptable addition salts include inorganic acids such as hydrochloric, hydrobromic, sulfuric, and phosphoric, and organic acids such as oxalic, maleic, succinic, and citric. Salts can also be formed by coordination of the compounds with an alkali metal or alkaline earth ion. Hence, the present disclosure contemplates sodium, potassium, magnesium, and calcium salts of the compounds disclosed herein, and the like.

[0106] Basic addition salts can be prepared during the final isolation and purification of the compounds by reacting a carboxy group with a suitable base such as the hydroxide, carbonate, or bicarbonate of a metal cation or with ammonia or an organic primary, secondary, or tertiary amine. The cations of therapeutically acceptable salts include lithium, sodium, potassium, calcium, magnesium, and aluminum, as well as nontoxic quaternary amine cations such as ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, ethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, dicyclohexylamine, procaine, dibenzylamine, N,N-dibenzylphenethylamine, 1-phenamine, and N,N'-dibenzylethylenediamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

[0107] A salt of a compound can be made by reacting the appropriate compound in the form of the free base with the appropriate acid.

Compounds

[0108] The present disclosure provides a compound of structural Formula I



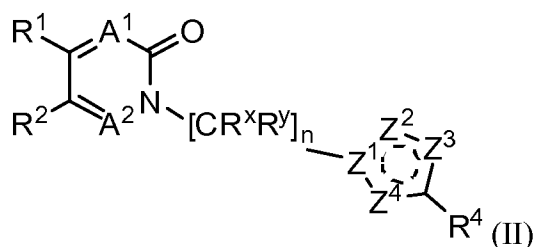
or a salt thereof, wherein: n is chosen from 3, 4, and 5; each R^{x} and R^{y} is independently chosen from alkyl, cyano, H, and halo, wherein two R^{x} groups together with the atoms to which they are

attached optionally form a cycloalkyl ring; A^1 and A^2 are independently chosen from C-H, C-F, and N; R^1 and R^4 are independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, hydroxyl, $C(R^3)_2C(O)R^3$, $C(R^3)_2C(O)N(R^3)_2$, $C(R^3)_2N(R^3)_2$, $C(R^3)_2NR^3C(O)R^3$, $C(R^3)_2NR^3C(O)OR^3$, $C(R^3)_2NR^3C(O)N(R^3)_2$, $C(R^3)_2NR^3S(O)R^3$, $C(R^3)_2NR^3S(O)_2R^3$, $N(R^3)_2$, $NR^3C(O)R^3$, $NR^3C(O)OR^3$, $NR^3C(O)N(R^3)_2$, $NR^3S(O)R^3$, $NR^3S(O)_2R^3$, $C(O)N(R^3)_2$, $S(O)N(R^3)_2$, $S(O)_2N(R^3)_2$, $C(O)R^3$, SR^3 , $S(O)R^3$, and $S(O)_2R^3$, wherein each R^1 and R^4 may be optionally substituted with between 0 and 3 R^Z groups; R^2 is chosen from alkyl, heterocycloalkyl, cyano, cycloalkyl, H, halo, and haloalkyl, wherein R^1 and R^2 together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups; each R^3 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein each R^3 may be optionally substituted with between 0 and 3 R^Z groups, wherein two R^3 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups; each R^Z group is independently chosen from alkenyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyarylalkyl, alkoxycycloalkyl, alkoxycycloalkylalkyl, alkoxyhaloalkyl, alkoxyheteroaryl, alkoxyheteroarylalkyl, alkoxyheterocycloalkyl, alkoxyheterocycloalkylalkyl, alkyl, alkylaryl, alkylarylalkyl, alkylcycloalkyl, alkylcycloalkylalkyl, alkylheteroaryl, alkylheteroarylalkyl, alkylheterocycloalkyl, alkylheterocycloalkylalkyl, aryl, arylalkyl, arylalkyloxy, arylhaloalkyl, aryloxy, cyano, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, cycloalkylhaloalkyl, cycloalkyloxy, H, halo, haloalkoxy, haloalkoxyalkyl, haloalkoxyaryl, haloalkoxyarylalkyl, haloalkoxycycloalkyl, haloalkoxycycloalkylalkyl, haloalkoxyheteroaryl, haloalkoxyheteroarylalkyl, haloalkoxyheterocycloalkyl, haloalkoxyheterocycloalkylalkyl, haloalkyl, haloalkylaryl, haloalkylarylalkyl, haloalkylcycloalkyl, haloalkylcycloalkylalkyl, haloalkylheteroaryl, haloalkylheteroarylalkyl, haloalkylheterocycloalkyl, haloalkylheterocycloalkylalkyl, haloaryl, haloarylalkyl, haloarylalkyloxy, haloaryloxy, halocycloalkyl, halocycloalkylalkyl, halocycloalkylalkyloxy, halocycloalkyloxy, haloheteroaryl, haloheteroarylalkyl, haloheteroarylalkyloxy, haloheteroaryloxy, haloheterocycloalkyl,

haloheterocycloalkylalkyl, haloheterocycloalkylalkyloxy, haloheterocycloalkyloxy, heteroaryl, heteroarylalkyl, heteroarylalkyloxy, heteroarylhaloalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkylalkyloxy, heterocycloalkylhaloalkyl, heterocycloalkyloxy, hydroxyl, oxo, $N(R^6)_2$, $NR^6C(O)C(R^6)_3$, $NR^6C(O)OC(R^6)_3$, $NR^6C(O)N(R^6)_2$, $NR^6S(O)C(R^6)_3$, $NR^6S(O)_2C(R^6)_3$, $C(O)N(R^6)_2$, $S(O)N(R^6)_2$, $S(O)_2N(R^6)_2$, $C(O)C(R^6)_3$, $SC(R^6)_3$, $S(O)C(R^6)_3$, and $S(O)_2C(R^6)_3$; each R^6 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein two R^6 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^x groups; and Z is heteroaryl, which may be optionally substituted..

[0109] In some embodiments, Z is a 5-6 membered monocyclic or 9-10 membered bicyclic heteroaryl, either of which contains one to four heteroatoms chosen from N, O, and S, and either of which may optionally be substituted by one to three substituents chosen from lower alkyl, halogen, CF_3 , OCF_3 , cyano, and hydroxyl.

[0110] In some embodiments, the compound, or a pharmaceutically acceptable salt thereof, has Formula II:



or a salt thereof, wherein; n is chosen from 3, 4, and 5; each R^x and R^y is independently chosen from alkyl, cyano, H, and halo, wherein two R^x groups together with the atoms to which they are attached optionally form a cycloalkyl ring; A^1 and A^2 are independently chosen from C-H, C-F, and N; Z^1 is chosen from C and N; Z^2 , Z^3 , and Z^4 are independently chosen from N, O, S, and CH, wherein at least one of Z^1 , Z^2 , Z^3 , and Z^4 is chosen from N, O, and S; R^1 and R^4 are independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, hydroxyl, $C(R^3)_2C(O)R^3$, $C(R^3)_2C(O)N(R^3)_2$, $C(R^3)_2N(R^3)_2$, $C(R^3)_2NR^3C(O)R^3$, $C(R^3)_2NR^3C(O)OR^3$, $C(R^3)_2NR^3C(O)N(R^3)_2$, $C(R^3)_2NR^3S(O)R^3$,

$C(R^3)_2NR^3S(O)_2R^3$, $N(R^3)_2$, $NR^3C(O)R^3$, $NR^3C(O)OR^3$, $NR^3C(O)N(R^3)_2$, $NR^3S(O)R^3$,
 $NR^3S(O)_2R^3$, $C(O)N(R^3)_2$, $S(O)N(R^3)_2$, $S(O)_2N(R^3)_2$, $C(O)R^3$, SR^3 , $S(O)R^3$, and $S(O)_2R^3$, wherein
each R^1 and R^4 may be optionally substituted with between 0 and 3 R^Z groups; R^2 is chosen from
alkyl, heterocycloalkyl, cyano, cycloalkyl, H, halo, and haloalkyl, wherein R^1 and R^2 together
with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl,
or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups;
each R^3 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl,
cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl,
heterocycloalkylalkyl, and hydroxyl, wherein each R^3 may be optionally substituted with
between 0 and 3 R^Z groups, wherein two R^3 groups together with the atoms to which they are
attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be
optionally substituted with between 0 and 3 R^Z groups; each R^Z group is independently chosen
from alkenyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyarylalkyl, alkoxycycloalkyl,
alkoxycycloalkylalkyl, alkoxyhaloalkyl, alkoxyheteroaryl, alkoxyheteroarylalkyl,
alkoxyheterocycloalkyl, alkoxyheterocycloalkylalkyl, alkyl, alkylaryl, alkylarylalkyl,
alkylcycloalkyl, alkylcycloalkylalkyl, alkylheteroaryl, alkylheteroarylalkyl,
alkylheterocycloalkyl, alkylheterocycloalkylalkyl, aryl, arylalkyl, arylalkyloxy, arylhaloalkyl,
aryloxy, cyano, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, cycloalkylhaloalkyl,
cycloalkyloxy, H, halo, haloalkoxy, haloalkoxyalkyl, haloalkoxyaryl, haloalkoxyarylalkyl,
haloalkoxycycloalkyl, haloalkoxycycloalkylalkyl, haloalkoxyheteroaryl,
haloalkoxyheteroarylalkyl, haloalkoxyheterocycloalkyl, haloalkoxyheterocycloalkylalkyl,
haloalkyl, haloalkylaryl, haloalkylarylalkyl, haloalkylcycloalkyl, haloalkylcycloalkylalkyl,
haloalkylheteroaryl, haloalkylheteroarylalkyl, haloalkylheterocycloalkyl,
haloalkylheterocycloalkylalkyl, haloaryl, haloarylalkyl, haloarylalkyloxy, haloaryloxy,
halocycloalkyl, halocycloalkylalkyl, halocycloalkylalkyloxy, halocycloalkyloxy, haloheteroaryl,
haloheteroarylalkyl, haloheteroarylalkyloxy, haloheteroaryloxy, haloheterocycloalkyl,
haloheterocycloalkylalkyl, haloheterocycloalkylalkyloxy, haloheterocycloalkyloxy, heteroaryl,
heteroarylalkyl, heteroarylalkyloxy, heteroarylhaloalkyl, heteroaryloxy, heterocycloalkyl,
heterocycloalkylalkyl, heterocycloalkylalkyloxy, heterocycloalkylhaloalkyl,
heterocycloalkyloxy, hydroxyl, oxo, $N(R^6)_2$, $NR^6C(O)C(R^6)_3$, $NR^6C(O)OC(R^6)_3$,
 $NR^6C(O)N(R^6)_2$, $NR^6S(O)C(R^6)_3$, $NR^6S(O)_2C(R^6)_3$, $C(O)N(R^6)_2$, $S(O)N(R^6)_2$, $S(O)_2N(R^6)_2$,

$C(O)C(R^6)_3$, $SC(R^6)_3$, $S(O)C(R^6)_3$, and $S(O)_2C(R^6)_3$; and each R^6 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein two R^6 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^x groups

[0111] In certain embodiments, n is 4; and A^1 and A^2 are CH.

[0112] In certain embodiments, n is 4; A^1 is N; and A^2 are CH.

[0113] In certain embodiments, Z_1 is C; Z_2 and Z_3 are N; Z_4 is S; and R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$.

[0114] In certain embodiments, n is 4; A^1 and A^2 are CH; Z^1 is C; Z^2 and Z^3 are N; Z^4 is S; and R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$.

[0115] In certain embodiments, Z^1 is C; Z^2 and Z^3 are N; Z^4 is S; and R^4 is $C(O)N(R^3)_2$.

[0116] In certain embodiments, n is 4; A^1 and A^2 are CH; Z^1 is C; Z^2 and Z^3 are N; Z^4 is S; and R^4 is $C(O)N(R^3)_2$.

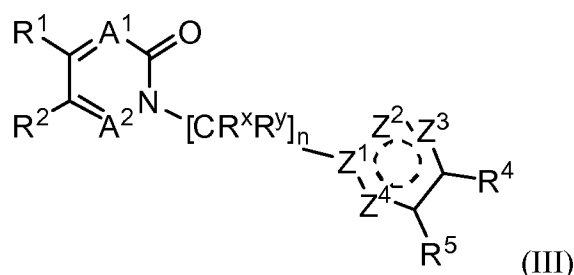
[0117] In certain embodiments, Z^1 , Z^2 , and Z^3 are N; Z^4 is CH; and R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$.

[0118] In certain embodiments, n is 4; A^1 and A^2 are CH; Z^1 , Z^2 , and Z^3 are N; Z^4 is CH; and R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$.

[0119] In certain embodiments, Z^1 , Z^2 , and Z^3 are N; Z^4 is CH; and R^4 is $C(O)N(R^3)_2$.

[0120] In certain embodiments, n is 4; A^1 and A^2 are CH; Z^1 , Z^2 , and Z^3 are N; Z^4 is CH; and R^4 is $C(O)N(R^3)_2$.

[0121] In some embodiments, the compound, or a pharmaceutically acceptable salt thereof, Formula III:



or a salt thereof, wherein: n is chosen from 3, 4, and 5; each R^x and R^y is independently chosen from alkyl, cyano, H, and halo, wherein two R^x groups together with the atoms to which they are

attached optionally form a cycloalkyl ring; A^1 and A^2 are independently chosen from C-H, C-F, and N; Z^1 is chosen from C and N; Z^2 is chosen from N, CH, and C(O); Z^3 , and Z^4 are independently chosen from N and CH, wherein at least one of Z^1 , Z^2 , Z^3 , and Z^4 is N; R^1 and R^4 are independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, hydroxyl, $C(R^3)_2C(O)R^3$, $C(R^3)_2C(O)N(R^3)_2$, $C(R^3)_2N(R^3)_2$, $C(R^3)_2NR^3C(O)R^3$, $C(R^3)_2NR^3C(O)OR^3$, $C(R^3)_2NR^3C(O)N(R^3)_2$, $C(R^3)_2NR^3S(O)R^3$, $C(R^3)_2NR^3S(O)_2R^3$, $N(R^3)_2$, $NR^3C(O)R^3$, $NR^3C(O)OR^3$, $NR^3C(O)N(R^3)_2$, $NR^3S(O)R^3$, $NR^3S(O)_2R^3$, $C(O)N(R^3)_2$, $S(O)N(R^3)_2$, $S(O)_2N(R^3)_2$, $C(O)R^3$, SR^3 , $S(O)R^3$, and $S(O)_2R^3$, wherein each R^1 and R^4 may be optionally substituted with between 0 and 3 R^Z groups; R^2 and R^5 are chosen from alkyl, heterocycloalkyl, cyano, cycloalkyl, H, halo, and haloalkyl, wherein R^1 and R^2 together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups, wherein R^4 and R^5 together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups; each R^3 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein each R^3 may be optionally substituted with between 0 and 3 R^Z groups, wherein two R^3 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups; each R^Z group is independently chosen from alkenyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyarylalkyl, alkoxycycloalkyl, alkoxycycloalkylalkyl, alkoxyhaloalkyl, alkoxyheteroaryl, alkoxyheteroarylalkyl, alkoxyheterocycloalkyl, alkoxyheterocycloalkylalkyl, alkyl, alkylaryl, alkylarylalkyl, alkylcycloalkyl, alkylcycloalkylalkyl, alkylheteroaryl, alkylheteroarylalkyl, alkylheterocycloalkyl, alkylheterocycloalkylalkyl, aryl, arylalkyl, arylalkyloxy, arylhaloalkyl, aryloxy, cyano, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, cycloalkylhaloalkyl, cycloalkyloxy, H, halo, haloalkoxy, haloalkoxyalkyl, haloalkoxyaryl, haloalkoxyarylalkyl, haloalkoxycycloalkyl, haloalkoxycycloalkylalkyl, haloalkoxyheteroaryl, haloalkoxyheteroarylalkyl, haloalkoxyheterocycloalkyl, haloalkoxyheterocycloalkylalkyl, haloalkyl, haloalkylaryl, haloalkylarylalkyl, haloalkylcycloalkyl, haloalkylcycloalkylalkyl,

haloalkylheteroaryl, haloalkylheteroarylalkyl, haloalkylheterocycloalkyl, haloalkylheterocycloalkylalkyl, haloaryl, haloarylalkyl, haloarylalkyloxy, haloaryloxy, halocycloalkyl, halocycloalkylalkyl, halocycloalkylalkyloxy, halocycloalkyloxy, haloheteroaryl, haloheteroarylalkyl, haloheteroarylalkyloxy, haloheteroaryloxy, haloheterocycloalkyl, haloheterocycloalkylalkyl, haloheterocycloalkylalkyloxy, haloheterocycloalkyloxy, heteroaryl, heteroarylalkyl, heteroarylalkyloxy, heteroarylhaloalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkylalkyloxy, heterocycloalkylhaloalkyl, heterocycloalkyloxy, hydroxyl, oxo, $N(R^6)_2$, $NR^6C(O)C(R^6)_3$, $NR^6C(O)OC(R^6)_3$, $NR^6C(O)N(R^6)_2$, $NR^6S(O)C(R^6)_3$, $NR^6S(O)_2C(R^6)_3$, $C(O)N(R^6)_2$, $S(O)N(R^6)_2$, $S(O)_2N(R^6)_2$, $C(O)C(R^6)_3$, $SC(R^6)_3$, $S(O)C(R^6)_3$, and $S(O)_2C(R^6)_3$; and each R^6 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein two R^6 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^x groups.

[0122] In certain embodiments, n is 4; and A^1 and A^2 are CH.

[0123] In certain embodiments, n is 4; A^1 is N; and A^2 are CH.

[0124] In certain embodiments, Z_1 is C; Z_2 and Z_3 are N; Z^4 is CH; R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$; and R^5 is H.

[0125] In certain embodiments, n is 4; A^1 and A^2 are CH; Z^1 is C; Z^2 and Z^3 are N; Z^4 is CH; R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$; and R^5 is H.

[0126] In certain embodiments, Z^1 is C; Z^2 and Z^3 are N; Z^4 is CH; R^4 is $C(O)N(R^3)_2$; and R^5 is H.

[0127] In certain embodiments, n is 4; A^1 and A^2 are CH; Z^1 is C; Z^2 and Z^3 are N; Z^4 is CH; R^4 is $C(O)N(R^3)_2$; and R^5 is H.

[0128] In certain embodiments, Z^1 is N; Z^2 is $C(O)$; Z^4 is CH; R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$; and R^5 is H.

[0129] In certain embodiments, n is 4; A^1 and A^2 are CH; Z^1 is N; Z^2 is $C(O)$; Z^4 is CH; R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$; and R^5 is H.

[0130] In certain embodiments, Z^1 is N; Z^2 is $C(O)$; Z^4 is CH; R^4 is $C(O)N(R^3)_2$; and R^5 is H.

[0131] In certain embodiments, n is 4; and A^1 and A^2 are CH; Z^1 is N; Z^2 is C(O); Z^4 is CH; R^4 is C(O)N(R³)₂; and R^5 is H.

[0132] Also provided are embodiments wherein any of embodiment above in paragraphs [0006] and [00107] – [0131] above may be combined with any one or more of these embodiments, provided the combination is not mutually exclusive.

Pharmaceutical Compositions

[0133] While it may be possible for the compounds of the subject disclosure to be administered as the raw chemical, it is also possible to present them as a pharmaceutical formulation. Accordingly, provided herein are pharmaceutical formulations which comprise one or more of certain compounds disclosed herein, or one or more pharmaceutically acceptable salts, esters, prodrugs, amides, or solvates thereof, together with one or more pharmaceutically acceptable carriers thereof and optionally one or more other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Proper formulation is dependent upon the route of administration chosen. Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; e.g., in Remington's Pharmaceutical Sciences. The pharmaceutical compositions disclosed herein may be manufactured in any manner known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[0134] The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous, intraarticular, and intramedullary), intraperitoneal, transmucosal, transdermal, rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Typically, these methods include the step of bringing into association a compound of the subject disclosure or a pharmaceutically acceptable salt, ester, amide, prodrug or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association the active

ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

[0135] Compounds described herein can be administered as follows:

Oral Administration

[0136] The compounds of the present invention may be administered orally, including swallowing, so the compound enters the gastrointestinal tract, or is absorbed into the blood stream directly from the mouth, including sublingual or buccal administration.

[0137] Suitable compositions for oral administration include solid formulations such as tablets, pills, cachets, lozenges and hard or soft capsules, which can contain liquids, gels, powders, or granules.

[0138] In a tablet or capsule dosage form the amount of drug present may be from about 0.05% to about 95% by weight, more typically from about 2% to about 50% by weight of the dosage form.

[0139] In addition, tablets or capsules may contain a disintegrant, comprising from about 0.5% to about 35% by weight, more typically from about 2% to about 25% of the dosage form. Examples of disintegrants include methyl cellulose, sodium or calcium carboxymethyl cellulose, croscarmellose sodium, polyvinylpyrrolidone, hydroxypropyl cellulose, starch and the like.

[0140] Suitable binders, for use in a tablet, include gelatin, polyethylene glycol, sugars, gums, starch, hydroxypropyl cellulose and the like. Suitable diluents, for use in a tablet, include mannitol, xylitol, lactose, dextrose, sucrose, sorbitol and starch.

[0141] Suitable surface active agents and glidants, for use in a tablet or capsule, may be present in amounts from about 0.1% to about 3% by weight, and include polysorbate 80, sodium dodecyl sulfate, talc and silicon dioxide.

[0142] Suitable lubricants, for use in a tablet or capsule, may be present in amounts from about 0.1% to about 5% by weight, and include calcium, zinc or magnesium stearate, sodium stearyl fumarate and the like.

[0143] Tablets may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with binders, inert diluents, or lubricating, surface active or dispersing agents. Molded

tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with a liquid diluent. Dyes or pigments may be added to tablets for identification or to characterize different combinations of active compound doses.

[0144] Liquid formulations can include emulsions, solutions, syrups, elixirs and suspensions, which can be used in soft or hard capsules. Such formulations may include a pharmaceutically acceptable carrier, for example, water, ethanol, polyethylene glycol, cellulose, or an oil. The formulation may also include one or more emulsifying agents and/or suspending agents.

[0145] Compositions for oral administration may be formulated as immediate or modified release, including delayed or sustained release, optionally with enteric coating.

[0146] In another embodiment, a pharmaceutical composition comprises a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Parenteral Administration

[0147] Compounds of the present invention may be administered directly into the blood stream, muscle, or internal organs by injection, e.g., by bolus injection or continuous infusion. Suitable means for parenteral administration include intravenous, intra-muscular, subcutaneous intraarterial, intraperitoneal, intrathecal, intracranial, and the like. Suitable devices for parenteral administration include injectors (including needle and needle-free injectors) and infusion methods. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials.

[0148] Most parenteral formulations are aqueous solutions containing excipients, including salts, buffering, suspending, stabilizing and/or dispersing agents, antioxidants, bacteriostats, preservatives, and solutes which render the formulation isotonic with the blood of the intended recipient, and carbohydrates.

[0149] Parenteral formulations may also be prepared in a dehydrated form (e.g., by lyophilization) or as sterile non-aqueous solutions. These formulations can be used with a suitable vehicle, such as sterile water. Solubility-enhancing agents may also be used in preparation of parenteral solutions.

[0150] Compositions for parenteral administration may be formulated as immediate or modified release, including delayed or sustained release. Compounds may also be formulated as

depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0151]

Topical Administration

[0152] Compounds of the present invention may be administered topically (for example to the skin, mucous membranes, ear, nose, or eye) or transdermally. Formulations for topical administration can include, but are not limited to, lotions, solutions, creams, gels, hydrogels, ointments, foams, implants, patches and the like. Carriers that are pharmaceutically acceptable for topical administration formulations can include water, alcohol, mineral oil, glycerin, polyethylene glycol and the like. Topical administration can also be performed by, for example, electroporation, iontophoresis, phonophoresis and the like.

[0153] Typically, the active ingredient for topical administration may comprise from 0.001% to 10% w/w (by weight) of the formulation. In certain embodiments, the active ingredient may comprise as much as 10% w/w; less than 5% w/w; from 2% w/w to 5% w/w; or from 0.1% to 1% w/w of the formulation.

[0154] Compositions for topical administration may be formulated as immediate or modified release, including delayed or sustained release.

Rectal, Buccal, and Sublingual Administration

[0155] Suppositories for rectal administration of the compounds of the present invention can be prepared by mixing the active agent with a suitable non-irritating excipient such as cocoa butter, synthetic mono-, di-, or triglycerides, fatty acids, or polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature, and which will therefore melt in the rectum and release the drug.

[0156] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

Administration by Inhalation

[0157] For administration by inhalation, compounds may be conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray or powder. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, the compounds according to the disclosure may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch. The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[0158] Other carrier materials and modes of administration known in the pharmaceutical art may also be used. Pharmaceutical compositions of the invention may be prepared by any of the well-known techniques of pharmacy, such as effective formulation and administration procedures. Preferred unit dosage formulations are those containing an effective dose, as herein recited, or an appropriate fraction thereof, of the active ingredient. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. The specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diets, time of administration, route of administration, rate of excretion, drug combination, the precise disorder being treated, and the severity of the indication or condition being treated. In addition, the route of administration may vary depending on the condition and its severity. The above considerations concerning effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pa., 1975; Liberman, et al., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and Kibbe, et al., Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington, 1999.

Methods of Treatment

[0159] The present disclosure provides compounds and pharmaceutical compositions that inhibit glutaminase activity, particularly GLS1 activity and are thus useful in the treatment or prevention of disorders associated with GLS1. Compounds and pharmaceutical compositions of the present disclosure selectively modulate GLS1 and are thus useful in the treatment or prevention of a range of disorders associated with GLS1 and include, but are not limited to, cancer, immunological or neurological diseases associated with GLS1.

Neurological Disorders

[0160] In some embodiments, the compounds and pharmaceutical compositions of the present disclosure may be useful in the treatment or prevention of neurological diseases.

[0161] The most common neurotransmitter is glutamate, derived from the enzymatic conversion of glutamine via glutaminase. High levels of glutamate have been shown to be neurotoxic. Following traumatic insult to neuronal cells, there occurs a rise in neurotransmitter release, particularly glutamate. Accordingly, inhibition of glutaminase has been hypothesized as a means of treatment following an ischemic insult, such as stroke.

[0162] Huntington's disease is a progressive, fatal neurological condition. In genetic mouse models of Huntington's disease, it was observed that the early manifestation of the disease correlated with dysregulated glutamate release (Raymond et al., Neuroscience, 2011). In HIV-associated dementia, HIV infected macrophages exhibit upregulated glutaminase activity and increased glutamate release, leading to neuronal damage (Huang et al., J. Neurosci., 2011). Similarly, in another neurological disease, the activated microglia in Rett Syndrome release glutamate causing neuronal damage. The release of excess glutamate has been associated with the up-regulation of glutaminase (Maezawa et al., J. Neurosci, 2010). In mice bred to have reduced glutaminase levels, sensitivity to psychotic-stimulating drugs, such as amphetamines, was dramatically reduced, thus suggesting that glutaminase inhibition may be beneficial in the treatment of schizophrenia (Gaisler-Salomon et al., Neuropsychopharmacology, 2009). Bipolar disorder is a devastating illness that is marked by recurrent episodes of mania and depression. This disease is treated with mood stabilizers such as lithium and valproate; however, chronic use of these drugs appear to increase the abundance of glutamate receptors (Nanavati et al., J. Neurochem., 2011), which may lead to a decrease in the drug's effectiveness over time. Thus, an alternative treatment may be to reduce the amount of glutamate by inhibiting glutaminase. This

may or may not be in conjunction with the mood stabilizers. Memantine, a partial antagonist of N-methyl-D-aspartate receptor (NMDAR), is an approved therapeutic in the treatment of Alzheimer's disease. Currently, research is being conducted looking at memantine as a means of treating vascular dementia and Parkinson's disease (Oliverares et al., Curr. Alzheimer Res., 2011). Since memantine has been shown to partially block the NMDA glutamate receptor also, it is not unreasonable to speculate that decreasing glutamate levels by inhibiting glutaminase could also treat Alzheimer's disease, vascular dementia and Parkinson's disease. Alzheimer's disease, bipolar disorder, HIV-associated dementia, Huntington's disease, ischemic insult, Parkinson's disease, schizophrenia, stroke, traumatic insult and vascular dementia are but a few of the neurological diseases that have been correlated to increased levels of glutamate. Thus, inhibiting glutaminase with a compound described herein can reduce or prevent neurological diseases. Therefore, in certain embodiments, the compounds may be used for the treatment or prevention of neurological diseases.

Immunological Disorders

[0163] In some embodiments, the compounds and pharmaceutical compositions of the present disclosure may be useful in the treatment or prevention of immunological diseases.

[0164] Activation of T lymphocytes induces cell growth, proliferation, and cytokine production, thereby placing energetic and biosynthetic demands on the cell. Glutamine serves as an amine group donor for nucleotide synthesis, and glutamate, the first component in glutamine metabolism, plays a direct role in amino acid and glutathione synthesis, as well as being able to enter the Krebs cycle for energy production (Carr et al., J. Immunol., 2010). Mitogen-induced T cell proliferation and cytokine production require high levels of glutamine metabolism, thus inhibiting glutaminase may serve as a means of immune modulation. In multiple sclerosis, an inflammatory autoimmune disease, the activated microglia exhibit up-regulated glutaminase and release increased levels of extracellular glutamate. Glutamine levels are lowered by sepsis, injury, burns, surgery and endurance exercise (Calder et al., Amino Acids, 1999). These situations put the individual at risk of immunosuppression. In fact, in general, glutaminase gene expression and enzyme activity are both increased during T cell activity. Patients given glutamine following bone marrow transplantation resulted in a lower level of infection and reduced graft v. host disease (Crowther, Proc. Nutr. Soc., 2009). T cell proliferation and activation is involved in many immunological diseases, such as inflammatory bowel disease,

Crohn's disease, sepsis, psoriasis, arthritis (including rheumatoid arthritis), multiple sclerosis, graft v. host disease, infections, lupus and diabetes. In an embodiment of the invention, the compounds described herein can be used to treat or prevent immunological diseases.

Cancer

[0165] In some embodiments, the compounds and pharmaceutical compositions of the present disclosure may be useful in the treatment or prevention of cancer.

[0166] In addition to serving as the basic building blocks of protein synthesis, amino acids have been shown to contribute to many processes critical for growing and dividing cells, and this is particularly true for cancer cells. Nearly all definitions of cancer include reference to dysregulated proliferation. Numerous studies on glutamine metabolism in cancer indicate that many tumors are avid glutamine consumers (Souba, *Ann. Surg.*, 1993; Collins et al., *J. Cell. Physiol.*, 1998; Medina, *J. Nutr.*, 2001; Shanware et al., *J. Mol. Med.*, 2011). An embodiment of the invention is the use of the compounds described herein for the treatment of cancer.

[0167] In some embodiments, the compounds of the present disclosure may be used to prevent or treat cancer, wherein the cancer is one or a variant of Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Adrenocortical Carcinoma, AIDS-Related Cancers (Kaposi Sarcoma and Lymphoma), Anal Cancer, Appendix Cancer, Atypical Teratoid/Rhabdoid Tumor, Basal Cell Carcinoma, Bile Duct Cancer (including Extrahepatic), Bladder Cancer, Bone Cancer (including Osteosarcoma and Malignant Fibrous Histiocytoma), Brain Tumor (such as Astrocytomas, Brain and Spinal Cord Tumors, Brain Stem Glioma, Central Nervous System Atypical Teratoid/Rhabdoid Tumor, Central Nervous System Embryonal Tumors, Craniopharyngioma, Ependymoblastoma, Ependymoma, Medulloblastoma, Medulloepithelioma, Pineal Parenchymal Tumors of Intermediate Differentiation, Supratentorial Primitive Neuroectodermal Tumors and Pineoblastoma), Breast Cancer, Bronchial Tumors, Burkitt Lymphoma, Basal Cell Carcinoma, Bile Duct Cancer (including Extrahepatic), Bladder Cancer, Bone Cancer (including Osteosarcoma and Malignant Fibrous Histiocytoma), Carcinoid Tumor, Carcinoma of Unknown Primary, Central Nervous System (such as Atypical Teratoid/Rhabdoid Tumor, Embryonal Tumors and Lymphoma), Cervical Cancer, Childhood Cancers, Chordoma, Chronic Lymphocytic Leukemia (CLL), Chronic Myelogenous Leukemia (CML), Chronic Myeloproliferative Disorders, Colon Cancer, Colorectal Cancer, Craniopharyngioma, Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome), Duct, Bile (Extrahepatic), Ductal

Carcinoma In Situ (DCIS), Embryonal Tumors (Central Nervous System), Endometrial Cancer, Ependymoblastoma, Ependymoma, Esophageal Cancer, Esthesioneuroblastoma, Ewing Sarcoma Family of Tumors, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer (like Intraocular Melanoma, Retinoblastoma), Fibrous Histiocytoma of Bone (including Malignant and Osteosarcoma) Gallbladder Cancer, Gastric (Stomach) Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Stromal Tumors (GIST), Germ Cell Tumor (Extracranial, Extragonadal, Ovarian), Gestational Trophoblastic Tumor, Glioma, Hairy Cell Leukemia, Head and Neck Cancer, Heart Cancer, Hepatocellular (Liver) Cancer, Histiocytosis, Langerhans Cell, Hodgkin Lymphoma, Hypopharyngeal Cancer, Intraocular Melanoma, Islet Cell Tumors (Endocrine, Pancreas), Kaposi Sarcoma, Kidney (including Renal Cell), Langerhans Cell Histiocytosis, Laryngeal Cancer, Leukemia (including Acute Lymphoblastic (ALL), Acute Myeloid (AML), Chronic Lymphocytic (CLL), Chronic Myelogenous (CML), Hairy Cell), Lip and Oral Cavity Cancer, Liver Cancer (Primary), Lobular Carcinoma In Situ (LCIS), Lung Cancer (Non-Small Cell and Small Cell), Lymphoma (AIDS-Related, Burkitt, Cutaneous T-Cell (Mycosis Fungoides and Sézary Syndrome), Hodgkin, Non-Hodgkin, Primary Central Nervous System (CNS), Macroglobulinemia, Waldenström, Male Breast Cancer, Malignant Fibrous Histiocytoma of Bone and Osteosarcoma, Medulloblastoma, Medulloepithelioma, Melanoma (including Intraocular (Eye)), Merkel Cell Carcinoma, Mesothelioma (Malignant), Metastatic Squamous Neck Cancer with Occult Primary, Midline Tract Carcinoma Involving NUT Gene, Mouth Cancer, Multiple Endocrine Neoplasia Syndromes, Multiple Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Neoplasms, Myelogenous Leukemia, Chronic (CML), Myeloid Leukemia, Acute (AML), Myeloma and Multiple Myeloma, Myeloproliferative Disorders (Chronic), Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin Lymphoma, Non-Small Cell Lung Cancer, Oral Cancer, Oral Cavity Cancer, Lip and, Oropharyngeal Cancer, Osteosarcoma and Malignant Fibrous Histiocytoma of Bone, Ovarian Cancer (such as Epithelial, Germ Cell Tumor, and Low Malignant Potential Tumor), Pancreatic Cancer (including Islet Cell Tumors), Papillomatosis, Paraganglioma, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pharyngeal Cancer, Pheochromocytoma, Pineal Parenchymal Tumors of Intermediate Differentiation, Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors,

Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Pleuropulmonary Blastoma, Pregnancy and Breast Cancer, Primary Central Nervous System (CNS) Lymphoma, Prostate Cancer, Rectal Cancer, Renal Cell (Kidney) Cancer, Renal Pelvis and Ureter, Transitional Cell Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoma (like Ewing Sarcoma Family of Tumors, Kaposi, Soft Tissue, Uterine), Sézary Syndrome, Skin Cancer (such as Melanoma, Merkel Cell Carcinoma, Nonmelanoma), Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary, Metastatic, Stomach (Gastric) Cancer, Supratentorial Primitive Neuroectodermal Tumors, T-Cell Lymphoma (Cutaneous, Mycosis Fungoides and Sézary Syndrome), Testicular Cancer, Throat Cancer, Thymoma and Thymic Carcinoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Trophoblastic Tumor (Gestational), Unknown Primary, Unusual Cancers of Childhood, Ureter and Renal Pelvis, Transitional Cell Cancer, Urethral Cancer, Uterine Cancer, Endometrial, Uterine Sarcoma, Waldenström Macroglobulinemia or Wilms Tumor.

[0168] In certain embodiments, the cancer to be treated is one specific to T-cells such as T-cell lymphoma and lymphoblastic T-cell leukemia.

[0169] In some embodiments, methods described herein are used to treat a disease condition comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula I or pharmaceutically acceptable salt thereof, wherein the condition is cancer which has developed resistance to chemotherapeutic drugs and/or ionizing radiation.

Combinations and Combination Therapy

[0170] The compounds of the present invention can be used, alone or in combination with other pharmaceutically active compounds, to treat conditions such as those previously described hereinabove. The compound(s) of the present invention and other pharmaceutically active compound(s) can be administered simultaneously (either in the same dosage form or in separate dosage forms) or sequentially. Accordingly, in one embodiment, the present invention comprises methods for treating a condition by administering to the subject a therapeutically-effective amount of one or more compounds of the present invention and one or more additional pharmaceutically active compounds.

[0171] In another embodiment, there is provided a pharmaceutical composition comprising one or more compounds of the present invention, one or more additional pharmaceutically active compounds, and a pharmaceutically acceptable carrier.

[0172] In another embodiment, the one or more additional pharmaceutically active compounds is selected from the group consisting of anti-cancer drugs, anti-proliferative drugs, and anti-inflammatory drugs.

[0173] GLS1 inhibitor compositions described herein are also optionally used in combination with other therapeutic reagents that are selected for their therapeutic value for the condition to be treated. In general, the compounds described herein and, in embodiments where combination therapy is employed, other agents do not have to be administered in the same pharmaceutical composition and, because of different physical and chemical characteristics, are optionally administered by different routes. The initial administration is generally made according to established protocols and then, based upon the observed effects, the dosage, modes of administration and times of administration subsequently modified. In certain instances, it is appropriate to administer a GLS1 inhibitor compound, as described herein, in combination with another therapeutic agent. By way of example only, the therapeutic effectiveness of a GLS1 inhibitor is enhanced by administration of another therapeutic agent (which also includes a therapeutic regimen) that also has therapeutic benefit. Regardless of the disease, disorder or condition being treated, the overall benefit experienced by the patient is either simply additive of the two therapeutic agents or the patient experiences an enhanced (i.e., synergistic) benefit. Alternatively, if a compound disclosed herein has a side effect, it may be appropriate to administer an agent to reduce the side effect; or the therapeutic effectiveness of a compound described herein may be enhanced by administration of an adjuvant.

[0174] Therapeutically effective dosages vary when the drugs are used in treatment combinations. Methods for experimentally determining therapeutically effective dosages of drugs and other agents for use in combination treatment regimens are documented methodologies. Combination treatment further includes periodic treatments that start and stop at various times to assist with the clinical management of the patient. In any case, the multiple therapeutic agents (one of which is a GLS1 inhibitor as described herein) may be administered in any order, or simultaneously. If simultaneously, the multiple therapeutic agents are optionally

provided in a single, unified form, or in multiple forms (by way of example only, either as a single pill or as two separate pills).

[0175] In some embodiments, one of the therapeutic agents is given in multiple doses, or both are given as multiple doses. If not simultaneous, the timing between the multiple doses optionally varies from more than zero weeks to less than twelve weeks.

[0176] In addition, the combination methods, compositions and formulations are not to be limited to the use of only two agents, the use of multiple therapeutic combinations are also envisioned. It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is optionally modified in accordance with a variety of factors. These factors include the disorder from which the subject suffers, as well as the age, weight, sex, diet, and medical condition of the subject. Thus, the dosage regimen actually employed varies widely, in some embodiments, and therefore deviates from the dosage regimens set forth herein.

[0177] The pharmaceutical agents which make up the combination therapy disclosed herein are optionally a combined dosage form or in separate dosage forms intended for substantially simultaneous administration. The pharmaceutical agents that make up the combination therapy are optionally also administered sequentially, with either agent being administered by a regimen calling for two-step administration. The two-step administration regimen optionally calls for sequential administration of the active agents or spaced-apart administration of the separate active agents. The time between the multiple administration steps ranges from a few minutes to several hours, depending upon the properties of each pharmaceutical agent, such as potency, solubility, bioavailability, plasma half-life and kinetic profile of the pharmaceutical agent.

[0178] In another embodiment, a GLS1 inhibitor is optionally used in combination with procedures that provide additional benefit to the patient. A GLS1 inhibitor and any additional therapies are optionally administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a GLS1 inhibitor varies in some embodiments. Thus, for example, a GLS1 inhibitor is used as a prophylactic and is administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. A GLS1 inhibitor and compositions are optionally administered to a subject during or as soon as possible after the onset of the symptoms. While embodiments of the present invention have been shown and described herein,

it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that in some embodiments of the invention various alternatives to the embodiments described herein are employed in practicing the invention.

[0179] A GLS1 inhibitor can be used in combination with anti-cancer drugs, including but not limited to the following classes: alkylating agents, anti-metabolites, plant alkaloids and terpenoids, topoisomerase inhibitors, cytotoxic antibiotics, angiogenesis inhibitors and tyrosine kinase inhibitors.

[0180] For use in cancer and neoplastic diseases a GLS1 inhibitor may be optimally used together with one or more of the following non-limiting examples of anti-cancer agents: (1) alkylating agents, including but not limited to cisplatin (PLATIN), carboplatin (PARAPLATIN), oxaliplatin (ELOXATIN), streptozocin (ZANOSAR), busulfan (MYLERAN) and cyclophosphamide (ENDOXAN); (2) anti-metabolites, including but not limited to mercaptopurine (PURINETHOL), thioguanine, pentostatin (NIPENT), cytosine arabinoside (ARA-C), gemcitabine (GEMZAR), fluorouracil (CARAC), leucovorin (FUSILEV) and methotrexate (RHEUMATREX); (3) plant alkaloids and terpenoids, including but not limited to vincristine (ONCOVIN), vinblastine and paclitaxel (TAXOL); (4) topoisomerase inhibitors, including but not limited to irinotecan (CAMPTOSAR), topotecan (HYCAMTIN) and etoposide (EPOSIN); (5) cytotoxic antibiotics, including but not limited to actinomycin D (COSMEGEN), doxorubicin (ADRIAMYCIN), bleomycin (BLENOXANE) and mitomycin (MITOSOL); (6) angiogenesis inhibitors, including but not limited to sunitinib (SUTENT) and bevacizumab (AVASTIN); and (7) tyrosine kinase inhibitors, including but not limited to imatinib (GLEEVEC), erlotinib (TARCEVA), lapatinib (TYKERB) and axitinib (INLYTA).

[0181] Where a subject is suffering from or at risk of suffering from an inflammatory condition, a GLS1 inhibitor compound described herein is optionally used together with one or more agents or methods for treating an inflammatory condition in any combination. Therapeutic agents/treatments for treating an autoimmune and/or inflammatory condition include, but are not limited to any of the following examples: (1) corticosteroids, including but not limited to cortisone, dexamethasone, and methylprednisolone; (2) nonsteroidal anti-inflammatory drugs (NSAIDs), including but not limited to ibuprofen, naproxen, acetaminophen, aspirin, fenoprofen

(NALFON), flurbiprofen (ANSAID), ketoprofen, oxaprozin (DAYPRO), diclofenac sodium (VOLTAREN), diclofenac potassium (CATAFLAM), etodolac (LODINE), indomethacin (INDOCIN), ketorolac (TORADOL), sulindac (CLINORIL), tolmetin (TOLECTIN), meclofenamate (MECLOMEN), mefenamic acid (PONSTEL), nabumetone (RELAFEN) and piroxicam (FELDENE); (3) immunosuppressants, including but not limited to methotrexate (RHEUMATREX), leflunomide (ARAVA), azathioprine (IMURAN), cyclosporine (NEORAL, SANDIMMUNE), tacrolimus and cyclophosphamide (CYTOXAN); (4) CD20 blockers, including but not limited to rituximab (RITUXAN); (5) Tumor Necrosis Factor (TNF) blockers, including but not limited to etanercept (ENBREL), infliximab (REMICADE) and adalimumab (HUMIRA); (6) interleukin-1 receptor antagonists, including but not limited to anakinra (KINERET); (7) interleukin-6 inhibitors, including but not limited to tocilizumab (ACTEMRA); (8) interleukin-17 inhibitors, including but not limited to AIN457; (9) Janus kinase inhibitors, including but not limited to tasocitinib; and (10) syk inhibitors, including but not limited to fostamatinib.

Compound Synthesis

[0182] Compounds of the present invention can be prepared using methods illustrated in general synthetic schemes and experimental procedures detailed below. General synthetic schemes and experimental procedures are presented for purposes of illustration and are not intended to be limiting. Starting materials used to prepare compounds of the present invention are commercially available or can be prepared using routine methods known in the art.

List of Abbreviations

[0183] Ac₂O = acetic anhydride; AcCl = acetyl chloride; AcOH = acetic acid; AIBN = azobisisobutyronitrile; aq. = aqueous; Bu₃SnH = tributyltin hydride; CD₃OD = deuterated methanol; CDCl₃ = deuterated chloroform; CDI = 1,1'-Carbonyldiimidazole; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DCM = dichloromethane; DEAD = diethyl azodicarboxylate; DIBAL-H = di-iso-butyl aluminium hydride; DIEA = DIPEA = N,N-diisopropylethylamine; DMAP = 4-dimethylaminopyridine; DMF = N,N-dimethylformamide; DMSO-d₆ = deuterated dimethyl sulfoxide; DMSO = dimethyl sulfoxide; DPPA = diphenylphosphoryl azide; EDC.HCl = EDCI.HCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; Et₂O = diethyl ether; EtOAc = ethyl

acetate; EtOH = ethanol; h = hour; HATU=2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate methanaminium; HMDS = hexamethyldisilazane; HOBT = 1-hydroxybenzotriazole; i-PrOH = isopropanol; LAH = lithium aluminiumhydride; LiHMDS = Lithium bis(trimethylsilyl)amide; MeCN = acetonitrile; MeOH = methanol; MP-carbonate resin = macroporous triethylammonium methylpolystyrene carbonate resin; MsCl = mesyl chloride; MTBE = methyl tertiary butyl ether; n-BuLi = n-butyllithium; NaHMDS = Sodium bis(trimethylsilyl)amide; NaOMe = sodium methoxide; NaOtBu = sodium t-butoxide; NBS = N-bromosuccinimide; NCS = N-chlorosuccinimide; NMP = N-Methyl-2-pyrrolidone; Pd(Ph₃)₄ = tetrakis(triphenylphosphine)palladium(0); Pd₂(dba)₃ = tris(dibenzylideneacetone)dipalladium(0); PdCl₂(PPh₃)₂ = bis(triphenylphosphine)palladium(II) dichloride; PG = protecting group; prep-HPLC = preparative high-performance liquid chromatography; PyBop = (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate; Pyr = pyridine; RT = room temperature; RuPhos = 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl; sat. = saturated; ss = saturated solution; t-BuOH = tert-butanol; T3P = Propylphosphonic Anhydride; TEA = Et₃N = triethylamine; TFA = trifluoroacetic acid; TFAA = trifluoroacetic anhydride; THF = tetrahydrofuran; Tol = toluene; TsCl = tosyl chloride; XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

General methods for preparing compounds

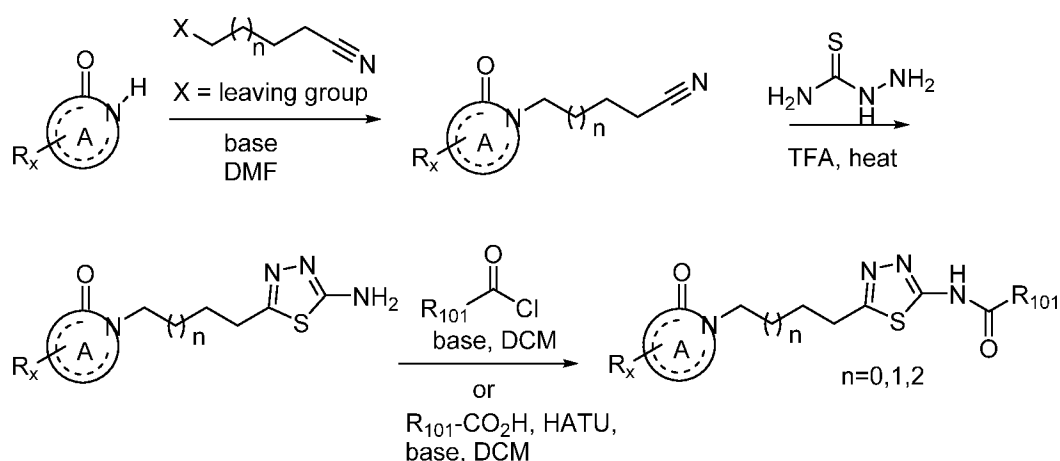
[0184] The following schemes can be used to practice the present invention. Additional structural groups, including but not limited to those defined elsewhere in the specification and not shown in the compounds described in the schemes can be incorporated to give various compounds disclosed herein, or intermediate compounds which can, after further manipulations using techniques known to those skilled in the art, be converted to compounds of the present invention. For example in certain embodiments the A and B rings in the structures described in the schemes – wherein A and B are heteroaromatic rings - can be substituted with various groups as defined herein.

[0185] One route for preparation of compounds of the present invention is described in Scheme 1. A substituted functionalized heteroaromatic ring containing a pyridone-like moiety can be functionalized by reaction with an alkyl nitrile containing a suitable leaving group such as halogen, mesylate or tosylate, in the presence of a base such as K₂CO₃ or

Cs_2CO_3 , in a polar solvent such as DMF or NMP, with or without heating. Typically mixtures of O- and N-alkylated products are obtained, and the two regio-isomeric products can be separated by means of SiO_2 gel or reverse phase chromatography. The addition of lithium salts, for example LiCl, to the reaction mixture can be employed to favor N- vs. O-alkylation. The obtained alkyl nitrile can be further converted to the corresponding 5-alkyl-2-amino thiadiazole by heating in the presence of TFA and hydrazinecarbothioamide.

Functionalization of the 2-amino group is then possible by employing standard methodologies known to those skilled in the art. For example, acylation with an acyl chloride in the presence of a base such as DIEA, pyridine, TEA and in a solvent such as DCM can afford the corresponding 2-carboxamides. Alternatively, the same transformation can be achieved by employing a carboxylic acid and coupling reagents such as EDC.HCl/HOBT, PyBOP, HATU or T3P in the presence of a base such as TEA or DIPEA, in a solvent such as DCM or DMF, with or without heating.

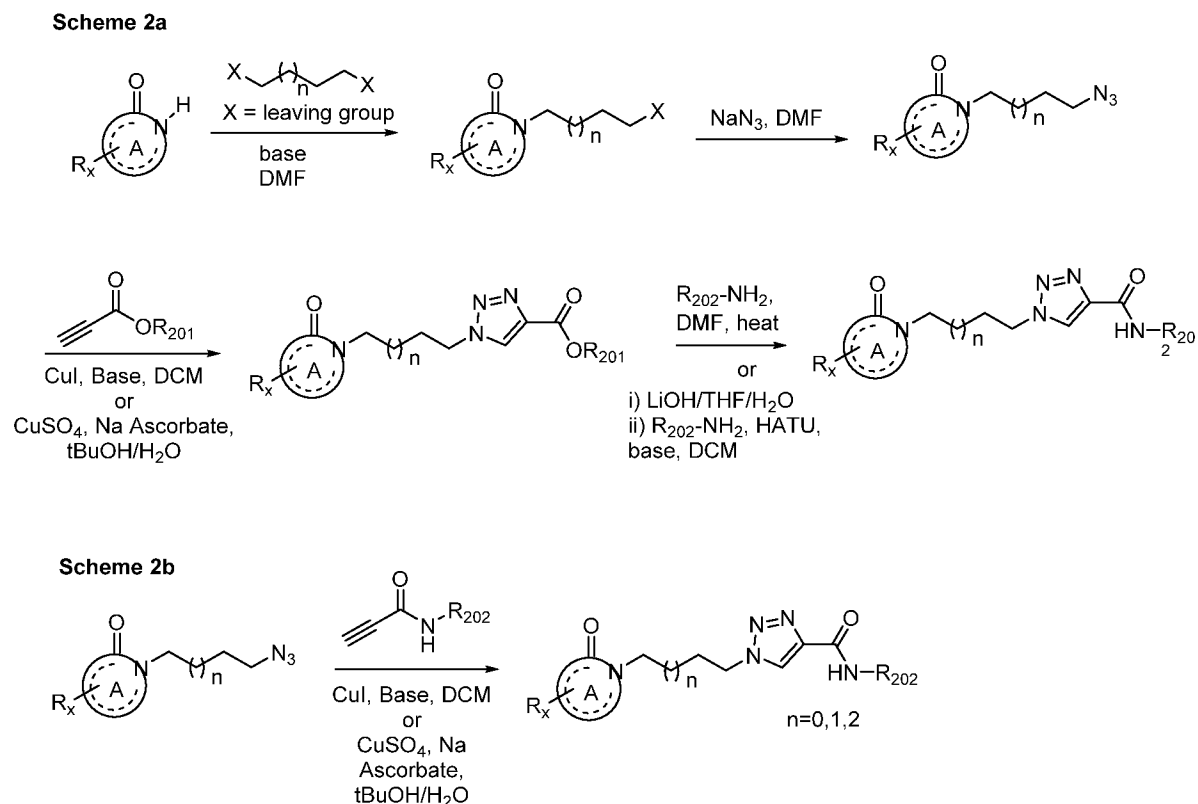
Scheme 1:



[0186] A further route of preparation of the compounds described in this invention is depicted in Scheme 2a and 2b. A substituted functionalized heteroaromatic ring containing a pyridone-like moiety can be functionalized by reaction with an alkyl compound containing two suitable leaving groups such as halogen, mesylate or tosylate, in the presence of a base such as K_2CO_3 or Cs_2CO_3 , in a polar solvent such as DMF or NMP, with or without heating. Controlled displacement of one of the two leaving groups can be achieved by adjusting the stoichiometry of the reagents. Similarly to what already described for Scheme 1, mixtures of

N- and *O*-alkylated products can be expected, and the two region-isomeric products can typically be separated by chromatography. The obtained alkyl compound can be further converted into the corresponding azide by displacement of the remaining leaving group with NaN_3 in a solvent such as DMF or THF/ H_2O , with or without heating. The obtained azide derivative can then be progressed to the corresponding triazole 4-carboxylic ester by copper-mediated azide-alkyne cycloaddition with a suitable alkyl propiolate in the presence of a base (e.g. TEA or DIEA), and a copper (I) salt such as CuI , or a copper (II) salt such as CuSO_4 in the presence of a reducing agent such as sodium ascorbate, in a solvent such as THF, DMSO, *t*BuOH or H_2O (H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angewandte Chemie International Edition*, 2001, 40 (11): 2004–2021). The triazole 4--carboxylic ester can then be converted into the corresponding 4-carboxamide by direct displacement with a suitable amine heating in a polar solvent such as DMF. Alternatively, the same transformation could be achieved with a two-step sequence involving the base-mediated hydrolysis of the carboxylic ester followed by coupling of the resulting carboxylic acid with an amine, using standard coupling reagents such as HATU, PyBOP or EDCI.HCl/HOBT, T3P in the presence of a suitable base such as TEA or DIEA, in a polar solvent such as DMF, with or without heating. An alternative way to obtain the derivatives described in this invention is described in Scheme 2b, whereby the functionalized alkyl-azide described in Scheme 2a can be be progressed directly to the corresponding triazole 4-carboxamides by copper-mediated azide-alkyne cycloaddition with a suitable propiolamide in similar conditions to those described for Scheme 2a.

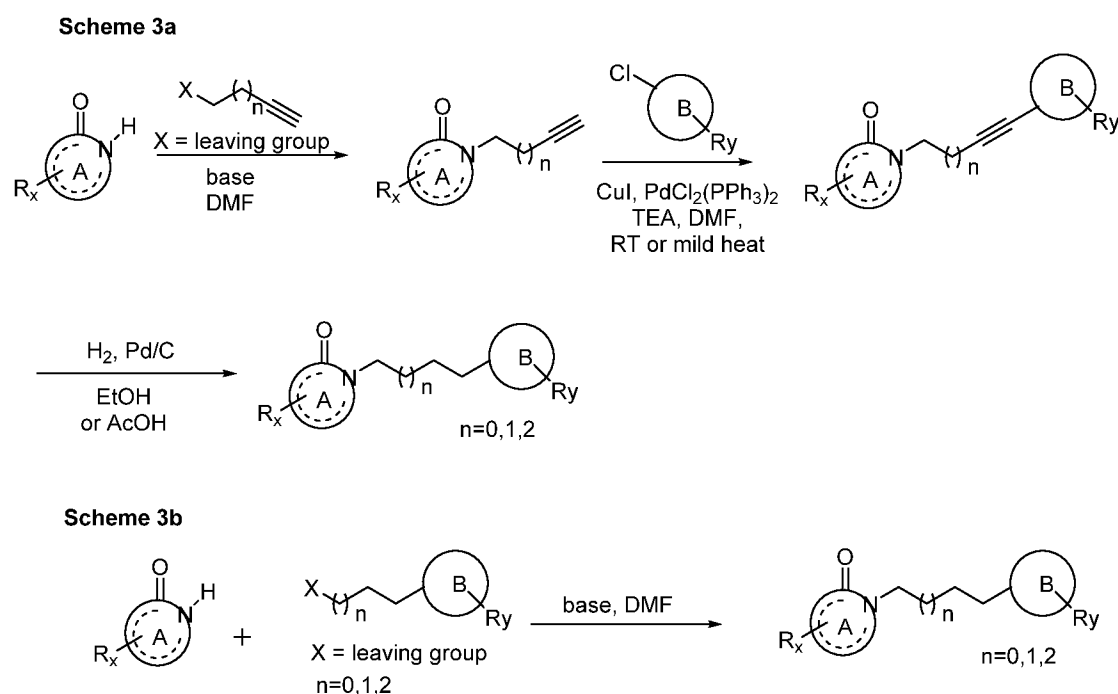
Scheme 2:



[0187] An additional route for the preparation of the compounds described in this invention is described in Scheme 3a. A substituted functionalized heteroaromatic ring containing a pyridone-like moiety can be functionalized by reaction with an alkyl compound containing an alkyne, in an analogous manner and using the same conditions to those described in Schemes 1 and 2. Like in those previously described routes, the *N*-alkylated product can be isolated from the *O*-alkylated regio-isomeric compound by means of chromatographic separation. The obtained alkyne can be further functionalized for example by Sonogashira cross-coupling reaction with a suitably functionalized heteroaromatic halide (Tetrahedron Lett. 16: 4467–4470). Typically, the above transformation is performed in the presence of a suitable Pd catalyst such as $\text{PdCl}_2(\text{PPh}_3)_2$ or $\text{Pd}(\text{PPh}_3)_4$, of a copper co-catalyst, typically a halide salt of copper (I), such as CuI or CuBr, and a base such as DIEA or TEA. The transformation can be run at RT or with mild heating in a variety of solvents, including DMF, toluene and EtOAc. Further functional group manipulations could include hydrogenation of the resulting heteroaromatic alkyne derivative in the presence of a suitable Pd catalyst (such as Pd/C or $\text{Pd}(\text{OH}_2)$) in a solvent such as EtOH.

[0188] An additional route to prepare the derivatives described in Scheme 3a is depicted in Scheme 3b. In this case, the functionalized heteroaromatic ring containing a pyridone-like moiety can be alkylated by reaction with suitably functionalized heteroalkyl compound containing a suitable leaving group, in an analogous manner and using the same conditions to those described in Schemes 1-3. As in the previous examples, the reaction results in the formation of a mixture of O- and N-alkylated products, which can be separated by chromatography.

Scheme 3:



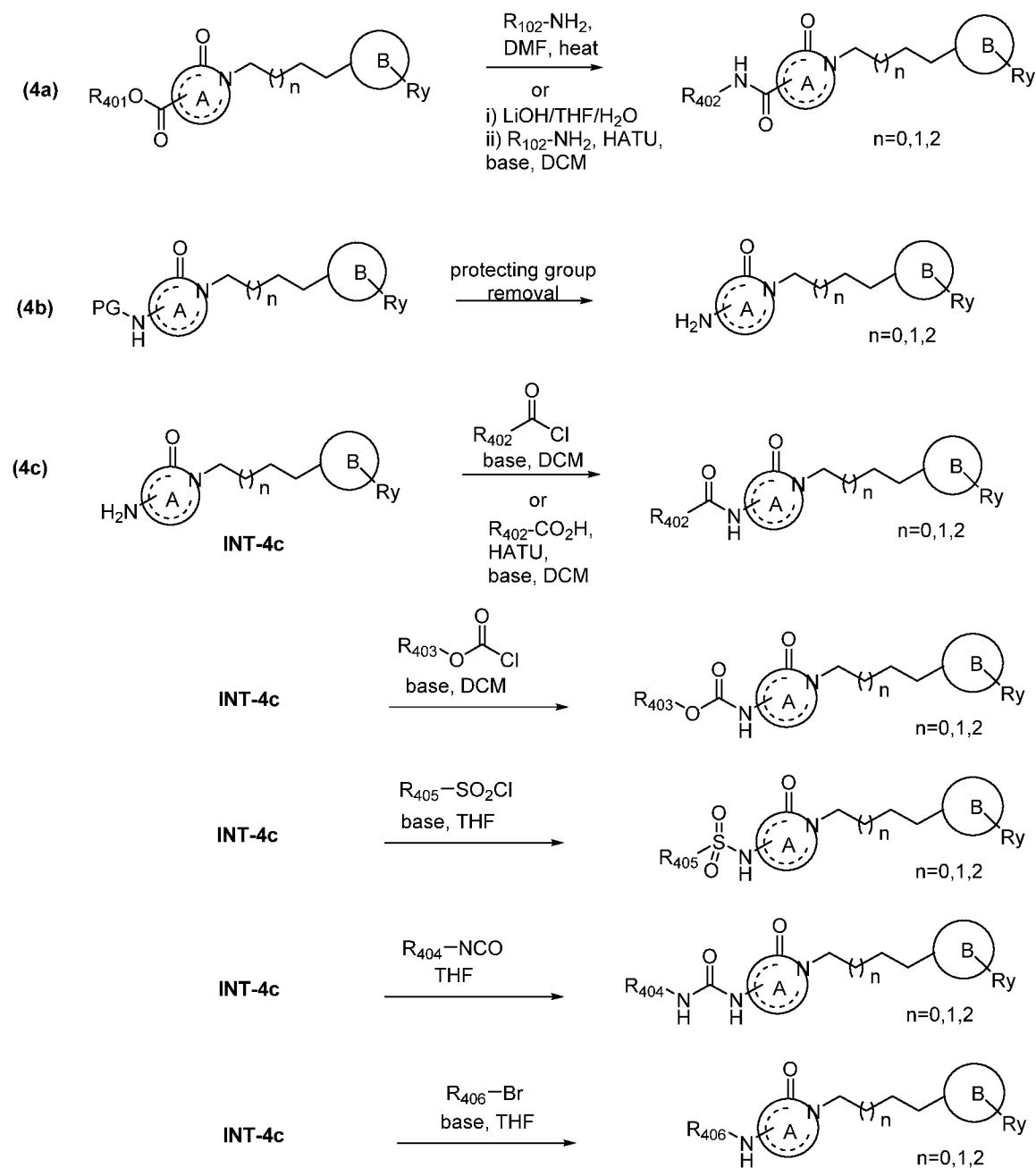
[0189] Standard functional group manipulations known to those skilled in the art can be performed with the Rx and Ry substituents groups of the structures reported in Schemes 1-3. A non-limiting number of examples of such transformations are exemplified in Scheme 4. For simplicity these transformations are described for the Rx group only, although they can be applied independently to one or both of the Rx and Ry groups.

[0190] In Scheme 4a, where Rx = carboxylic ester, the corresponding carboxamides can be obtained either by direct displacement with a suitable amine heating in a polar solvent such as DMF, or with a two-step sequence involving the base-mediated hydrolysis of the carboxylic ester followed by coupling of the resulting carboxylic acid with an amine. The

coupling reaction can be performed using standard coupling reagents such as HATU, PyBOP or EDCI.HCl/HOBT or T3P in the presence of a suitable base such as TEA or DIEA, in a polar solvent such as DMF, with or without heating.

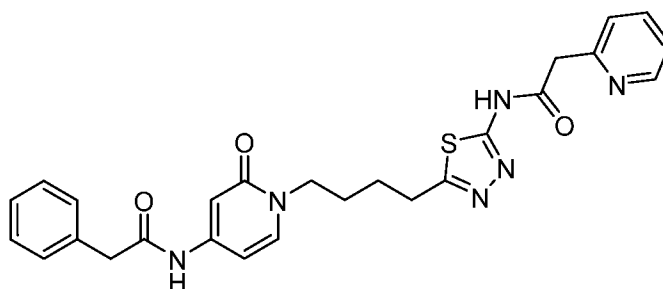
[0191] In Scheme 4b the Rx group is a protected amine group. Suitable protecting groups for the amine moiety can be chosen amongst substituted carbamates, amides and amines (e.g. benzyl amine, 3,4-dimethoxy-benzylamine, t-butyl carbamate, trifluoroacetamide) or amongst other suitable functional groups known to those skilled in the art (see also: P.G.M. Wutz, T.W. Greene, "Greene's protective Groups in Organic Synthesis", Fourth Edition, John Wiley & Sons). The free amino group can be obtained by removal of the amine protecting group with techniques known to those skilled in the art (for example: reductive removal of a benzyl group; acid-mediated removal of the tert-butyl carbamoyl group and other conditions reported by P.G.M. Wutz, T.W. Greene in the reference cited above). The obtained amino derivatives can be further functionalized according to the non-limiting reaction examples reported in Scheme 4c. Thus, the corresponding carboxamides can be prepared by acylation with a carboxylic chloride in the presence of a base such as DIEA, pyridine or TEA in a solvent such as DCM, or employing a carboxylic acid and coupling reagents such as EDC.HCl/HOBT, PyBOP, HATU or T3P in the presence of a base such as TEA or DIPEA, in a solvent such as DCM or DMF, with or without heating. Similarly, carbamate and sulfamides derivatives can be obtained by reaction of the amine compounds with a suitable carbamoyl- or sulfonyl chloride respectively, in the presence of a base such as TEA or DIPEA in a solvent such as DCM. Urea derivatives can be prepared by reaction of the amine moiety with a suitable isocyanate, in a solvent such as THF or DCM. Alkylation of the amino group can be achieved by treatment with a suitable alkylating agent, for example an alkyl, benzyl or heterobenzyl bromide in the presence of a base of a suitable strength, for example NaH, in a solvent such as THF.

Scheme 4:

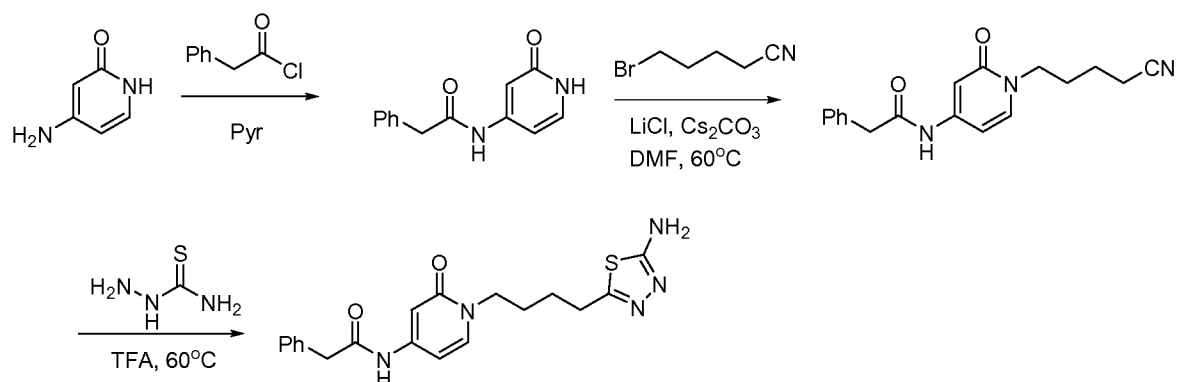


[0192] Non-limiting examples include the following compounds and pharmaceutically acceptable salts thereof.

EXAMPLE 1: N-(2-oxo-1-(4-(5-(2-(pyridin-2-yl)acetamido)-1,3,4-thiadiazol-2-yl)butyl)-1,2-dihydropyridin-4-yl)-2-phenylacetamide



Steps 1 to 3



Step 1: *N*-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

[0193] To a mixture of pyridine (0.220 ml, 2.72 mmol) and 4-aminopyridin-2(1H)-one (0.20 g, 1.8 mmol) in DMF (2 ml) was added 2-phenylacetyl chloride (0.290 ml, 2.36 mmol). The resulting mixture was allowed to stir at RT for 24 h, diluted with water (20 mL), stirred at 0°C for 10 minutes and filtered. The solid was washed with cold water (5 mL) followed by Et₂O (5 mL) to give the title compound as a white solid (261 mg, 63%). MS (ES⁺) C₁₃H₁₂N₂O₂ requires: 228, found: 229 [M+H]⁺.

Step 2: *N*-(1-(4-cyanobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

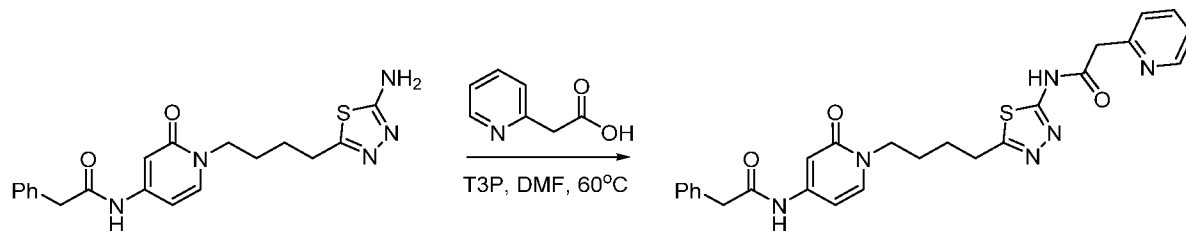
[0194] A vial was charged with LiCl (0.037 g, 0.88 mmol), Cs₂CO₃ (0.171 g, 0.526 mmol), *N*-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (0.10 g, 0.44 mmol), 5-bromopentanenitrile (0.061 ml, 0.526 mmol) and DMF (1.7 ml). The resulting mixture was heated at 60 °C for 15 h, concentrated under reduced pressure and the residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 minutes; Column: C18) to give the title compound

as an off-white solid (49 mg, 36 % yield). MS (ES^+) $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2$ requires: 309, found: 310 $[\text{M}+\text{H}]^+$.

Step 3: *N*-(1-(4-(5-amino-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

[0195] To a solution of *N*-(1-(4-cyanobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (49 mg, 0.16 mmol) in trifluoroacetic acid (122 μl , 1.58 mmol) was added hydrazinecarbothioamide (16 mg, 0.17 mmol) and the resulting mixture was stirred at 60 °C for 4 h. The reaction was then diluted with toluene (5 mL) and concentrated under reduced pressure. The residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 20 - 60%; 12 minutes; Column: C18) to give the title compound as a thick oil (54 mg, 68%). MS (ES^+) $\text{C}_{19}\text{H}_{21}\text{N}_5\text{O}_2\text{S}$ requires: 383, found: 384 $[\text{M}+\text{H}]^+$; ^1H NMR (600 MHz, Methanol- d_4) δ 7.57 (d, J = 7.4 Hz, 1H), 7.34 – 7.28 (m, 4H), 7.25 (m, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.66 (dd, J = 7.4, 2.4 Hz, 1H), 3.98 (t, J = 7.0 Hz, 2H), 3.68 (s, 2H), 2.94 (t, J = 7.3 Hz, 2H), 1.84 – 1.70 (m, 4H).

Step 4

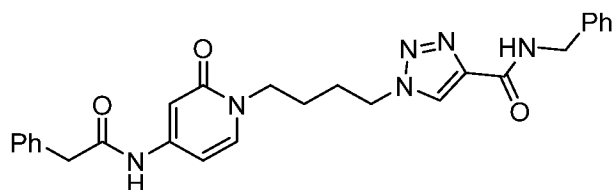


Step 4: *N*-(2-oxo-1-(4-(5-(2-(pyridin-2-yl)acetamido)-1,3,4-thiadiazol-2-yl)butyl)-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

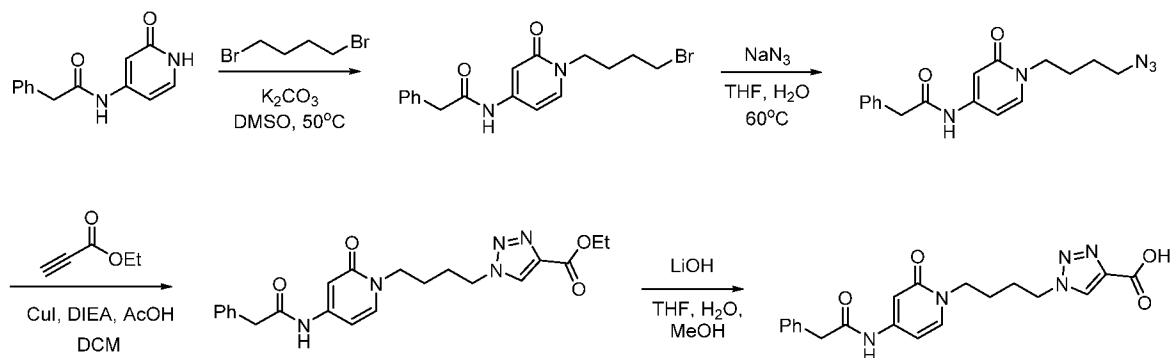
[0196] To a suspension of 2-(pyridin-2-yl)acetic acid hydrochloride (10 mg, 0.058 mmol) and *N*-(1-(4-(5-amino-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (17 mg, 0.044 mmol) in DMF (222 μl) was added T3P (36.7 mg, 0.058 mmol, 50% solution in DMF) and the resulting mixture was stirred at 60 °C for 3 h. The reaction was quenched with MeOH (1 mL) and concentrated under reduced pressure. The residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 20 - 50%; 16 minutes; Column: C18) to give the title compound as a pale yellow solid. MS (ES^+) $\text{C}_{26}\text{H}_{26}\text{N}_6\text{O}_3\text{S}$ requires: 502, found: 503 $[\text{M}+\text{H}]^+$; ^1H NMR (600 MHz, DMSO- d_6) δ 12.61 (s, 1H), 10.25 (s, 1H), 8.51 (m, 1H),

7.76 (m, 1H), 7.56 (d, $J = 7.4$ Hz, 1H), 7.39 (d, $J = 7.8$ Hz, 1H), 7.35 – 7.21 (m, 6H), 6.72 (d, $J = 2.3$ Hz, 1H), 6.36 (dd, $J = 7.4, 2.4$ Hz, 1H), 3.98 (s, 2H), 3.85 – 3.75 (m, 2H), 3.65 (s, 2H), 3.02 – 2.93 (m, 2H), 1.69 – 1.58 (m, 4H).

EXAMPLE 2: N-benzyl-1-(4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxamide



Steps 1 to 4



Step 1: N-(1-(4-bromobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

[0197] To a suspension of K_2CO_3 (0.945 g, 6.83 mmol) and *N*-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (0.78 g, 3.42 mmol) in DMSO (6.83 ml) was added 1,4-dibromobutane (0.816 ml, 6.83 mmol) and the resulting mixture was stirred at 50 °C for 6 h. The mixture was diluted with EtOAc (50 mL) and washed with water (2x 20 mL) and brine (2 x 10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified via SiO_2 gel chromatography (0 - 20% MeOH in DCM) to give the title compound as a yellow thick oil that solidified upon standing (0.67 mg, 43%). MS (ES^+) $C_{17}H_{19}BrN_2O_2$ requires: 362, found: 363 $[M+H]^+$; ^1H NMR (600 MHz, $DMSO-d_6$) δ 10.27 (s, 1H), 7.57 (d, $J = 7.4$ Hz, 1H), 7.33 – 7.26 (m, 4H), 7.28 – 7.23 (m, 1H), 6.74 (d, $J = 2.3$ Hz, 1H), 6.38 (dd, $J = 7.4, 2.3$ Hz, 1H), 3.83 (t, $J = 6.7$ Hz, 2H), 3.65 (s, 2H), 3.54 (t, $J = 6.4$ Hz, 2H), 1.79 – 1.66 (m, 4H).

Step 2: N-(1-(4-azidobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

[0198] To a solution of *N*-(1-(4-bromobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (0.665 g, 1.83 mmol) in THF (7.32 ml) and water (1.83 ml) was added NaN₃ (0.131 g, 2.01 mmol) and the resulting mixture was stirred at 60 °C for 6 h. The reaction mixture was concentrated under reduced pressure, the residue was taken up in EtOAc (50 mL), and washed with water (2x20 mL) and brine (20mL). The organic layers were dried (MgSO₄) and concentrated under reduced pressure to give the title compound as an off-white solid (0.58 g, 98%). MS (ES⁺) C₁₇H₁₉N₅O₂ requires: 325, found: 326 [M+H]⁺.

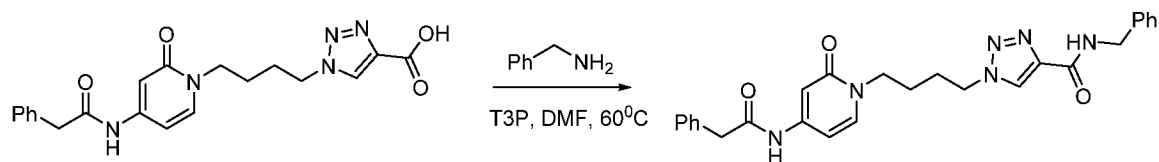
[0199] Step 3: Ethyl 1-(4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate.

[0200] To a solution of acetic acid (2.9 µl, 0.051 mmol), DIEA (8.9 µl, 0.051 mmol), ethyl propiolate (0.078 ml, 0.77 mmol), and *N*-(1-(4-azidobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (0.167 g, 0.513 mmol) in DCM (2.57 ml) was added copper(I) iodide (4.9 mg, 0.026 mmol) and the resulting mixture was stirred at RT for 3 h. The volatiles were removed under reduced pressure and the residue was purified via silica gel chromatography (0 - 15% MeOH in DCM with 1% NH₄OH) to give the title compound as a white solid (123 mg, 54%). MS (ES⁺) C₂₂H₂₅N₅O₄ requires: 423, found: 424 [M+H]⁺.

Step 4: 1-(4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid.

[0201] To a solution of ethyl 1-(4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate (0.117 g, 0.276 mmol) in THF (1.10 ml) and MeOH (0.276 ml) was added LiOH (2M solution in water, 0.152 ml, 0.304 mmol,) and the resulting mixture was stirred at RT for 3 h. The reaction was concentrated under reduced pressure to give the title compound as an off-white solid (109 mg, 100%, Li salt). MS (ES⁺) C₂₀H₂₁N₅O₄ requires: 395, found: 396 [M+H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.64 (s, 1H), 8.04 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.33 – 7.28 (m, 4H), 7.28 – 7.21 (m, 1H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.40 (dd, *J* = 7.5, 2.3 Hz, 1H), 4.32 (t, *J* = 7.0 Hz, 2H), 3.81 (t, *J* = 7.6 Hz, 2H), 3.67 (s, 2H), 3.17 (d, *J* = 4.8 Hz, 1H), 1.77 – 1.74 (m, 2H), 1.57 – 1.48 (m, 2H).

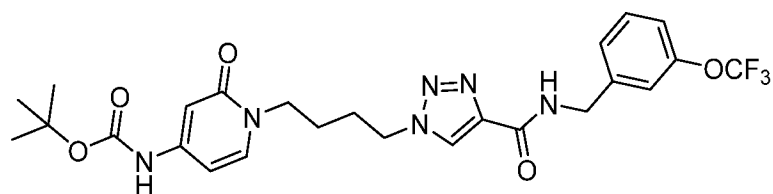
Step 5



N-benzyl-1-(4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxamide:

[0202] To a suspension of 1-(4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid lithium salt (20 mg, 0.051 mmol) and benzylamine (6.6 μ l, 0.061 mmol) in DMF (253 μ l) was T3P (39 mg, 0.061 mmol, 50% solution in DMF) and the resulting mixture was stirred at 60 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 minutes; Column: C18) to give the title compound as an off-white solid (3.5 mg, 12 %). MS (ES⁺) C₂₇H₂₈N₆O₃ requires: 484, found: 485 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.29 (s, 1H), 9.06 (t, *J* = 6.3 Hz, 1H), 8.57 (s, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.31 – 7.27 (m, 8H), 7.26 – 7.24 (m, 2H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.37 (dd, *J* = 7.4, 2.3 Hz, 1H), 4.45 – 4.40 (m, 4H), 3.82 (t, *J* = 7.1 Hz, 2H), 3.65 (s, 2H), 1.81 – 1.79 (m, 2H), 1.57 -1.48 (m, 2H).

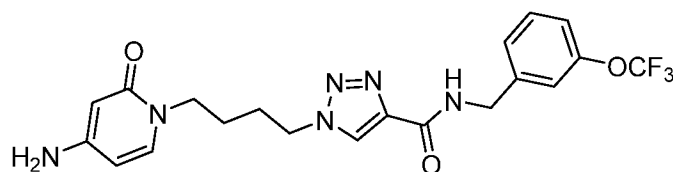
EXAMPLE 3: Tert-butyl (2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridin-4-yl)carbamate



[0203] To a solution of tert-butyl (1-(4-azidobutyl)-2-oxo-1,2-dihydropyridin-4-yl)carbamate (Example 2, Step 2, 80 mg, 0.26 mmol) in DCM (3 ml) were added DIEA (4.5 μ l, 0.026 mmol), AcOH (1.5 μ l, 0.026 mmol), N-(3-(trifluoromethoxy)benzyl)propiolamide (63.3 mg, 0.260 mmol), and CuI (2.5 mg, 0.013 mmol) and the resulting mixture was stirred at RT for 2.5 h. The reaction mixture was directly loaded on SiO₂ and was purified via silica gel chromatography (0 - 100% EtOAc in hexane with 10% MeOH) to give the title compound as a white solid (112 mg, 78 %). MS (ES⁺) C₂₅H₂₉F₃N₆O₅ requires: 550.2, found:

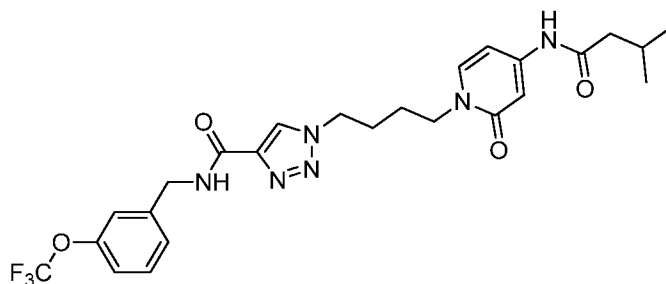
551 [M+H]⁺. ¹H NMR (600 MHz, DMSO-d₆) δ: 9.56 (s, 1H), 9.16 (t, J = 6.2 Hz, 1H), 8.58 (s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.44 (m, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.29 (s, 1H), 7.23 (d, J = 8.3 Hz, 1H), 6.49 (d, J = 2.3 Hz, 1H), 6.31 (dd, J = 7.2, 2.3 Hz, 1H), 4.48 (d, J = 6.4 Hz, 2H), 4.43 (t, J = 7.0 Hz, 2H), 3.80 (t, J = 7.0 Hz, 2H), 1.76 - 1.83 (m, 2H), 1.57 - 1.53 (m, 2H), 1.46 (s, 9H).

EXAMPLE 4: 1-(4-(4-Amino-2-oxopyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



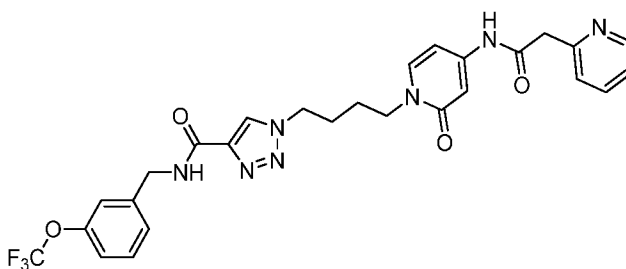
[0204] To a solution of *tert*-butyl (2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridin-4-yl)carbamate (Example 3, 95 mg, 0.178 mmol) in DCM (3 mL) was added TFA (1 mL) and the reaction stirred at RT for 45 minutes. The reaction mixture was then concentrated under reduced pressure, the residue was dissolved in DCM/MeOH (1:1 v:v, 8 mL) and stirred with 1 g of MP-carbonate resin (3 mmol/g) at RT for 15 minutes. The mixture was filtered through a cotton plug and a syringe filter (13 mm PP 0.45 μm), the filtrate was concentrated under reduced pressure to give the title compound as a white solid (78 mg, 97%). MS (ES⁺) C₂₀H₂₁F₃N₆O₃ requires: 450.2, found: 451 [M+H]⁺. ¹H NMR (600 MHz, DMSO-d₆) δ 9.16 (t, J = 6.2 Hz, 1H), 8.58 (s, 1H), 7.45 (m, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.29 (s, 1H), 7.21 - 7.25 (m, 2H), 5.93 (s, 2H), 5.63 (dd, J = 7.2, 2.3 Hz, 1H), 5.21 (d, J = 2.3 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 4.43 (t, J = 7.2 Hz, 2H), 3.70 (t, J = 7.0 Hz, 2H), 1.81 - 1.76 (m, 2H), 1.52 - 1.48 (m, 2H).

EXAMPLE 5: 1-(4-(4-(3-methylbutanamido)-2-oxopyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



[0205] To a solution of 1-(4-(4-amino-2-oxopyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (Example 4, 15 mg, 0.033 mmol) and DIEA (7.6 μ L, 0.043 mmol) in DMF (0.5 mL) at 0°C was added 3-methylbutanoyl chloride (4.8 mg, 0.040 mmol). The resulting mixture was stirred at RT for 16 h, diluted with DCM and the pH was adjusted to ~7-8 by addition of 1 N aqueous NaOH. The organic layer was washed with water, dried over Na₂SO₄, filtered, concentrated under reduced pressure and purified by silica gel column chromatography (DCM:MeOH = 10:0 to 10:1) to give the title compound (2.2 mg, 12%). MS (ES⁺) C₂₅H₂₉F₃N₆O₄ requires: 534, found: 535 [M+H]⁺; ¹H NMR (600 MHz, DMSO-d₆) δ 9.95 (s, 1H), 9.16 (t, *J* = 6.0 Hz, 1H), 8.59 (s, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.45 (m, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.29 (s, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.35 (dd, *J* = 7.8, 2.4 Hz, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.47 – 4.42 (m, 2H), 3.84 – 3.86 (m, 2H), 2.18 (d, *J* = 7.2 Hz, 2H), 2.04 (m, 1H), 1.83 – 1.79 (m, 2H), 1.57 – 1.54 (m, 2H), 0.91 (d, *J* = 7.2 Hz, 6H).

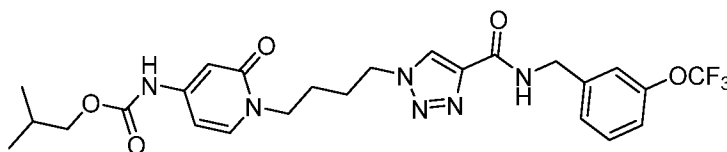
EXAMPLE 6: 1-(4-(2-oxo-4-(2-(pyridin-2-yl)acetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



[0206] To a solution of 1-(4-(4-amino-2-oxopyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (Example 4, 15 mg, 0.033 mmol) and 2-(pyridin-2-yl)acetic acid hydrochloride (7.5 mg, 0.043 mmol) in DMF (0.3 mL)

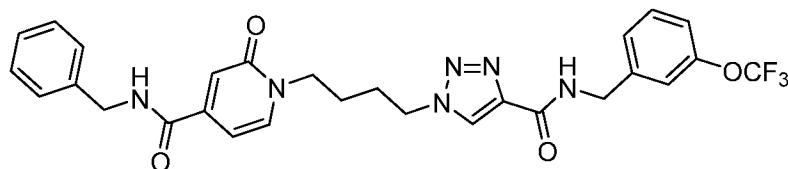
were added HATU (19 mg, 0.050 mmol) and DIEA (15 μ L, 0.083 mmol). The resulting mixture was stirred at RT for 16 h, diluted with DCM, and the pH was adjusted to ~7-8 by addition of 1 N aqueous NaOH. The organic layer was washed with water, dried over Na_2SO_4 , filtered, concentrated under reduced pressure and purified by silica gel column chromatography (DCM:MeOH = 10:0 to 10:1) to give the title compound (5.7 mg, 30%). MS (ES^+) $\text{C}_{27}\text{H}_{26}\text{F}_3\text{N}_7\text{O}_4$ requires: 569, found: 570 $[\text{M}+\text{H}]^+$; ^1H NMR (600 MHz, DMSO- d_6) δ 10.48 (s, 1H), 9.16 (t, J = 6.0 Hz, 1H), 8.71 (s, 1H), 8.57 (s, 1H), 8.17 (m, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.63 (m, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.45 (m, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.29 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H), 6.37 (dd, J = 7.8, 2.4 Hz, 1H), 4.48 (d, J = 6.0 Hz, 2H), 4.44 (t, J = 7.2 Hz, 2H), 4.06 (s, 2H), 3.84 (d, J = 7.2 Hz, 2H), 1.84-1.80 (m, 2H), 1.59 – 1.55 (m, 2H).

EXAMPLE 7: Isobutyl (2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridin-4-yl)carbamate

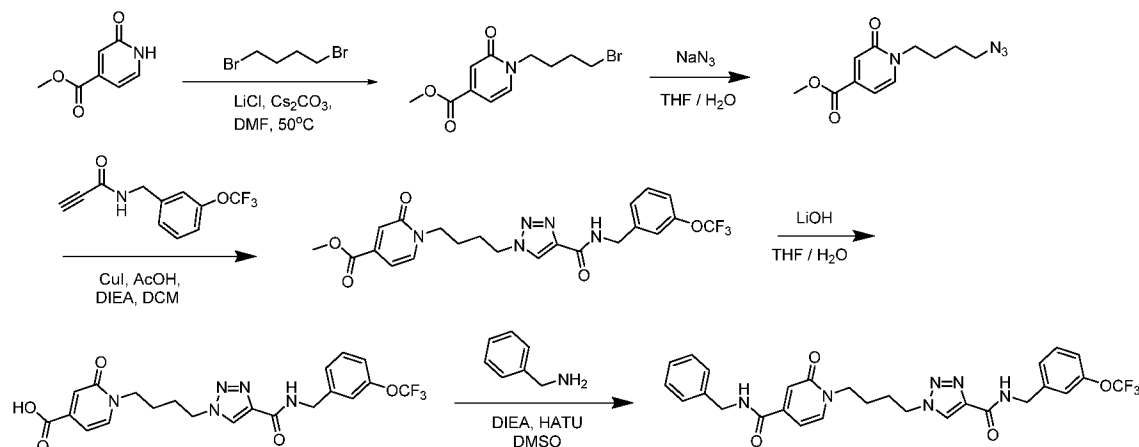


[0207] To a solution of 1-(4-(4-amino-2-oxopyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (Example 4, 12.2 mg, 0.027 mmol) in pyridine (0.25 ml) was added isobutyl carbonochloridate (7.0 μ l, 0.054 mmol) and the resulting mixture was stirred at RT for 16 h. The reaction mixture was then concentrated under reduced pressure, the residue was taken up in DMSO and purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 min; Column: C18) to give the title compound as a white solid (7.6 mg, 51%). MS (ES^+) $\text{C}_{25}\text{H}_{29}\text{F}_3\text{N}_6\text{O}_5$ requires: 550.2, found: 551 $[\text{M}+\text{H}]^+$. ^1H NMR (600 MHz Methanol- d_4) δ : 8.38 (s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.39 - 7.44 (m, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.27 (s, 1H), 7.16 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 2.3 Hz, 1H), 6.62 (dd, J = 7.2, 2.3 Hz, 1H), 4.60 (s, 2H), 4.50 (t, J = 7.0 Hz, 2H), 3.99 (t, J = 7.2 Hz, 2H), 3.96 - 3.92 (m, 2H), 1.90 - 2.01 (m, 2H), 1.76 - 1.72 (m, 2H), 0.97 (d, J = 6.8 Hz, 6H).

EXAMPLE 8: N-Benzyl-2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridine-4-carboxamide



Steps 1 to 5:



Step 1: methyl 1-(4-bromobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate.

[0208] To a solution of methyl 2-oxo-1,2-dihydropyridine-4-carboxylate (500 mg, 3.27 mmol) in DMF (10 ml) were added Cs_2CO_3 (2.13 g, 6.53 mmol), LiCl (138 mg, 3.27 mmol) and 1,4-dibromobutane (1.17 ml, 9.80 mmol), and the resulting mixture was stirred at 50 °C for 3.5 h. The reaction mixture was then concentrated under reduced pressure, diluted with DCM and filtered. The solid was washed sequentially with DCM, DCM/MeOH, DCM, and the filtrate was concentrated under reduced pressure. The residue was taken up in DCM and adsorbed onto Celite® and purified via SiO_2 gel chromatography (0 - 75% EtOAc in hexane with 10% MeOH) to give the title compound as a pale yellow solid (498 mg, 53%). MS (ES^+) $\text{C}_{11}\text{H}_{14}\text{BrNO}_3$ requires: 287.0, found: 288 $[\text{M}+\text{H}]^+$. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) 7.84 (d, $J = 7.2$ Hz, 1H), 6.86 (s, 1H), 6.57 (dd, $J = 7.0, 1.3$ Hz, 1H), 3.95 (t, $J = 6.6$ Hz, 2H), 3.84 (s, 3H), 3.58 - 3.52 (m, 2H), 1.83 - 1.73 (m, 4H).

Step 2: methyl 1-(4-azidobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate.

[0209] To a solution of methyl 1-(4-bromobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (494 mg, 1.71 mmol) in THF (4 ml) and water (1.00 ml) was added NaN_3 (223

mg, 3.43 mmol) and the resulting mixture was stirred in at 60 °C for 17 h. The reaction mixture was then diluted with water (30 mL) and extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound (415 mg, 97%). MS (ES⁺) C₁₁H₁₄N₄O₃ requires: 250.1, found: 251 [M+H]⁺. ¹H NMR (600 MHz, DMSO-d₆) 7.84 (d, *J* = 6.8 Hz, 1H), 6.86 (s, 1H), 6.57 (dd, *J* = 7.0, 1.3 Hz, 1H), 3.94 (t, *J* = 7.2 Hz, 2H), 3.84 (s, 3H), 3.36 (t, *J* = 7.0 Hz, 2H), 1.72 – 1.66 (m, 2H), 1.56 - 1.47 (m, 2H).

Step 3: methyl 2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridine-4-carboxylate.

[0210] To a solution of *N*-(3-(trifluoromethoxy)benzyl)propiolamide (401 mg, 1.65 mmol) in DCM (8 ml) was added to methyl 1-(4-azidobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (413 mg, 1.65 mmol) were added AcOH (9.45 μl, 0.165 mmol), DIEA (0.029 ml, 0.165 mmol), and CuI (15.7 mg, 0.0830 mmol). The resulting mixture was stirred at RT for 24 h. The reaction mixture was diluted with MeOH, loaded on Celite® and purified by SiO₂ gel chromatography (0 to 100% EtOAc in hexane with 10% MeOH) to give the title compound as an off white solid (481 mg, 59%). MS (ES⁺) C₂₂H₂₂F₃N₅O₅ requires: 493.2, found: 494 [M+H]⁺. ¹H NMR (600 MHz, DMSO-d₆) δ 9.16 (t, *J* = 6.2 Hz, 1H), 8.59 (s, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.45 (m, 1H), 7.34 (d, *J* = 7.9 Hz, 1H), 7.28 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 1.1 Hz, 1H), 6.55 (dd, *J* = 6.8, 1.5 Hz, 1H), 4.51 - 4.40 (m, 4H), 3.94 (t, *J* = 7.0 Hz, 2H), 3.84 (s, 3H), 1.86 - 1.81 (m, 2H), 1.64 - 1.59 (m, 2H).

Step 4: 2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridine-4-carboxylic acid.

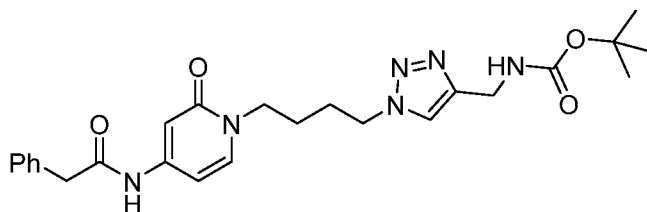
[0211] To a suspension of methyl 2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridine-4-carboxylate (476 mg, 0.965 mmol) in THF (3 ml) was added MeOH (3.00 ml), water (3.00 ml) and lithium hydroxide hydrate (46.5 mg, 1.11 mmol) and the resulting mixture was stirred at RT for 2.5 h. The reaction mixture was then concentrated, diluted with water and brought to pH ~2-3 with 1 N aq. HCl. The resulting precipitate was filtered and washed sequentially with water, hexanes, ether/hexanes (1:1 v/v), hexanes, and dried under reduced pressure to give the title compound as a white solid (420 mg, 91%). MS (ES⁺)

$C_{21}H_{20}F_3N_5O_5$ requires: 479.1, found: 480 $[M+H]^+$. ^1H NMR (600 MHz, DMSO- d_6) 9.16 (t, $J = 6.2$ Hz, 1H), 8.59 (s, 1H), 7.77 (d, $J = 6.8$ Hz, 1H), 7.45 (m, 1H), 7.34 (d, $J = 7.9$ Hz, 1H), 7.29 (s, 1H), 7.23 (d, $J = 7.9$ Hz, 1H), 6.82 (s, 1H), 6.54 (dd, $J = 7.0, 1.3$ Hz, 1H), 4.40 - 4.52 (m, 4H), 3.93 (t, $J = 7.2$ Hz, 2H), 1.87 - 1.82 (m, 2H), 1.63 - 1.60 (m, 2H).

Step 5: N-benzyl-2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridine-4-carboxamide.

[0212] To a solution of 2-oxo-1-(4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-1,2-dihydropyridine-4-carboxylic acid (10.4 mg, 0.022 mmol) in DMSO (0.1 ml) were added phenylmethanamine (4.65 mg, 0.043 mmol), DIEA (0.015 ml, 0.087 mmol), and HATU (24.7 mg, 0.065 mmol) and the resulting mixture was stirred at RT for 13 h. The reaction mixture was then diluted with water (4 mL) and the resulting precipitate was filtered, washed with water, hexanes and dried under reduced pressure to give the title compound as a white solid (12.6 mg, 100%). MS (ES^+) $C_{28}H_{27}F_3N_6O_4$ requires: 568.2, found: 569 $[M+H]^+$. ^1H NMR (600 MHz, DMSO- d_6) : 9.21 - 9.09 (m, 2H), 8.59 (s, 1H), 7.76 (d, $J = 7.2$ Hz, 1H), 7.46 (m, 1H), 7.37 - 7.31 (m, 3H), 7.29 (m, 3H), 7.27 - 7.20 (m, 2H), 6.83 (s, 1H), 6.52 - 6.57 (m, 1H), 4.38 - 4.51 (m, 6H), 3.93 (t, $J = 7.0$ Hz, 2H), 1.86 - 1.80 (m, 2H), 1.64 - 1.61 (m, 2H).

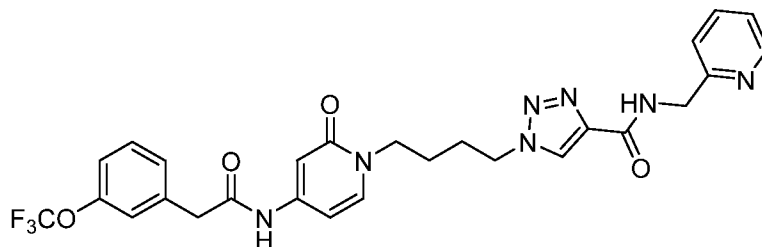
EXAMPLE 9: *tert*-Butyl N-[(1-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazol-4-yl)methyl]carbamate



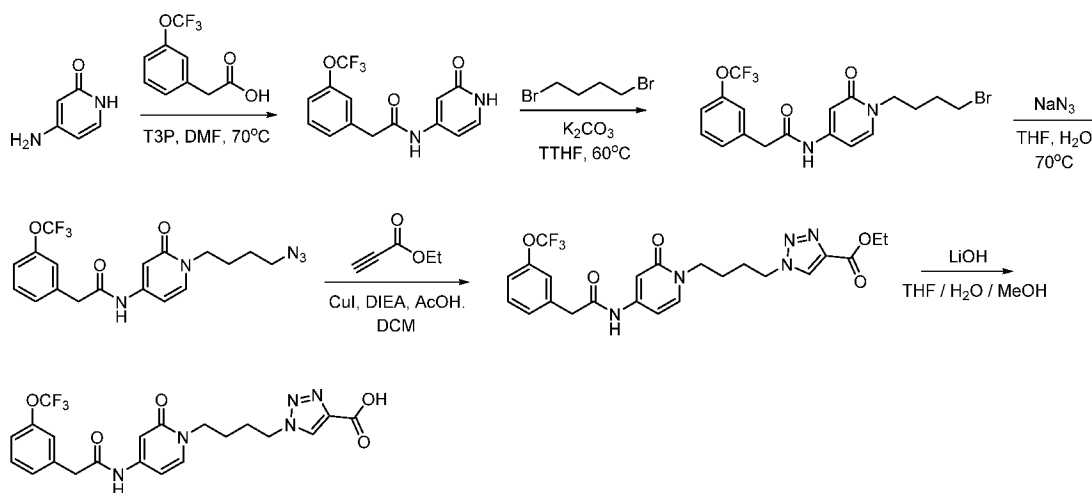
[0213] To a mixture of *tert*-butyl prop-2-yn-1-ylcarbamate (21.5 mg, 0.138 mmol), DIEA (1.61 μ l, 9.22 μ mol), AcOH (0.53 μ l, 9.2 μ mol), and *N*-(1-(4-azidobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (Example 2, Step 2; 30 mg, 0.092 mmol) in DCM (922 μ l) was added copper(I) iodide (0.88 mg, 4.6 μ mol). The resulting reaction mixture was stirred at RT for 6 h, then loaded directly onto SiO_2 and purified via silica gel chromatography (0 - 15% MeOH in DCM with 1% NH_4OH) to give the title compound as a white solid (25 mg, 56%). MS (ES^+) $C_{25}H_{32}N_6O_4$ requires: 480, found: 481 $[M+H]^+$; ^1H

NMR (600 MHz, DMSO-*d*₆) δ 10.25 (s, 1H), 7.84 (s, 1H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.34 – 7.22 (m, 6H), 6.73 (d, *J* = 2.3 Hz, 1H), 6.36 (dd, *J* = 7.5, 2.3 Hz, 1H), 4.34 (t, *J* = 7.1 Hz, 2H), 4.14 (d, *J* = 5.9 Hz, 2H), 3.80 (t, *J* = 7.1 Hz, 2H), 3.64 (s, 2H), 1.75 -1.72 (m, 2H), 1.56 - 1.54 (m, 2H), 1.37 (s, 9H).

EXAMPLE 10: 1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridin-1(2H)-yl)butyl)-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide



Steps 1 to 5



Step 1: N-(2-oxo-1,2-dihydropyridin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide.

[0214] T3P in DMF (1.39 g, 2.18 mmol, 50% wt solution) was added to 4-aminopyridin-2(1H)-one (0.20 g, 1.8 mmol) and 2-(3-(trifluoromethoxy)phenyl)acetic acid (0.400 g, 1.82 mmol) and the mixture stirred at 70 °C for 3 h. The reaction mixture was cooled to RT, diluted with EtOAc (20 mL) and washed with sat. NaHCO₃ (2 x 10 mL) and brine (10 mL). The organic layer was dried over MgSO₄ and concentrated under reduced pressure to give the title compound as a light brown solid (0.35 g, 62%). MS (ES⁺) C₁₄H₁₁F₃N₂O₃ requires: 312, found: 313 [M+H]⁺.

Step 2: N-(1-(4-bromobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide.

[0215] To a suspension of K₂CO₃ (0.155 g, 1.12 mmol) and *N*-(2-oxo-1,2-dihydropyridin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (0.35 g, 1.1 mmol) in THF (2.24 ml) was added 1,4-dibromobutane (0.268 ml, 2.24 mmol) and the resulting mixture was stirred at 70 °C for 12 h. The reaction mixture was cooled to RT and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 10% MeOH in DCM) to give the title compound as an orange solid (72 mg, 14%). MS (ES⁺) C₁₈H₁₈BrF₃N₂O₃ requires: 446, found: 447 [M+H]⁺.

Step 3: N-(1-(4-azidobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide.

[0216] To a solution of *N*-(1-(4-bromobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (72 mg, 0.16 mmol) in THF (644 µl) and water (161 µl) was added NaN₃ (12.6 mg, 0.190 mmol) and the resulting mixture was stirred at 70 °C for 4 h. The reaction mixture was cooled to RT, concentrated under reduced pressure. The residue was taken up in EtOH and concentrated again to give the title compound as a light yellow solid (66 mg, 100 % yield). MS (ES⁺) C₁₈H₁₈F₃N₅O₃ requires: 409, found: 410 [M+H]⁺.

Step 4: ethyl 1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate.

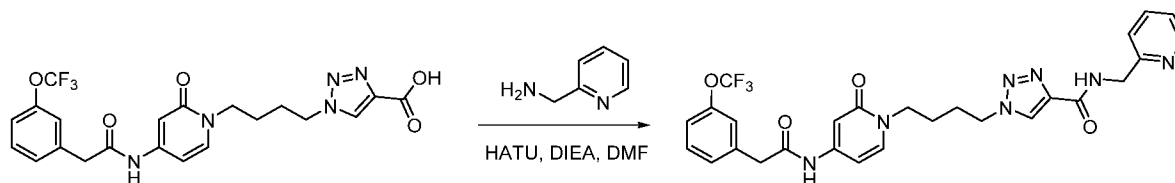
[0217] To a mixture of AcOH (0.92 µl, 0.016 mmol), DIEA (2.8 µl, 0.016 mmol), ethyl propiolate (0.025 ml, 0.24 mmol), and *N*-(1-(4-azidobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (0.066 g, 0.16 mmol) in DCM (0.8 ml) was added copper(I) iodide (1.5 mg, 8.1 µmol) and the resulting mixture was stirred at RT for 3 h. The reaction mixture was then concentrated under reduced pressure and purified via silica gel chromatography (0 - 15% MeOH in DCM with 1% NH₄OH) to give the title compound as a yellow solid (72 mg, 88%). MS (ES⁺) C₂₃H₂₄F₃N₅O₅ requires: 507, found: 508 [M+H]⁺.

Step 5: 1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid.

[0218] To a solution of ethyl 1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate (72 mg, 0.14 mmol) in THF (568 µl) and MeOH (142 µl) was added aq. LiOH (2M, 78 µl,

0.15 mmol) and the resulting mixture was stirred at RT for 4 h. The reaction mixture was then concentrated under reduced pressure to give the title compound as a light green solid (70 mg, 100%, Li salt). MS (ES^+) $\text{C}_{21}\text{H}_{20}\text{F}_3\text{N}_5\text{O}_3$ requires: 479, found: 480 $[\text{M}+\text{H}]^+$.

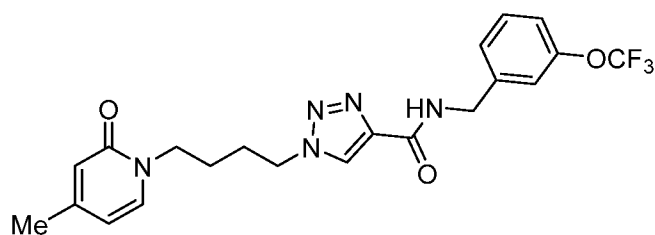
Step 6



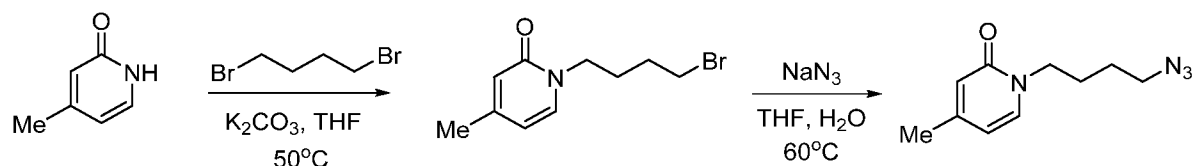
1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridin-1(2H)-yl)butyl)-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide:

[0219] To a mixture of 1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid (20 mg, 0.042 mmol), pyridin-2-ylmethanamine (5.2 μl , 0.050 mmol) and HATU (24 mg, 0.063 mmol) in DMF (209 μl) was added DIEA (14.6 μl , 0.0830 mmol) and the resulting mixture was stirred at RT for 2 h. The reaction was then concentrated under reduced pressure and the residue was purified via silica gel chromatography (0 - 15% MeOH in DCM with 1% NH_4OH) to give the title compound as a pink solid (12 mg, 51%). MS (ES^+) $\text{C}_{27}\text{H}_{26}\text{N}_7\text{O}_4$ requires: 569, found: 570 $[\text{M}+\text{H}]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.31 (s, 1H), 9.04 (t, $J = 6.1$ Hz, 1H), 8.61 (s, 1H), 8.50 (m, 1H), 7.75 (m, 1H), 7.57 (d, $J = 7.4$ Hz, 1H), 7.47 (m, 1H), 7.37 – 7.20 (m, 4H), 6.72 (d, $J = 2.2$ Hz, 1H), 6.36 (dd, $J = 7.5, 2.4$ Hz, 1H), 4.55 (d, $J = 6.0$ Hz, 1H), 4.44 (t, $J = 7.0$ Hz, 2H), 3.83 (t, $J = 7.1$ Hz, 2H), 3.75 (s, 2H), 1.85 – 1.78 (m, 2H), 1.60 – 1.52 (m, 2H).

EXAMPLE 11: 1-(4-(4-methyl-2-oxopyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



Steps 1 to 2



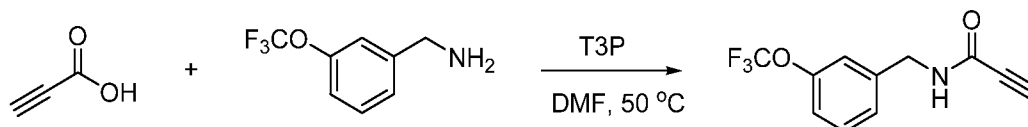
Step 1: 1-(4-bromobutyl)-4-methylpyridin-2(1H)-one.

[0220] To a suspension of K_2CO_3 (0.127 g, 0.916 mmol) and 4-methylpyridin-2(1H)-one (0.10 g, 0.92 mmol) in THF (1.83 ml) was added 1,4-dibromobutane (0.164 ml, 1.38 mmol) and the resulting mixture was stirred at 50 °C for 12 h. The reaction mixture was then cooled to RT and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 10% MeOH in DCM) to give the title compound as a pale yellow liquid (116 mg, 47%). MS (ES^+) $C_{10}H_{14}BrNO$ requires: 243, found: 244 $[M+H]^+$.

Step 2: 1-(4-azidobutyl)-4-methylpyridin-2(1H)-one.

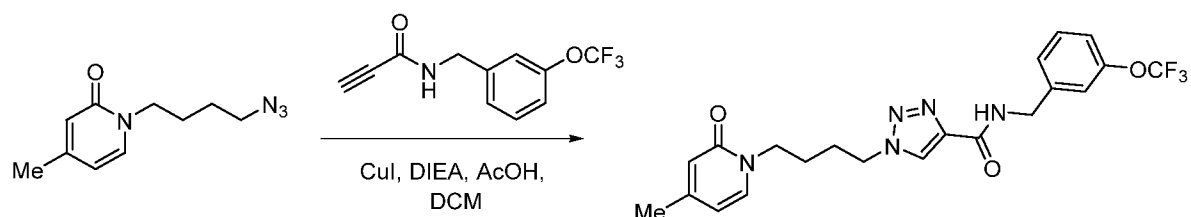
[0221] To a solution of 1-(4-bromobutyl)-4-methylpyridin-2(1H)-one (115 mg, 0.471 mmol) in THF (1884 μ l) and water (471 μ l) were added NaN_3 (33.7 mg, 0.518 mmol) and the resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was then concentrated under reduced pressure, the residue was taken up in EtOH and concentrated again. The residue was purified via silica gel chromatography (0 - 10% MeOH in DCM) to give the title compound as a pale yellow liquid (68 mg, 70%). MS (ES^+) $C_{10}H_{14}N_4O$ requires: 206, found: 207 $[M+H]^+$.

Step 3: N-(3-(trifluoromethoxy)benzyl)propiolamide.



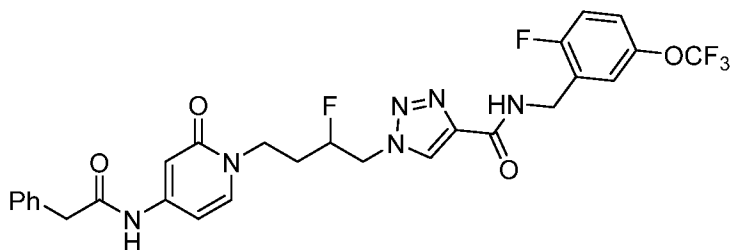
[0222] A vial was charged with T3P in DMF (3.72 g, 5.84 mmol, 50 wt% solution), propiolic acid (0.264 ml, 4.28 mmol), and 3-(trifluoromethoxy)phenylmethanamine (0.744 ml, 3.89 mmol) and allowed to stir at 50 °C for 12 h. The orange viscous solution was concentrated under reduced pressure, and the residue was purified via silica gel chromatography (0 - 100 % EtOAc in hexanes) to give the title compound as a pale yellow liquid (506 mg, 53%). MS (ES^+) $C_{11}H_8F_3NO_2$ requires: 243, found: 244 $[M+H]^+$; ^1H NMR (600 MHz, $DMSO-d_6$) δ 9.30 (t, J = 5.8 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.28 (d, J = 7.7 Hz, 1H), 7.26 (m, 1H), 7.22 (s, 1H), 4.34 (d, J = 6.2 Hz, 2H), 4.20 (s, 1H).

Step 4: 1-(4-(4-methyl-2-oxopyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

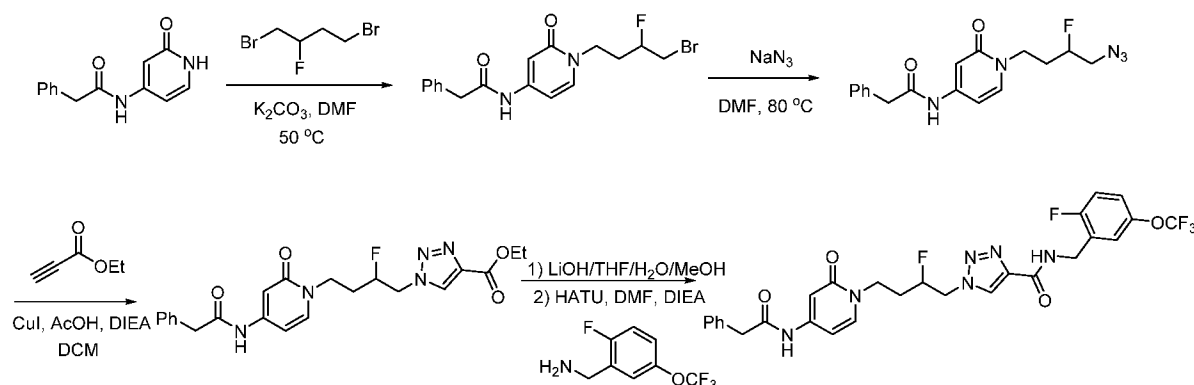


[0223] To a mixture of AcOH (0.471 μ l, 8.22 μ mol), DIEA (1.43 μ l, 8.22 μ mol), *N*-(3-(trifluoromethoxy)benzyl)propiolamide (20 mg, 0.082 mmol), and 1-(4-azidobutyl)-4-methylpyridin-2(1H)-one (17 mg, 0.082 mmol) in DCM (411 μ l) was added copper(I) iodide (0.78 mg, 4.1 μ mol) and the resulting mixture was stirred at RT for 3 h. The reaction mixture was concentrated under reduced pressure and the residue was purified via silica gel chromatography (0 - 10% MeOH in DCM with 1% NH_4OH) to give the title compound as a tan solid (32 mg, 74%). MS (ES^+) $\text{C}_{21}\text{H}_{22}\text{F}_3\text{N}_5\text{O}_3$ requires: 449, found: 450 $[\text{M}+\text{H}]^+$; ^1H NMR (600 MHz, Methanol- d_4) δ 8.38 (s, 1H), 7.47 (d, $J = 6.9$ Hz, 1H), 7.41 (t, $J = 7.9$ Hz, 1H), 7.35 (d, $J = 7.7$ Hz, 1H), 7.27 (s, 1H), 7.15 (m, 1H), 6.34 (s, 1H), 6.24 (dd, $J = 6.9, 1.8$ Hz, 1H), 4.60 (s, 2H), 4.50 (t, $J = 7.0$ Hz, 2H), 3.98 (t, $J = 7.2$ Hz, 2H), 2.20 (s, 3H), 1.99 – 1.90 (m, 2H), 1.77 – 1.69 (m, 2H).

EXAMPLE 12: 1-(2-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(2-fluoro-5-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



Steps 1 to 5



Step 1: *N*-(1-(4-bromo-3-fluorobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

[0224] To a suspension of K_2CO_3 (0.36 g, 2.6 mmol) and *N*-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (0.30 g, 1.3 mmol) in DMF (2.6 ml) was added 1,4-dibromo-2-fluorobutane (0.62 g, 2.6 mmol, prepared according to WO2013/020993 A1, p. 156) and the resulting mixture was stirred at 50 °C for 5 h. The mixture was then concentrated under reduced pressure and the residue was purified via silica gel chromatography (0 - 10 % MeOH in DCM) to give the title compound as a pale yellow, viscous liquid (0.45 g, 90%). MS (ES^+) $C_{17}H_{18}BrFN_2O_2$ requires: 380, found: 381 $[M+H]^+$.

Step 2: *N*-(1-(4-azido-3-fluorobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

[0225] To a suspension of *N*-(1-(4-bromo-3-fluorobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (0.45 g, 1.2 mmol) in DMF (5.0 mL) was added NaN_3 (0.084 g, 1.3 mmol) and the resulting mixture was stirred at 80 °C for 3 h. The reaction was concentrated under reduced pressure and the residue was purified via silica gel chromatography (0 - 10% MeOH in DCM) to give the title compound as an off-white solid (0.33 g, 82%). MS (ES^+) $C_{17}H_{18}FN_5O_2$ requires: 343, found: 344 $[M+H]^+$.

Step 3: Ethyl 1-(2-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate.

[0226] To a suspension of AcOH (10.0 μ l, 0.175 mmol), DIEA (0.031 mL, 0.18 mmol), ethyl propiolate (0.103 g, 1.05 mmol), and *N*-(1-(4-azido-3-fluorobutyl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (0.30 g, 0.87 mmol) in DCM (4.37 ml) was added copper(I) iodide (8.3 mg, 0.044 mmol) and the resulting mixture was stirred at RT for 6 h. The reaction mixture was loaded onto a SiO_2 column and purified via silica gel

chromatography (0 - 15% MeOH in DCM with 1% NH₄OH) to give the title compound as a white solid (0.23 g, 60%). MS (ES⁺) C₂₂H₂₄FN₅O₄ requires: 441, found: 442 [M+H]⁺.

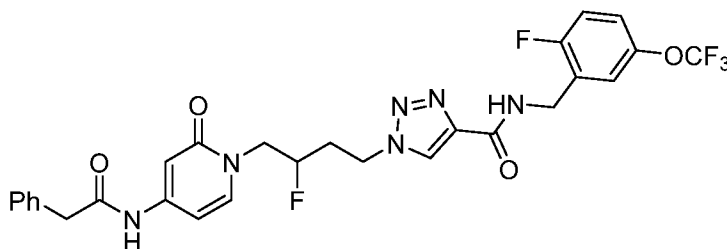
Step 4: 1-(2-Fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid.

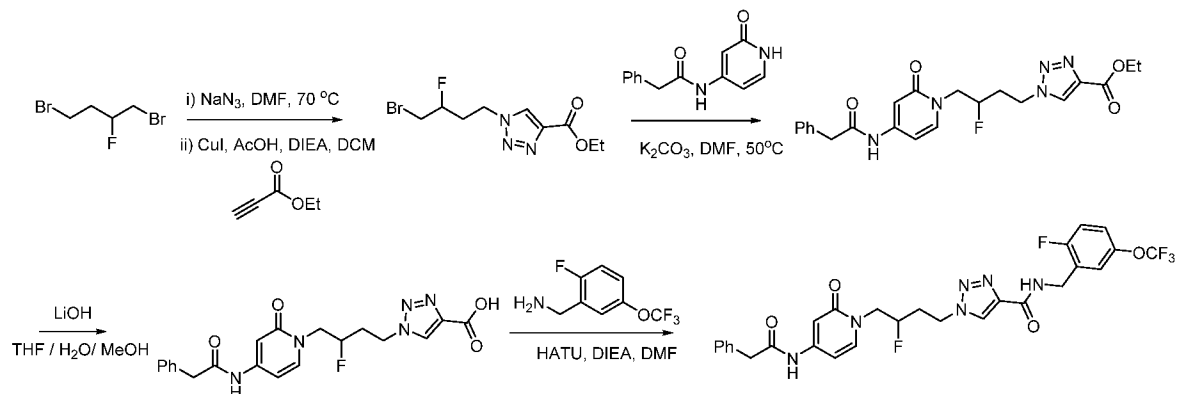
[0227] To a suspension of ethyl 1-(2-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate (0.23 g, 0.52 mmol) in THF (2.1 mL) and MeOH (0.52 mL) was added aq. LiOH (0.29 mL, 0.57 mmol, 2M) and the resulting mixture was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to give the title compound as an off-white solid (0.22 g, >100%, Li salt). MS (ES⁺) C₂₀H₂₀FN₅O₄ requires: 413, found: 414 [M+H]⁺.

Step 5: 1-(2-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(2-fluoro-5-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

[0228] To a suspension of 1-(2-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid (20 mg, 0.048 mmol), (2-fluoro-5-(trifluoromethoxy)phenyl)methanamine (10 mg, 0.048 mmol) and HATU (24 mg, 0.063 mmol) in DMF (242 µl) was added DIEA (17 µl, 0.097 mmol) and the resulting mixture was stirred at RT for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 min; Column: C18) to give the title compound as a white solid (22 mg, 75%). MS (ES⁺) C₂₈H₂₅F₅N₆O₄ requires: 604, found: 605 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.28 (s, 1H), 9.18 (t, *J* = 6.2 Hz, 1H), 8.58 (s, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.37 – 7.28 (m, 7H), 7.25 (m, 1H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.37 (dd, *J* = 7.6, 2.2 Hz, 1H), 5.04 – 4.88 (m, 1H), 4.84 – 4.66 (m, 2H), 4.51 (d, *J* = 6.0 Hz, 2H), 3.99 - 3.91 (m, 2H), 3.65 – 3.50 (m, 2H), 2.12 – 1.83 (m, 2H).

EXAMPLE 13: 1-(3-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(2-fluoro-5-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



Steps 1 to 4Step 1: Ethyl 1-(4-bromo-3-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate.

[0229] To a solution of 1,4-dibromo-2-fluorobutane (1.0 g, 4.3 mmol; prepared according to WO2013/020993 A1, p. 156) in DMF (1.94 mL) was added NaN₃ (0.28 g, 4.3 mmol) and the resulting mixture was stirred at 70 °C for 1 h. The reaction was then cooled to RT and diluted with DCM (19 mL) before adding AcOH (0.049 mL, 0.86 mmol), DIEA (0.15 mL, 0.86 mmol), and ethyl propiolate (0.84 mL, 8.6 mmol). Finally, copper(I) iodide (0.041 g, 0.21 mmol) was added and the resulting mixture was stirred at RT for 5 h. The mixture was loaded directly onto SiO₂ and purified via silica gel chromatography (0 - 100 % EtOAc in hexanes) to give the title compound as a pale yellow solid (0.49 g, 39%). MS (ES⁺) C₉H₁₃BrFN₃O₂ requires: 293, found: 294 [M+H]⁺.

Step 2: Ethyl 1-(3-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate.

[0230] To a suspension of K₂CO₃ (0.24 g, 1.8 mmol) and *N*-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (0.20 g, 0.88 mmol) in DMF (1.8 mL) was added ethyl 1-(4-bromo-3-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate (0.26 g, 0.88 mmol) and the resulting mixture was stirred at 50 °C for 5 h. The mixture was concentrated under reduced pressure and the residue was purified via silica gel chromatography (0 - 10% MeOH in DCM) to give the title compound as a white solid (0.17 g, 43%). MS (ES⁺) C₂₂H₂₄FN₅O₄ requires: 441, found: 442 [M+H]⁺.

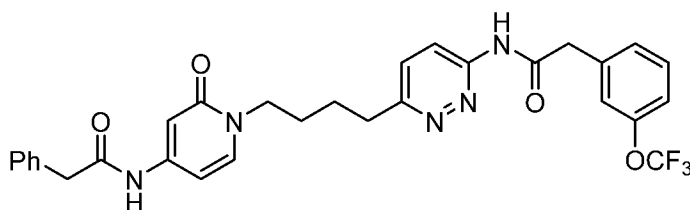
Step 3: 1-(3-Fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid.

[0231] To a suspension of ethyl 1-(3-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate (0.17 g, 0.37 mmol) in THF (1.5 mL) and MeOH (0.37 mL) was added aq. LiOH (2M, 0.21 mL, 0.41 mmol,) and the resulting mixture was stirred at RT for 2 h. The mixture was concentrated under reduced pressure to give the title compound as an off-white solid (160 mg, >100%, Li salt). MS (ES⁺) C₂₀H₂₀FN₅O₄ requires: 413, found: 414 [M+H]⁺.

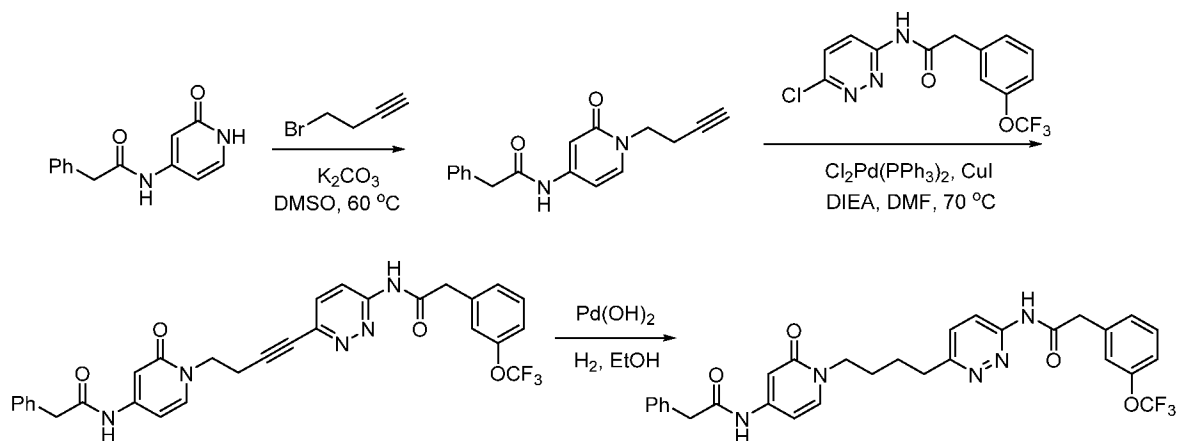
Step 4: 1-(3-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(2-fluoro-5-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

[0232] To a suspension of 1-(3-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid (20 mg, 0.048 mmol), (2-fluoro-5-(trifluoromethoxy)phenyl)methanamine (10 mg, 0.048 mmol) and HATU (24 mg, 0.063 mmol) in DMF (242 μ l) was added DIEA (17 μ l, 0.097 mmol) and the resulting mixture was stirred at RT for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 min; Column: C18) to give the title compound as an off-white solid (16 mg, 55%). MS (ES⁺) C₂₈H₂₅F₅N₆O₄ requires: 604, found: 605 [M+H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.32 (s, 1H), 9.17 (t, *J* = 6.1 Hz, 1H), 8.64 (s, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.40 – 7.18 (m, 8H), 6.79 (d, *J* = 2.3 Hz, 1H), 6.37 (dd, *J* = 7.5, 2.3 Hz, 1H), 4.88 – 4.69 (m, 1H), 4.58 (t, *J* = 7.1 Hz, 2H), 4.50 (d, *J* = 6.1 Hz, 2H), 4.17 (ddd, *J* = 29.6, 14.2, 2.8 Hz, 1H), 4.01 (ddd, *J* = 18.3, 14.2, 7.7 Hz, 1H), 3.65 – 3.50 (m, 2H), 2.35 – 2.08 (m, 2H).

EXAMPLE 14: N-(2-oxo-1-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridazin-3-yl)butyl)-1,2-dihydropyridin-4-yl)-2-phenylacetamide



Steps 1 to 3



Step 1: N-(1-(but-3-yn-1-yl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

[0233] To a mixture of *N*-(2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (Example 1, Step 1; 1.2 g, 5.3 mmol) and K_2CO_3 (1.45 g, 10.5 mmol) in DMSO (10.5 ml) at 60 °C was added 4-bromobut-1-yne (0.987 ml, 10.5 mmol) in four equal portions over 4 h. The reaction mixture was then diluted with EtOAc (100mL) and washed with water (3 x 10 mL) and brine (2 x 10 mL). The combined organic layers were concentrated under reduced pressure and the residue was adsorbed onto SiO_2 and purified via SiO_2 gel chromatography (0 - 20% MeOH in DCM) to give the title compound as a brown solid (407 mg, 17%). MS (ES^+) $C_{17}H_{16}N_2O_2$ requires: 280, found: 281 $[M+H]^+$; ^1H NMR (600 MHz, DMSO- d_6) δ 10.30 (s, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.35 – 7.28 (m, 4H), 7.25 (m, 1H), 6.75 (d, J = 2.3 Hz, 1H), 6.36 (dd, J = 7.4, 2.4 Hz, 1H), 3.90 (t, J = 6.7 Hz, 2H), 3.66 (s, 2H), 2.88 (t, J = 2.6 Hz, 1H), 2.53 (td, J = 6.8, 2.7 Hz, 2H).

Step 2: N-(2-oxo-1-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridazin-3-yl)but-3-yn-1-yl)-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

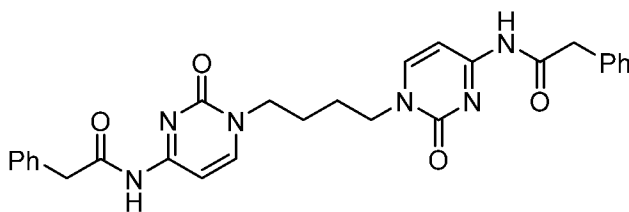
[0234] A mixture of bis(triphenylphosphine)palladium(II) chloride (15 mg, 0.021 mmol), DIEA (748 μ l, 4.28 mmol), CuI (8.1 mg, 0.043 mmol), *N*-(1-(but-3-yn-1-yl)-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide (120 mg, 0.428 mmol) and *N*-(6-chloropyridazin-3-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (170 mg, 0.514 mmol) in DMF (1.43 mL) was degassed with N_2 for 5 minutes. The reaction mixture was then heated to 70 °C and stirred for 2 h, concentrated under reduced pressure and the residue was purified via silica gel chromatography (0 - 15% MeOH in DCM) to give the title compound as a tan solid (35 mg, 14%). MS (ES^+) $C_{30}H_{24}F_3N_5O_4$ requires: 575, found: 576 $[M+H]^+$; ^1H NMR (600 MHz,

DMSO-*d*₆) δ 11.55 (s, 1H), 10.28 (s, 1H), 8.26 (d, *J* = 9.3 Hz, 1H), 7.68 (m, 2H), 7.47 (m, 1H), 7.37 (m, 2H), 7.34 – 7.22 (m, 6H), 6.78 (d, *J* = 2.3 Hz, 1H), 6.38 (dd, *J* = 7.5, 2.3 Hz, 1H), 4.05 (t, *J* = 6.7 Hz, 2H), 3.88 (s, 2H), 3.65 (s, 2H), 2.88 (t, *J* = 6.7 Hz, 2H).

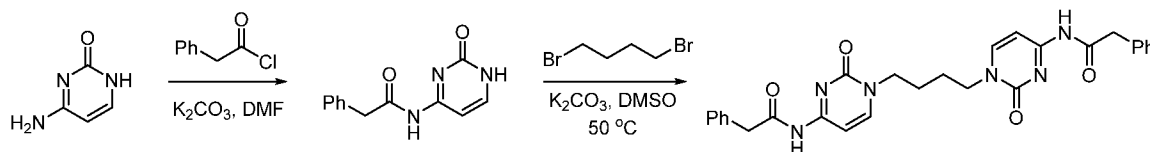
Step 3: N-(2-oxo-1-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridazin-3-yl)butyl)-1,2-dihydropyridin-4-yl)-2-phenylacetamide.

[0235] A reaction vessel was charged with palladium hydroxide on carbon (85 mg, 0.030 mmol, 5% w/w), *N*-(2-oxo-1-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridazin-3-yl)but-3-yn-1-yl)-1,2-dihydropyridin-4-yl)-2-phenylacetamide (35 mg, 0.061 mmol) and EtOH (608 μ l) under an atmosphere of N₂. The suspension was degassed with N₂ for 5 minutes and purged with H₂ for 10 minutes. The reaction mixture was stirred under an H₂ balloon for 2 h at RT, then purged with N₂, filtered through a pad of Celite®, and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 15 % MeOH in DCM) to give the title compound as a white solid (16 mg, 45%). MS (ES⁺) C₃₀H₂₈F₃N₅O₄ requires: 579, found: 580 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.28 (s, 1H), 10.24 (s, 1H), 8.18 (d, *J* = 9.1 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.47 (m, 1H), 7.39 – 7.22 (m, 8H), 6.72 (d, *J* = 2.3 Hz, 1H), 6.36 (dd, *J* = 7.4, 2.4 Hz, 1H), 3.88 – 3.77 (m, 4H), 3.64 (s, 2H), 2.89 – 2.82 (m, 2H), 1.67 – 1.59 (m, 4H).

EXAMPLE 15: N,N'-(butane-1,4-diylbis(2-oxo-1,2-dihydropyrimidine-1,4-diyl))bis(2-phenylacetamide)



Steps 1 to 2



Step 1: N-(2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide.

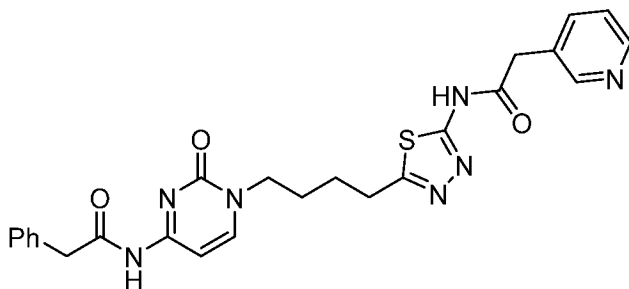
[0236] To a suspension of 4-aminopyrimidin-2(1H)-one (1.0 g, 9.0 mmol) and K₂CO₃ (1.24 g, 9.00 mmol) in DMF (36.0 ml) at 0 °C was added 2-phenylacetyl chloride (2.21 ml,

18.0 mmol). The resulting mixture was stirred at RT for 48 h, diluted with water (200 mL) and allowed to stir at RT for 5 minutes. The mixture was then filtered through a Buchner funnel and the filter cake was washed with water (10 mL) to give the title compound as a light yellow solid (1.12 g, 54%). MS (ES^+) $\text{C}_{12}\text{H}_{11}\text{N}_3\text{O}_2$ requires: 229, found: 230 $[\text{M}+\text{H}]^+$.

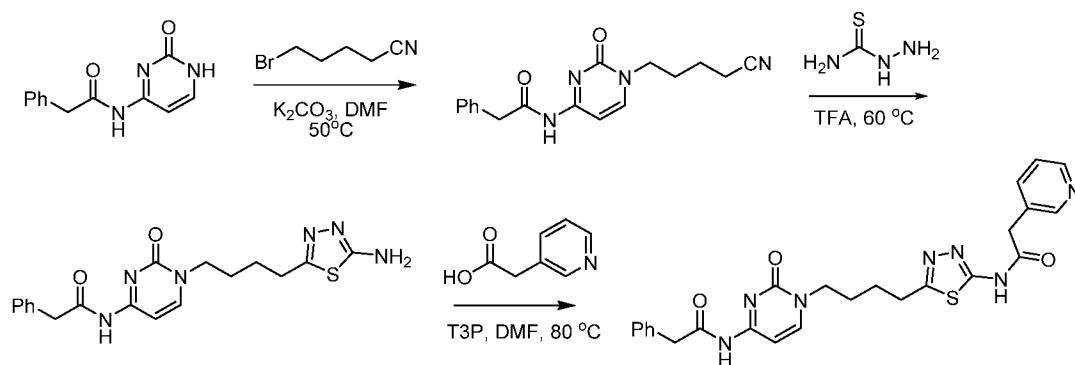
Step 2: N,N'-(butane-1,4-diylbis(2-oxo-1,2-dihydropyrimidine-1,4-diyl))bis(2-phenylacetamide).

[0237] To a suspension of *N*-(2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide (21 mg, 0.093 mmol) and K_2CO_3 (13 mg, 0.093 mmol) in DMSO (0.18 mL) was added 1,4-dibromobutane (0.0055 mL, 0.046 mmol), and the resulting mixture was heated at 50 °C for 1 h. The reaction mixture was then filtered and purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 20 minutes; Column: C18) to give the title compound as an off-white solid (8 mg, 34% yield). MS (ES^+) $\text{C}_{28}\text{H}_{28}\text{N}_6\text{O}_4$ requires: 512, found: 513 $[\text{M}+\text{H}]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.04 (s, 2H), 8.08 (d, $J = 7.2$ Hz, 2H), 7.36 – 7.28 (m, 8H), 7.28 – 7.22 (m, 2H), 7.10 (d, $J = 7.2$ Hz, 2H), 3.84 – 3.77 (m, 4H), 3.71 (s, 4H), 1.66 – 1.53 (m, 4H).

EXAMPLE 16: *N*-(2-oxo-1-(4-(5-(2-(pyridin-3-yl)acetamido)-1,3,4-thiadiazol-2-yl)butyl)-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide



Steps 1 to 3



Step 1: N-(1-(4-cyanobutyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide.

[0238] To a suspension of *N*-(2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide (Example 15, Step 1; 0.480 g, 2.09 mmol) and K₂CO₃ (0.289 g, 2.09 mmol) in DMF (10.5 ml) was added 5-bromopentanenitrile (0.293 ml, 2.51 mmol). The resulting mixture was heated at 50 °C for 1 h. The reaction mixture was filtered, concentrated under reduced pressure, and the residue purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 minutes; Column: C18) to give the title compound (0.241 g, 37%) as a pale yellow solid. MS (ES⁺) C₁₇H₁₈N₄O₂ requires: 310, found: 311 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.04 (s, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 7.34 – 7.28 (m, 4H), 7.28 – 7.21 (m, 1H), 7.12 (d, *J* = 7.2 Hz, 1H), 3.81 (t, *J* = 7.0 Hz, 2H), 3.72 (s, 2H), 3.69 (s, 2H), 2.53 (t, *J* = 7.1 Hz, 2H), 1.77 – 1.67 (m, 2H), 1.58 – 1.49 (m, 2H).

Step 2: N-(1-(4-(5-amino-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide.

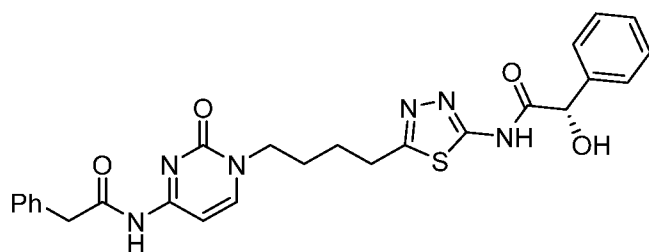
[0239] To a solution of *N*-(1-(4-cyanobutyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide (240 mg, 0.773 mmol) in trifluoroacetic acid (596 µl, 7.73 mmol) was added hydrazinecarbothioamide (70.5 mg, 0.773 mmol) and the resulting mixture was stirred at 60 °C for 12 h. The reaction was diluted with toluene (5 mL) and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 20 % MeOH in DCM) to give the title compound as a light yellow solid (72 mg, 24% yield). MS (ES⁺) C₁₈H₂₀N₆O₂S requires: 384, found: 385 [M+H]⁺; ¹H NMR (600 MHz, Methanol-*d*₄) δ 8.00 (d, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.33 – 7.30 (m, 4H), 7.28 – 7.24 (m, 1H), 3.94 (t, *J* = 7.0 Hz, 2H), 3.75 (s, 2H), 2.96 (t, *J* = 7.3 Hz, 2H), 1.88 – 1.72 (m, 4H).

Step 3: N-(2-oxo-1-(4-(5-(2-(pyridin-3-yl)acetamido)-1,3,4-thiadiazol-2-yl)butyl)-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide.

[0240] To a suspension of *N*-(1-(4-(5-amino-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide (35 mg, 0.091 mmol) and 2-(pyridin-3-yl)acetic acid hydrochloride (17.4 mg, 0.100 mmol) in DMF (910 µl) was added T3P (63.7 µl, 0.100 mmol, 50% solution in DMF) and the resulting mixture was stirred at 80 °C for 8 h. The reaction mixture was then concentrated under reduced pressure and the residue purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1%

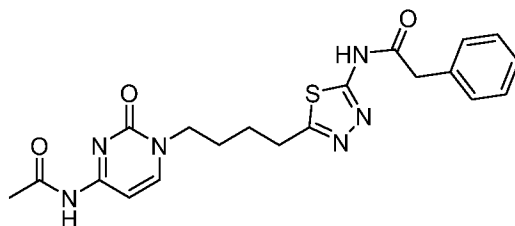
TFA/MeCN; Gradient: B = 20 - 60%; 12 minutes; Column: C18) to give the title compound as a pale yellow solid (5 mg, 9%). MS (ES⁺) C₂₅H₂₅N₇O₃ requires: 503, found: 504 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 12.78 (s, 1H), 11.03 (s, 1H), 8.83 – 8.73 (m, 2H), 8.32 (dd, *J* = 8.0, 1.9 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 7.88 (dd, *J* = 8.0, 5.4 Hz, 1H), 7.33 – 7.29 (m, 4H), 7.27 – 7.24 (m, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 4.08 (s, 2H), 3.82 (t, *J* = 6.6 Hz, 2H), 3.71 (s, 2H), 3.00 (t, *J* = 7.0 Hz, 2H), 1.73 – 1.61 (m, 4H).

EXAMPLE 17: (S)-2-hydroxy-N-(5-(4-(2-oxo-4-(2-phenylacetamido)pyrimidin-1(2H)-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-phenylacetamide



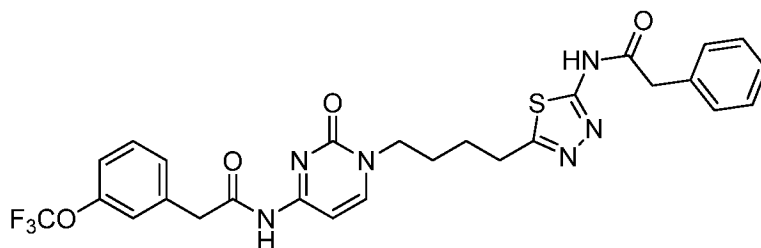
[0241] A vial was charged with *N*-methylmorpholine (14.6 μl, 0.133 mmol), *N*-(1-(4-(5-amino-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide (Step 3, Example 16; 51 mg, 0.13 mmol), (*S*)-2-hydroxy-2-phenylacetic acid (26.2 mg, 0.172 mmol), EDC (30.5 mg, 0.159 mmol), HOBT (24.4 mg, 0.159 mmol), and DMF (663 μl). The resulting mixture was stirred at RT for 15 h. The reaction was concentrated under reduced pressure and the residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 minutes; Column: C18). The residual TFA was neutralized using Agilent StratoSpheres PL-HCO₃ MP resin before concentrating to give the title compound (11 mg, 13% yield) as a colorless thick oil. MS (ES⁺) C₂₆H₂₆N₆O₄S requires: 518, found: 519 [M+H]⁺; ¹H NMR (600 MHz, Methanol-*d*₄) δ 7.55 – 7.48 (m, 2H), 7.37 – 7.26 (m, 10H), 5.32 (d, *J* = 4.1 Hz, 1H), 3.93 (t, *J* = 6.6 Hz, 2H), 3.91 – 3.84 (m, 1H), 3.75 (s, 1H), 3.59 (s, 1H), 3.09 – 3.03 (m, 2H), 1.84 – 1.76 (m, 4H).

EXAMPLE 18: N-(2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyrimidin-4-yl)-2-[3-(trifluoromethoxy)phenyl]acetamide

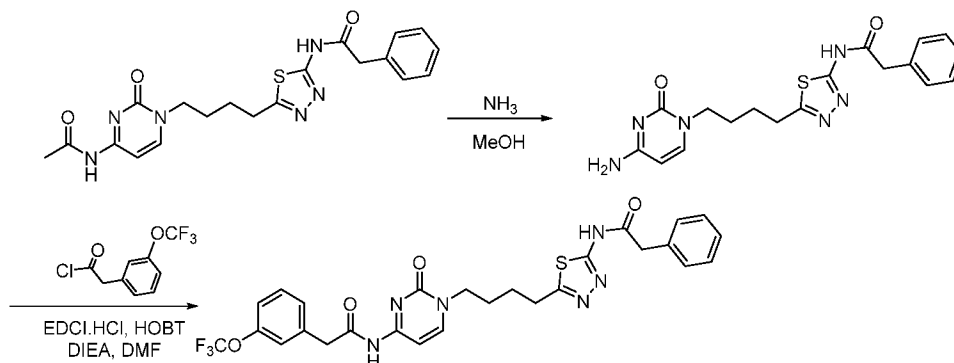


[0242] Prepared as Example 16 (405 mg, 95%); MS (ES⁺) C₂₀H₂₂N₆O₃S requires: 426, found: 427 [M+H]⁺. ¹H NMR (600 MHz, DMSO-d₆) δ 12.65 (s, 1H), 10.78 (s, 1H), 8.07 (d, *J*= 7.2 Hz, 1H), 7.35-7.24 (m, 5H), 7.11 (d, *J*= 7.2 Hz, 1H), 3.83-3.78 (m, 4H), 2.99 (t, *J*= 7.2 Hz, 2H), 2.08 (s, 3H), 1.72-1.62 (m, 4H).

EXAMPLE 19: N-(2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyrimidin-4-yl)-2-[3-(trifluoromethoxy)phenyl]acetamide



Steps 1 and 2



Step 1: N-(5-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-phenylacetamide.

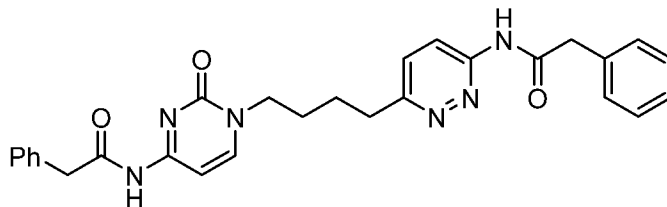
[0243] A suspension of *N*-(5-(4-(4-acetamido-2-oxopyrimidin-1(2H)-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-phenylacetamide (Example 18; 85 mg, 0.20 mmol) in ammonia in MeOH (7N, 3 ml) was stirred at 20 °C for 16 h. The precipitate was filtered to give *N*-(5-(4-(4-

amino-2-oxopyrimidin-1(2H)-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-phenylacetamide (52 mg, 68%) as a white solid. MS (ES^+) $\text{C}_{18}\text{H}_{20}\text{N}_6\text{O}_2\text{S}$ requires: 384, found: 385 $[\text{M}+\text{H}]^+$.

Step 2: N-(2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyrimidin-4-yl)-2-[3-(trifluoromethoxy)phenyl]acetamide.

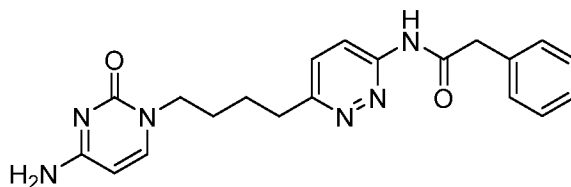
[0244] To a suspension of *N*-(5-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-phenylacetamide (40 mg, 0.10 mmol) in DMF (1 ml) were added 2-(3-(trifluoromethoxy)phenyl)acetic acid (27.5 mg, 0.125 mmol), HOBT (19.1 mg, 0.125 mmol), DIEA (0.035 mL, 0.19 mmol) and EDC.HCl (23.9 mg, 0.125 mmol) and the resulting mixture was stirred at 20 °C for 16 h. The volatiles were removed under reduced pressure. The crude residue was taken up in DMSO and purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 minutes; Column: C18) to give the title compound (30 mg, 49%) as a white solid. MS (ES^+) $\text{C}_{27}\text{H}_{25}\text{F}_3\text{N}_6\text{O}_4\text{S}$ requires: 586, found: 587 $[\text{M}+\text{H}]^+$. ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 12.67 (s, 1H), 11.08 (s, 1H), 8.09 (d, J = 7.2 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.35-7.24 (m, 8 H), 7.09 (d, J = 7.2 Hz, 1H), 3.83-3.78 (m, 6H), 2.99 (t, J = 7.2 Hz, 2H), 1.72-1.62 (m, 4H).

EXAMPLE 20: N-(2-oxo-1-(4-(6-(2-phenylacetamido)pyridazin-3-yl)butyl)-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide

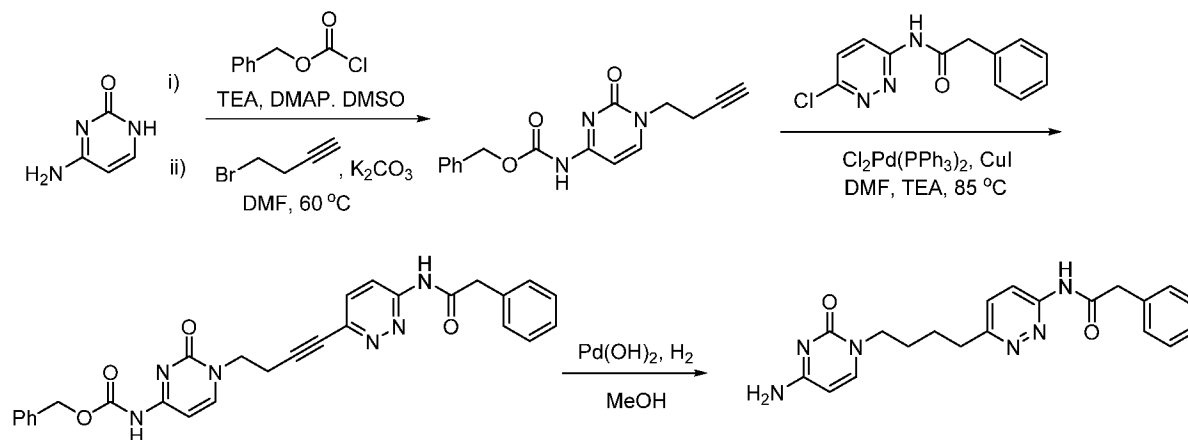


[0245] Prepared as Example 1; MS (ES^+) $\text{C}_{28}\text{H}_{28}\text{F}_3\text{N}_6\text{O}_3$ requires: 496, found: 497 $[\text{M}+\text{H}]^+$; ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 11.16 (m, 2H), 8.18 (d, J = 9.1 Hz, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 9.1 Hz, 1H), 7.39 – 7.18 (m, 10H), 7.08 (d, J = 7.2 Hz, 1H), 3.85 – 3.78 (m, 2H), 3.76 (s, 2H), 3.70 (s, 2H), 2.90 – 2.82 (m, 2H), 1.71 – 1.58 (m, 4H).

EXAMPLE 21: N-(6-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-phenylacetamide



Steps 1 to 4



Step 1: Benzyl (2-oxo-1,2-dihydropyrimidin-4-yl)carbamate.

[0246] To a suspension of 4-aminopyrimidin-2(1H)-one (1.0 g, 9.0 mmol), TEA (1.88 mL, 13.5 mmol), and DMAP (110 mg, 0.90 mmol) in DMSO (30 mL) at 0 °C was added dropwise Cbz-Cl (1.93 mL, 13.5 mmol) and the mixture was stirred at RT for 5 days. The reaction mixture was then poured into ice-water (100 mL) and cooled to 0 °C for 10 minutes. The precipitate was filtered, washed with water (50 mL) and Et₂O (50 mL) to give the title compound as a white solid (1.6 g, 72%). MS (ES⁺) C₁₂H₁₁N₃O₃ requires: 245, found: 246 [M+H]⁺.

Step 2: Benzyl (1-(but-3-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate.

A mixture of benzyl (2-oxo-1,2-dihydropyrimidin-4-yl)carbamate (3.0 g, 12 mmol), 4-bromobut-1-yne (1.7 mL, 18 mmol) and K₂CO₃ (1.7 g, 12 mmol) in DMF (50 mL) was heated at 60 °C for 16 h. The mixture was concentrated under reduced pressure and the residue was purified by SiO₂ gel column chromatography (0 to 10% MeOH in DCM) to give the title compound (2.3 g, 80%). MS (ES⁺) C₁₆H₁₅N₃O₃ requires: 297, found: 298 [M+H]⁺.

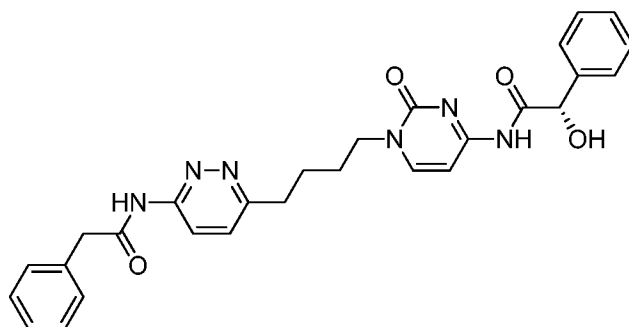
Step 3: Benzyl (2-oxo-1-(4-(6-(2-phenylacetamido)pyridazin-3-yl)but-3-yn-1-yl)-1,2-dihydropyrimidin-4-yl)carbamate.

[0247] To a solution of benzyl (1-(but-3-yn-1-yl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate (2.2 g, 5.9 mmol) in DMF (30 mL) was added TEA (8.25 mL, 59.2 mmol) and the mixture was degassed with a stream of N₂ for 2 minutes. CuI (56 mg, 0.30 mmol), *N*-(6-chloropyridazin-3-yl)-2-phenylacetamide (1.47 g, 5.92 mmol), and bis(triphenylphosphine)palladium(II) chloride (208 mg, 0.300 mmol) were then added, and the resulting mixture was heated at 85 °C for 4 h under N₂. The mixture was concentrated under reduced pressure at 60 °C, and the residue was purified by silica gel column chromatography (DCM:MeOH = 10:0 to 10:1) to give the title compound (1.68 g, 56%). MS (ES⁺) C₂₈H₂₄N₆O₄ requires: 508, found: 509 [M+H]⁺.

Step 4: N-(6-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-phenylacetamide.

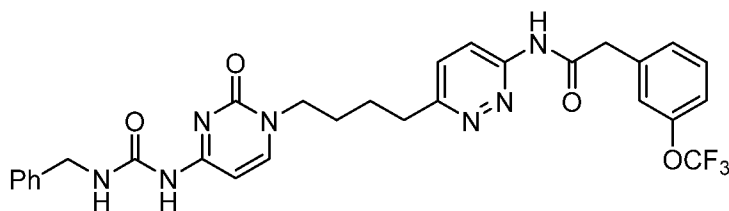
A reaction vessel was charged with palladium hydroxide on carbon (20% w/w, 1.16 g, 1.65 mmol), benzyl (2-oxo-1-(4-(6-(2-phenylacetamido)pyridazin-3-yl)but-3-yn-1-yl)-1,2-dihydropyrimidin-4-yl)carbamate (1.68 g, 3.30 mmol) and MeOH (50 mL) under an atmosphere of N₂. The suspension was degassed with N₂ for 5 minutes, purged with H₂ and shaken under H₂ (40 PSI) at RT for 10 h in a Parr apparatus. The mixture was then purged with N₂, filtered through a pad of Celite® and washed with MeOH. The filtrate was concentrated under reduced pressure, the residue was taken up in MeOH/DCM/Hex (1:1:10), stirred with for 30 minutes, filtered and washed with hexanes to give the title compound (950 mg, 76%). MS (ES⁺) C₂₀H₂₂N₆O₂ requires: 378, found: 379 [M+H]⁺. ¹H NMR (600 MHz, Methanol-*d*₄) δ 8.39 (d, *J* = 9.2 Hz, 1H), 7.92 (d, *J* = 7.7 Hz, 1H), 7.65 (d, *J* = 9.2 Hz, 1H), 7.38 – 7.24 (m, 5H), 6.02 (d, *J* = 7.7 Hz, 1H), 3.88 (t, *J* = 6.4 Hz, 2H), 3.79 (s, 2H), 3.00 – 2.93 (m, 2H), 1.83 – 1.74 (m, 4H).

EXAMPLE 22: (S)-2-hydroxy-N-(2-oxo-1-(4-(6-(2-phenylacetamido)pyridazin-3-yl)butyl)-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide



[0248] To a mixture of *N*-(6-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-phenylacetamide (Example 21; 24 mg, 0.063 mmol) and (*S*)-2-hydroxy-2-phenylacetic acid (12 mg, 0.082 mmol) and DIEA (0.020 mL, 0.19 mmol) in DMF (0.5 mL) were added EDC.HCl (15 mg, 0.076 mmol) and HOBT (12 mg, 0.11 mmol). The mixture was stirred at RT for 6 h, then diluted with DCM. The pH was adjusted to ~7-8 by addition of aq. 1 N NaOH. The two layers were separated, the organic layer was washed with water, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by SiO₂ gel column chromatography (DCM:MeOH = 10:0 to 10:1) to give the title compound (8.5 mg, 26%). MS (ES⁺) C₂₈H₂₈N₆O₄ requires: 512, found: 513 [M+H]⁺; ¹H NMR (600 MHz, DMSO-d₆) δ 11.23 (s, 1H), 10.34 (s, 1H), 8.17 (d, *J* = 9.0 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 1H), 7.48 (d, *J* = 7.2 Hz, 2H), 7.37-7.30 (m, 7H), 7.25 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.40 (bs, 1H), 5.22 (bs, 1H), 3.82-3.81 (m, 2H), 3.76 (s, 2H), 2.87-2.85 (m, 2H), 1.66-1.64 (m, 4H).

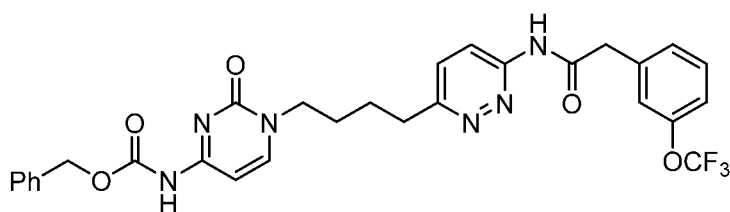
EXAMPLE 23: *N*-(6-(4-(4-(3-benzylureido)-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide



[0249] To a solution of *N*-(6-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (Example 21; 34 mg, 0.074 mmol) in THF (294 μl) was added (isocyanatomethyl)benzene (12 μl, 0.096 mmol) and the resulting mixture was stirred at RT for 12 h. The mixture was concentrated under reduced pressure and the residue

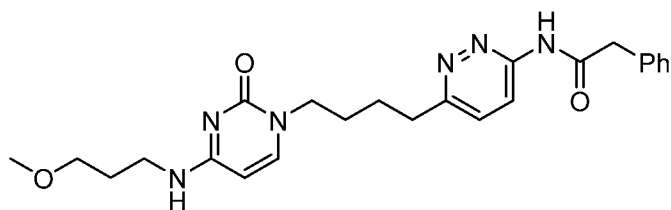
was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 minutes; Column: C18) to give the title compound as a white solid (3 mg, 7%). MS (ES⁺) C₂₉H₂₈ F₃N₇O₄ requires: 595, found: 596 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.31 (s, 1H), 9.90 (s, 1H), 9.36 (s, 1H), 8.19 (d, *J* = 9.1 Hz, 1H), 7.93 (d, *J* = 7.1 Hz, 1H), 7.56 (d, *J* = 9.2 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.39 – 7.23 (m, 8H), 6.20 (s, 1H), 4.43 (s, 2H), 3.85 (s, 2H), 3.79 – 3.73 (m, 2H), 2.91 – 2.82 (m, 2H), 1.69 – 1.58 (m, 4H).

EXAMPLE 24: Benzyl (2-oxo-1-(4-(6-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyridazin-3-yl)butyl)-1,2-dihydropyrimidin-4-yl)carbamate



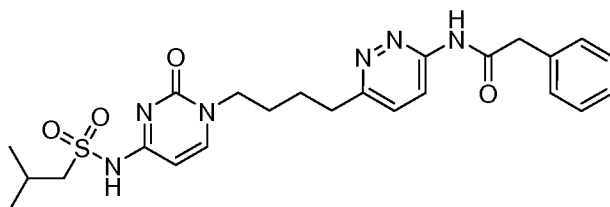
[0250] To a mixture of *N*-(6-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (Example 21; 20 mg, 0.043 mmol) and pyridine (7.0 μl, 0.087 mmol) in DMF (216 μl) was added benzyl carbonochloridate (9.2 μl, 0.065 mmol). The orange solution was allowed to stir at RT for 24 h. The reaction was concentrated under reduced pressure and the residue was purified via silica gel chromatography (0 - 20 % MeOH in DCM) to give the title compound as an off-white solid (10 mg, 39%). MS (ES⁺) C₂₉H₂₇ F₃N₆O₅ requires: 596, found: 597 [M+H]⁺; ¹H NMR (600 MHz, Methanol-*d*₄) δ 8.34 (d, *J* = 9.1 Hz, 1H), 7.95 (d, *J* = 7.3 Hz, 1H), 7.57 (d, *J* = 9.2 Hz, 1H), 7.46 – 7.28 (m, 8H), 7.24 (d, *J* = 7.3 Hz, 1H), 7.21 – 7.14 (m, 1H), 5.21 (s, 2H), 3.92 (t, *J* = 6.6 Hz, 2H), 3.85 (s, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 1.82 – 1.72 (m, 4H).

EXAMPLE 25: *N*-(6-(4-(4-((3-methoxypropyl)amino)-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-phenylacetamide



[0251] To a suspension of NaH (3.80 mg, 0.095 mmol) in DMF (793 μ l) was added dropwise *N*-(6-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-phenylacetamide (Example 21; 30 mg, 0.079 mmol) and the resulting mixture was stirred at RT for 30 minutes. A solution of 1-bromo-3-methoxypropane (11 μ L, 0.095 mmol) in DMF (793 μ l) was added dropwise, and the resulting mixture was stirred at RT for 2 h. The reaction mixture was then diluted with EtOAc (10 mL) and washed with H₂O (10 mL). The layers were separated, and the organic layer was washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 10 - 40%; 12 minutes; Column: C18) to give the title compound as a white solid (5 mg, 11%); MS (ES⁺) C₂₄H₃₀N₆O₃ requires: 450, found: 451 [M+H]⁺; ¹H NMR (600 MHz, CD₃OD) δ 8.70 (d, *J* = 9.4 Hz, 1H), 8.11 (d, *J* = 9.3 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.32 (m, 3H), 7.34 – 7.26 (m, 2H), 6.04 (d, *J* = 7.6 Hz, 1H), 4.72 (t, *J* = 6.8 Hz, 2H), 3.96 (s, 2H), 3.91–3.89 (m, 2H), 3.43 (t, *J* = 5.7 Hz, 2H), 3.25 (s, 3H), 3.02 (t, *J* = 6.9 Hz, 2H), 2.22 (p, *J* = 6.3 Hz, 2H), 1.86 – 1.80 (m, 4H).

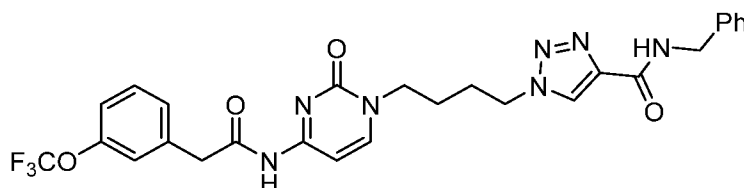
EXAMPLE 26: *N*-(6-(4-(4-(2-methylpropylsulfonamido)-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-phenylacetamide



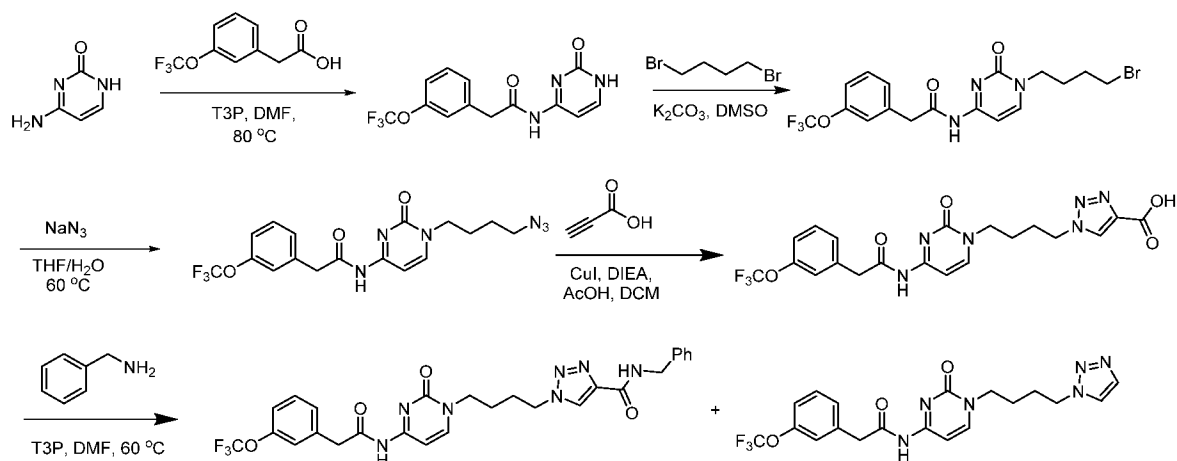
[0252] To a suspension of *N*-(6-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)butyl)pyridazin-3-yl)-2-phenylacetamide (Example 21; 30 mg, 0.079 mmol) in THF (0.4 mL) was added NaH (60 % mineral oil dispersion; 8.4 mg, 0.21 mmol). The resulting mixture was stirred at RT for 1 h, 2-methylpropane-1-sulfonyl chloride (10 μ l, 0.079 mmol) was added and the resulting mixture was stirred at RT for another 16 h. The reaction mixture was then diluted with DMSO (1 mL), filtered, and the filtrate was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 minutes; Column: C18) to give the title compound as an off-white solid (5 mg, 13%). MS (ES⁺) C₂₄H₃₀N₆O₄S requires: 498.2, found: 499 [M+H]⁺. ¹H NMR (DMSO-d₆) δ : 11.87 (br s, 1H), 11.26 (s, 1H), 8.21 (d, *J* =

9.4 Hz, 1H), 7.81 (d, $J = 7.9$ Hz, 1H), 7.58 (d, $J = 9.1$ Hz, 1H), 7.29 - 7.38 (m, 4H), 7.20 - 7.28 (m, 1H), 6.40 (d, $J = 7.9$ Hz, 1H), 3.68 - 3.81 (m, 4H), 2.82 - 2.95 (m, 4H), 2.08 - 2.21 (m, 1H), 1.57 - 1.73 (m, 4H), 0.97 - 1.07 (m, 6H).

EXAMPLE 27: N-benzyl-1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyrimidin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxamide.



Steps 1 to 5



Step 1: N-(2-oxo-1,2-dihydropyrimidin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide.

T3P in DMF (6.87 g, 10.8 mmol, 50% solution) was added to 4-aminopyrimidin-2(1H)-one (1.0 g, 9.0 mmol) and the mixture stirred at 80 °C for 4 h. The orange solution was cooled to 0 °C and diluted with water (70 mL). After stirring at 0 °C for 10 minutes the mixture was filtered on a Buchner funnel. The solid was washed with Et₂O (10 mL), and the title compound as collected as a yellow-orange solid (1.64 g, 55%). MS (ES⁺) C₁₃H₁₀F₃N₃O₃ requires: 313, found: 314 [M+H]⁺.

Step 2: N-(1-(4-bromobutyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide.

To a mixture of K₂CO₃ (0.35 g, 2.5 mmol) and N-(2-oxo-1,2-dihydropyrimidin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (0.80 g, 2.5 mmol) in DMSO (5.1 mL) was added 1,4-

dibromobutane (0.30 mL, 0.64 mmol) and the resulting mixture was stirred at RT for 4 h. The reaction mixture was then filtered, diluted with EtOAc (50 mL) and washed with brine (5x10mL) before concentrating under reduced pressure. The residue was purified via silica gel chromatography (0 - 20% MeOH in DCM) to give the title compound as a colorless oil (249 mg, 22%). MS (ES^+) $C_{17}H_{17}BrF_3N_3O_3$ requires: 447, found: 448 $[M+H]^+$.

Step 3: N-(1-(4-azidobutyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide.

To a solution of N-(1-(4-bromobutyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (0.25 g, 0.56 mmol) in THF (2.2 ml) and water (0.56 ml) was added sodium azide (0.040 g, 0.61 mmol) and the resulting mixture was stirred at 60 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give the title compound as a light yellow solid (0.25 g, >100%). MS (ES^+) $C_{17}H_{17}F_3N_6O_3$ requires: 410, found: 411 $[M+H]^+$.

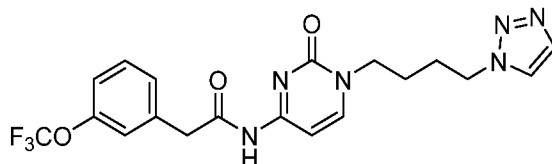
Step 4: 1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyrimidin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid.

[0253] To a mixture of DIEA (98 μ l, 0.56 mmol), AcOH (6.4 μ l, 0.11 mmol), and N-(1-(4-azidobutyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide (230 mg, 0.560 mmol) in DCM (2.2 mL) were added CuI (11 mg, 0.056 mmol) and propiolic acid (44.8 μ l, 0.729 mmol). The resulting mixture was stirred at RT for 15 h. The reaction mixture was concentrated under reduced pressure and the residue purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 20 minutes; Column: C18) to give the title compound as an off-white solid (62 mg, 23%). MS (ES^+) $C_{20}H_{19}F_3N_6O_5$ requires: 480, found: 481 $[M+H]^+$.

Step 5: N-benzyl-1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyrimidin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxamide.

To a suspension of 1-(4-(2-oxo-4-(2-(3-(trifluoromethoxy)phenyl)acetamido)pyrimidin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid (20 mg, 0.042 mmol) and phenylmethanamine (5.5 μ l, 0.050 mmol) in DMF (208 μ l) was added T3P (26 mg, 0.042 mmol, 50% wt. solution) and the resulting mixture was heated at 60 °C for 3 h. The mixture was concentrated under reduced pressure and the residue was purified by mass-triggered

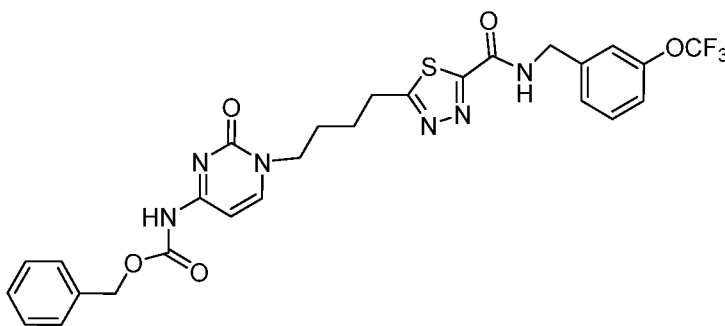
preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 20 minutes; Column: C18) to give the title compound as a white solid (3.1 mg, 13%). MS (ES⁺) C₂₇H₂₆F₃N₇O₄ requires: 569, found: 570 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.06 (s, 1H), 9.03 (m, 1H), 8.57 (s, 1H), 8.06 (d, *J* = 7.2 Hz, 1H), 7.46 (m, 1H), 7.34 – 7.29 (m, 6H), 7.27 – 7.20 (m, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 4.47 – 4.39 (m, 4H), 3.86 – 3.75 (m, 4H), 1.87 – 1.77 (m, 2H), 1.65 – 1.52 (m, 2H).



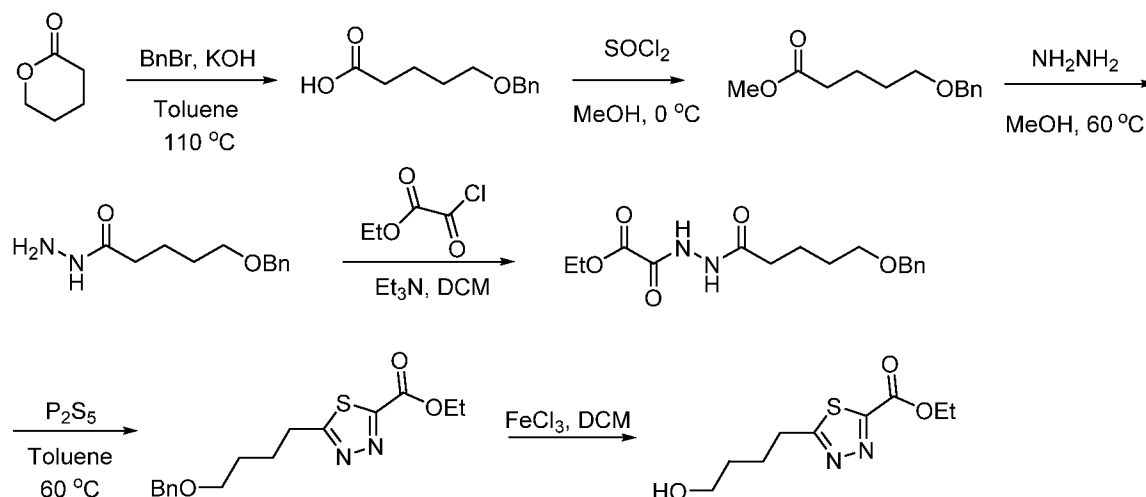
N-(1-(4-(1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)-2-(3-(trifluoromethoxy)phenyl)acetamide.

[0254] The title compound was also isolated from the above reaction as an off-white solid (3 mg, 17%). MS (ES⁺) C₁₉H₁₉F₃N₆O₃ requires: 436, found: 437 [M+H]⁺; ¹H NMR (600 MHz, Methanol-*d*₄) δ 7.99 – 7.95 (m, 2H), 7.71 (d, *J* = 1.0 Hz, 1H), 7.42 (m, 1H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.27 (s, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 4.49 (t, *J* = 7.0 Hz, 2H), 3.93 (t, *J* = 7.2 Hz, 2H), 3.81 (s, 2H), 1.99 – 1.89 (m, 2H), 1.78 – 1.70 (m, 2H).

EXAMPLE 28: Benzyl 2-oxo-1-(4-(5-(3-(trifluoromethoxy)benzylcarbamoyl)-1,3,4-thiadiazol-2-yl)butyl)-1,2-dihydropyrimidin-4-ylcarbamate



Steps 1 to 6



Step 1: 5-(benzyloxy)pentanoic acid.

[0255] To a solution of tetrahydro-2H-pyran-2-one (5.0 g, 50 mmol) in toluene (50 mL) were added KOH (15.8 g, 28.2 mmol) and benzylbromide (17.8 mL, 150 mmol), and the mixture was stirred at 110 °C for 16 h. The solution was cooled to RT and diluted with ice-cold H₂O (70 mL). The organic layer was separated and the aqueous layer was washed with MTBE (3x 30 mL). The aqueous layer was then cooled to 0 °C and the pH was adjusted to 3-4 by addition of concentrated aq. HCl (15 mL) and 6 N aq. HCl (8 mL). The mixture was extracted with EtOAc (4x 50 mL) and the combined organic layers were washed with brine (20 mL), dried (Na₂SO₄) and concentrated under reduced pressure to give the title compound as a light yellow oil (10 g, 96%). MS (ES⁺) C₁₂H₁₆O₃ requires: 208, found: 209[M+H]⁺.

Step 2: methyl 5-(benzyloxy)pentanoate.

[0256] To a solution of 5-(benzyloxy)pentanoic acid (1.0 g, 4.8 mmol) in MeOH (40 mL) at 0 °C was slowly added SOCl₂ (0.39 mL, 5.3 mmol) and the mixture was stirred at RT for 1 h. The mixture was then treated with saturated aq. NaHCO₃ (5 mL), the volatiles were removed under reduced pressure, and the aqueous layer was extracted with DCM (3x 10 mL). The combined organic layers were washed with brine (5 mL), dried (Na₂SO₄) and concentrated under reduced pressure to afford the title compound as a light yellow oil (1.0 g, 94%). MS (ES⁺) C₁₃H₁₈O₃ requires: 222, found: 223[M+H]⁺.

Step 3: 5-(benzyloxy)pentanehydrazide.

[0257] A mixture of methyl 5-(benzyloxy)pentanoate (1.0 g, 4.5 mmol) and NH_2NH_2 (35% wt. solution in H_2O , 1.3 mL, 13 mmol) in MeOH (15 mL) was heated at reflux in a pressure safe vial for 18 h. The mixture was cooled to RT and the volatiles were removed under reduced pressure. The residue was taken up in toluene (2 x 5 mL), concentrated again, and the resulting solid was triturated with hexane (2 x 5 mL) and filtered to give the title compound as a white solid (840 mg, 84%). MS (ES^+) $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}_2$ requires: 222, found: 223 $[\text{M}+\text{H}]^+$.

Step 4: ethyl 2-(2-(5-(benzyloxy)pentanoyl)hydrazinyl)-2-oxoacetate.

[0258] To a solution of 5-(benzyloxy)pentanehydrazide (500 mg, 2.25 mmol) and TEA (0.63 mL, 4.5 mmol) in DCM (5.0 mL) at 0 °C was added ethyl 2-chloro-2-oxoacetate (0.45 mL, 4.0 mmol), and the resulting mixture was stirred at RT for 30 minutes. The volatiles were removed under reduced pressure to give the title compound as a white solid (800 mg, 100%). MS (ES^+) $\text{C}_{16}\text{H}_{22}\text{N}_2\text{O}_5$ requires: 322, found: 323 $[\text{M}+\text{H}]^+$.

Step 5: ethyl 5-(4-(benzyloxy)butyl)-1,3,4-thiadiazole-2-carboxylate.

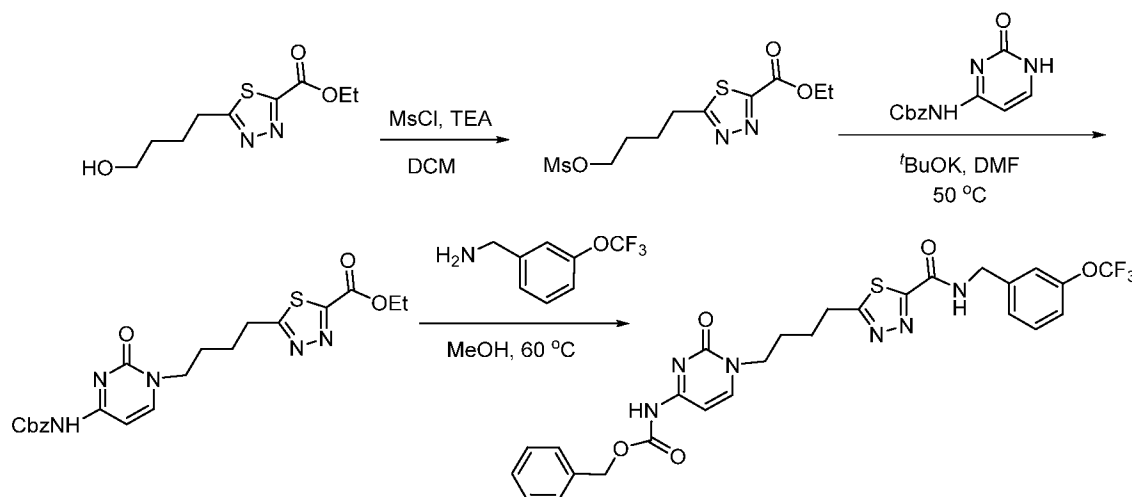
[0259] To a mixture of ethyl 2-(2-(5-(benzyloxy)pentanoyl)hydrazinyl)-2-oxoacetate (400 mg, 2.3 mmol) in toluene (5 mL) at 60 °C was added P_2S_5 (500 mg, 2.3 mmol). The reaction mixture was stirred at 60 °C for 15 minutes, cooled to RT, and partitioned between saturated aq. NaHCO_3 (30 mL) and EtOAc (50 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by SiO_2 gel chromatography (5 - 20% EtOAc in hexanes) to give the title compound as a yellow oil (1.3 g, 48%). MS (ES^+) $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ requires: 320, found: 321 $[\text{M}+\text{H}]^+$.

Step 6: ethyl 5-(4-hydroxybutyl)-1,3,4-thiadiazole-2-carboxylate.

[0260] To a solution of ethyl 5-(4-(benzyloxy)butyl)-1,3,4-thiadiazole-2-carboxylate (1.0 g, 3.1 mmol) in DCM (30 mL) was added anhydrous FeCl_3 (2.0 g, 12 mmol) portionwise. The reaction mixture was stirred at RT for 25 minutes, a further aliquot of anhydrous FeCl_3 (1.0 g, 6.3 mmol) was added, and the mixture was stirred for an additional 10 minutes. The mixture was then treated with saturated aq. NH_4Cl (10 mL), the layers were separated, and the aqueous phase was extracted with DCM /MeOH = 10/1 v/v (3x 50 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by SiO_2 gel chromatography (0 - 2% MeOH in

DCM) to give the title compound as a brown oil (730 mg, 100%). MS (ES^+) $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ requires: 230, found: 231 $[\text{M}+\text{H}]^+$.

Steps 7 to 9



Step 7: ethyl 5-(4-(methylsulfonyloxy)butyl)-1,3,4-thiadiazole-2-carboxylate.

[0261] To a mixture of ethyl 5-(4-hydroxybutyl)-1,3,4-thiadiazole-2-carboxylate (100 mg, 0.43 mmol) and TEA (131 mg, 1.30 mmol) in DCM (1.5 mL) at 0 °C was added dropwise MsCl (75 mg, 0.65 mmol) as a solution in DCM (0.5 mL). The resulting mixture was stirred for 10 minutes at 0 °C and for a further 10 minutes at RT, then washed diluted with DCM (5 mL) and washed with brine (3 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure to give the title compound as a brown oil (130 mg, 97%). MS (ES^+) $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_5\text{S}_2$ requires: 308, found: 309 $[\text{M}+\text{H}]^+$.

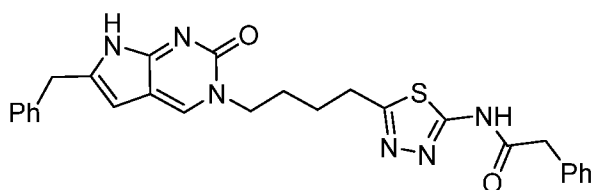
Step 8: ethyl 5-(4-(4-(benzyloxycarbonylamino)-2-oxopyrimidin-1(2H)-yl)butyl)-1,3,4-thiadiazole-2-carboxylate.

[0262] A mixture of ethyl 5-(4-(methylsulfonyloxy)butyl)-1,3,4-thiadiazole-2-carboxylate (640 mg, 2.08 mmol), benzyl 2-oxo-1,2-dihydropyrimidin-4-ylcarbamate (764 mg, 3.11 mmol) and *t*-BuOK (349 mg, 3.11 mmol) in DMF (8.0 mL) was stirred at 50 °C for 2 h. The mixture was filtered, and the filtrate was purified by preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 min; Column: C18) to give the title compound as a white solid (155 mg, 27%). MS (ES^+) $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_5\text{S}$ requires: 457, found: 458 $[\text{M}+\text{H}]^+$.

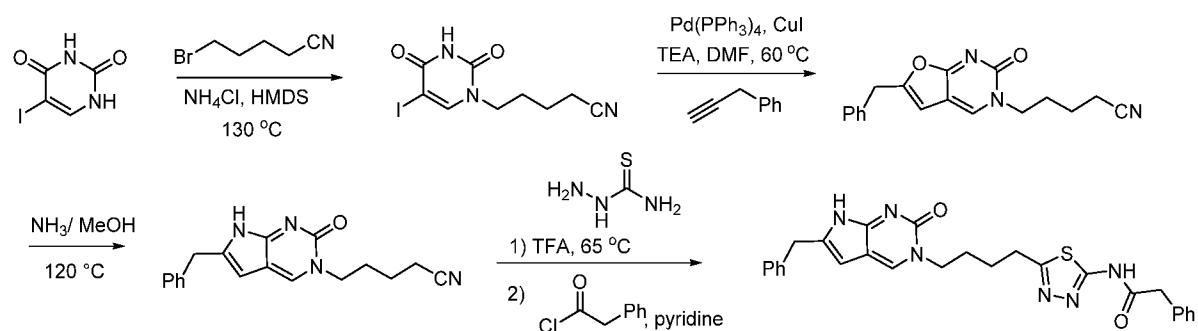
Step 9: benzyl 2-oxo-1-(4-(5-(3-(trifluoromethoxy)benzylcarbamoyl)-1,3,4-thiadiazol-2-yl)butyl)-1,2-dihydropyrimidin-4-ylcarbamate.

[0263] A mixture of ethyl 5-(4-(4-(benzyloxycarbonylamino)-2-oxopyrimidin-1(2H)-yl)butyl)-1,3,4-thiadiazole-2-carboxylate (30 mg, 0.060 mmol) and (3-(trifluoromethoxy)phenyl)methanamine (75 mg, 0.40 mmol) in MeOH (0.5 mL) was stirred at 60 °C in a sealed vial for 5 h. The mixture was then cooled to RT, the volatiles were removed under reduced pressure, and the residue was purified by preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 min; Column: C18) to give the title compound as a white solid (6.8 mg, 17%). MS (ES⁺) C₂₇H₂₅F₃N₆O₅S requires: 602, found: 603 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.75 (bs, 1H), 9.85 (t, *J* = 6.2 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 7.48 (m, 1H), 7.48-7.20 (m, 8H), 6.98 (d, *J* = 7.6 Hz, 1H), 5.18 (s, 2H), 4.51 (d, *J* = 6.0 Hz, 2H), 3.86 - 3.80 (m, 2H), 3.25 - 3.15 (m, 2H), 1.78 - 1.70 (m, 4H).

EXAMPLE 29: N-(5-(4-(6-benzyl-2-oxo-2,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-3-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-phenylacetamide



Steps 1 to 4



Step 1: 5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)pentanenitrile.

[0264] A mixture of NH₄Cl (0.45 g, 4.40 mmol), HMDS (17.9 ml, 84.0 mmol), and 5-iodopyrimidine-2,4(1H,3H)-dione (2.0 g, 8.4 mmol) was heated at 130 °C for 4 h. The resulting clear solution was cooled to RT and concentrated under reduced pressure. 5-

Bromopentanenitrile (0.98 mL, 8.4 mmol) was then added and the mixture was heated at 130 °C for 2 h. The reaction mixture was cooled to RT, diluted with EtOAc (20 mL) and *i*-PrOH (10 mL), stirred for 10 minutes at RT and filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure and purified via SiO₂ gel chromatography (0 -10% MeOH in DCM) to give the title compound as a light yellow solid (2.02 g, 75%). MS (ES⁺) C₉H₁₀IN₃O₂ requires: 319, found: 320 [M+H]⁺.

Step 2: 5-(6-benzyl-2-oxofuro[2,3-d]pyrimidin-3(2H)-yl)pentanenitrile.

[0265] A mixture of Pd(PPh₃)₄ (0.362 g, 0.313 mmol), triethylamine (5.0 mL, 36 mmol), CuI (1.19 g, 6.27 mmol), prop-2-yn-1-ylbenzene (1.01 mL, 8.15 mmol), and 5-(5-iodo-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)pentanenitrile (2.0 g, 6.3 mmol) in DMF (100 mL) was degassed with a stream of N₂ for 10 minutes. The reaction mixture was heated to 70 °C and stirred for 6 h, then cooled to RT and concentrated under reduced pressure. The residue was purified via silica gel chromatography (0 - 15% MeOH in DCM) to give a brown oil (1.25 g). The residue was further purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 minutes; Column: C18) to give the title compound as a brown solid (170 mg, 9%). MS (ES⁺) C₁₈H₁₇N₃O₂ requires: 307, found: 308 [M+H]⁺.

Step 3: 5-(6-benzyl-2-oxo-2,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-3-yl)pentanenitrile.

[0266] Ammonia in MeOH (7N, 7.7 mL, 54 mmol) was added to 5-(6-benzyl-2-oxofuro[2,3-d]pyrimidin-3(2H)-yl)pentanenitrile (165 mg, 0.537 mmol) and the resulting solution was heated at 120 °C for 4 h in a pressure safe vial. The reaction mixture was concentrated under reduced pressure and the residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 20 - 50%; 16 minutes; Column: C18) to give the title compound as a brown thick oil (72 mg, 44%). MS (ES⁺) C₁₈H₁₈N₄O requires: 306, found: 307 [M+H]⁺.

Step 4: 3-(4-(5-amino-1,3,4-thiadiazol-2-yl)butyl)-6-benzyl-3,7-dihydro-2H-pyrrolo[2,3-d]pyrimidin-2-one.

[0267] A mixture of TFA (0.063 mL, 0.082 mmol), hydrazinecarbothioamide (8.2 mg, 0.090 mmol) and 5-(6-benzyl-2-oxo-2,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-3-yl)pentanenitrile (25 mg, 0.082 mmol) was heated at 60 °C for 2 h. The reaction was

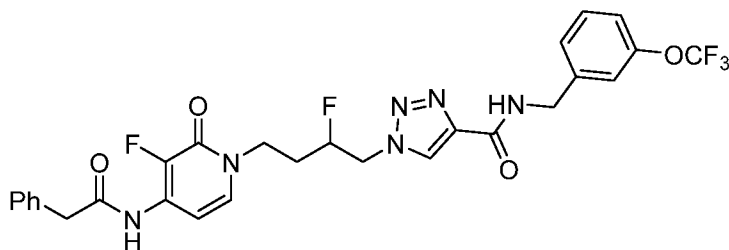
concentrated under reduced pressure and the residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 20 - 50%; 12 minutes; Column: C18) to give the title compound as a pale yellow solid (38 mg, 94%). MS (ES⁺) C₁₉H₂₀N₆O₂S requires: 380, found: 381 [M+H]⁺.

Step 5: N-(5-(4-(6-benzyl-2-oxo-2,7-dihydro-3H-pyrrolo[2,3-d]pyrimidin-3-yl)butyl)-1,3,4-thiadiazol-2-yl)-2-phenylacetamide.

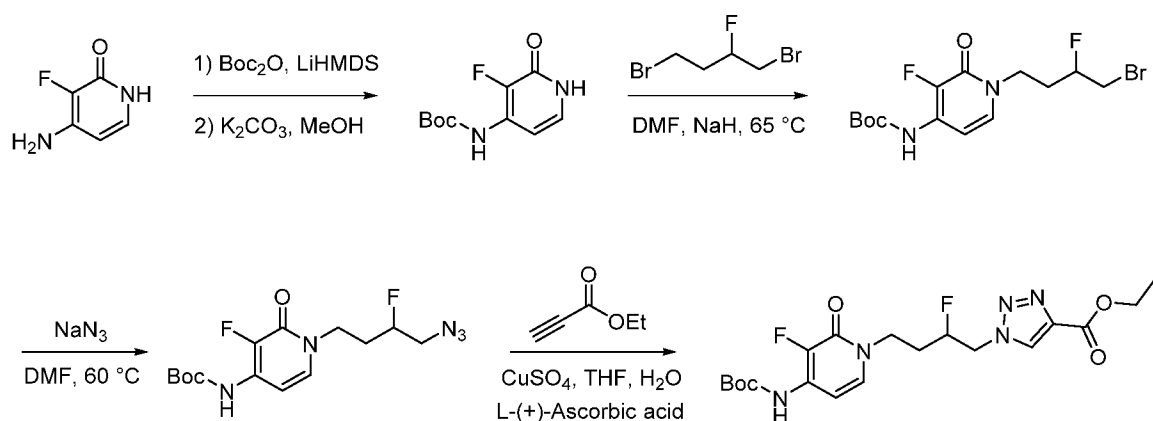
[0268] To a mixture of pyridine (14.0 μ l, 0.173 mmol) and 3-(4-(5-amino-1,3,4-thiadiazol-2-yl)butyl)-6-benzyl-3,7-dihydro-2H-pyrrolo[2,3-d]pyrimidin-2-one (33 mg, 0.087 mmol) in DMF (434 μ l) was added 2-phenylacetyl chloride (16 μ l, 0.13 mmol). The resulting mixture was stirred at RT for 12 h and concentrated under reduced pressure. The residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 minutes; Column: C18) to give the title compound as an off-white solid after neutralizing residual TFA with Agilent StratoSpheres PL-HCO₃ MP resin (3 mg, 7%). MS (ES⁺) C₂₇H₂₆N₆O₂S requires: 498, found: 499 [M+H]⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 12.67 (s, 1H), 11.17 (s, 1H), 8.28 (s, 1H), 7.35 – 7.21 (m, 10H), 5.83 (s, 1H), 3.90 (t, *J* = 6.8 Hz, 2H), 3.86 (s, 2H), 3.78 (s, 2H), 2.97 (t, *J* = 7.2 Hz, 2H), 1.74 – 1.61 (m, 4H).

[0269] Additional non-limiting examples include the following compounds and pharmaceutically acceptable salts thereof.

EXAMPLE 180: 1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



Steps 1 to 4



Step 1: tert-butyl (3-fluoro-2-oxo-1,2-dihydropyridin-4-yl)carbamate.

[0270] To a suspension of 4-amino-3-fluoropyridin-2(1H)-one (4.43 g, 34.6 mmol, prepared according to J. Med. Chem. 1987, 30, 340-347) and di-tert-butyl dicarbonate (16.6 g, 76 mmol) in THF (50 mL) was added LiHMDS in THF (76 mL, 76 mmol, 1.0 M) and the resulting mixture was stirred at 50 °C for 4 h. The reaction was concentrated, diluted with DCM (100 mL), and washed with ice-cold 1 M HCl (100 mL). The organic layer was concentrated to give a yellow oil (11.1 g, 99%). The crude oil was diluted with MeOH (60 mL) and K₂CO₃ (5.13 g, 37.1 mmol) was added. The resulting mixture was stirred at 50 °C for 45 min and then allowed to warm to RT overnight. The reaction was filtered and the filtrate was adsorbed on Celite® and purified via silica gel chromatography (0 - 30 % MeOH in DCM) to give the title compound as a yellow solid (5.92 g, 77%). MS (ES⁺) C₁₀H₁₃FN₂O₃ requires: 228, found: 229 [M+H]⁺.

Step 2: tert-butyl 1-(4-bromo-3-fluorobutyl)-3-fluoro-2-oxo-1,2-dihydropyridin-4-ylcarbamate.

[0271] NaH (5.26 g, 131 mmol) was added to a solution of ethyl tert-butyl 3-fluoro-2-oxo-1,2-dihydropyridin-4-ylcarbamate (20.0 g, 87.7 mmol) in DMF (400 mL) at RT and stirred for 1 h, then 1,4-dibromo-2-fluorobutane (30.5 g, 131 mmol) was added. The mixture was stirred for 15 h at RT. The reaction solution was poured into water (2000 mL), extracted with EtOAc (500 mL x 3), and the combined organics were washed with water (500 mL). The volatiles were concentrated and the residue purified via silica gel chromatography (Pet. Ether:EtOAc = from 10:1 to 1:2, v/v) to give the title compound as a solid (16.8 g, 50%). MS (ES⁺) C₁₄H₁₉BrF₂N₂O₃ requires: 380, found: 381 [M+H]⁺.

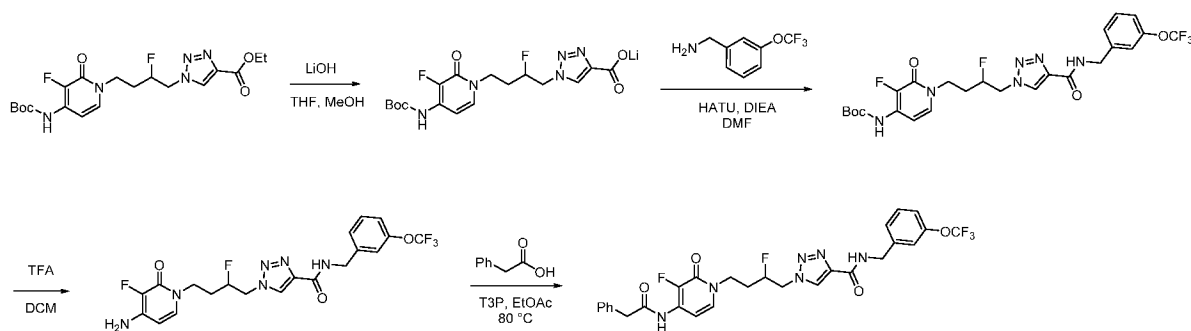
Step 3: tert-butyl 1-(4-azido-3-fluorobutyl)-3-fluoro-2-oxo-1,2-dihydropyridin-4-ylcarbamate.

[0272] NaN₃ (1.10 g, 19.7 mmol) was added to a solution of tert-butyl 1-(4-bromo-3-fluorobutyl)-3-fluoro-2-oxo-1,2-dihydropyridin-4-ylcarbamate (5.0 g, 13.1 mmol) in DMF (100 mL) and heated at 60-65 °C for 15 h. The mixture was cooled to RT, poured into water (800 mL), and extracted with EtOAc (100 mL x 3). The combined organics were washed with water (100 mL x 2) and brine (100 mL), dried over Na₂SO₄, and concentrated to give the title compound as an oil (4.2 g, 93%). MS (ES⁺) C₁₄H₁₉F₂N₅O₃ requires: 343, found: 344 [M+H]⁺.

Step 4: ethyl 1-(4-(4-(tert-butoxycarbonylamino)-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate.

[0273] Tert-butyl 1-(4-azido-3-fluorobutyl)-3-fluoro-2-oxo-1,2-dihydropyridin-4-ylcarbamate (20 g, 58 mmol), CuSO₄·5H₂O (4.0 g, 16 mmol), L(+)-ascorbic acid (8.0 g, 45 mmol) and water (300 mL) were added to t-BuOH (300 mL). The reaction mixture was stirred for 5 min, then ethyl propiolate (6.85 g, 69.9 mmol) was added at RT. The mixture was stirred for 15 h at RT. The reaction mixture was concentrated in vacuo at 40-50°C, the residue was diluted with water (1000 mL) and extracted with EtOAc (200 mL x 3). The combined organics were washed with water (300 mL x 2), dried over Na₂SO₄, and concentrated in vacuo. The residue was purified via silica gel chromatography (Pet. Ether:EtOAc = from 1:1 to 1:2, v/v) to give the title compound as a white solid (18.5 g, 72%). MS (ES⁺) C₁₉H₂₅F₂N₅O₅ requires: 441, found: 442 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.48 (s, 1H), 8.76 (s, 1H), 7.45 (dd, *J* = 7.8, 1.5 Hz, 1H), 6.87 (dd, *J* = 7.7, 6.5 Hz, 1H), 5.06 – 4.90 (m, 1H), 4.84 – 4.66 (m, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 4.11 – 3.94 (m, 2H), 2.15 – 1.82 (m, 2H), 1.47 (s, 9H), 1.30 (t, *J* = 7.1 Hz, 3H). The regioisomer ethyl 1-(4-(4-((tert-butoxycarbonyl)amino)-3-fluoro-2-oxopyridin-1(2H)-yl)-3-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate was also isolated as a minor side product (435 mg, 2%). MS (ES⁺) C₁₉H₂₅F₂N₅O₅ requires: 441, found: 442 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 9.47 (s, 1H), 8.92 (s, 1H), 7.32 (dd, *J* = 7.8, 1.6 Hz, 1H), 6.84 (dd, *J* = 7.7, 6.4 Hz, 1H), 5.03 (ddt, *J* = 15.7, 10.6, 5.2 Hz, 1H), 4.87 – 4.71 (m, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.90 – 3.75 (m, 2H), 2.41 – 2.23 (m, 2H), 1.46 (s, 9H), 1.32 (t, *J* = 7.1 Hz, 3H).

Steps 5 to 8



Step 5: lithium 1-(4-(4-((tert-butoxycarbonyl)amino)-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate.

[0274] To a suspension of ethyl 1-(4-(4-((tert-butoxycarbonyl)amino)-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate (1.0 g, 2.26 mmol) in THF (9.1 mL) and MeOH (2.3 mL) was added aqueous LiOH (1.25 mL, 2.49 mmol, 2.0 M) and the resulting mixture was stirred at RT for 2 h. The reaction was concentrated to give the title compound as a green amorphous material (0.896 g, 100%, Li salt). MS (ES^+) $C_{17}H_{21}F_2N_5O_5$ requires: 413, found: 414 $[M+H]^+$.

Step 6: tert-butyl (3-fluoro-1-(3-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)carbamate.

[0275] To a suspension of 1-(4-(4-((tert-butoxycarbonyl)amino)-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylic acid (0.896 g, 2.17 mmol), (3-(trifluoromethoxy)phenyl)methanamine (0.456 g, 2.38 mmol) and HATU (0.989 g, 2.60 mmol) in DMF (10.8 mL) at 0 °C was added DIEA (0.757 mL, 4.34 mmol) and the resulting mixture was stirred at RT for 2 h. The volatiles were removed under reduced pressure. The residue was purified via silica gel chromatography (0 - 15 % MeOH in DCM with 1% NH_4OH) to give the title compound as an off-white solid (1.8 g, >100%, 70% purity). MS (ES^+) $C_{25}H_{27}F_5N_6O_5$ requires: 586, found: 587 $[M+H]^+$.

Step 7: 1-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

[0276] To a suspension of tert-butyl (3-fluoro-1-(3-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)carbamate (1.27 g, 2.16 mmol) in DCM (10.8 mL) was added trifluoroacetic acid (3.34 mL, 43.3 mmol) and the resulting mixture was stirred at RT for 4 h. The reaction was concentrated

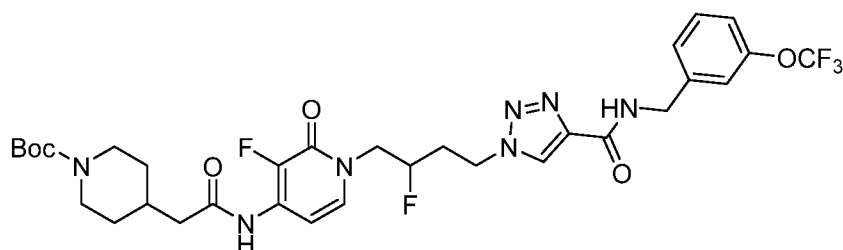
and the residue was purified via silica gel chromatography (0 - 15 % MeOH in DCM with 1% NH₄OH) to give the title compound as an off-white solid (880 mg, 84%). MS (ES⁺)

C₂₀H₁₉F₅N₆O₃ requires: 486, found: 487 [M+H]⁺.

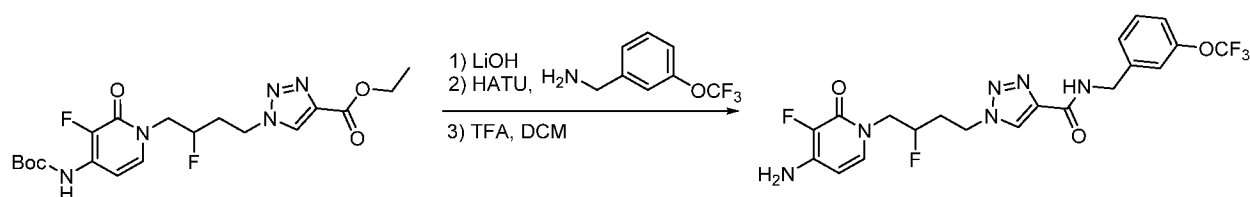
Step 8: 1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

[0277] To a suspension of 1-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (50 mg, 0.10 mmol) and 2-phenylacetic acid (28.0 mg, 0.206 mmol) was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (327 mg, 0.514 mmol, 50 wt.% in EtOAc) and the resulting mixture was stirred at 80 °C for 2 h. The reaction was concentrated briefly and purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 min; Column: C18) to give the title compound as a white solid (20 mg, 32%). MS (ES⁺) C₂₈H₂₅F₅N₆O₄ requires: 604, found: 605 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.21 (s, 1H), 9.20 (t, *J* = 6.4 Hz, 1H), 8.56 (s, 1H), 7.49 – 7.37 (m, 2H), 7.36 – 7.17 (m, 8H), 7.05 (dd, *J* = 7.7, 6.3 Hz, 1H), 4.99 (dddt, *J* = 49.6, 9.9, 6.7, 3.0 Hz, 1H), 4.84 – 4.66 (m, 2H), 4.48 (d, *J* = 6.2 Hz, 2H), 4.15 – 3.95 (m, 2H), 3.78 (s, 2H), 2.16 – 1.87 (m, 2H).

EXAMPLE 365: tert-butyl 4-(2-((3-fluoro-1-(2-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)amino)-2-oxoethyl)piperidine-1-carboxylate

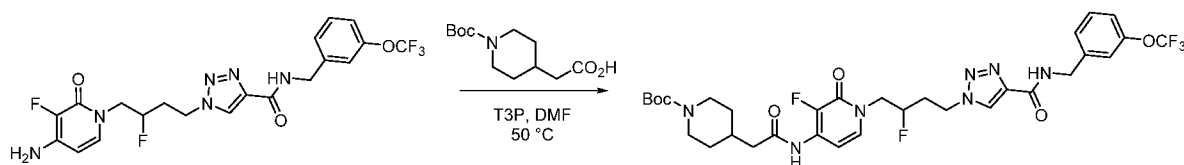


Steps 1 to 3



Steps 1 to 3: 1-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)-3-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

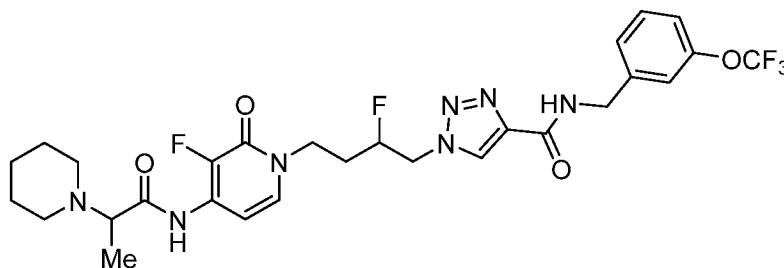
[0278] Using steps 5 to 7 of EXAMPLE 180, the title compound was obtained as a tan solid (98 mg, 20% overall). MS (ES⁺) C₂₀H₁₉F₅N₆O₃ requires: 486, found: 487 [M+H]⁺.

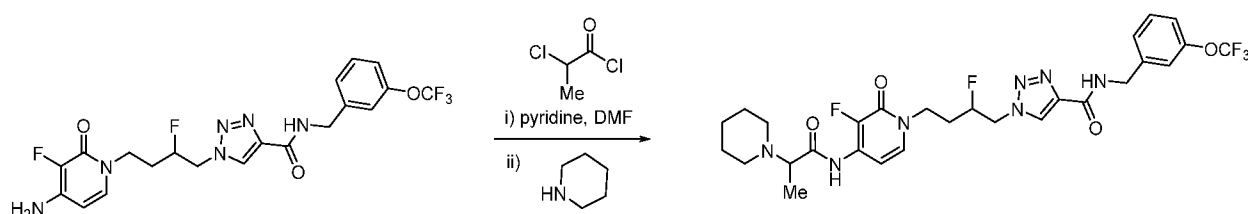


Step 4: tert-butyl 4-(2-((3-fluoro-1-(2-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)amino)-2-oxoethyl)piperidine-1-carboxylate.

[0279] To a solution of 1-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)-3-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (20 mg, 0.041 mmol), pyridine (16.56 μ l, 0.206 mmol), and T3P® in DMF (122 μ l, 0.206 mmol, 50% wt) in DMF (411 μ l) was added 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid (20 mg, 0.082 mmol) and the resulting mixture was stirred at 50 °C overnight. The reaction mixture was concentrated and the residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 min; Column: C18) to give the title compound as a white solid (2.2 mg, 7.5%). MS (ES⁺) C₃₂H₃₈F₅N₇O₆ requires: 711, found: 612 [M-Boc+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.73 (s, 1H), 9.69 (s, 1H), 9.21 (t, *J* = 6.3 Hz, 1H), 8.56 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 0H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 0H), 6.97 (t, *J* = 6.5 Hz, 1H), 5.09 – 4.87 (m, 1H), 4.85 – 4.68 (m, 2H), 4.48 (d, *J* = 6.2 Hz, 2H), 4.27 – 4.20 (m, 1H), 4.17 – 4.11 (m, 1H), 4.09 – 4.03 (m, 1H), 3.55 (d, *J* = 13.0 Hz, 1H), 3.36 (d, *J* = 9.7 Hz, 1H), 3.09 – 2.91 (m, 2H), 2.18 – 2.02 (m, 1H), 2.01 – 1.88 (m, 1H), 1.86 – 1.74 (m, 3H), 1.73 – 1.61 (m, 2H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.47 – 1.39 (m, 1H).

EXAMPLE 337: 1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-(piperidin-1-yl)propanamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide

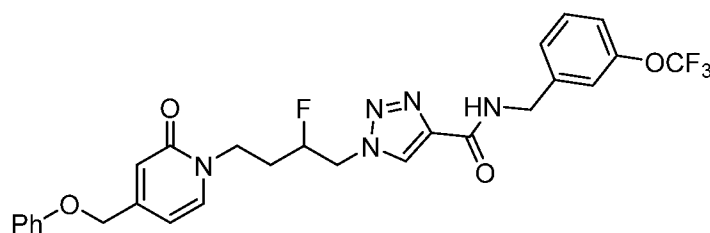




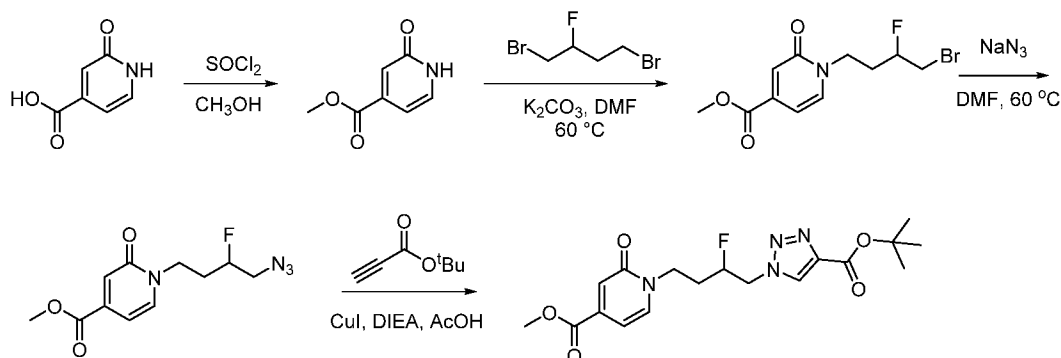
Step 1: 1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-(piperidin-1-yl)propanamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

[0280] To a solution of 1-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (30 mg, 0.062 mmol) and pyridine (15 μ l, 0.18 mmol) in DMF (308 μ l) at 0 $^{\circ}$ C was added 2-chloropropanoyl chloride (15 mg, 0.12 mmol). The resulting mixture was stirred at RT for 1 h. The reaction was cooled to 0 $^{\circ}$ C and piperidine (61 μ l, 0.62 mmol) was added before warming to RT and stirring for 12 h. The reaction was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 30 - 70%; 12 min; Column: C18) to give the title compound as a pale yellow solid (35 mg, 91% yield, TFA salt). MS (ES⁺) C₂₈H₃₂F₅N₇O₄ requires: 625 found: 626 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.73 (s, 1H), 9.69 (s, 1H), 9.21 (t, *J* = 6.3 Hz, 1H), 8.56 (s, 1H), 7.56 (d, *J* = 7.7 Hz, 0H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 1H), 7.23 (d, *J* = 8.0 Hz, 0H), 6.97 (t, *J* = 6.5 Hz, 1H), 5.09 – 4.87 (m, 1H), 4.85 – 4.68 (m, 2H), 4.48 (d, *J* = 6.2 Hz, 2H), 4.27 – 4.20 (m, 1H), 4.17 – 4.11 (m, 1H), 4.09 – 4.03 (m, 1H), 3.55 (d, *J* = 13.0 Hz, 1H), 3.36 (d, *J* = 9.7 Hz, 1H), 3.09 – 2.91 (m, 2H), 2.18 – 2.02 (m, 1H), 2.01 – 1.88 (m, 1H), 1.86 – 1.74 (m, 3H), 1.73 – 1.61 (m, 2H), 1.53 (d, *J* = 6.8 Hz, 3H), 1.47 – 1.39 (m, 1H).

EXAMPLE 414: 1-(2-fluoro-4-(2-oxo-4-(phenoxyethyl)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



Steps 1 to 5



Step 1: 1, 4-dibromo-2-fluorobutane.

[0281] To a solution of 1, 4-dibromobutan-2-ol (15 g, 65.5 mmol) in DCM (100 mL) at 0 °C was added DAST (20 mL, 131 mmol). The reaction mixture was stirred at 0 °C for 10 min, then at RT for 12 h. The reaction was quenched with sat. NaHCO₃ (30 mL) and extracted with the EtOAc (3 x 50 mL). The combined organics were dried over Na₂SO₄ and concentrated to gave the title compound as an orange oil (14.7 g, 98%). ¹F NMR (500 MHz, MeOH-*d*₄) δ 192.3.

Step 2: methyl 2-oxo-1,2-dihydropyridine-4-carboxylate.

[0282] To a solution of 2-oxo-1,2-dihydropyridine-4-carboxylic acid (10 g, 72 mmol) in CH₃OH (100 mL) was added SOCl₂ (21 mL, 180 mmol) slowly at 0 °C. The reaction mixture was stirred at 0 °C for 10 min, then at 65 °C for 12 h. The reaction mixture was concentrated, then washed with water (30 mL), and the solid filtered to give the title compound as an orange solid (9.0 g, 78%). MS (ES⁺) C₇H₇NO₃ requires: 153 found: 154 [M+H]⁺.

Step 3: methyl 1-(4-bromo-3-fluorobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate.

[0283] A mixture of methyl 2-oxo-1,2-dihydropyridine-4-carboxylate (8.0 g, 52 mmol), 1,4-dibromo-2-fluorobutane (24 g, 104 mmol), and K₂CO₃ (14 g, 104 mmol) in DMF (30 mL) was stirred at 60 °C for 12 h. The mixture was filtered and poured into water (100 mL), extracted with EtOAc (3 x 50 mL), washed with brine (3 x 50 mL), and dried over Na₂SO₄. Concentration gave the title compound as an orange solid (9.1 g, 50%). MS (ES⁺) C₁₁H₁₃BrFNO₃ requires: 305 found: 306 [M+H]⁺.

Step 4: methyl 1-(4-azido-3-fluorobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate.

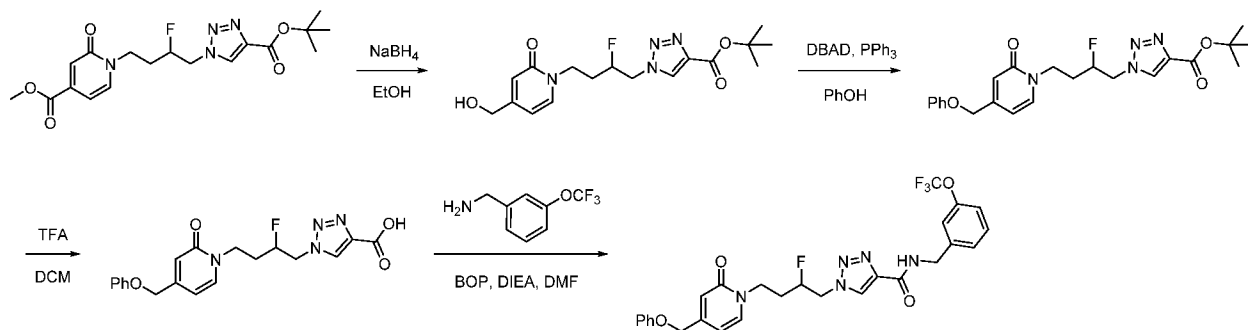
[0284] A mixture of methyl 1-(4-bromo-3-fluorobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (9.0 g, 29.5 mmol) and NaN₃ (3.8 g, 59 mmol) in DMF (40 mL) was stirred at 60 °C

for 12 h. The mixture was filtered off and poured into water (100 mL), extracted with EtOAc (3 x 50 mL), washed with brine (3 x 50 mL), then dried by Na₂SO₄, filtered off and concentrated to give the title compound as an orange solid (7.9 g, 98%). MS (ES⁺) C₁₁H₁₃FN₄O₃ requires: 268 found: 269 [M+H]⁺.

Step 5: methyl 1-(4-(4-(tert-butoxycarbonyl)-1H-1,2,3-triazol-1-yl)-3-fluorobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate.

[0285] A mixture of methyl 1-(4-azido-3-fluorobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (7.9 g, 29 mmol), tert-butyl propiolate (7.5 g, 59.7 mmol), CuSO₄ (1.6 g, 10 mmol) and L-sodium ascorbate (3.2 mg, 16 mmol) in t-BuOH (20 mL) and water (20 mL) was stirred at RT for 1 h. The mixture was filtered off and poured into water, extracted with EtOAc (3 x 50 mL), dried over Na₂SO₄, and concentrated. The resulting residue was purified via the silica gel chromatography to give the title compound as a white solid (9 g, 85%). MS (ES⁺) C₁₈H₂₃FN₄O₅ requires: 394, found: 395 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 7.79 (s, 1H), 6.87 (s, 1H), 6.57 (s, 1H), 5.65-4.93 (m, 1H), 4.82-4.73 (m, 2H), 4.13-4.02 (m, 2H), 3.85 (s, 3H), 1.67 (s, 2H), 1.53 (s, 9H).

Steps 6 to 9



Step 6: tert-butyl 1-(2-fluoro-4-(4-(hydroxymethyl)-2-oxopyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate.

[0286] To a suspension of methyl 1-(4-(4-(tert-butoxycarbonyl)-1H-1,2,3-triazol-1-yl)-3-fluorobutyl)-2-oxo-1,2-dihydropyridine-4-carboxylate (1.0 g, 2.5 mmol) in EtOH (12.7 mL) was added sodium borohydride (0.288 g, 7.61 mmol) and the resulting mixture was stirred at RT for 24 h. At that time an additional amount of NaBH₄ was added (0.288 g) and allowed to stir at RT for another 24 h. The reaction mixture was concentrated. The residue was adsorbed onto Celite® and purified via silica gel chromatography (0 - 15 % MeOH in DCM with 1% NH₄OH) to give

the title compound as a colorless amorphous material (710 mg, 76%). MS (ES^+) $\text{C}_{17}\text{H}_{23}\text{FN}_4\text{O}_4$ requires: 366 found: 367 $[\text{M}+\text{H}]^+$.

Step 7: tert-butyl 1-(2-fluoro-4-(2-oxo-4-(phenoxymethyl)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate.

[0287] To a solution of phenol (19.3 mg, 0.205 mmol), tert-butyl 1-(2-fluoro-4-(4-(hydroxymethyl)-2-oxopyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate (50 mg, 0.14 mmol), and di-tert-butyl hydrazine-1,2-dicarboxylate (63 mg, 0.27 mmol) in THF (682 μL) was added triphenylphosphine (72 mg, 0.27 mmol) and the resulting mixture was stirred at RT for 2 h. The reaction was concentrated. The residue was purified via silica gel chromatography (0 - 10 % MeOH in DCM with 1% NH_4OH) to give the title compound as a colorless amorphous material (117 mg, >100%, ~50% purity). MS (ES^+) $\text{C}_{23}\text{H}_{27}\text{FN}_4\text{O}_4$ requires: 442 found: 443 $[\text{M}+\text{H}]^+$.

Step 8: 1-(2-fluoro-4-(2-oxo-4-(phenoxymethyl)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid.

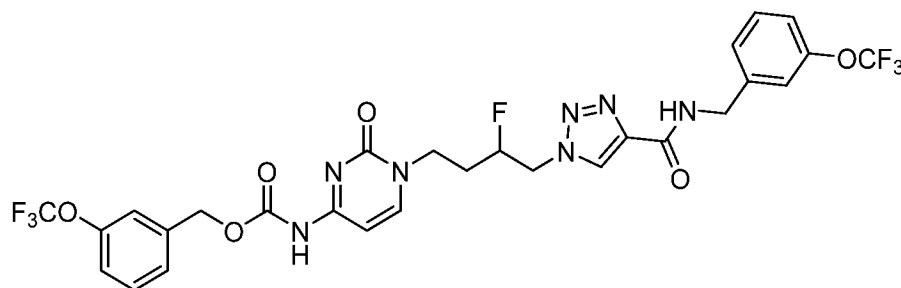
[0288] A reaction vessel was charged with tert-butyl 1-(2-fluoro-4-(2-oxo-4-(phenoxymethyl)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylate (117 mg, 0.264 mmol), trifluoroacetic acid (1.0 mL, 13 mmol) and DCM (1 mL) under an atmosphere of N_2 . The resulting solution was allowed to stir at RT for 1 h. The solution was concentrated to give the title compound as an amorphous material (102 mg, 100%). MS (ES^+) $\text{C}_{19}\text{H}_{19}\text{FN}_4\text{O}_4$ requires: 386 found: 387 $[\text{M}+\text{H}]^+$.

Step 9: 1-(2-fluoro-4-(2-oxo-4-(phenoxymethyl)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

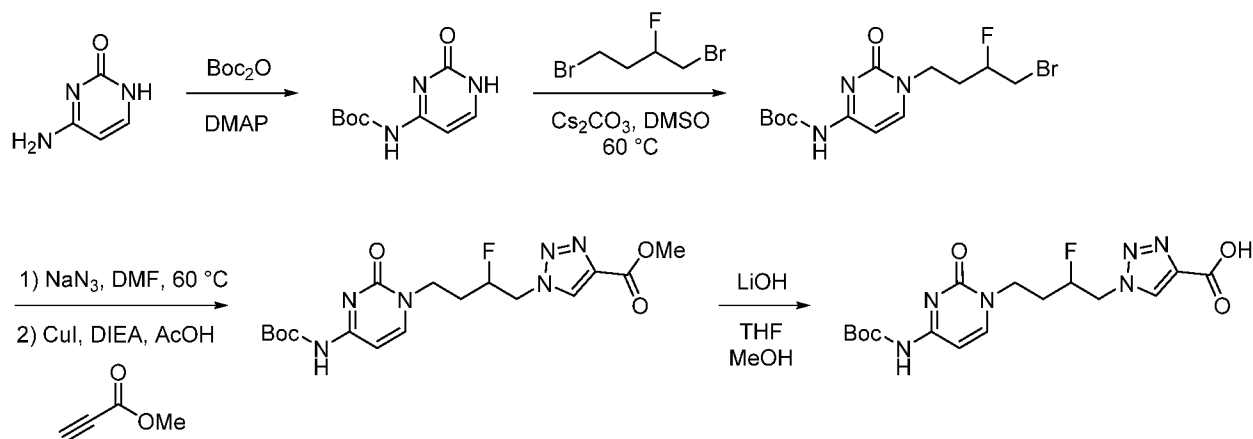
[0289] To a suspension of 1-(2-fluoro-4-(2-oxo-4-(phenoxymethyl)pyridin-1(2H)-yl)butyl)-1H-1,2,3-triazole-4-carboxylic acid (50 mg, 0.13 mmol), (3-(trifluoromethoxy)phenyl)methanamine (27 mg, 0.14 mmol) and BOP (74 mg, 0.17 mmol) in DMF (647 μL) was added DIEA (45 μL , 0.26 mmol) and the resulting mixture was stirred at RT for 1 h. The reaction mixture was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 min; Column: C18) to give the title compound as a white solid (3.2 mg, 3.7%). MS (ES^+) $\text{C}_{27}\text{H}_{25}\text{F}_4\text{N}_5\text{O}_4$ requires: 559, found: 560 $[\text{M}+\text{H}]^+$; ^1H NMR (500 MHz, Methanol- d_4) δ 9.11 (t, J = 6.4 Hz, 1H), 8.41 (d, J = 1.2

Hz, 1H), 7.45 – 7.39 (m, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.31 – 7.23 (m, 3H), 7.16 (d, $J = 8.2$ Hz, 1H), 6.96 (dd, $J = 13.7, 7.5$ Hz, 3H), 6.63 (s, 1H), 6.44 (d, $J = 6.9$ Hz, 1H), 5.01 (s, 2H), 4.85 (s, 1H), 4.66 (t, $J = 7.0$ Hz, 2H), 4.60 (d, $J = 5.5$ Hz, 2H), 4.37 (dd, $J = 29.5, 14.4$ Hz, 1H), 4.17 – 4.03 (m, 1H), 2.44 – 2.19 (m, 2H).

EXAMPLE 491: 3-(trifluoromethoxy)benzyl (1-(3-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate



Steps 1 to 4



Step 1: tert-butyl 2-oxo-1,2-dihydropyrimidin-4-ylcarbamate.

[0290] To a solution of 4-aminopyrimidin-2(1H)-one (10 g, 90 mmol) in DMF (100 mL), DMAP (1.1 g, 9.0 mmol) and Boc_2O (29.5 g, 135 mmol) were added. The resulted mixture was stirred at RT for 15 h. To the mixture was added water (200 mL) and the solid filtered off to obtain the title compound as a white solid (7.0 g, 37%). MS (ES^+) $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_3$ requires: 211, found: 212 $[\text{M}+\text{H}]^+$.

Step 2: tert-butyl 1-(4-bromo-3-fluorobutyl)-2-oxo-1,2-dihydropyrimidin-4-ylcarbamate.

[0291] To a solution of tert-butyl 2-oxo-1,2-dihydropyrimidin-4-ylcarbamate (5 g, 24 mmol) in DMSO (100 mL), 1,4-dibromo-2-fluorobutane (6.65 g, 28.4 mmol) and Cs₂CO₃ (15.4 g, 47.4 mmol) were added. The resulting mixture was stirred at 60 °C for 15 h. The resulted mixture was poured into water (500 mL), extracted with EtOAc (200 mL x 2), concentrated, and purified by silica gel chromatography (DCM : MeOH = 19:1) to give the title compound as a yellow solid (1.5 g, 17%). MS (ES+) C₁₃H₁₉BrFN₃O₃ requires: 363, found: 364 [M+H]⁺.

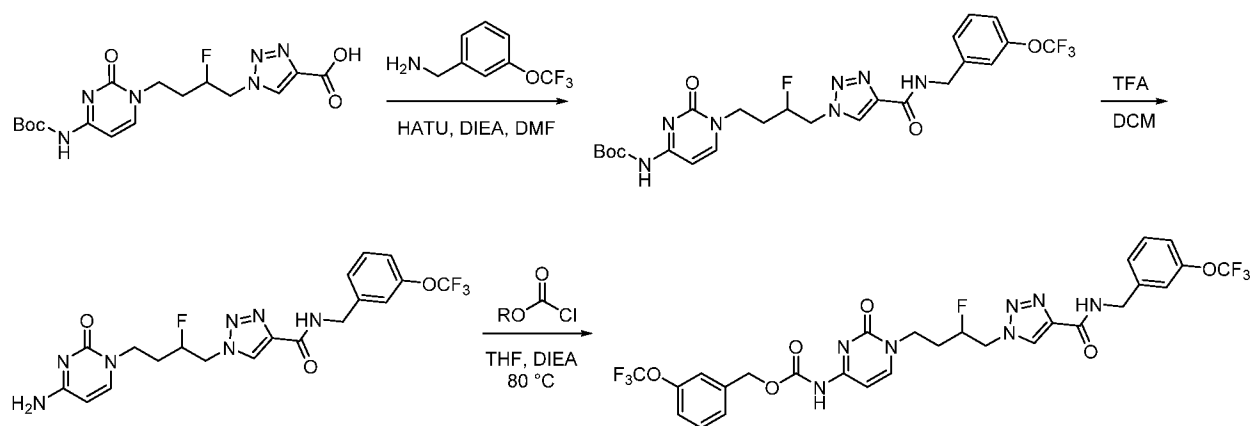
Step 3: tert-butyl 1-(4-azido-3-fluorobutyl)-2-oxo-1,2-dihydropyrimidin-4-ylcarbamate

[0292] To a solution of tert-butyl 1-(4-bromo-3-fluorobutyl)-2-oxo-1,2-dihydropyrimidin-4-ylcarbamate (1.5 g, 4.13 mmol) in DMF (15 mL), NaN₃ (270 mg, 4.13 mmol) was added. The resulting mixture was stirred at 60 °C overnight. The resulting mixture was cooled to RT, and DCM (20 mL), methyl propiolate (347 mg, 4.13 mmol), AcOH (51 mg, 0.83 mmol), DIEA (51 mg, 0.83 mmol) and CuI (39 mg, 0.21 mmol) were added. The resulting mixture was stirred at RT for 2 h. The mixture was concentrated, then water (20 mL) was added, and the solid was filtered off to give the title compound as a white solid (1.6 g, 95% overall). MS (ES+) C₁₇H₂₃FN₆O₅ requires: 410, found: 411 [M+H]⁺.

Step 4: 1-(4-(4-(tert-butoxycarbonylamino)-2-oxopyrimidin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylic acid.

[0293] To a solution of methyl 1-(4-(4-(tert-butoxycarbonylamino)-2-oxopyrimidin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate (1.6 g, 3.9 mmol) in THF (4 mL) and MeOH (4 mL), a solution of aqueous LiOH (94 mg, 3.9 mmol) was added. The resulting mixture was stirred at RT for 3 h. The mixture was concentrated, the pH adjusted with 1 N HCl, and the precipitate was filtered off to give the title compound as a yellow solid (1.25 g, 81%). MS (ES+) C₁₆H₂₁FN₆O₅ requires: 396, found: 397 [M+H]⁺.

Steps 5 to 7



Step 5: tert-butyl 1-(3-fluoro-4-(4-(3-(trifluoromethoxy)benzylcarbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-ylcarbamate.

[0294] To a solution of 1-(4-(4-(tert-butoxycarbonylamino)-2-oxopyrimidin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylic acid (600 mg, 1.52 mmol) and (3-(trifluoromethoxy)phenyl)methanamine (345 mg, 1.82 mmol) in DMF (4 mL), HATU (691 mg, 1.82 mmol) and DIEA (489 mg, 3.8 mmol) were added. The resulting mixture was stirred at RT for 2 h. The reaction mixture was diluted with water (20 mL), and the precipitate was filtered off to give the title compound as a yellow solid (800 mg, 90%). MS (ES⁺) C₂₄H₂₇F₄N₇O₅ requires: 569, found: 570 [M+H]⁺.

Step 6: 1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

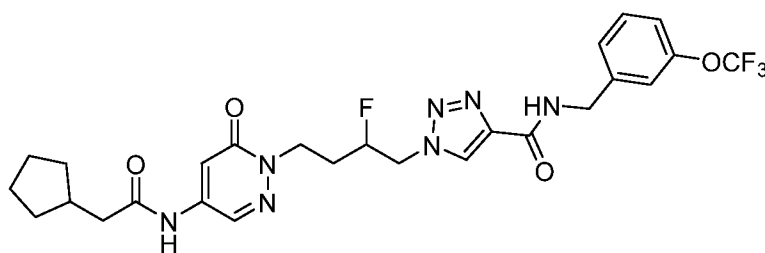
[0295] To a solution of tert-butyl 1-(3-fluoro-4-(4-(3-(trifluoromethoxy)benzylcarbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-ylcarbamate (800 mg, 1.41 mmol) in DCM (2 mL), TFA (10 mL) was added. The resulting mixture was stirred at RT for 3 h. The mixture was concentrated, diluted with sat. NaHCO₃, extracted with EtOAc (150 mL x 2), and concentrated to give the title compound as a yellow solid (550 mg, 83%). MS (ES⁺) C₁₉H₁₉F₄N₇O₃ requires: 469, found: 470 [M+H]⁺.

Step 7: 3-(trifluoromethoxy)benzyl 1-(3-fluoro-4-(4-(3-(trifluoromethoxy)benzylcarbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyrimidin-4-ylcarbamate.

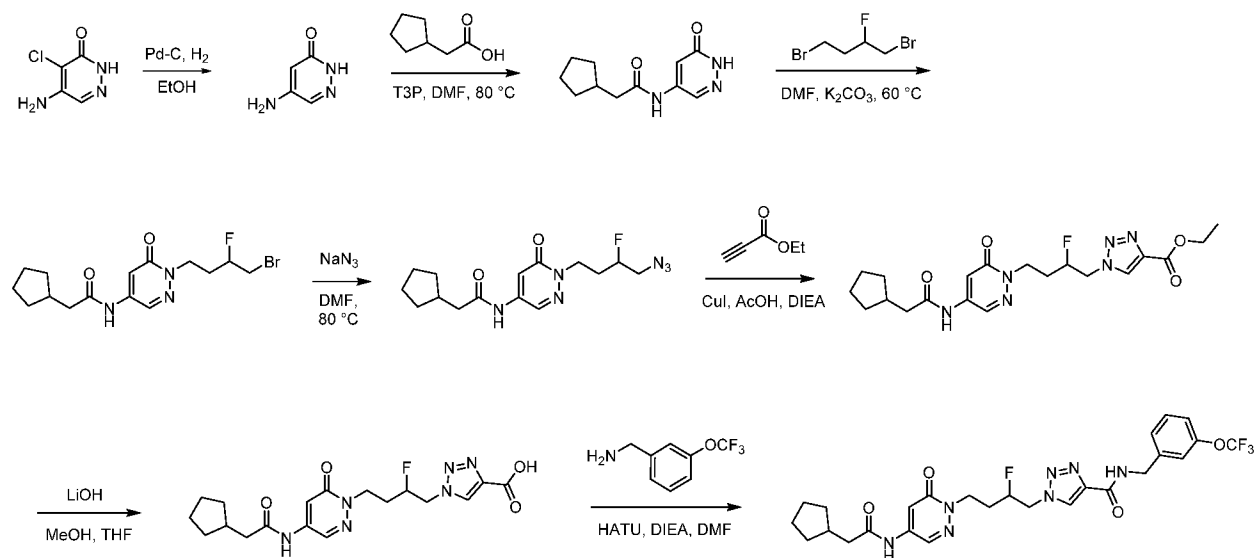
[0296] To a solution of tert (3-(trifluoromethoxy)phenyl)methanol (123 mg, 0.64 mmol) and DIEA (1.37 g, 10.7 mmol) in THF (3 mL), triphosgene (127 mg, 0.43 mmol) was added. The resulting mixture was stirred at RT for 3 h. Then 1-(4-(4-amino-2-oxopyrimidin-1(2H)-yl)-2-

fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (51 mg, 0.11 mmol) was added. The mixture was stirred at 80 °C overnight. The resulting mixture was concentrated and the residue purified by silica gel chromatography (0 – 100% EtOAc/Pet. Ether) to give the crude product which was further purified by prep-HPLC (Mobile phase: A = +0.1% ammonium hydroxide /H₂O, B = acetonitrile; Gradient: B = 5%-95% in 18 min; Column: XBridge C18, 5 μ m, 30 mm x 150 mm) to give the title compound as a white solid (20 mg, 26%). MS (ES⁺) C₂₈H₂₄F₇N₇O₆ requires: 687, found: 688 [M+H]⁺; ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.26 (t, *J* = 6.3 Hz, 1H), 8.58 (s, 1H), 8.07 (d, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 8.1 Hz, 1H), 7.46 (dd, *J* = 9.7, 6.1 Hz, 3H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.29 (s, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 7.3 Hz, 1H), 5.23 (s, 2H), 5.07 – 4.97 (m, 1H), 4.88 – 4.58 (m, 2H), 4.48 (d, *J* = 6.2 Hz, 2H), 3.95 (ddd, *J* = 20.5, 13.1, 6.5 Hz, 2H), 2.19 – 1.92 (m, 2H).

EXAMPLE 386: 1-(4-(4-(2-cyclopentylacetamido)-6-oxopyridazin-1(6H)-yl)-2-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



Steps 1 to 7



Step 1: 5-aminopyridazin-3(2H)-one.

[0297] A reaction vessel was charged with 5-amino-4-chloropyridazin-3(2H)-one (0.60 g, 4.1 mmol), palladium on carbon (2.19 g, 2.061 mmol, 10 wt.%) and EtOH (21 mL) under an atmosphere of N₂. The solution was degassed with N₂ for 5 min and purged with H₂ for 5 min. The reaction mixture was then heated at 50 °C for 6 h under 1 atm of H₂. The reaction mixture was purged with N₂, filtered through Celite®, and concentrated under reduced pressure to give the title compound as a light gray solid (460 mg, 100). MS (ES⁺) C₄H₅N₃O requires: 111, found: 112 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 13.10 (s, 1H), 7.75 (s, 1H), 7.57 – 6.74 (m, 2H), 5.97 (s, 1H).

Step 2: 2-cyclopentyl-N-(6-oxo-1,6-dihydropyridazin-4-yl)acetamide.

[0298] To a suspension of 2-cyclopentylacetic acid (0.124 mL, 0.990 mmol) and 5-aminopyridazin-3(2H)-one (0.10 g, 0.90 mmol) in pyridine (0.080 mL, 0.99 mmol) was added T3P® in DMF (0.687 g, 1.08 mmol, 50 wt.%) and the resulting mixture was stirred at 80 °C for 1 h. The reaction was cooled and diluted with EtOAc (15 mL), allowed to stir at 0 °C for 10 min, and filtered. The solid was washed with cold EtOAc (10 mL). The filtrate was concentrated and the residue was purified via silica gel chromatography (0 - 15 % MeOH in DCM with 1% NH₄OH) to give the title compound as a yellow amorphous material (130 mg, 65%). MS (ES⁺) C₁₁H₁₅N₃O₂ requires: 221, found: 222 [M+H]⁺.

Step 3: N-(1-(4-bromo-3-fluorobutyl)-6-oxo-1,6-dihydropyridazin-4-yl)-2-cyclopentylacetamide.

[0299] To a suspension of 2-cyclopentyl-N-(6-oxo-1,6-dihydropyridazin-4-yl)acetamide (0.130 g, 0.588 mmol) and potassium carbonate (0.162 g, 1.17 mmol) in DMF (1.2 mL) was added 1,4-dibromo-2-fluorobutane (0.275 g, 1.17 mmol) and the resulting mixture was stirred at 60 °C for 5 h. The reaction was concentrated, and the residue was purified via silica gel chromatography (0 - 15 % MeOH in DCM) to give the title compound as a tan solid (101 mg, 46%). MS (ES⁺) C₁₅H₂₁BrFN₃O₂ requires: 373, found: 374 [M+H]⁺.

Step 4: N-(1-(4-azido-3-fluorobutyl)-6-oxo-1,6-dihydropyridazin-4-yl)-2-cyclopentylacetamide.

[0300] To a solution of N-(1-(4-bromo-3-fluorobutyl)-6-oxo-1,6-dihydropyridazin-4-yl)-2-cyclopentylacetamide (101 mg, 0.270 mmol) in DMF (540 µl) was added sodium azide (21 mg, 0.32 mmol) and the resulting mixture was stirred at 80 °C for 1 h. The reaction was concentrated (bath temperature < 40 °C) to give the title compound as a off-white residue (91 mg, 100%). MS (ES⁺) C₁₅H₂₁FN₆O₄ requires: 336, found: 337 [M+H]⁺.

Step 5: ethyl 1-(4-(4-(2-cyclopentylacetamido)-6-oxopyridazin-1(6H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate.

[0301] To a suspension of acetic acid (3.1 μ l, 0.054 mmol), DIEA (9.4 μ l, 0.054 mmol), ethyl propiolate (53 mg, 0.54 mmol), and N-(1-(4-azido-3-fluorobutyl)-6-oxo-1,6-dihydropyridazin-4-yl)-2-cyclopentylacetamide (91 mg, 0.27 mmol) in DCM (1.3 mL) was added copper(I) iodide (2.6 mg, 0.014 mmol) and the resulting mixture was stirred at RT for 12 h. The reaction mixture was adsorbed onto silica gel and purified via silica gel chromatography (0 - 15 % MeOH in DCM with 1% NH_4OH) to give the title compound as a yellow solid (35 mg, 30%). MS (ES^+) $\text{C}_{20}\text{H}_{27}\text{FN}_6\text{O}_4$ requires: 434, found: 435 $[\text{M}+\text{H}]^+$.

Step 6: 1-(4-(4-(2-cyclopentylacetamido)-6-oxopyridazin-1(6H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylic acid.

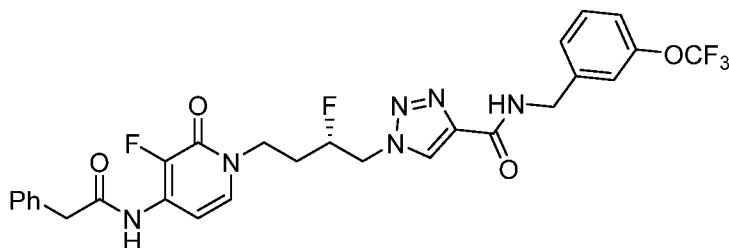
[0302] To a suspension of ethyl 1-(4-(4-(2-cyclopentylacetamido)-6-oxopyridazin-1(6H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate (35 mg, 0.081 mmol) in THF (322 μ l) and MeOH (81 μ l) was added aqueous LiOH (44 μ l, 0.089 mmol, 2.0 M) and the resulting mixture was stirred at RT for 2 h. The reaction was concentrated to give the title compound as a yellow amorphous material (33 mg, 100%, Li salt). MS (ES^+) $\text{C}_{18}\text{H}_{23}\text{FN}_6\text{O}_4$ requires: 406, found: 407 $[\text{M}+\text{H}]^+$.

Step 7: 1-(4-(4-(2-cyclopentylacetamido)-6-oxopyridazin-1(6H)-yl)-2-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

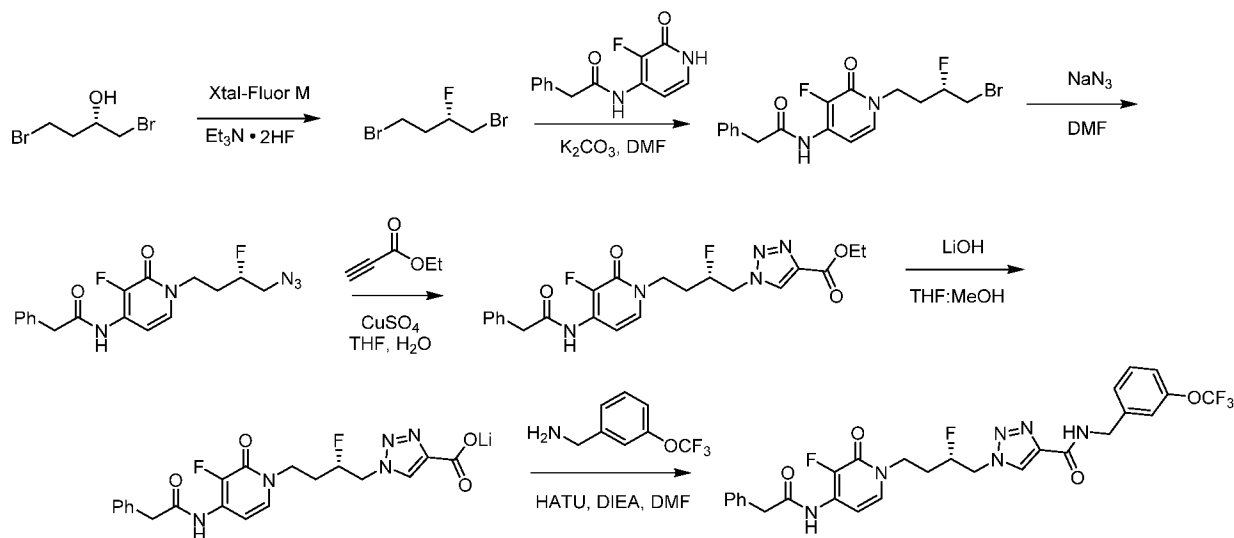
[0303] To a suspension of 1-(4-(4-(2-cyclopentylacetamido)-6-oxopyridazin-1(6H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylic acid (33 mg, 0.081 mmol), (3-(trifluoromethoxy)phenyl)methanamine (15 mg, 0.081 mmol) and HATU (46 mg, 0.12 mmol) in DMF (406 μ l) was added DIEA (28 μ l, 0.16 mmol) and the resulting mixture was stirred at RT for 1 h. The reaction mixture was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 40 - 80%; 12 min; Column: C18) to give the title compound as a off-white solid (8.0 mg, 17%). MS (ES^+) $\text{C}_{26}\text{H}_{29}\text{F}_4\text{N}_7\text{O}_4$ requires: 579, found: 580 $[\text{M}+\text{H}]^+$; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ 10.34 (s, 1H), 9.20 (t, J = 6.3 Hz, 1H), 8.56 (s, 1H), 7.90 (d, J = 2.4 Hz, 1H), 7.46 (t, J = 7.9 Hz, 1H), 7.35 (dt, J = 7.8, 1.2 Hz, 1H), 7.29 (d, J = 2.0 Hz, 1H), 7.26 – 7.20 (m, 2H), 5.01 (dddt, J = 49.4, 10.1, 6.7, 3.0 Hz, 1H), 4.84 – 4.67 (m, 2H), 4.48 (d, J = 6.2 Hz, 2H), 4.21 – 4.07 (m, 2H), 2.36 (d, J = 7.4 Hz, 2H), 2.24

– 2.03 (m, 2H), 1.95 (dddd, $J = 21.7, 15.0, 9.3, 6.9$ Hz, 1H), 1.78 – 1.70 (m, 2H), 1.64 – 1.45 (m, 4H), 1.21 – 1.11 (m, 2H).

EXAMPLE 127: (S)-1-(2-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide



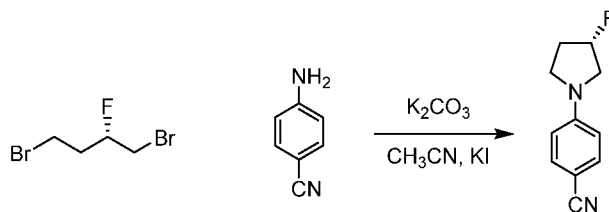
Steps 1 to 6



Step 1: (S)-1,4-dibromo-2-fluorobutane.

[0304] To a cooled solution of triethylamine trihydrofluoride (2.81 mL, 17.2 mmol) in DCM (43.1 mL) at 0 °C was added triethylamine (1.20 mL, 8.62 mmol). After 5 min, XtalFluor-M (3.14 g, 12.9 mmol) was added. After an additional 5 min (S)-1,4-dibromobutan-2-ol (1.00 mL, 8.62 mmol) was added and the resulting mixture was stirred as it warmed to RT over 7 h. The reaction was quenched with 5 % aqueous NaHCO₃ (20 mL), the layers were separated, and the aqueous layer was extracted with DCM (2 x 20 mL). The organic layers were combined, dried over Na₂SO₄, and the volatiles were removed under reduced pressure to give the title compound as a light yellow oil (1.35 g, 67%). ¹H NMR (600 MHz, Chloroform-*d*) δ 4.90 (ddtd, $J = 47.6, 9.5, 4.9, 2.9$ Hz, 1H), 3.59 – 3.46 (m, 4H), 2.40 – 2.28 (m, 1H), 2.27 – 2.13 (m, 1H).

[0305] To determine absolute stereochemistry and enantiopurity, an analytical sample was derivatized as follows:

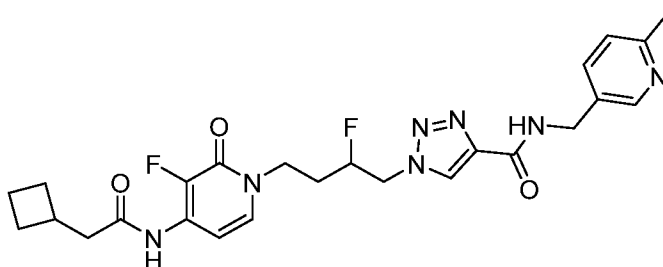


[0306] A microwave vial was charged with K_2CO_3 (591 mg, 4.28 mmol), KI (71 mg, 0.43 mmol), 4-aminobenzonitrile (303 mg, 2.57 mmol), (*S*)-1,4-dibromo-2-fluorobutane (400 mg, 1.71 mmol) and MeCN (1710 μ l). The vial was sealed and the reaction mixture was heated to 170 $^{\circ}C$ in the microwave reactor for 3 h. The volatiles were removed under reduced pressure and the residue was purified via mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/ H_2O , B = 0.1% TFA/MeCN; Gradient: B = 20 - 60%; 12 min; Column: C18) to give (*S*)-4-(3-fluoropyrrolidin-1-yl)benzonitrile (45 mg, 14%, TFA salt) as a white crystalline solid. MS (ES^+) $C_{11}H_{11}FN_2$ requires: 190, found: 191 $[M+H]^+$; ^1H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, 2H, J = 8.7 Hz), 6.53 (d, 2H, J = 8.7 Hz), 5.40 (dm, 1H, J = 53 Hz), 3.63 (m, 1H), 3.56 - 3.60 (m, 1H), 3.53 - 3.56 (m, 1H), 3.52 (m, 1H), 2.43 (m, 1H), 2.10 - 2.25 (m, 1H). Analytical chiral HPLC (Phenomenex Lux-3 250 x 4.6 mm @ 1.0mL/min, 20% EtOH in Hexane with 0.1% TFA) determined the sample to be 85% ee. Racemic and enantiopure standards were synthesized from 3-fluoropyrrolidine hydrochloride, 4-fluorobenzonitrile, and potassium carbonate in MeCN. The standard derived from commercially available (*S*)-3-fluoropyrrolidine hydrochloride matched the sample prepared above, which allowed assignment of the (*S*)-configuration.

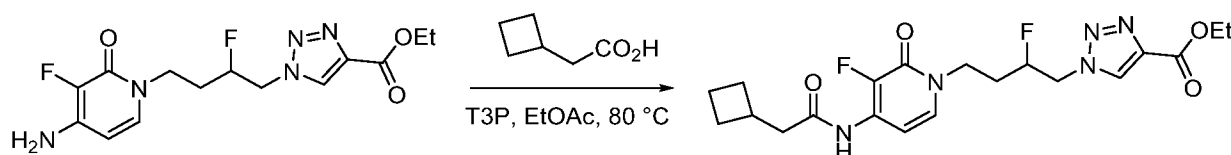
Step 2 to 6: (*S*)-1-(2-fluoro-4-(2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

[0307] Following EXAMPLE 180, steps 2 to 8, gave the title compound as a white solid. MS (ES^+) $C_{28}H_{25}F_5N_6O_4$ requires: 604, found: 605 $[M+H]^+$

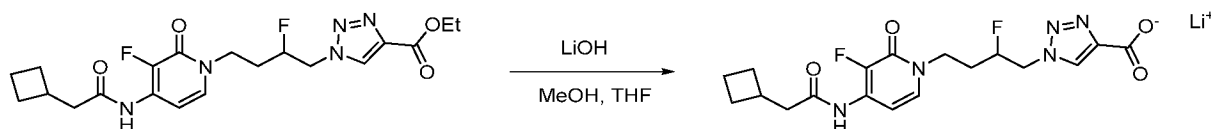
EXAMPLE 304: 1-(4-(4-(2-cyclobutylacetamido)-3-fluoro-2-oxypyridin-1(2H)-yl)-2-fluorobutyl)-N-((6-methylpyridin-3-yl)methyl)-1H-1,2,3-triazole-4-carboxamide



Step 1: 1-(4-(4-(2-cyclobutylacetamido)-3-fluoro-2-oxypyridin-1(2H)-yl)-2-fluorobutyl)-N-((6-methylpyridin-3-yl)methyl)-1H-1,2,3-triazole-4-carboxamide.



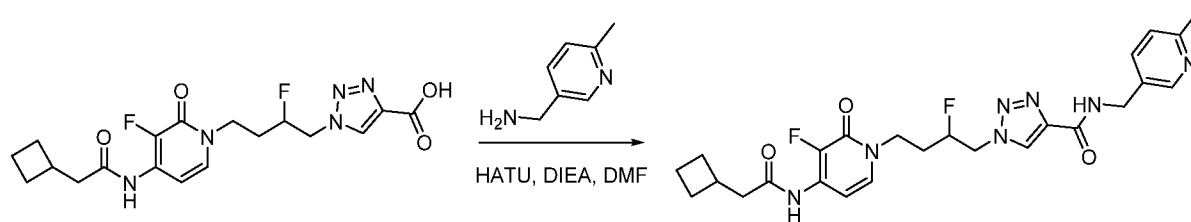
[0308] To a solution of ethyl 1-(4-(4-amino-3-fluoro-2-oxypyridin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate (0.30 g, 0.88 mmol), and 2-cyclobutylacetic acid (0.15 g, 1.3 mmol) was added 2,4,6-tripropyl-1,3,5,2,4,6-trioxatriphosphinane 2,4,6-trioxide (T3P®) in EtOAc (2.80 g, 4.39 mmol, 50 wt.%) and pyridine (0.213 mL, 2.64 mmol). The resulting mixture was stirred for 1 h at 80 °C. The reaction was cooled to RT and the resulting thick white suspension was diluted with EtOAc (10 mL) and filtered. The collected solids were washed with EtOAc and dried to give the title compound as a white solid (326 mg, 76 %). MS(ES⁺) C₂₀H₂₅F₂N₅O₄ requires: 437, found: 438 [M+H]⁺.



Step 2: lithium 1-(4-(4-(2-cyclobutylacetamido)-3-fluoro-2-oxypyridin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate.

[0309] To a suspension of ethyl 1-(4-(4-(2-cyclobutylacetamido)-3-fluoro-2-oxypyridin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylate (0.325 g, 0.743 mmol) in THF (2.97 mL) and MeOH (0.74 mL) was added aq. lithium hydroxide (0.409 mL, 0.817 mmol, 2.0 M) and the resulting mixture was stirred at RT for 2 h. The reaction was concentrated, azeotroping with

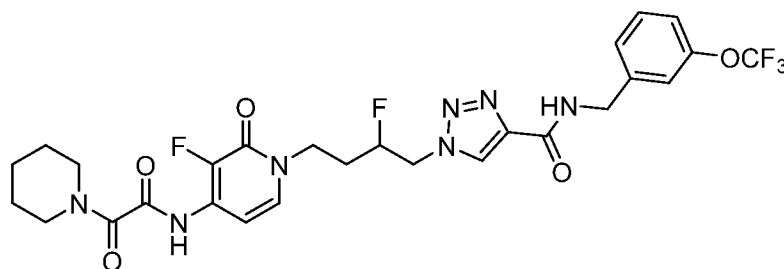
EtOH, to give the title compound (0.304 g, 100 %) as a green foam. MS(ES⁺) C₁₈H₂₁F₂N₅O₄ requires: 409, found: 410 [M+H]⁺.

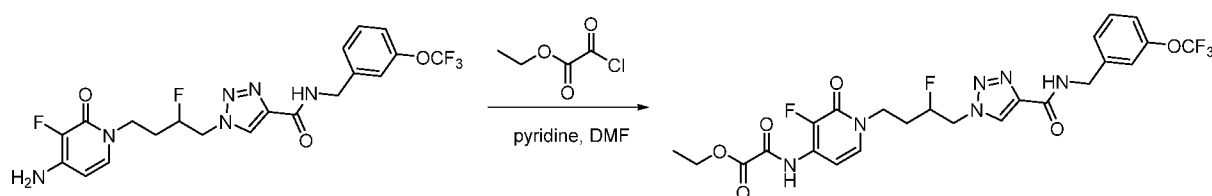


Step 3: 1-(4-(4-(2-cyclobutylacetamido)-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-N-((6-methylpyridin-3-yl)methyl)-1H-1,2,3-triazole-4-carboxamide.

[0310] To a suspension of (6-methylpyridin-3-yl)methanamine (28.6 mg, 0.234 mmol), 1-(4-(4-(2-cyclobutylacetamido)-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-1H-1,2,3-triazole-4-carboxylic acid (80 mg, 0.195 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (111 mg, 0.293 mmol) in DMF (977 μ l) was added *N*-ethyl-*N*-isopropylpropan-2-amine (68 μ l, 0.39 mmol) and the resulting mixture was stirred at RT for 1 h. The reaction mixture was concentrated and the residue was purified via silica gel chromatography (0–15 % MeOH in DCM with 1% NH₄OH) to give the title compound as an off-white solid (22 mg, 21%). MS(ES⁺) C₂₅H₂₉F₂N₇O₃ requires: 513, found: 514 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.91 (s, 1H), 9.16 (t, *J* = 6.2 Hz, 1H), 8.55 (s, 1H), 8.39 (d, *J* = 2.2 Hz, 1H), 7.60 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.44 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.05 (dd, *J* = 7.7, 6.4 Hz, 1H), 5.09 – 4.88 (m, 1H), 4.85 – 4.66 (m, 2H), 4.41 (d, *J* = 6.1 Hz, 2H), 4.04 (ddt, *J* = 44.4, 13.5, 7.2 Hz, 2H), 2.69 – 2.56 (m, 1H), 2.53 (d, *J* = 7.5 Hz, 3H), 2.16 – 1.63 (m, 8H).

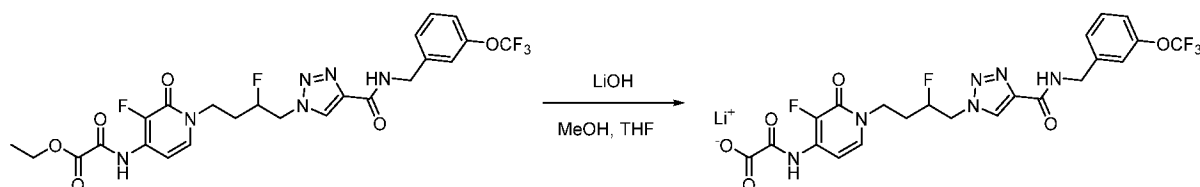
EXAMPLE 358: 1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-oxo-2-(piperidin-1-yl)acetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide





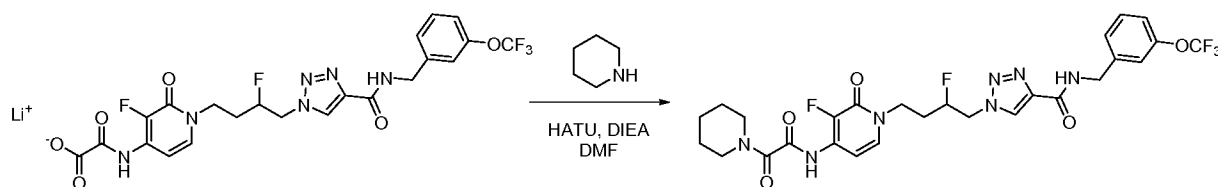
Step 1: ethyl 2-((3-fluoro-1-(3-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)amino)-2-oxoacetate.

[0311] To a solution of 1-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (100 mg, 0.206 mmol) in DMF (0.2 mL) was added pyridine (0.067 mL, 0.822 mmol). The reaction mixture was cooled to 0 °C in an ice bath, and ethyl 2-chloro-2-oxoacetate (33.7 mg, 0.247 mmol) added. The resulting mixture was removed from the bath and stirred at RT for 2 h. An additional amount of ethyl 2-chloro-2-oxoacetate (33.7 mg, 0.247 mmol) was added and the reaction mixture was stirred at RT for an additional 2 h. The reaction mixture was quenched with MeOH, concentrated, and the resulting solids were taken up into a minimal amount of MeOH, the suspension was filtered, and the collected solids were washed with a minimal amount of MeOH, then hexanes to give the title compound as a white solid (99 mg, 82%). MS (ES⁺) C₂₄H₂₃F₅N₆O₆ requires: 586, found: 587 [M+H]⁺.



Step 2: Lithium 2-((3-fluoro-1-(3-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)amino)-2-oxoacetate.

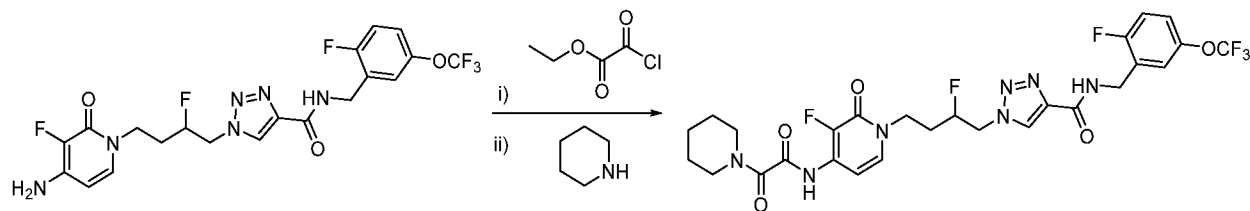
[0312] To a suspension of ethyl 2-((3-fluoro-1-(3-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)amino)-2-oxoacetate (38 mg, 0.065 mmol) in THF (2.6 mL) and MeOH (65 µL) was added aq. lithium hydroxide (35.6 µL, 0.071 mmol, 2.0 M) and the resulting mixture was stirred at RT for 1 h. The reaction mixture was concentrated to give the title compound as a white solid (36 mg, 100%). MS (ES⁺) C₂₂H₁₉F₅N₆O₆ requires: 558, found: 559 [M+H]⁺.



Step 3: 1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-oxo-2-(piperidin-1-yl)acetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide.

[0313] To a suspension of piperidine (7.66 μ l, 0.077 mmol), lithium 2-((3-fluoro-1-(3-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)amino)-2-oxoacetate (36 mg, 0.064 mmol) and 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate(V) (37 mg, 0.097 mmol) in DMF (0.65 mL) was added DIEA (23 μ l, 0.13 mmol) and the resulting mixture was stirred at RT for 1 h. The reaction mixture was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 40–80%; 12 min; Column: C18) to give the title compound as a white solid (10 mg, 25%). MS (ES⁺) C₂₇H₂₈F₅N₇O₅ requires: 625, found: 626 [M+H]⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.92 (s, 1H), 9.20 (t, J = 6.2 Hz, 1H), 8.57 (s, 1H), 7.54 (dd, J = 7.6, 1.6 Hz, 1H), 7.46 (t, J = 7.9 Hz, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.29 (s, 1H), 7.26 – 7.18 (m, 1H), 6.92 (t, J = 6.9 Hz, 1H), 5.01 (dddt, J = 49.8, 10.0, 6.7, 3.0 Hz, 1H), 4.86 – 4.67 (m, 2H), 4.48 (d, J = 6.2 Hz, 2H), 4.17 – 4.01 (m, 2H), 3.41 (dt, J = 69.8, 5.5 Hz, 4H), 2.19 – 1.89 (m, 2H), 1.68 – 1.50 (m, 6H).

EXAMPLE 422: 11-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-oxo-2-(piperidin-1-yl)acetamido)pyridin-1(2H)-yl)butyl)-N-(2-fluoro-5-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide

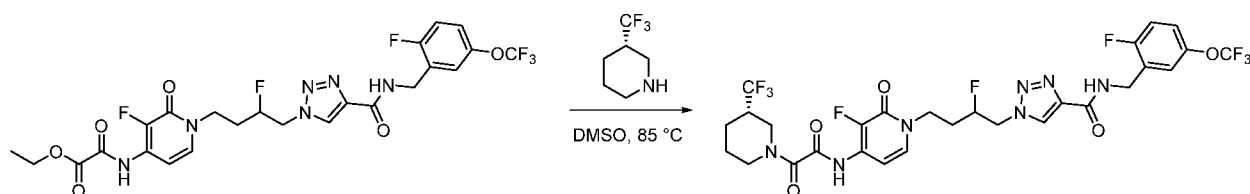


[0314] To a suspension of 1-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)-2-fluorobutyl)-N-(2-fluoro-5-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide (122 mg, 0.242 mmol) and DIEA (211 μ l, 1.21 mmol) in THF (4.8 mL) at 0 °C was added oxalyl chloride (151 μ l, 0.302 mmol). The resulting mixture was stirred as it warmed to RT for 25 min. The reaction was cooled to 0°C again and piperidine (48 μ l, 0.48 mmol) was added. The resulting mixture was stirred as it warmed to RT for 1 h. The volatiles were removed under reduced pressure and the

residue was purified via silica gel chromatography (0–10 % MeOH in DCM with 1 % NH₄OH) to give the title compound (67 mg, 43%) as an off-white crystalline solid. MS (ES⁺)

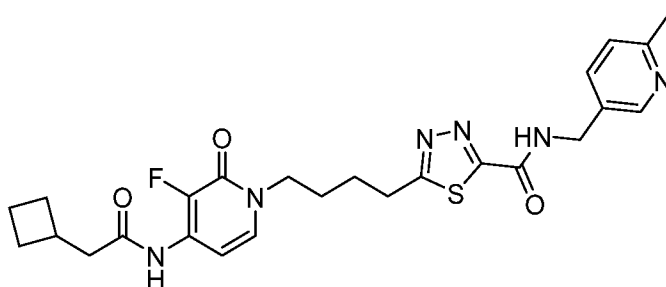
C₂₇H₂₇F₆N₇O₅ requires: 643, found: 644 [M+H]⁺; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.93 (s, 1H), 9.20 (t, *J* = 6.1 Hz, 1H), 8.59 (s, 1H), 7.56 – 7.51 (m, 1H), 7.37 – 7.31 (m, 3H), 6.93 (t, *J* = 6.8 Hz, 1H), 5.02 (dt, *J* = 49.4, 8.5 Hz, 1H), 4.85 – 4.69 (m, 2H), 4.52 (d, *J* = 6.1 Hz, 2H), 4.10 (ddt, *J* = 50.8, 13.7, 6.9 Hz, 2H), 3.51 – 3.37 (m, 4H), 2.19 – 1.89 (m, 2H), 1.67 – 1.50 (m, 6H).

EXAMPLE 435: 1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-oxo-2-(piperidin-1-yl)acetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethyl)benzyl)-1H-1,2,3-triazole-4-carboxamide

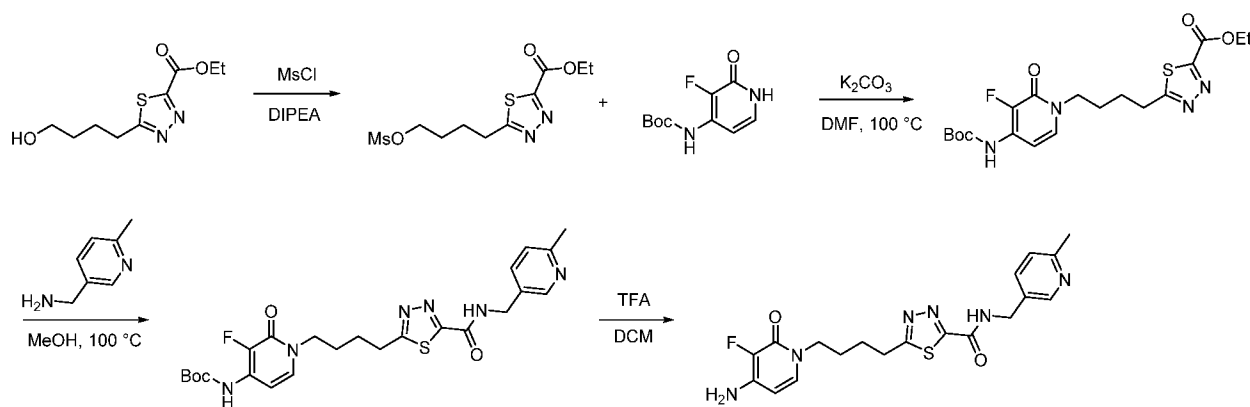


[0315] To a solution of ethyl 2-((3-fluoro-1-(3-fluoro-4-(4-((2-fluoro-5-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)amino)-2-oxoacetate (33 mg, 0.055 mmol) in DMSO (1 mL) was added (*S*)-3-(trifluoromethyl)piperidine (52 mg, 0.340 mmol) and the resulting mixture was stirred at 85 °C for 5 h. The residue was purified by mass-triggered preparative HPLC (Mobile phase: A = 0.1% TFA/H₂O, B = 0.1% TFA/MeCN; Gradient: B = 40–80%; 12 min; Column: C18) and lyophilized to give the title compound as a white powder (26 mg, 67 % yield, 1:1 mixture of diastereomers). MS(ES⁺) C₂₈H₂₆F₉N₇O₅ requires: 711, found: 712 [M+H]⁺. ¹H NMR (600 MHz, DMSO-*d*₆) δ ppm 10.94 (s, 2H), 9.20 (m, 2H), 8.59 (s, 2H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.36–7.31 (m, 6H), 6.95 (m, 1H), 6.83 (m, 1H), 5.05 (m, 1H), 4.97 (m, 1H), 4.84–4.69 (m, 4H), 4.50 (d, *J* = 6.1 Hz, 4H), 4.36 (m, 1H), 4.22–4.00 (m, 5H), 3.83 (d, *J* = 13 Hz, 1H), 3.63 (d, *J* = 13.4 Hz, 1H), 3.27 (dd, *J* = 11.3 Hz, 1H), 3.18 (t, *J* = 12.6 Hz, 1H), 2.91–2.81 (m, 2H), 2.18–1.91 (m, 6H), 1.78 (m, 2H), 1.66–1.46 (m, 4H).

EXAMPLE 464: 5-(4-(4-(2-cyclobutylacetamido)-3-fluoro-2-oxopyridin-1(2H)-yl)butyl)-N-((6-methylpyridin-3-yl)methyl)-1,3,4-thiadiazole-2-carboxamide



Steps 1 to 4



Step 1: ethyl 5-(4-(methylsulfonyloxy)butyl)-1,3,4-thiadiazole-2-carboxylate.

[0316] To a solution of ethyl 5-(4-hydroxybutyl)-1,3,4-thiadiazole-2-carboxylate (4.2 g, 18 mmol, see EXAMPLE 28) and DIEA (7.1 g, 54.8 mmol) in DCM (50 mL), MsCl (3.1g, 27.4 mmol) was slowly added. The mixture was stirred at RT for 3 h. The solution was diluted with water (100 mL) and extracted with DCM (2 × 100 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to obtain the title compound as a brown oil (5.2 g, 95%). MS (ES⁺) C₁₀H₁₆N₂O₅S₂ requires: 308, found: 309 [M+H]⁺.

Step 2: ethyl 5-(4-(4-(tert-butoxycarbonylamino)-3-fluoro-2-oxopyridin-1(2H)-yl)butyl)-1,3,4-thiadiazole-2-carboxylate.

[0317] A mixture of ethyl 5-(4-(methylsulfonyloxy)butyl)-1,3,4-thiadiazole-2-carboxylate (5.2 g, 17.1 mmol), tert-butyl 3-fluoro-2-oxo-1,2-dihydropyridin-4-ylcarbamate (3.12 g, 13.7 mmol), and K₂CO₃ (5.6 g, 41.1 mmol) in DMF (20 mL) was stirred at 100 °C for 1 h. The mixture was concentrated and the residue was purified by silica gel chromatography (Pet. Ether:

EtOAc = 1:1-1:2) to obtain the title compound as a brown solid (1.7 g, 30%). MS (ES+)

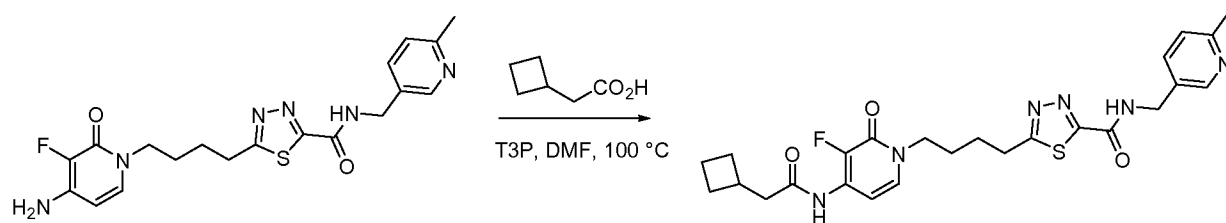
$C_{19}H_{25}FN_4O_5S$ requires: 440, found: 441 $[M+H]^+$.

Step 3: tert-butyl 3-fluoro-1-(4-(5-((6-methylpyridin-3-yl)methylcarbamoyl)-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyridin-4-ylcarbamate.

[0318] A solution of ethyl 5-(4-(4-(tert-butoxycarbonylamino)-3-fluoro-2-oxopyridin-1(2H)-yl)butyl)-1,3,4-thiadiazole-2-carboxylate (500 mg, 1.14 mmol) and (6-methylpyridin-3-yl)methanamine (416 mg, 3.4 mmol) in MeOH (5 mL) was stirred at 100 °C for 4 h. The reaction mixture was concentrated and the residue was purified by eluting through a short plug of silica gel (eluting with EtOAc) to obtain the title compound as white solid (540 mg, 70%). MS (ES+) $C_{24}H_{29}FN_6O_4S$ requires: 516, found: 517 $[M+H]^+$.

Step 5: 5-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)butyl)-N-((6-methylpyridin-3-yl)methyl)-1,3,4-thiadiazole-2-carboxamide.

[0319] To a solution of tert-butyl 3-fluoro-1-(4-(5-((6-methylpyridin-3-yl)methylcarbamoyl)-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyridin-4-ylcarbamate (540 mg, 0.97 mmol) in DCM (5 mL) was added TFA (5 mL) and the resulting solution was stirred at RT for 3 h. The mixture was concentrated to give the title compound as a brown oil (600 mg, >100%, TFA salt). MS (ES+) $C_{19}H_{21}FN_6O_2S$ requires: 416, found: 417 $[M+H]^+$.

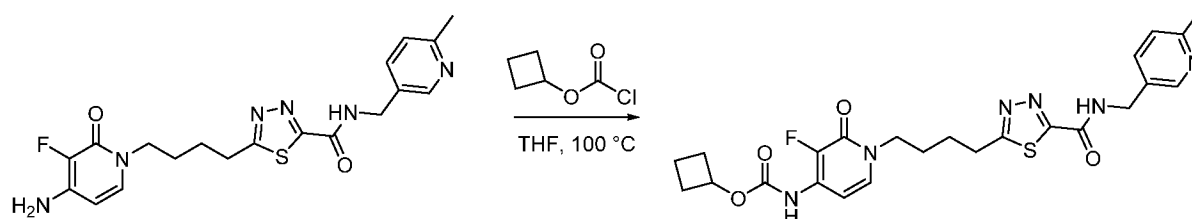


Step 5: 5-(4-(4-(2-cyclobutylacetamido)-3-fluoro-2-oxopyridin-1(2H)-yl)butyl)-N-((6-methylpyridin-3-yl)methyl)-1,3,4-thiadiazole-2-carboxamide.

[0320] To a solution of 5-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)butyl)-N-((6-methylpyridin-3-yl)methyl)-1,3,4-thiadiazole-2-carboxamide (100 mg, 0.24 mmol, TFA salt) and 2-cyclobutylacetic acid (72 mg, 0.72 mmol) in DMF (5 mL) was added T3P® in EtOAc (759 mg, 1.20 mmol, 50 wt.%). The resulting mixture was stirred at 100 °C overnight. The mixture was purified by Prep-HPLC (Mobile phase: A = +0.1% NH_4OH / H_2O , B = acetonitrile; Gradient: B = 5%-95% in 18 min; Column: C18) to obtain the title compound as a white solid (20 mg, 27%). MS (ES+) $C_{25}H_{29}FN_6O_3S$ requires: 512, found: 513 $[M+H]^+$. ^1H NMR (500 MHz, $DMSO-d_6$) δ 9.90 (s, 1H), 9.85 (s, 1H), 8.62 (s, 1H), 8.09 (s, 1H), 7.61 (s, 1H), 7.47 (d, J = 7.4

Hz, 1H), 7.05 (s, 1H), 4.54 (d, J = 5.3 Hz, 2H), 3.93 (s, 2H), 3.18 (s, 2H), 2.58 (t, J = 21.9 Hz, 6H), 2.03 (s, 2H), 1.82 (d, J = 8.5 Hz, 2H), 1.71 (s, 6H).

EXAMPLE 468: cyclobutyl (3-fluoro-1-(4-(5-(((6-methylpyridin-3-yl)methyl)carbamoyl)-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)carbamate

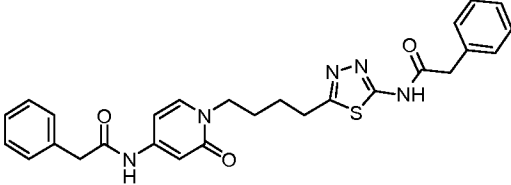
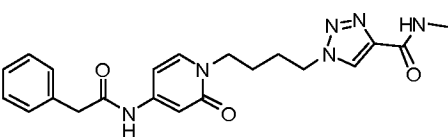
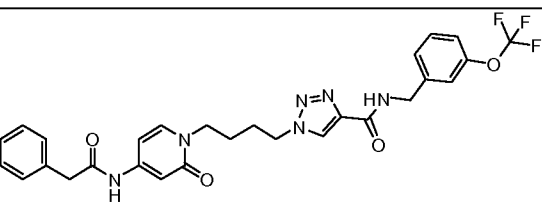
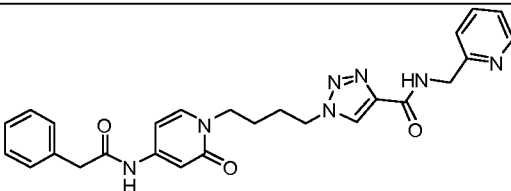
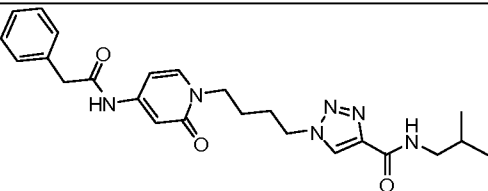
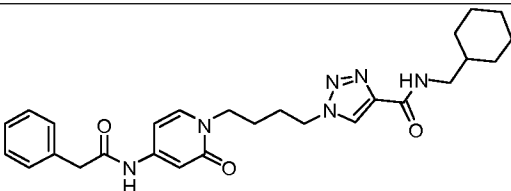
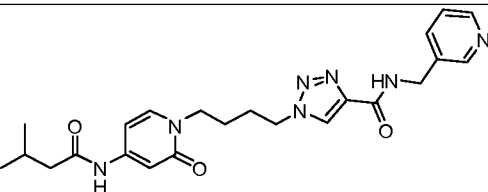


[0321] To a solution of cyclobutanol (52 mg, 0.43 mmol) and DIEA (155 mg, 1.202 mmol) in THF (10 mL) was added bis(trichloromethyl) carbonate (128 mg, 0.721 mmol) at 0 °C. The reaction was stirred at RT for 6 h. The mixture was then added to a solution of 5-(4-(4-amino-3-fluoro-2-oxopyridin-1(2H)-yl)butyl)-N-((6-methylpyridin-3-yl)methyl)-1,3,4-thiadiazole-2-carboxamide (100 mg, 0.24 mmol) in THF (10 mL) and stirred at 100 °C for 24 h. The mixture was concentrated and purified by Prep-HPLC (Mobile phase: A = +0.1% NH₄OH /H₂O, B = acetonitrile; Gradient: B = 5%-95% in 18 min; Column: C18) to obtain the title compound as a white solid (12 mg, 10%). MS (ES⁺) C₂₄H₂₇FN₆O₄S requires: 514, found: 515 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 9.86 (t, J = 6.1 Hz, 1H), 9.82 (s, 1H), 8.66 (s, 1H), 8.18 (d, J = 6.7 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.48 (d, J = 6.9 Hz, 1H), 6.96 – 6.63 (m, 1H), 4.93 (p, J = 7.3 Hz, 1H), 4.56 (d, J = 6.1 Hz, 2H), 3.92 (s, 2H), 3.18 (s, 2H), 2.62 (s, 3H), 2.29 (dd, J = 16.2, 8.2 Hz, 2H), 2.11 – 1.97 (m, 2H), 1.80 – 1.50 (m, 6H).

[0322] Non-limiting examples include the following compounds and pharmaceutically acceptable salts thereof:

Table 1: Synthesized Compounds

Ex.	Structure	IUPAC Name
30		N-{1-[4-(5-amino-1,3,4-thiadiazol-2-yl)butyl]-2-oxo-1,2-dihydropyridin-4-yl}-2-phenylacetamide

31		N-(2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyridin-4-yl)-2-phenylacetamide
32		N-methyl-1-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
33		1-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
34		1-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide
35		N-(2-methylpropyl)-1-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
36		N-(cyclohexylmethyl)-1-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
37		1-{4-[4-(3-methylbutanamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-(pyridin-3-ylmethyl)-1H-1,2,3-triazole-4-carboxamide

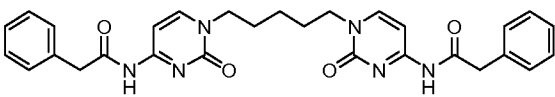
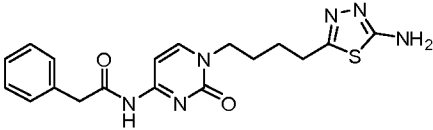
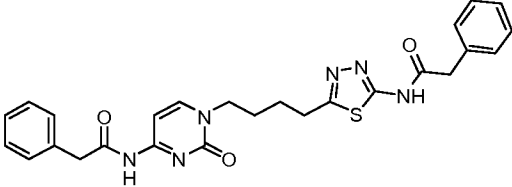
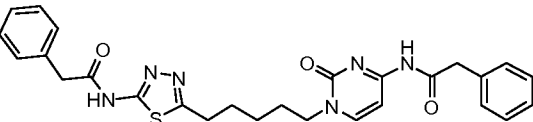
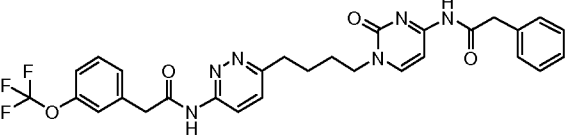
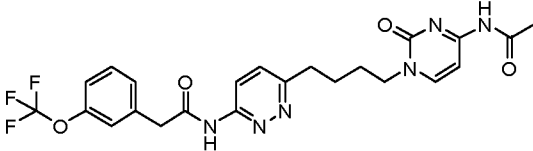
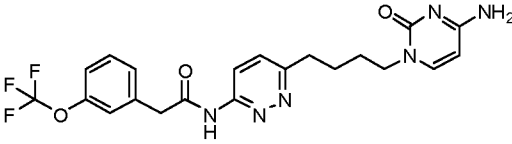
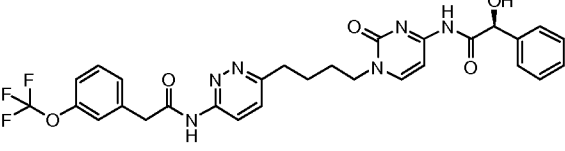
38		1-{4-[4-(3-methylbutanamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide
39		N-(cyclohexylmethyl)-1-{4-[4-(3-methylbutanamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
40		N-methyl-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide
41		N-(cyclohexylmethyl)-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide
42		benzyl N-(2-oxo-1-{4-[4-({3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridin-4-yl)carbamate
43		propan-2-yl N-(2-oxo-1-{4-[4-({3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridin-4-yl)carbamate
44		cyclohexyl N-(2-oxo-1-{4-[4-({3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridin-4-yl)carbamate

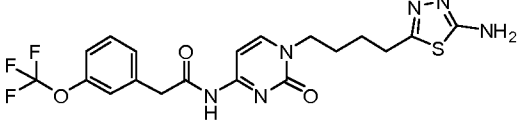
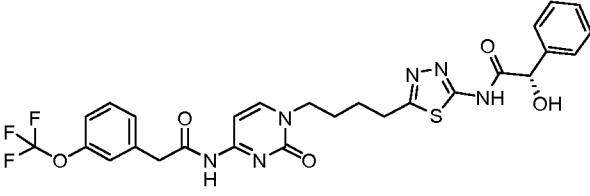
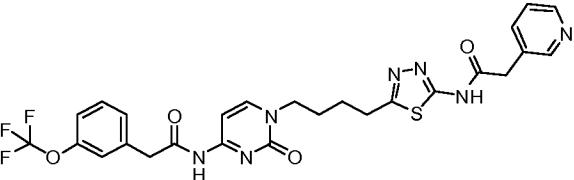
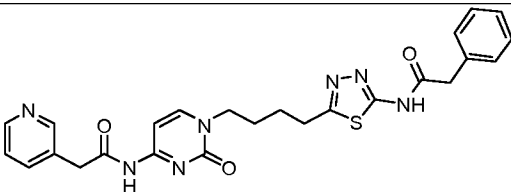
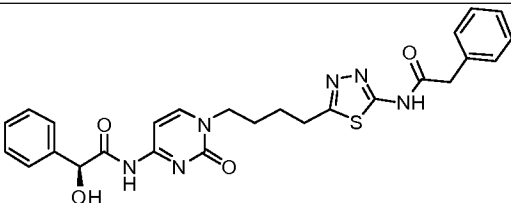
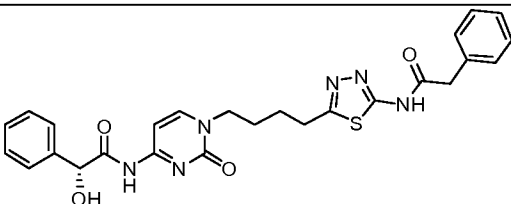
45		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
46		1-(4-{4-[2-(1-methyl-1H-pyrazol-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
47		1-(4-{2-oxo-4-[2-(oxolan-3-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
48		1-(4-{4-[2-(oxan-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
49		2-oxo-N-(pyridin-2-ylmethyl)-1-{4-[4-({[3-(trifluoromethoxy)phenyl]methyl}carbonyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridine-4-carboxamide
50		1-[4-(4-acetamido-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
51		N-benzyl-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide

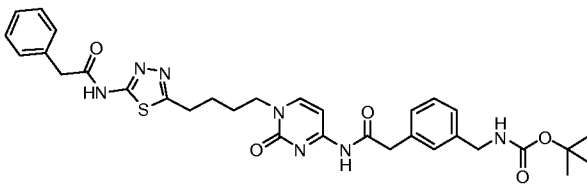
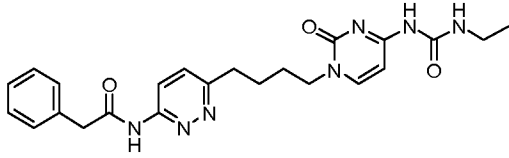
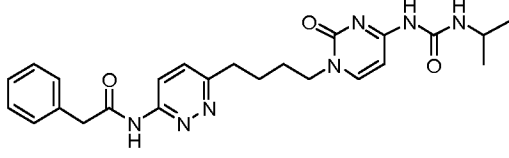
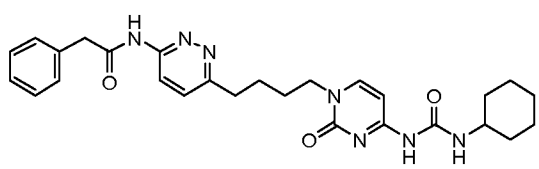
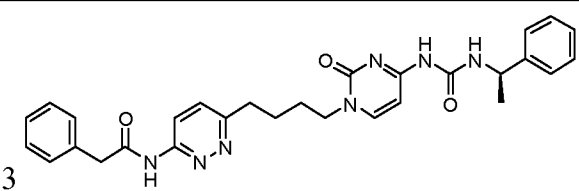
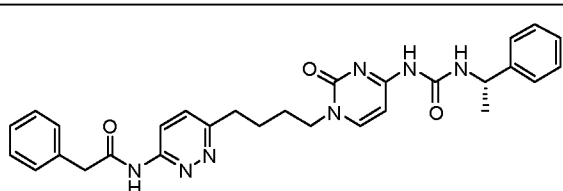
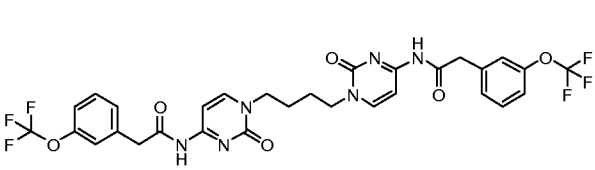
52		1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
53		N-[(3-methanesulfonylphenyl)methyl]-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide
54		1-{4-[4-(2-methylpropanamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
55		1-(4-{4-[2-(2-fluorophenyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
56		1-(4-{4-[2-(2-oxan-3-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
57		benzyl N-[2-oxo-1-(4-{4-[(pyridin-2-yl)methyl]carbamoyl}-1H-1,2,3-triazol-1-yl}butyl)-1,2-dihydropyridin-4-yl]carbamate

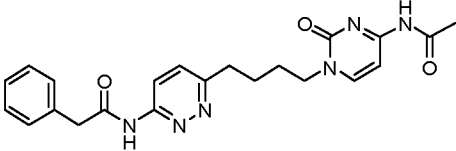
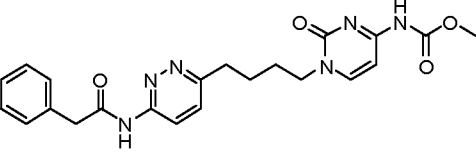
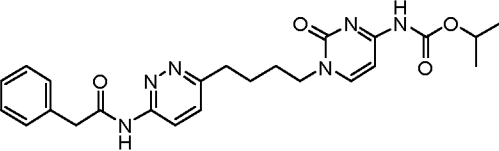
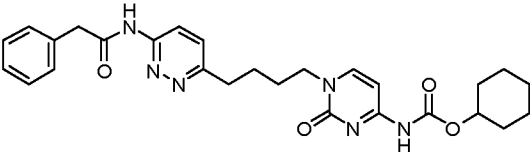
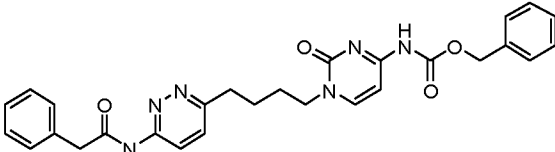
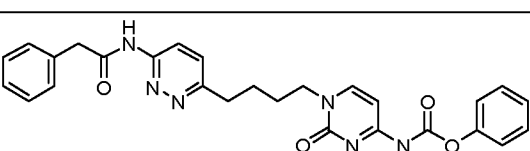
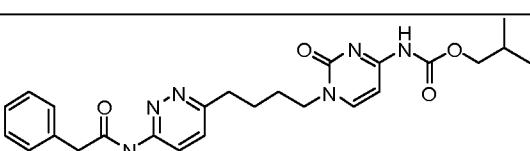
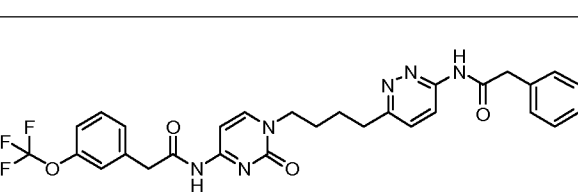
58		N-methyl-2-oxo-1-{4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridine-4-carboxamide
59		2-oxo-N-{[3-(trifluoromethoxy)phenyl]methyl}-1-{4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridine-4-carboxamide
60		2-oxo-N-(pyridin-3-ylmethyl)-1-{4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridine-4-carboxamide
61		N-[(2,4-dimethoxyphenyl)methyl]-2-oxo-1-{4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridine-4-carboxamide
62		N-(2-methylpropyl)-2-oxo-1-{4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridine-4-carboxamide
63		N-(cyclohexylmethyl)-2-oxo-1-{4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridine-4-carboxamide

64		[3-(trifluoromethoxy)phenyl]methyl N-(2-oxo-1-{4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbonyl]-1H-1,2,3-triazol-1-yl}butyl)-1,2-dihydropyridin-4-yl)carbamate
65		N-[(3-methoxyphenyl)methyl]-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide
66		N-[(3-fluorophenyl)methyl]-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide
67		N-[(4-methoxyphenyl)methyl]-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide
68		N-[(4-methanesulfonylphenyl)methyl]-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide
69		1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N-(pyridin-3-ylmethyl)-1H-1,2,3-triazole-4-carboxamide
70		N-[(6-methylpyridin-3-yl)methyl]-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide

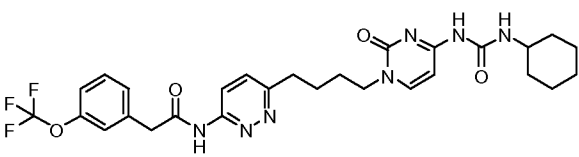
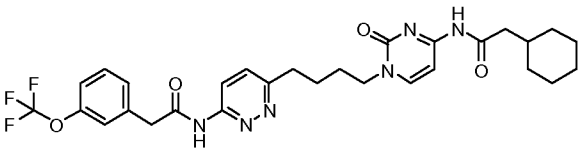
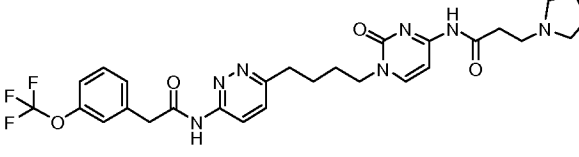
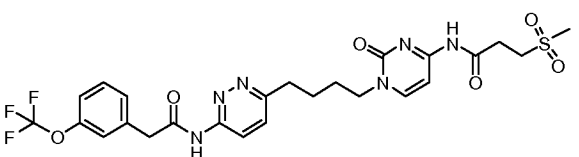
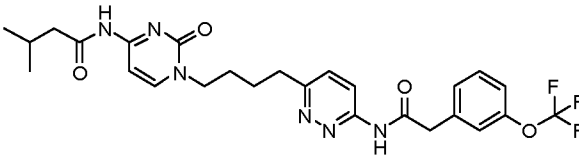
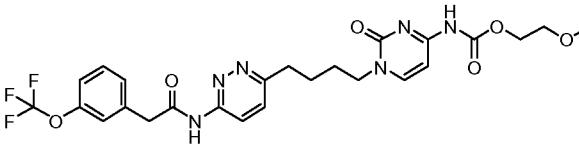
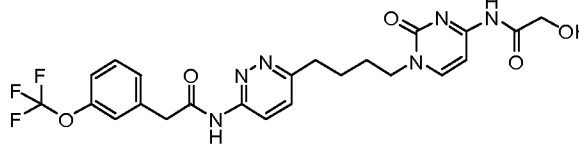
71		N-(2-oxo-1-{5-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyrimidin-1-yl]pentyl}-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide
72		N-{1-[4-(5-amino-1,3,4-thiadiazol-2-yl)butyl]-2-oxo-1,2-dihydropyrimidin-4-yl}-2-phenylacetamide
73		N-(2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide
74		N-(2-oxo-1-{5-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]pentyl}-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide
75		N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}-2-phenylacetamide
76		N-{6-[4-(4-acetamido-2-oxo-1,2-dihydropyrimidin-1-yl)butyl]pyridazin-3-yl}-2-[3-(trifluoromethoxy)phenyl]acetamide
77		N-{6-[4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)butyl]pyridazin-3-yl}-2-[3-(trifluoromethoxy)phenyl]acetamide
78		(2S)-2-hydroxy-N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}-2-phenylacetamide

		dihydropyrimidin-4-yl}-2-phenylacetamide
79		N-{1-[4-(5-amino-1,3,4-thiadiazol-2-yl)butyl]-2-oxo-1,2-dihydropyrimidin-4-yl}-2-[3-(trifluoromethoxy)phenyl]acetamide
80		(2S)-2-hydroxy-N-{5-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyrimidin-1-yl)butyl]-1,3,4-thiadiazol-2-yl}-2-phenylacetamide
81		N-[2-oxo-1-(4-{5-[2-(pyridin-3-yl)acetamido]-1,3,4-thiadiazol-2-yl}butyl)-1,2-dihydropyrimidin-4-yl]-2-[3-(trifluoromethoxy)phenyl]acetamide
82		N-[5-(4-{2-oxo-4-[2-(pyridin-3-yl)acetamido]-1,2-dihydropyrimidin-1-yl}butyl)-1,3,4-thiadiazol-2-yl]-2-phenylacetamide
83		(2S)-2-hydroxy-N-(2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide
84		(2R)-2-hydroxy-N-(2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide

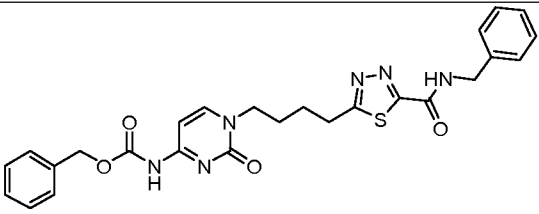
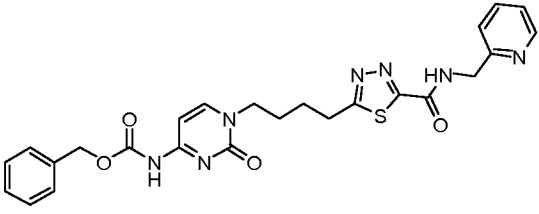
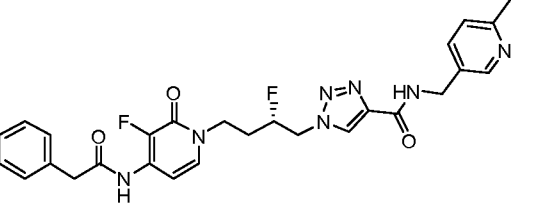
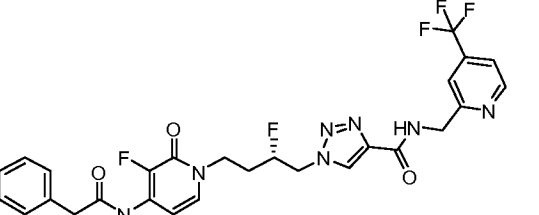
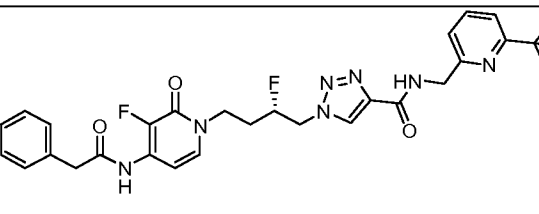
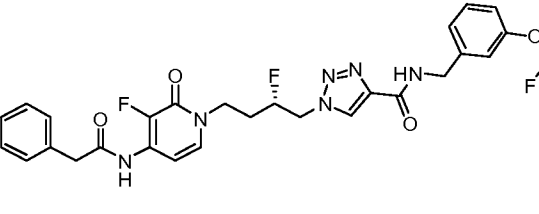
85		tert-butyl N-[(3-{[(2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyrimidin-4-yl)carbamoyl]methyl}phenyl)methyl]carbamate
86		N-[6-(4-{4-[(ethylcarbamoyl)amino]-2-oxo-1,2-dihydropyrimidin-1-yl}butyl)pyridazin-3-yl]-2-phenylacetamide
87		N-{6-[4-(2-oxo-4-{[(propan-2-yl)carbamoyl]amino}-1,2-dihydropyrimidin-1-yl)butyl]pyridazin-3-yl}-2-phenylacetamide
88		N-[6-(4-{4-[(cyclohexylcarbamoyl)amino]-2-oxo-1,2-dihydropyrimidin-1-yl}butyl)pyridazin-3-yl]-2-phenylacetamide
89		N-(6-{4-[2-oxo-4-({[(1R)-1-phenylethyl]carbamoyl}amino)-1,2-dihydropyrimidin-1-yl]butyl}pyridazin-3-yl)-2-phenylacetamide
90		N-(6-{4-[2-oxo-4-({[(1S)-1-phenylethyl]carbamoyl}amino)-1,2-dihydropyrimidin-1-yl]butyl}pyridazin-3-yl)-2-phenylacetamide
91		N-{2-oxo-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyrimidin-1-yl)butyl]-1,2-dihydropyrimidin-4-yl}-2-[3-(trifluoromethoxy)phenyl]acetamide

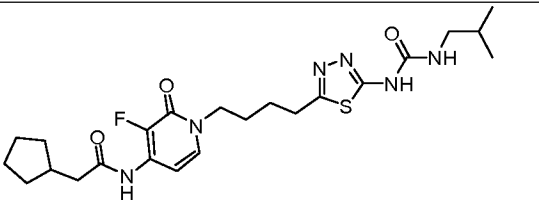
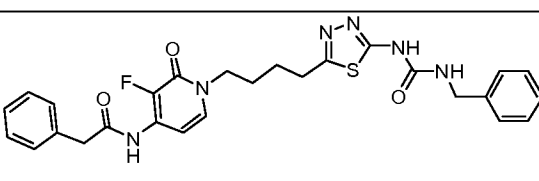
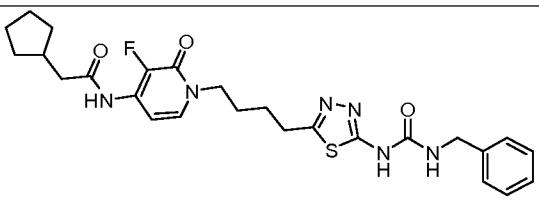
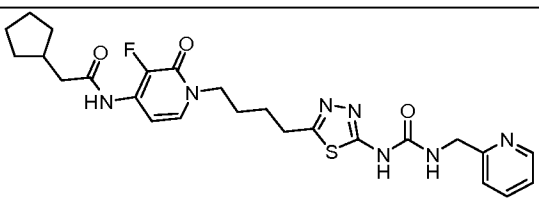
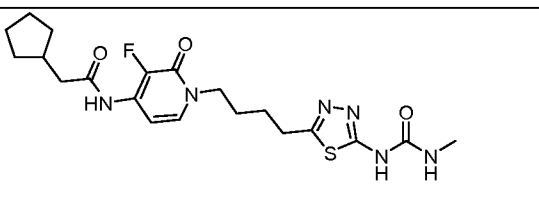
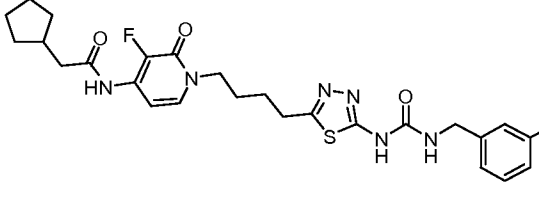
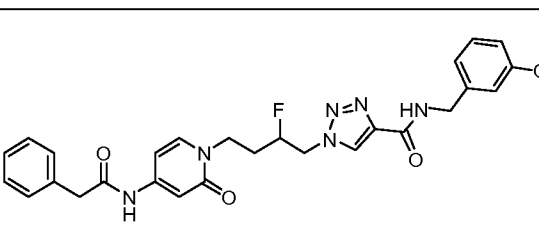
92		N-{6-[4-(4-acetamido-2-oxo-1,2-dihydropyrimidin-1-yl)butyl]pyridazin-3-yl}-2-phenylacetamide
93		methyl N-(2-oxo-1-{4-[6-(2-phenylacetamido)pyridazin-3-yl]butyl}-1,2-dihydropyrimidin-4-yl)carbamate
94		propan-2-yl N-(2-oxo-1-{4-[6-(2-phenylacetamido)pyridazin-3-yl]butyl}-1,2-dihydropyrimidin-4-yl)carbamate
95		cyclohexyl N-(2-oxo-1-{4-[6-(2-phenylacetamido)pyridazin-3-yl]butyl}-1,2-dihydropyrimidin-4-yl)carbamate
96		benzyl N-(2-oxo-1-{4-[6-(2-phenylacetamido)pyridazin-3-yl]butyl}-1,2-dihydropyrimidin-4-yl)carbamate
97		phenyl N-(2-oxo-1-{4-[6-(2-phenylacetamido)pyridazin-3-yl]butyl}-1,2-dihydropyrimidin-4-yl)carbamate
98		2-methylpropyl N-(2-oxo-1-{4-[6-(2-phenylacetamido)pyridazin-3-yl]butyl}-1,2-dihydropyrimidin-4-yl)carbamate
99		N-{6-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyrimidin-1-yl)butyl]pyridazin-3-yl}-2-phenylacetamide

100		(2R)-2-hydroxy-N-(2-oxo-1-{4-[6-(2-phenylacetamido)pyridazin-3-yl]butyl}-1,2-dihydropyrimidin-4-yl)-2-phenylacetamide
101		(2R)-2-hydroxy-N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}-2-phenylacetamide
102		propan-2-yl N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl} carbamate
103		cyclohexyl N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl} carbamate
104		2-methylpropyl N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl} carbamate
105		oxan-4-yl N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl} carbamate
106		N-{6-[4-(2-oxo-4-{[(propan-2-yl)carbamoyl]amino}-1,2-dihydropyrimidin-1-yl)butyl]pyridazin-3-yl}-2-[3-(trifluoromethoxy)phenyl]acetamide

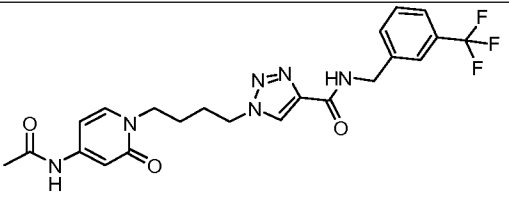
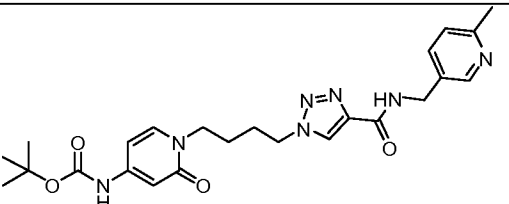
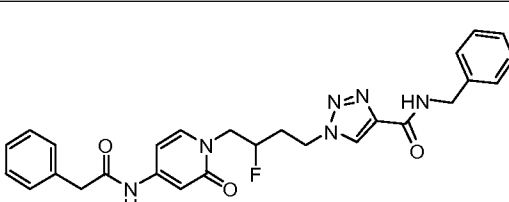
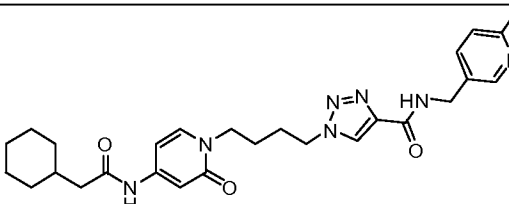
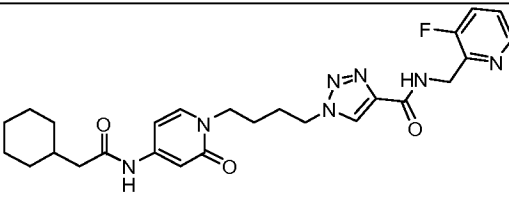
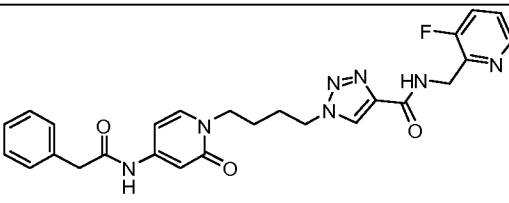
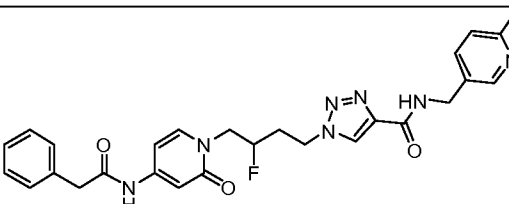
107		N-[6-(4-{4-[(cyclohexylcarbamoyl)amino]-2-oxo-1,2-dihydropyrimidin-1-yl}butyl)pyridazin-3-yl)-2-[3-(trifluoromethoxy)phenyl]acetamide
108		N-(6-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyrimidin-1-yl]butyl}pyridazin-3-yl)-2-[3-(trifluoromethoxy)phenyl]acetamide
109		N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}-3-(pyrrolidin-1-yl)propanamide
110		3-methanesulfonyl-N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}propanamide
111		3-methyl-N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}butanamide
112		2-methoxyethyl N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}carbamate
113		2-hydroxy-N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}acetamide

114		N-[6-(4-{4-[2-(1-methyl-1H-pyrazol-4-yl)acetamido]-2-oxo-1,2-dihydropyrimidin-1-yl} butyl)pyridazin-3-yl]-2-[3-(trifluoromethoxy)phenyl]acetamide
115		N-benzyl-1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyrimidin-1-yl)butyl]-1H-1,2,3-triazole-4-carboxamide
116		N-[6-(4-{2-oxo-4-[2-(pyridin-3-yl)acetamido]-1,2-dihydropyrimidin-1-yl} butyl)pyridazin-3-yl]-2-[3-(trifluoromethoxy)phenyl]acetamide
117		3-hydroxy-N-{2-oxo-1-[4-(6-{2-[3-(trifluoromethoxy)phenyl]acetamido}pyridazin-3-yl)butyl]-1,2-dihydropyrimidin-4-yl}propanamide
118		N-[6-(4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyrimidin-1-yl} butyl)pyridazin-3-yl]-2-[3-(trifluoromethoxy)phenyl]acetamide
119		benzyl N-[1-(4-{5-[(2-hydroxyethyl)carbamoyl]-1,3,4-thiadiazol-2-yl} butyl)-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate
120		benzyl N-[2-oxo-1-(4-{5-[(pyridin-2-yl)methyl]carbamoyl]-1,3,4-thiadiazol-2-yl} butyl)-1,2-dihydropyrimidin-4-yl]carbamate
121		benzyl N-[1-(4-{5-[(2-methoxyethyl)carbamoyl]-1,3,4-thiadiazol-2-yl} butyl)-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate

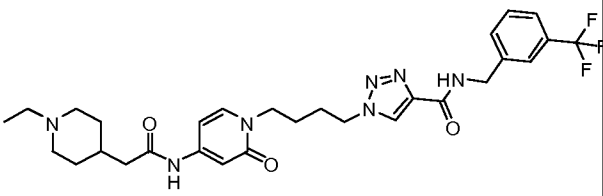
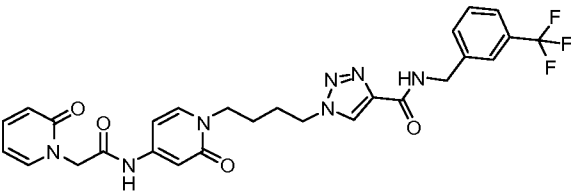
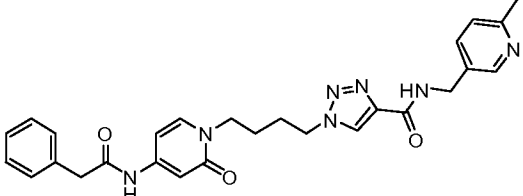
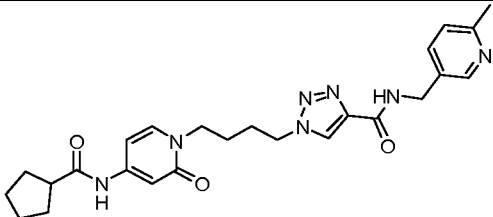
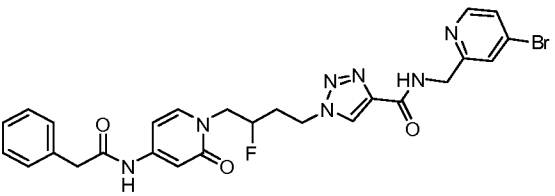
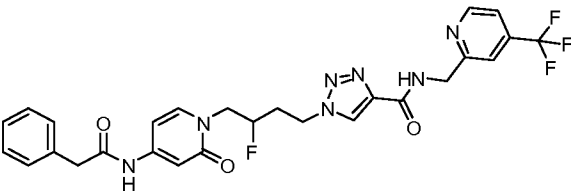
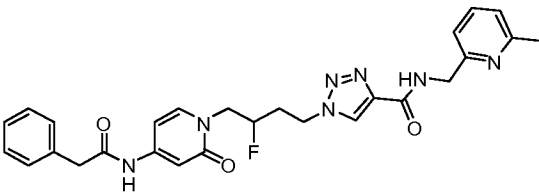
122		benzyl N-(1-{4-[5-(benzylcarbamoyl)-1,3,4-thiadiazol-2-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
123		benzyl N-[2-oxo-1-(4-{5-[(pyridin-2-ylmethyl)carbamoyl]-1,3,4-thiadiazol-2-yl}butyl)-1,2-dihydropyrimidin-4-yl]carbamate
124		(S)-1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-((6-methylpyridin-3-yl)methyl)-1H-1,2,3-triazole-4-carboxamide
125		(S)-1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-((4-(trifluoromethyl)pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide
126		(S)-1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-((6-(trifluoromethyl)pyridin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide
127		(S)-1-(2-fluoro-4-(3-fluoro-2-oxo-4-(2-phenylacetamido)pyridin-1(2H)-yl)butyl)-N-(3-(trifluoromethoxy)benzyl)-1H-1,2,3-triazole-4-carboxamide

128		2-cyclopentyl-N-(3-fluoro-1-(4-(5-(3-isobutylureido)-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)acetamide
129		N-(1-(4-(5-(3-benzylureido)-1,3,4-thiadiazol-2-yl)butyl)-3-fluoro-2-oxo-1,2-dihydropyridin-4-yl)-2-phenylacetamide
130		N-(1-(4-(5-(3-benzylureido)-1,3,4-thiadiazol-2-yl)butyl)-3-fluoro-2-oxo-1,2-dihydropyridin-4-yl)-2-cyclopentylacetamide
131		2-cyclopentyl-N-(3-fluoro-2-oxo-1-(4-(5-(3-(pyridin-2-ylmethyl)ureido)-1,3,4-thiadiazol-2-yl)butyl)-1,2-dihydropyridin-4-yl)acetamide
132		2-cyclopentyl-N-(3-fluoro-1-(4-(5-(3-methylureido)-1,3,4-thiadiazol-2-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)acetamide
133		2-cyclopentyl-N-(3-fluoro-2-oxo-1-(4-(5-(3-(3-(trifluoromethyl)benzyl)ureido)-1,3,4-thiadiazol-2-yl)butyl)-1,2-dihydropyridin-4-yl)acetamide
134		1-{2-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[[3-(trifluoromethoxy)phenyl]methyl]-1H-1,2,3-triazole-4-carboxamide

135		benzyl N-{1-[4-(4-{{(6-methylpyridin-3-yl)methyl}carbamoyl}-1H-1,2,3-triazol-1-yl)butyl]-2-oxo-1,2-dihydropyridin-4-yl} carbamate
136		2-({1-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1H-1,2,3-triazol-4-yl} formamido)acetamide
137		1-[4-(4-{{(1R)-1-carbamoylethyl}carbamoyl}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
138		1-[4-(4-{{(1S)-1-carbamoylethyl}carbamoyl}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
139		tert-butyl N-(2-oxo-1-{4-[4-({3-(trifluoromethyl)phenyl}methyl}carbonyl)-1H-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridin-4-yl) carbamate
140		1-[4-(4-amino-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{{3-(trifluoromethyl)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
141		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{{3-(trifluoromethyl)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide

142		1-[4-(4-acetamido-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
143		tert-butyl N-{1-[4-(4-{[(6-methylpyridin-3-yl)methyl]carbamoyl}-1H-1,2,3-triazol-1-yl)butyl]-2-oxo-1,2-dihydropyridin-4-yl} carbamate
144		1-{3-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
145		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
146		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
147		N-[(3-fluoropyridin-2-yl)methyl]-1-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
148		1-{3-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide

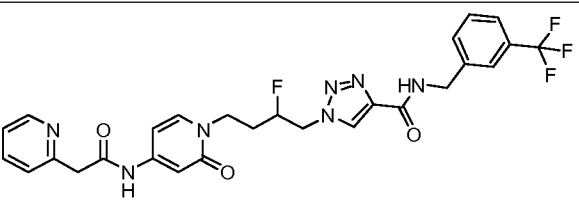
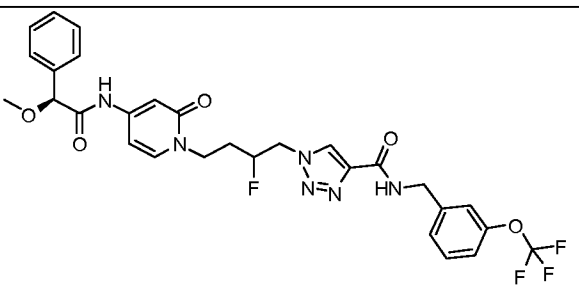
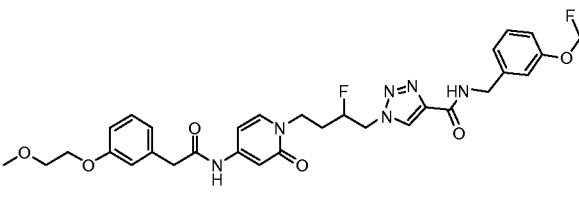
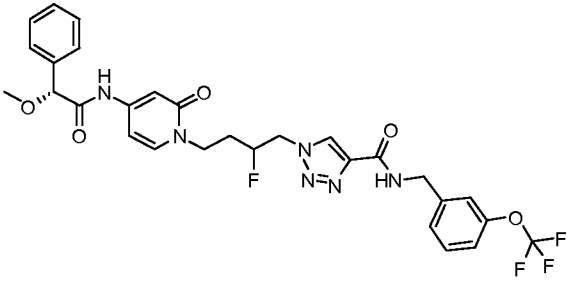
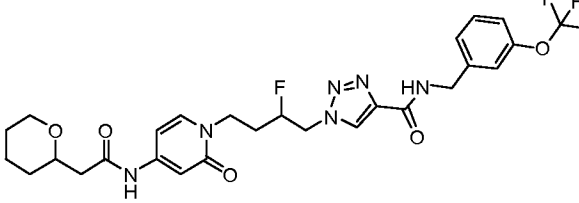
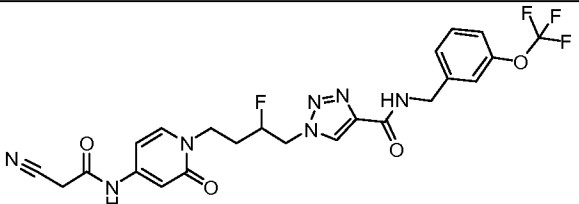
149		1-{3-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
150		1-{2-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
151		1-{2-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
152		1-[4-(4-cyclohexaneamido-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
153		1-{4-[4-(2-cyclopentylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
154		1-{4-[4-(2-cyclopropylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
155		1-(4-{2-oxo-4-[2-(2-oxopyrrolidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

156		1-(4-{4-[2-(1-ethylpiperidin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
157		1-(4-{2-oxo-4-[2-(2-oxo-1,2-dihydropyridin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
158		N-[(6-methylpyridin-3-yl)methyl]-1-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
159		1-[4-(4-cyclopentaneamido-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
160		N-[(4-bromopyridin-2-yl)methyl]-1-{3-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
161		1-{3-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
162		1-{3-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[(6-methylpyridin-2-yl)methyl]-1H-1,2,3-triazole-4-carboxamide

163		N-[(4-bromopyridin-2-yl)methyl]-1-{2-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
164		1-{2-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
165		1-{2-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[(6-methylpyridin-2-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
166		1-(4-{4-[2-(4,4-difluorocyclohexyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
167		1-{4-[4-(2-fluoro-2-phenylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
168		1-(4-{4-[2-(2,2-difluorocyclopropyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
169		1-(4-{2-oxo-4-[2-(thian-4-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

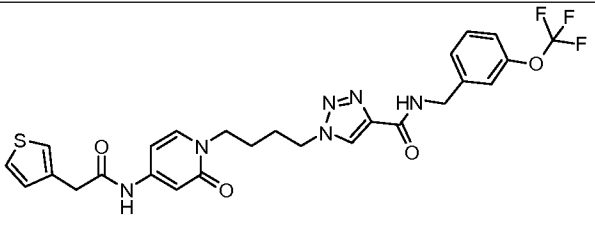
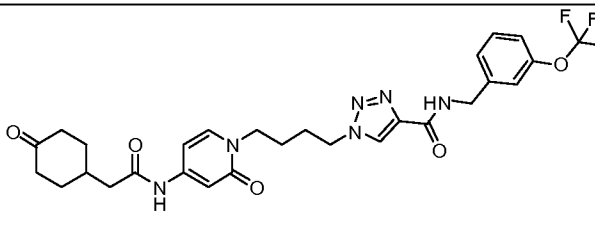
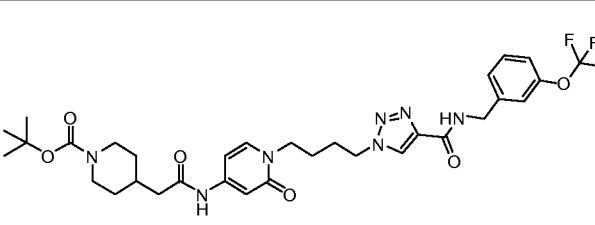
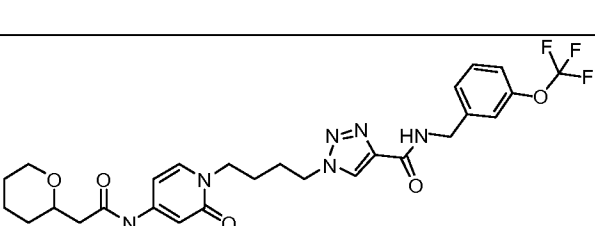
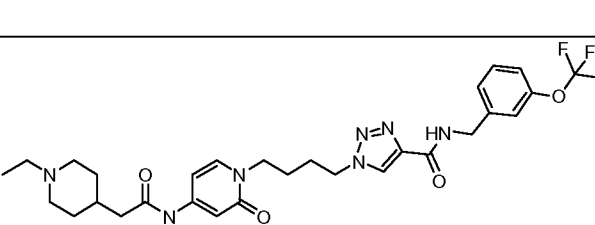
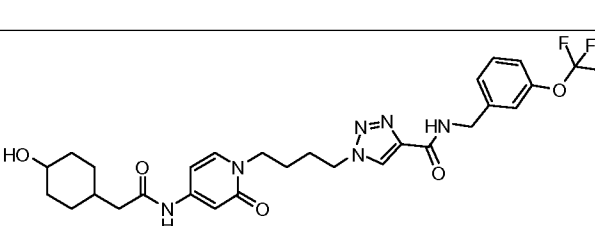
170		1-(4-{4-[2-(4-methoxycyclohexyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
171		(S)-[(2-oxo-1-{4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbonyl]-1H-1,2,3-triazol-1-yl}butyl)-1,2-dihydropyridin-4-yl]carbamoyl(phenyl)methyl acetate
172		1-{4-[6-oxo-4-(2-phenylacetamido)-1,6-dihydropyridazin-1-yl]butyl}-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
173		1-{4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
174		4,4-difluorocyclohexyl N-(2-oxo-1-{4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbonyl]-1H-1,2,3-triazol-1-yl}butyl)-1,2-dihydropyridin-4-yl)carbamate
175		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide

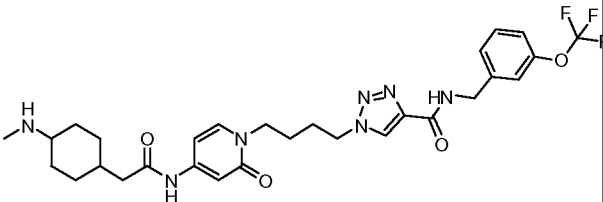
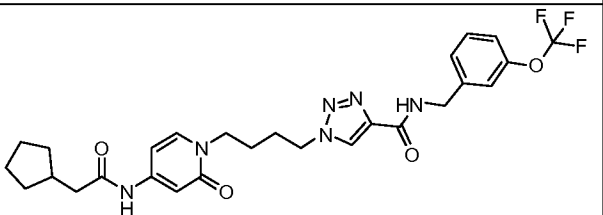
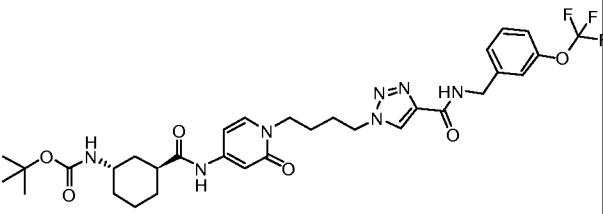
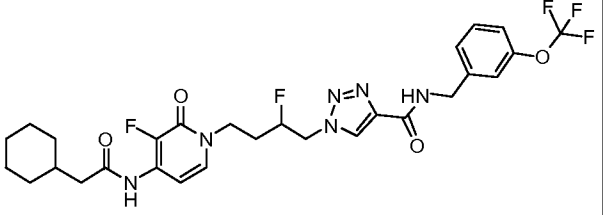
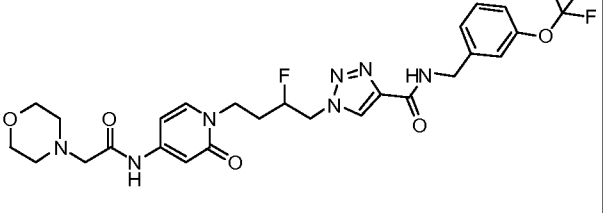
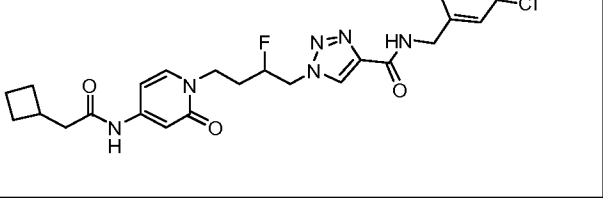
176		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
177		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
178		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
179		1-(4-{4-[2-(1,1-dioxo-1,4-thian-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
180		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
181		N-[(5-chloro-2-fluorophenyl)methyl]-1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
182		1-(2-fluoro-4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

183		1-(2-fluoro-4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethyl)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
184		1-(2-fluoro-4-{4-[(2S)-2-methoxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
185		1-[2-fluoro-4-(4-{2-[3-(2-methoxyethoxy)phenyl]acetamido}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
186		1-(2-fluoro-4-{4-[(2R)-2-methoxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
187		1-(2-fluoro-4-{4-[2-(oxan-2-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
188		1-{4-[4-(2-cyanoacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide

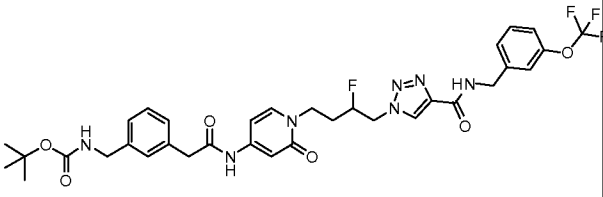
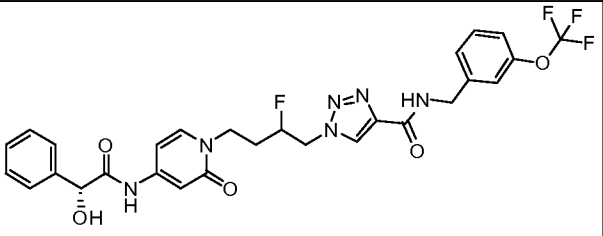
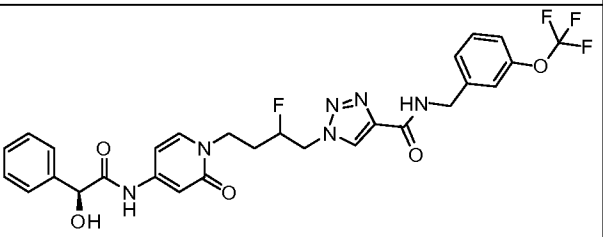
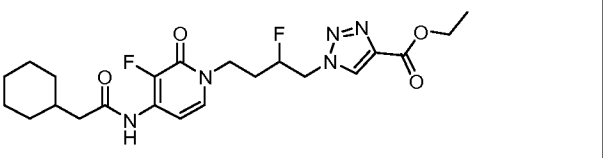
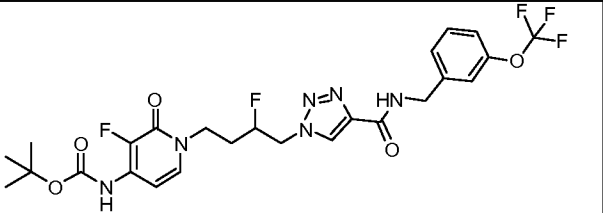
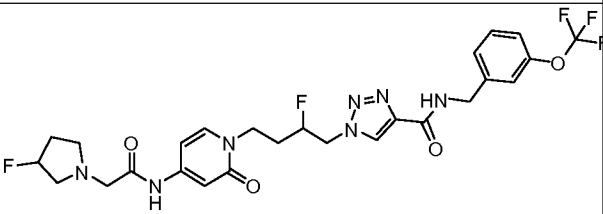
189		1-(2-fluoro-4-{4-[2-(1-methyl-1H-imidazol-2-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
190		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide
191		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-(pyridin-3-ylmethyl)-1H-1,2,3-triazole-4-carboxamide
192		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-(2-hydroxy-1-phenylethyl)-1H-1,2,3-triazole-4-carboxamide
193		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{1-[3-(trifluoromethoxy)phenyl]ethyl}-1H-1,2,3-triazole-4-carboxamide
194		1-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
195		1-(2-fluoro-4-{4-[2-(oxan-2-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide

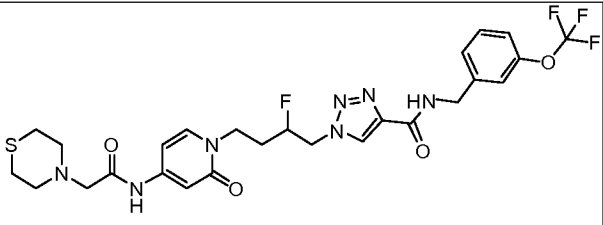
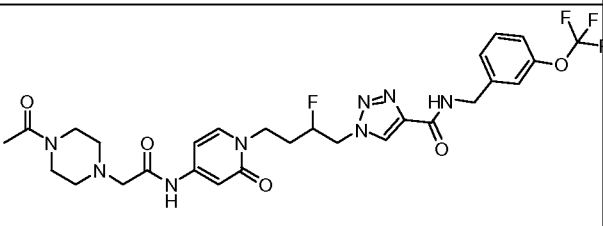
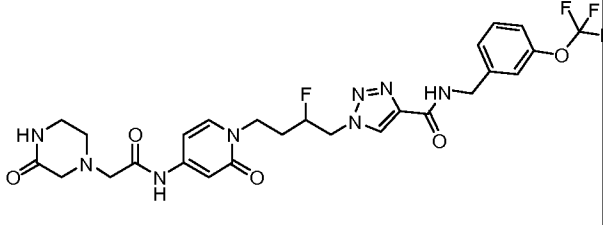
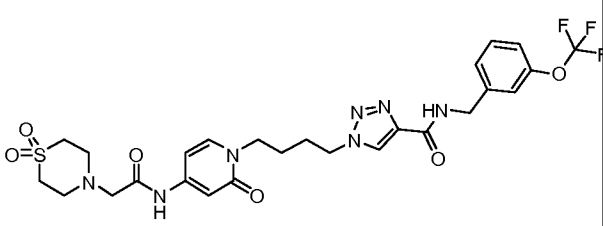
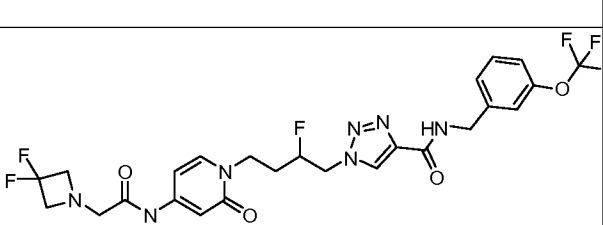
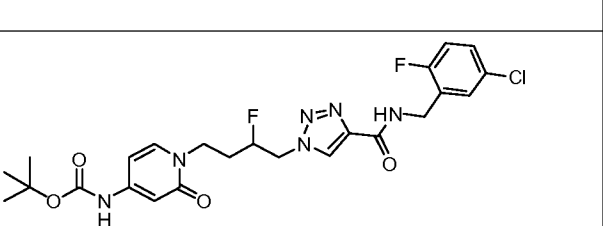
196		1-(2-fluoro-4-{4-[2-(oxan-3-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
197		1-(2-fluoro-4-{4-[2-(oxan-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
198		1-(2-fluoro-4-{2-oxo-4-[2-(thian-4-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
199		1-{4-[4-(2-cyclopentylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
200		1-(2-fluoro-4-{2-oxo-4-[2-(oxolan-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
201		1-{4-[4-(2-cyclobutylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
202		1-(4-{2-oxo-4-[2-(thiophen-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

203		1-(4-{2-oxo-4-[2-(thiophen-3-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
204		1-(4-{2-oxo-4-[2-(4-oxocyclohexyl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
205		tert-butyl 4-{[(2-oxo-1-{4-[4-([3-(trifluoromethoxy)phenyl]methyl)carbonyl]-1H-1,2,3-triazol-1-yl}butyl)-1,2-dihydropyridin-4-yl]carbonyl}piperidine-1-carboxylate
206		1-(4-{4-[2-(oxan-2-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
207		1-(4-{4-[2-(1-ethylpiperidin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
208		1-(4-{4-[2-(4-hydroxycyclohexyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

209		1-[4-(4-{2-[4-(methylamino)cyclohexyl]acetamido}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
210		1-{4-[4-(2-cyclopentylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
211		tert-butyl N-[(1S,3S)-3-[(2-oxo-1-{4-([3-(trifluoromethoxy)phenyl)methyl]carbonyl)-1,2,3-triazol-1-yl]butyl}-1,2-dihydropyridin-4-yl)carbonyl]cyclohexyl]carbamate
212		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
213		1-(2-fluoro-4-{4-[2-(morpholin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl]butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
214		N-[(5-chloro-2-fluorophenyl)methyl]-1-{4-[4-(2-cyclobutylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-1H-1,2,3-triazole-4-carboxamide

215		N-[(5-chloro-2-fluorophenyl)methyl]-1-(2-fluoro-4-{4-[2-(oxan-2-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-1H-1,2,3-triazole-4-carboxamide
216		N-[(5-chloro-2-fluorophenyl)methyl]-1-{2-fluoro-4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
217		1-{4-[4-(2-cyclobutylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
218		1-(4-{4-[2-(1-ethylpiperidin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
219		tert-butyl 4-{{[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperidine-1-carboxylate
220		1-{4-[4-(2-cyclopentylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
221		tert-butyl 3-{{[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperidine-1-carboxylate

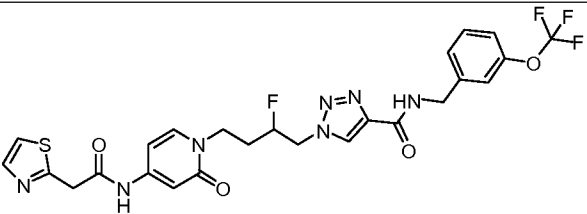
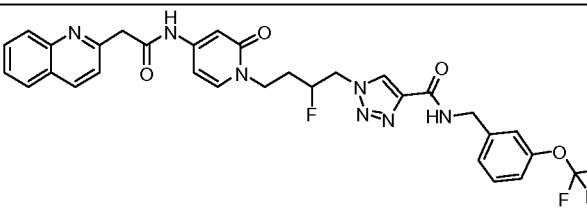
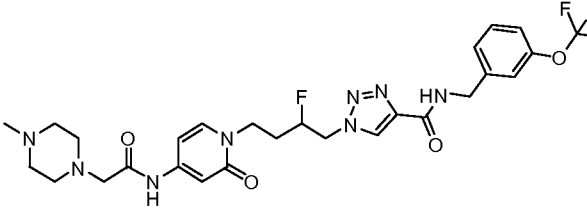
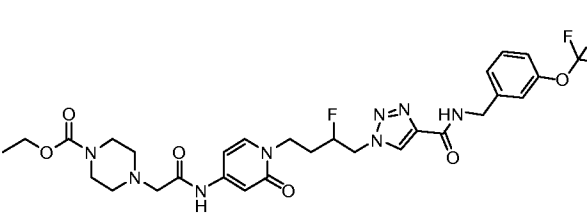
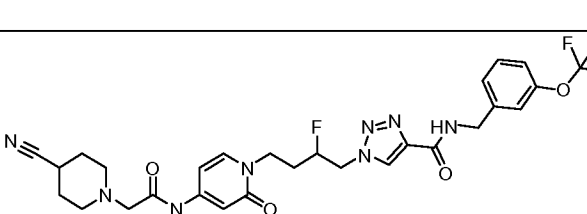
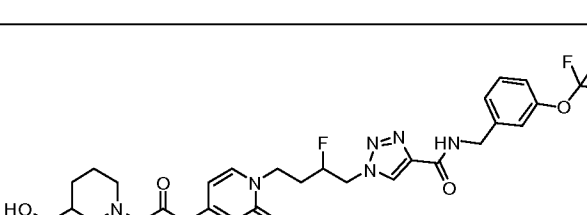
		yl)carbamoyl]methyl}pyrrolidine-1-carboxylate
222		tert-butyl N-[(3-{{(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl)methyl}carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}phenyl)methyl]carbamate
223		1-(2-fluoro-4-{4-[(2R)-2-hydroxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
224		1-(2-fluoro-4-{4-[(2S)-2-hydroxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
225		ethyl 1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-1H-1,2,3-triazole-4-carboxylate
226		tert-butyl N-(3-fluoro-1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl)methyl}carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamate
227		1-(2-fluoro-4-{4-[2-(3-fluoropyrrolidin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

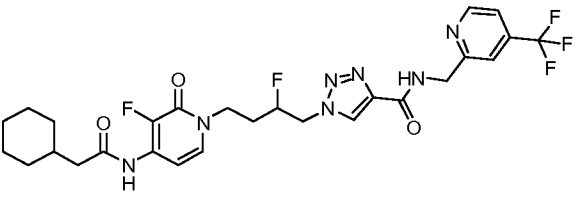
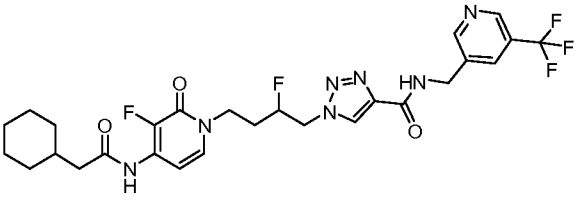
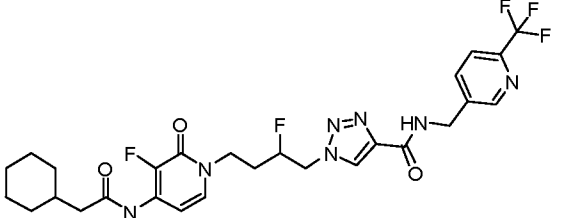
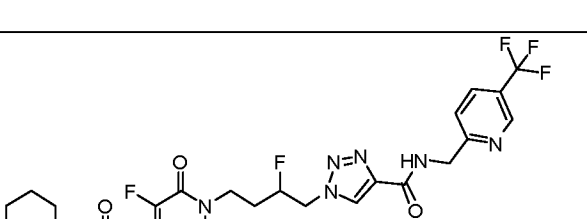
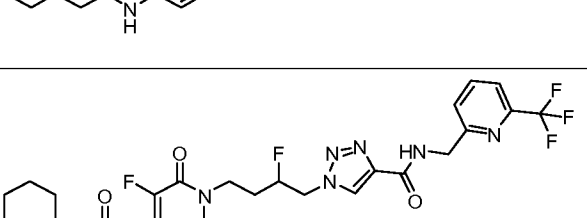
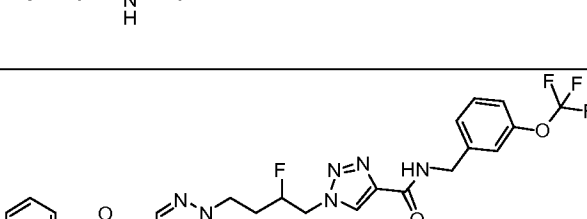
228		1-(2-fluoro-4-{2-oxo-4-[2-(thiomorpholin-4-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
229		1-(4-{4-[2-(4-acetylpiperazin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
230		1-(2-fluoro-4-{2-oxo-4-[2-(3-oxopiperazin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
231		1-(4-{4-[2-(1,1-dioxo-1,4-thiomorpholin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
232		1-(4-{4-[2-(3,3-difluoroazetidin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
233		tert-butyl N-{1-[4-(4-{[(5-chloro-2-fluorophenyl)methyl]carbamoyl}-1H-1,2,3-triazol-1-yl)-3-fluorobutyl]-2-oxo-1,2-dihydropyridin-4-yl}carbamate

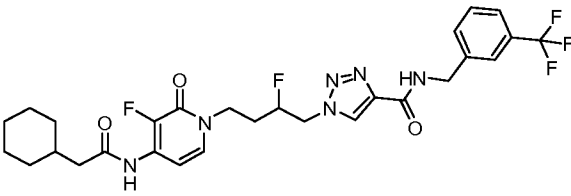
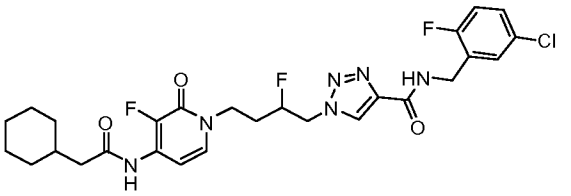
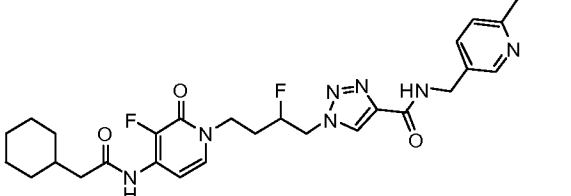
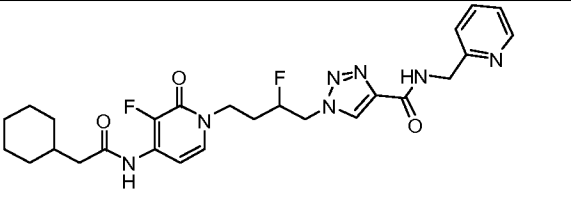
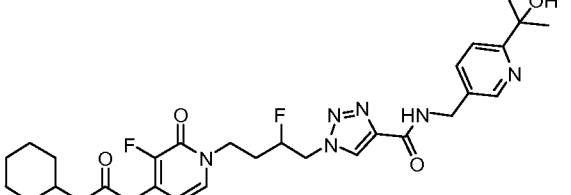
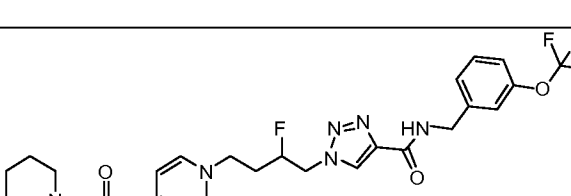
234		tert-butyl N-(1-({3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamate
235		1-(4-{4-[2-(3-cyanophenyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
236		1-(4-{4-[2-(2-chloropyridin-3-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
237		1-[2-fluoro-4-(4-{2-[3-(morpholin-4-yl)phenyl]acetamido}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
238		1-(4-{4-[2-(6-chloropyridin-3-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
239		tert-butyl N-[(1r,4r)-4-{[(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}cyclohexyl]carbamate

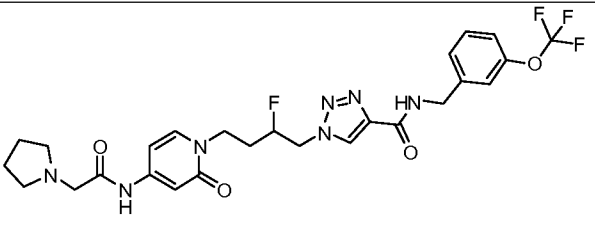
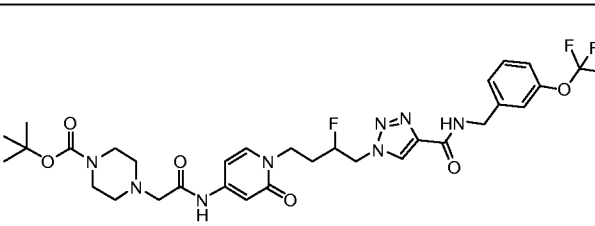
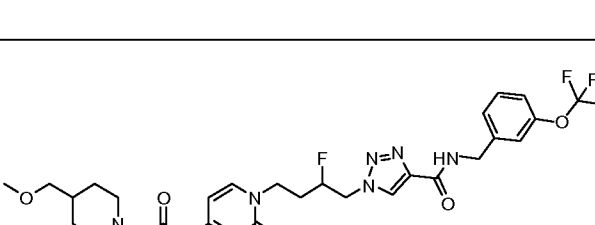
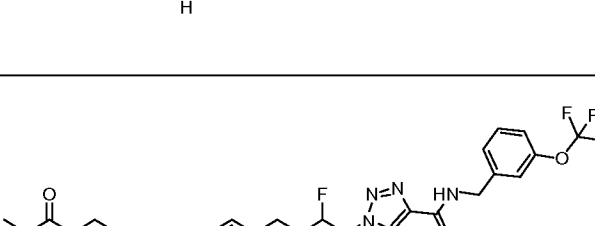
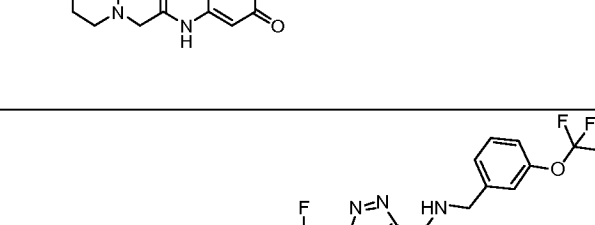
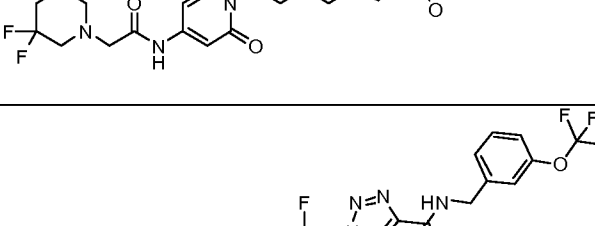
240		1-(2-fluoro-4-{4-[2-(6-methoxypyridin-3-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
241		tert-butyl N-[(1s,4s)-4-{[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}cyclohexyl]carbamate
242		1-[4-(4-{2-[1-(2,2-difluoroethyl)piperidin-4-yl]acetamido}-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
243		1-(4-{4-[2-(5-chloro-3-fluoropyridin-2-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
244		1-(4-{4-[2-(1-acetylpiperidin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
245		tert-butyl 3-{[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperidine-1-carboxylate

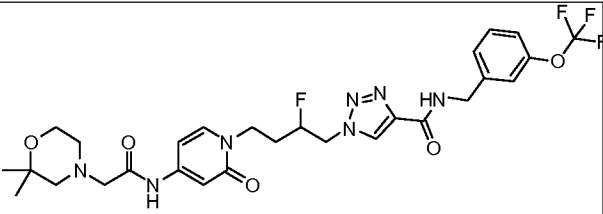
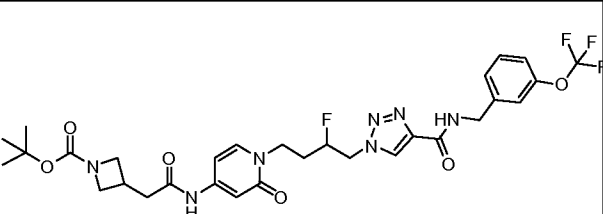
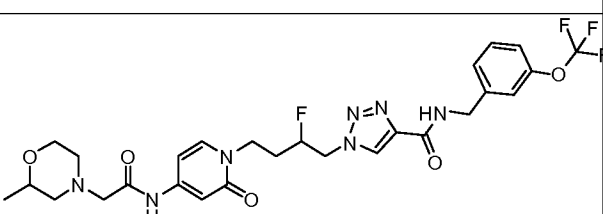
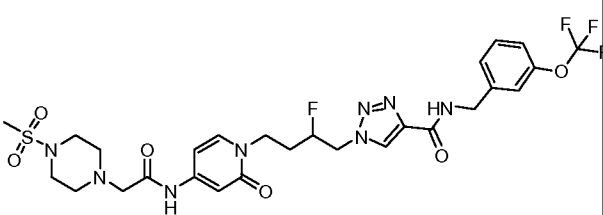
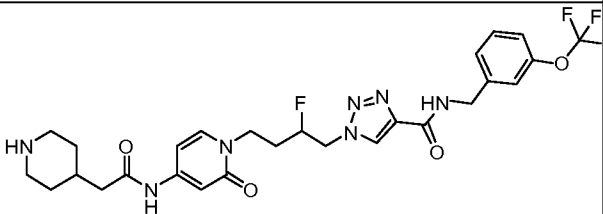
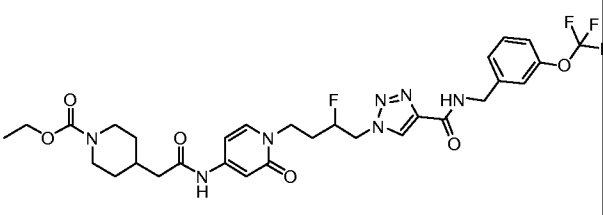
246		1-(2-fluoro-4-{2-oxo-4-[2-(pyridin-3-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
247		1-(2-fluoro-4-{2-oxo-4-[2-(1,3-thiazol-4-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
248		1-(2-fluoro-4-{4-[2-(6-methylpyridin-3-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
249		tert-butyl N-[(1R,3R)-3-[(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbamoyl]-1H-1,2,3-triazol-1-yl}butyl)-2-oxo-1,2-dihydropyridin-4-yl]carbamoyl]cyclohexyl]carbamate
250		1-(2-fluoro-4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
251		1-(2-fluoro-4-{4-[2-(6-methoxypyridin-2-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide

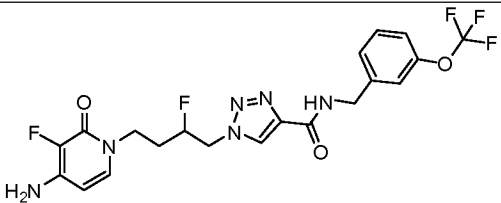
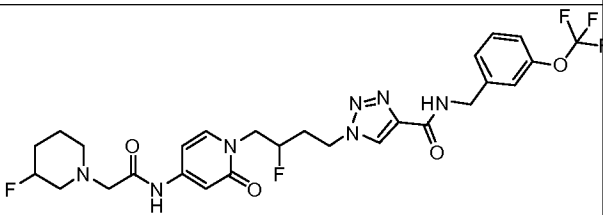
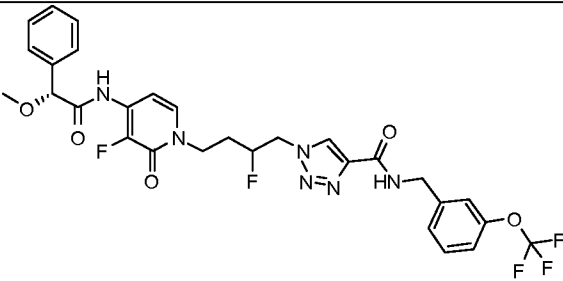
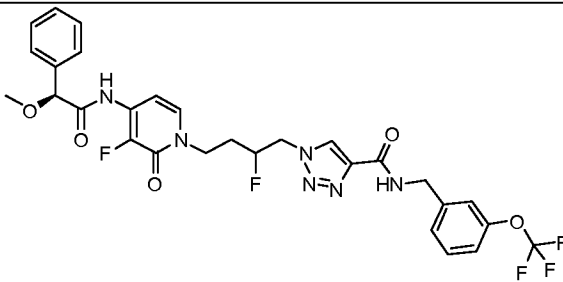
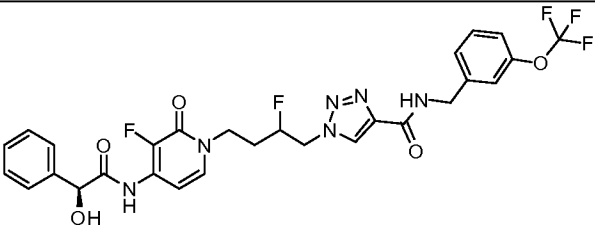
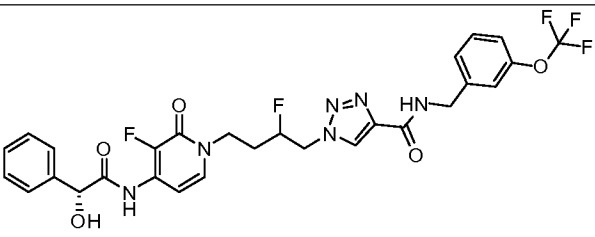
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253		1-(2-fluoro-4-{2-oxo-4-[2-(quinolin-2-yl)acetamido]-1,2-dihydropyridin-1-yl} butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
254		1-(2-fluoro-4-{4-[2-(4-methylpiperazin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl} butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
255		ethyl 4-{[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperazine-1-carboxylate
256		1-(4-{4-[2-(4-cyanopiperidin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
257		1-[2-fluoro-4-(4-{2-[3-(hydroxymethyl)piperidin-1-yl]acetamido}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

258		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
259		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
260		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
261		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[5-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
262		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
263		1-{2-fluoro-4-[6-oxo-4-(2-phenylacetamido)-1,6-dihydropyridazin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

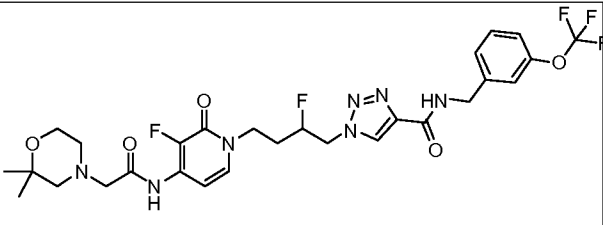
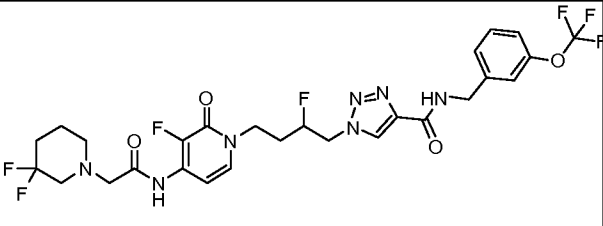
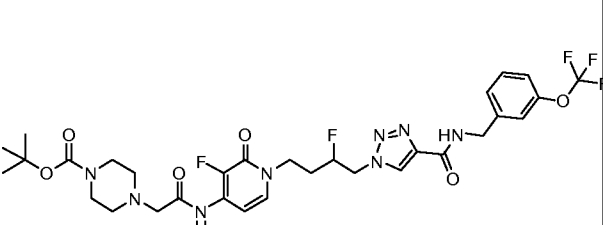
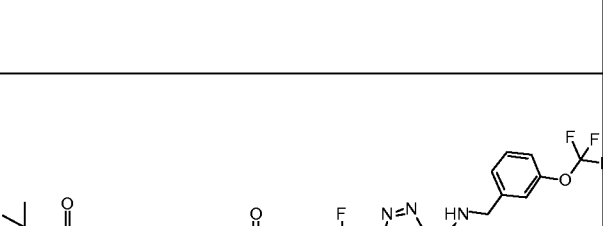
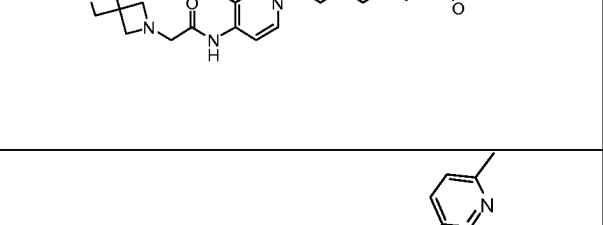
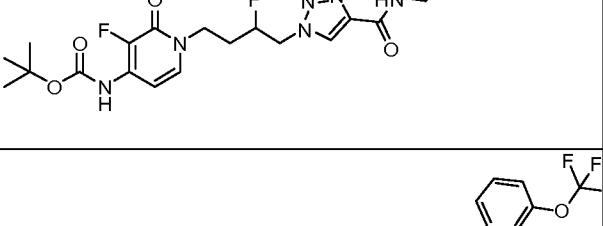
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265		N-[(5-chloro-2-fluorophenyl)methyl]-1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-1H-1,2,3-triazole-4-carboxamide
266		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
267		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide
268		1-{4-[4-(2-cyclohexylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[6-(2-hydroxypropan-2-yl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
269		1-(2-fluoro-4-{2-oxo-4-[2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

270		1-(2-fluoro-4-{2-oxo-4-[2-(pyrrolidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
271		tert-butyl 4-[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperazine-1-carboxylate
272		1-[2-fluoro-4-(4-{2-[4-(methoxymethyl)piperidin-1-yl]acetamido}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
273		methyl 1-[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperidine-4-carboxylate
274		1-(4-{4-[2-(3,3-difluoropiperidin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
275		1-(2-fluoro-4-{4-[2-(3-fluoropiperidin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

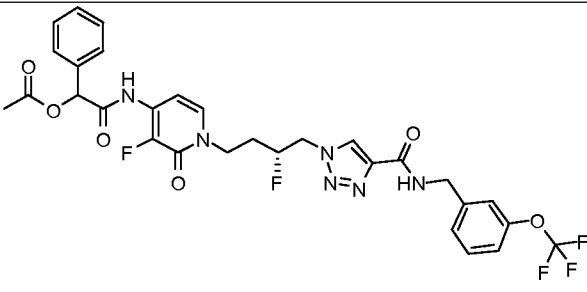
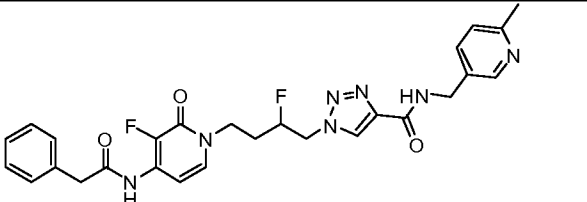
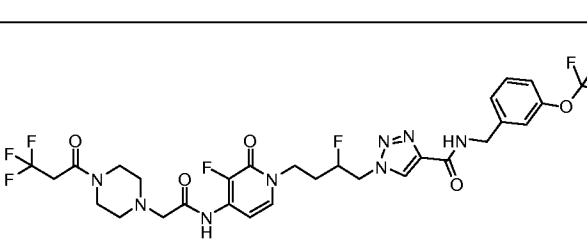
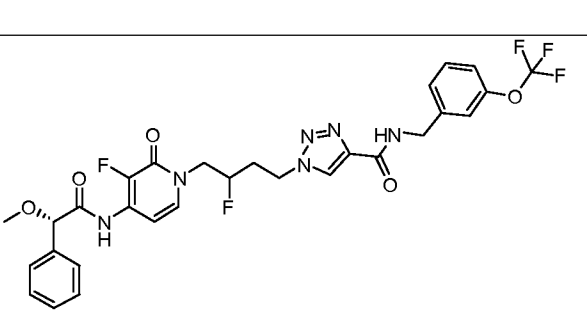
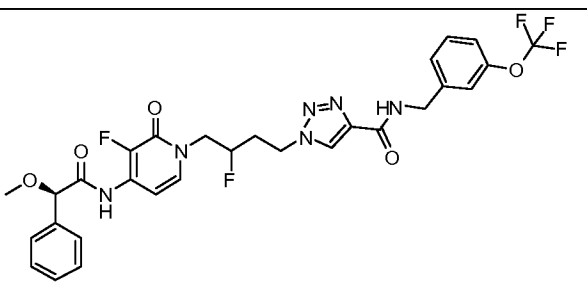
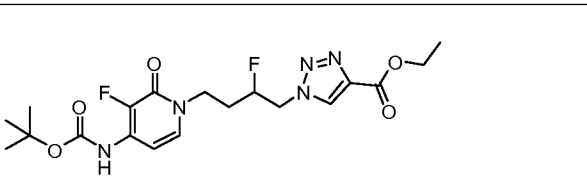
276		1-(4-{4-[2-(2,2-dimethylmorpholin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
277		tert-butyl 3-[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl]azetidine-1-carboxylate
278		1-(2-fluoro-4-{4-[2-(2-methylmorpholin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
279		1-(2-fluoro-4-{4-[2-(4-methanesulfonylpiperazin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
280		1-(2-fluoro-4-{2-oxo-4-[2-(piperidin-4-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
281		ethyl 4-[(1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl]piperidine-1-carboxylate

282		1-[4-(4-amino-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
283		1-(3-fluoro-4-{4-[2-(3-fluoropiperidin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
284		1-(2-fluoro-4-{3-fluoro-4-[(2R)-2-methoxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
285		1-(2-fluoro-4-{3-fluoro-4-[(2S)-2-methoxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
286		1-(2-fluoro-4-{3-fluoro-4-[(2S)-2-hydroxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
287		1-(2-fluoro-4-{3-fluoro-4-[(2R)-2-hydroxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide

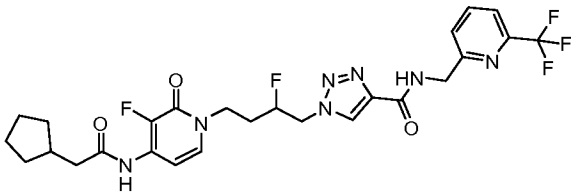
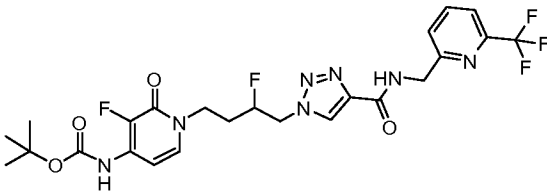
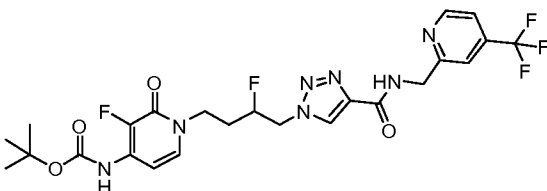
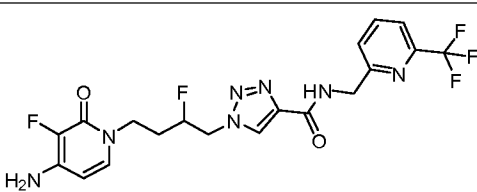
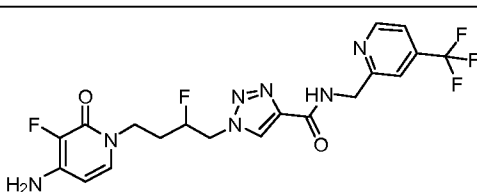
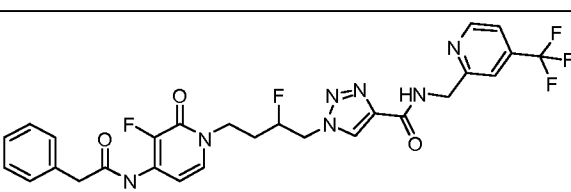
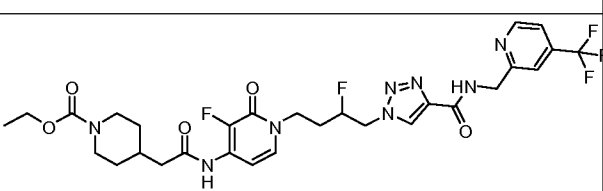
288		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
289		tert-butyl 4-{{[(3-fluoro-1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperidine-1-carboxylate
290		1-(4-{4-[2-(4,4-difluoropiperidin-1-yl)acetamido]-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
291		1-(2-fluoro-4-{3-fluoro-4-[2-(3-fluoropiperidin-1-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
292		ethyl 4-{{[(3-fluoro-1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperazine-1-carboxylate
293		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(pyrrolidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide

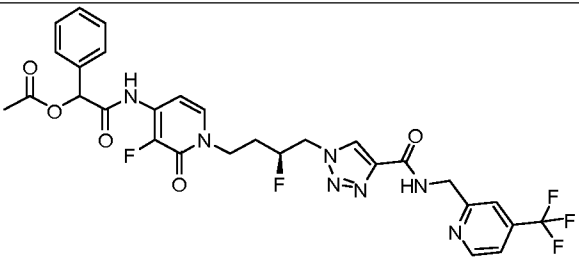
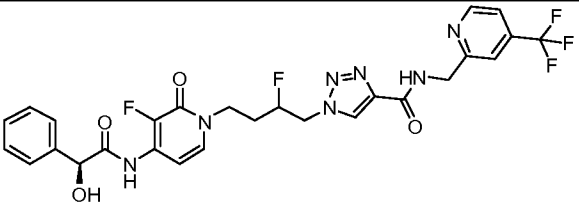
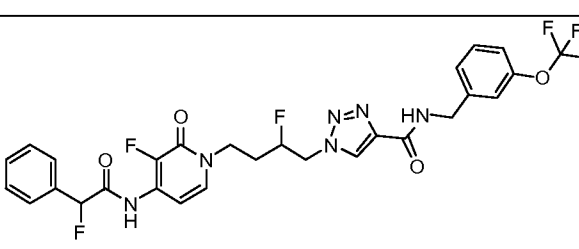
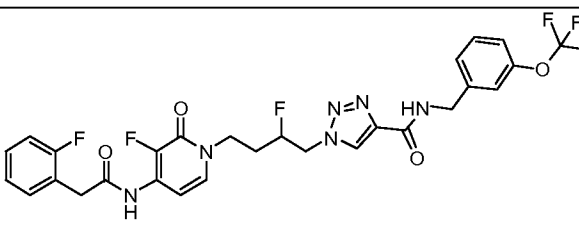
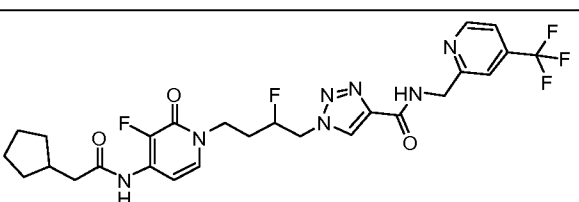
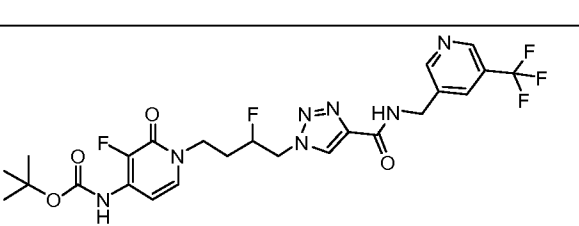
294		1-(4-{4-[2-(2,2-dimethylmorpholin-4-yl)acetamido]-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
295		1-(4-{4-[2-(3,3-difluoropiperidin-1-yl)acetamido]-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
296		tert-butyl 4-[[{(3-fluoro-1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl]piperazine-1-carboxylate
297		tert-butyl 6-[[{(3-fluoro-1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl]-2,6-diazaspiro[3.3]heptane-2-carboxylate
298		tert-butyl N-{3-fluoro-1-[3-fluoro-4-(4-{{[6-methylpyridin-3-yl]methyl} carbamoyl]-1H-1,2,3-triazol-1-yl)butyl]-2-oxo-1,2-dihydropyridin-4-yl} carbamate
299		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(piperidin-4-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

300		ethyl 4-{{[(3-fluoro-1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperidine-1-carboxylate
301		1-[2-fluoro-4-(3-fluoro-2-oxo-4-{2-[1-(3,3,3-trifluoropropanoyl)piperidin-4-yl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N-{{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
302		1-(2-fluoro-4-{3-fluoro-4-[2-(1-methanesulfonylpiperidin-4-yl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
303		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
304		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
305		(S)-[(3-fluoro-1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl](phenyl)methyl acetate

306		(R)-[(3-fluoro-1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl](phenyl)methyl acetate
307		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
308		1-[2-fluoro-4-(3-fluoro-2-oxo-4-{2-[4-(3,3,3-trifluoropropanoyl)piperazin-1-yl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
309		1-(3-fluoro-4-{3-fluoro-4-[(2S)-2-methoxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
310		1-(3-fluoro-4-{3-fluoro-4-[(2R)-2-methoxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
311		ethyl 1-[4-(4-{{(tert-butoxy)carbonyl}amino}-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-1H-1,2,3-triazole-4-carboxylate

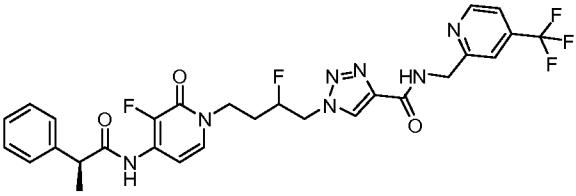
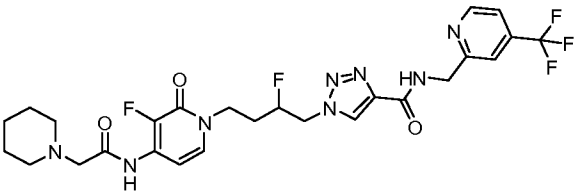
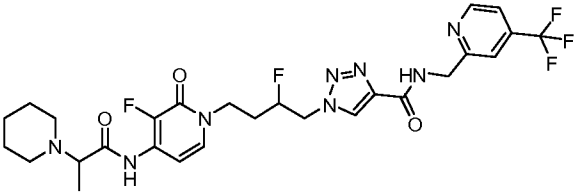
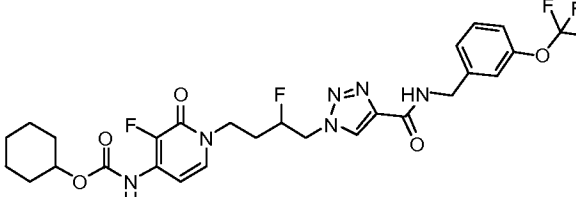
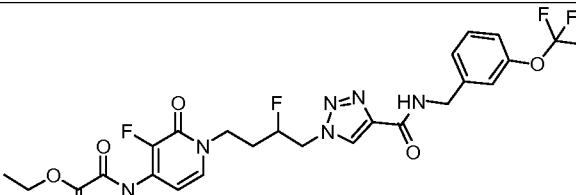
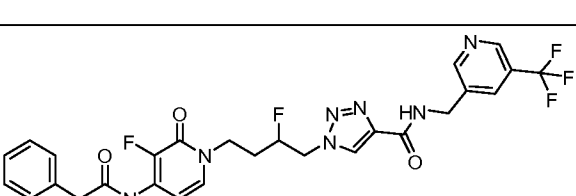
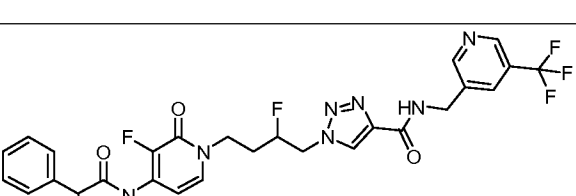
312		1-(2-fluoro-4-{3-fluoro-4-[(2S)-2-methoxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
313		1-(2-fluoro-4-{3-fluoro-4-[(2R)-2-methoxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
314		tert-butyl 4-[[{(3-fluoro-1-{2-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperidine-1-carboxylate
315		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-oxo-2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
316		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylpropanamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
317		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide

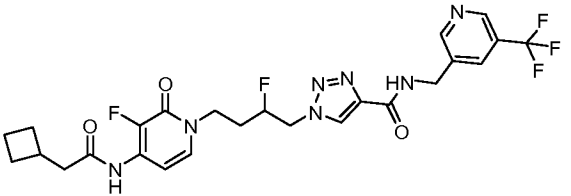
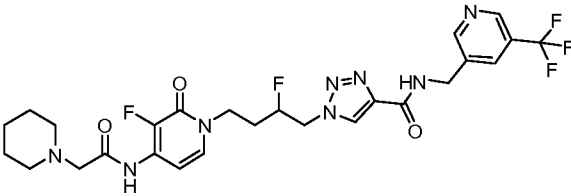
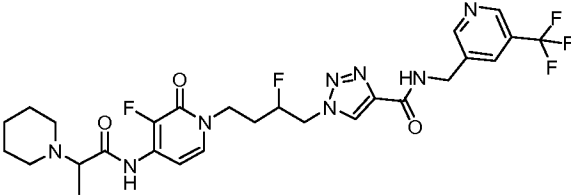
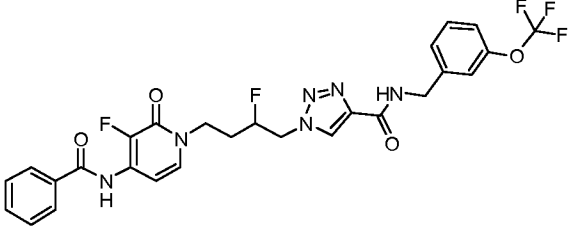
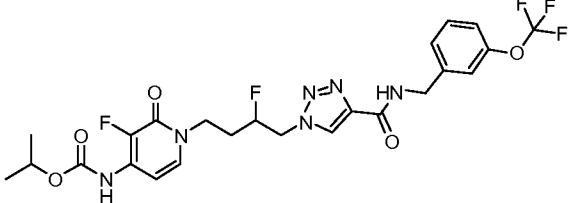
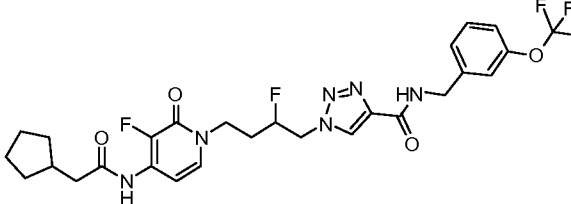
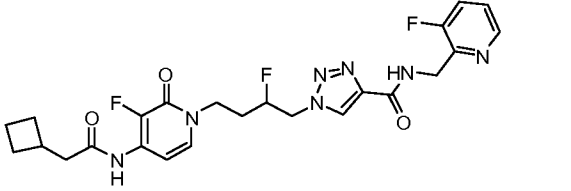
318		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{[6-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
319		tert-butyl N-(3-fluoro-1-{3-fluoro-4-[4-({[6-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamate
320		tert-butyl N-(3-fluoro-1-{3-fluoro-4-[4-({[4-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamate
321		1-[4-(4-amino-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{{[6-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
322		1-[4-(4-amino-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
323		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
324		ethyl 4-{{[(3-fluoro-1-{3-fluoro-4-[4-({[4-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl

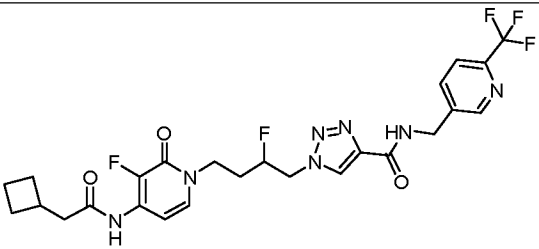
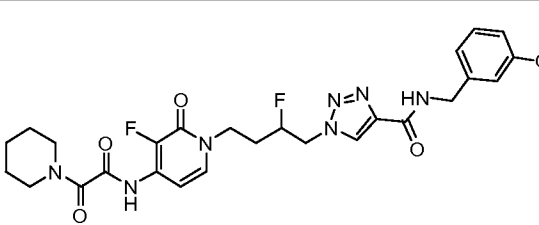
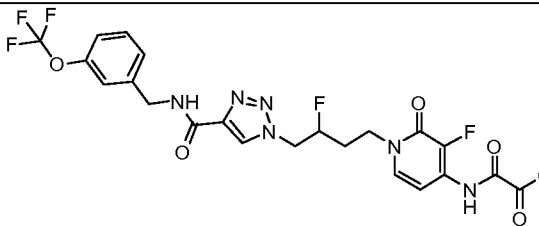
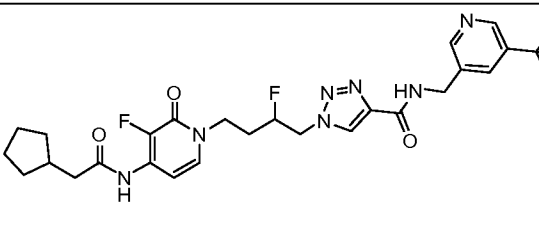
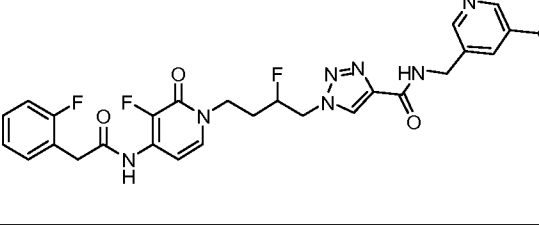
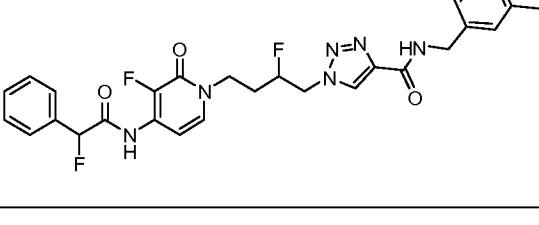
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325		(S)-[(3-fluoro-1-{3-fluoro-4-[4-({[4-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl](phenyl)methyl acetate
326		1-(2-fluoro-4-{3-fluoro-4-[(2S)-2-hydroxy-2-phenylacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
327		1-{2-fluoro-4-[3-fluoro-4-(2-fluoro-2-phenylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
328		1-(2-fluoro-4-{3-fluoro-4-[2-(2-fluorophenyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
329		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
330		tert-butyl N-(3-fluoro-1-{3-fluoro-4-[4-({[5-(trifluoromethyl)pyridin-3-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamate

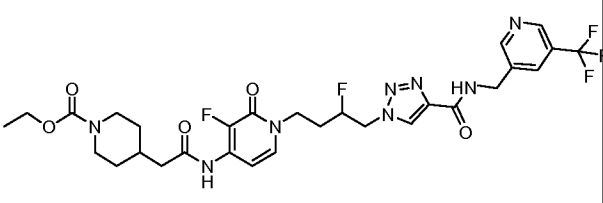
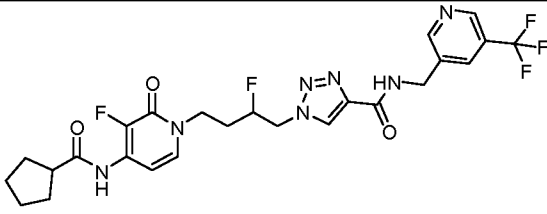
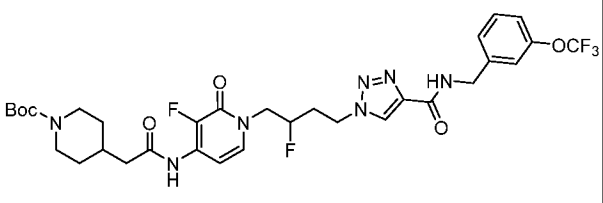
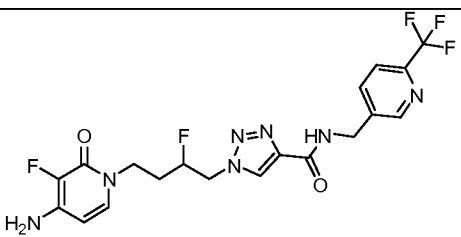
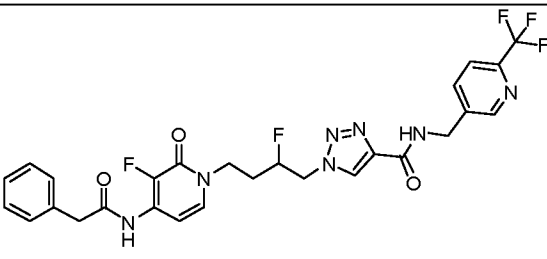
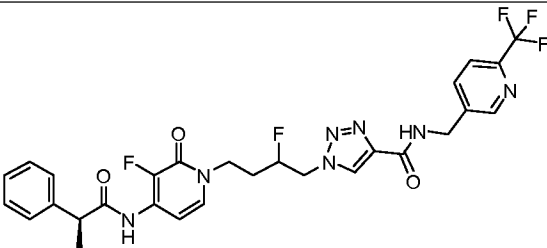
331		1-[4-(4-amino-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
332		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
333		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-oxo-2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
334		1-(4-{4-[2-(2,4-difluorophenyl)acetamido]-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
335		1-(4-{4-[2-(2,6-difluorophenyl)acetamido]-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
336		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide

337		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)propanamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
338		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[6-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
339		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
340		1-{4-[4-(3,3-dimethylbutanamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
341		1-[4-(4-cyclohexaneamido-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
342		1-[4-(4-cyclopentaneamido-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

343		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[(2S)-2-phenylpropanamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
344		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
345		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)propanamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
346		cyclohexyl N-(3-fluoro-1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl}carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamate
347		ethyl [(3-fluoro-1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl}carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]formate
348		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
349		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[(2S)-2-phenylpropanamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide

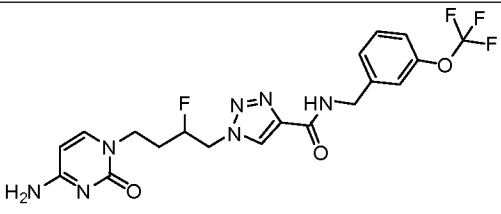
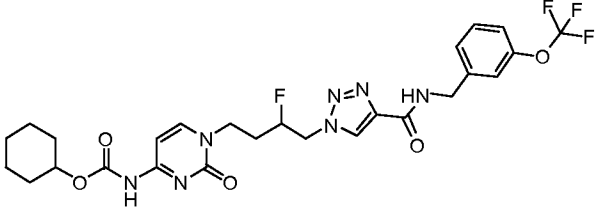
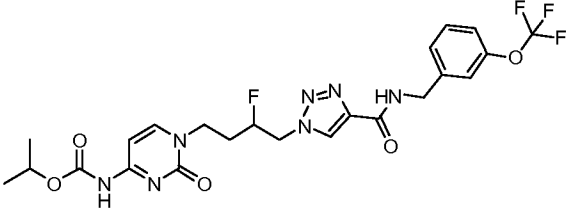
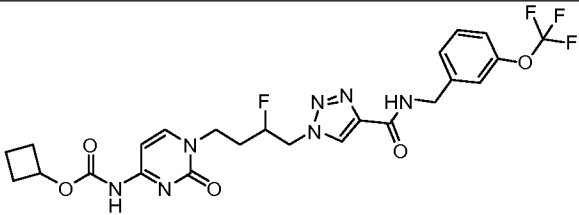
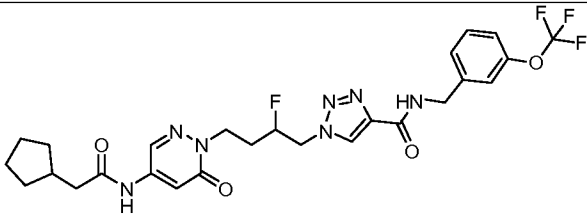
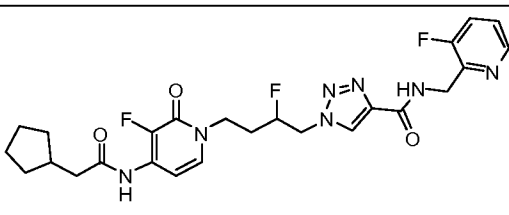
350		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{5-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
351		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{5-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
352		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)propanamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{5-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
353		1-[4-(4-benzamido-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
354		propan-2-yl N-(3-fluoro-1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbamoyl]-1H-1,2,3-triazol-1-yl}butyl)-2-oxo-1,2-dihydropyridin-4-yl)carbamate
355		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
356		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,3-triazole-4-carboxamide

		yl)methyl]-1H-1,2,3-triazole-4-carboxamide
357		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{6-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
358		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
359		[(3-fluoro-1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbonyl]-1H-1,2,3-triazol-1-yl}butyl)-2-oxo-1,2-dihydropyridin-4-yl]carbonyl]formic acid
360		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{5-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
361		1-(2-fluoro-4-{3-fluoro-4-[2-(2-fluorophenyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{5-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
362		1-{2-fluoro-4-[3-fluoro-4-(2-fluoro-2-phenylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{{5-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide

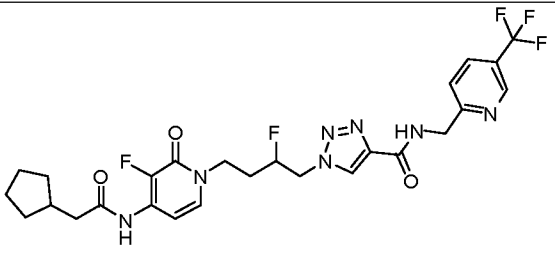
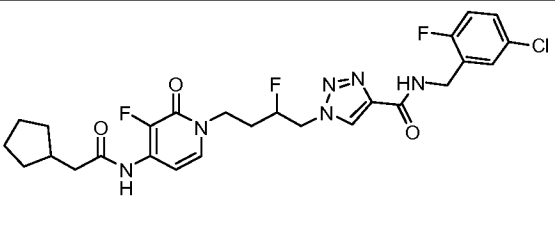
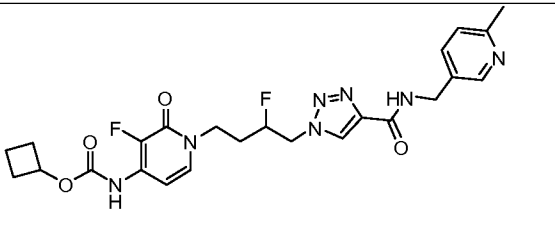
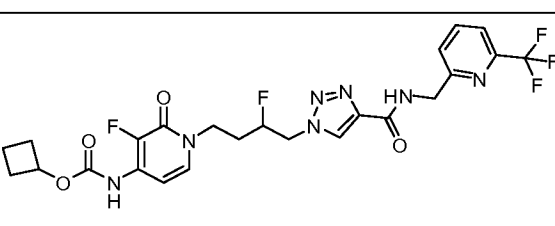
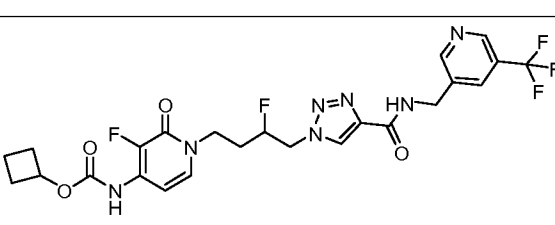
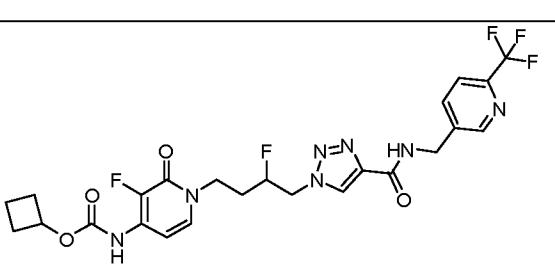
363		ethyl 4-([(3-fluoro-1-{3-fluoro-4-[4-([5-(trifluoromethyl)pyridin-3-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperidine-1-carboxylate
364		1-[4-(4-cyclopentaneamido-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{[5-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
365		tert-butyl 4-(2-((3-fluoro-1-(2-fluoro-4-(4-((3-(trifluoromethoxy)benzyl)carbamoyl)-1H-1,2,3-triazol-1-yl)butyl)-2-oxo-1,2-dihydropyridin-4-yl)amino)-2-oxoethyl)piperidine-1-carboxylate
366		1-[4-(4-amino-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
367		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
368		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[(2S)-2-phenylpropanamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide

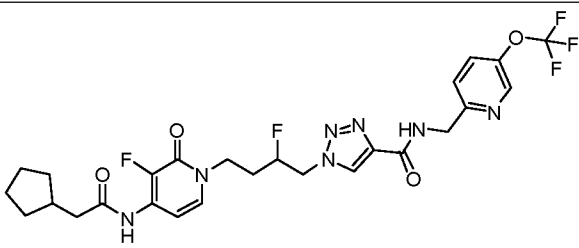
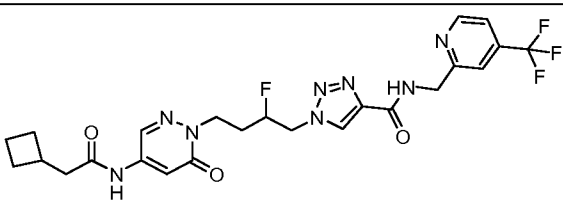
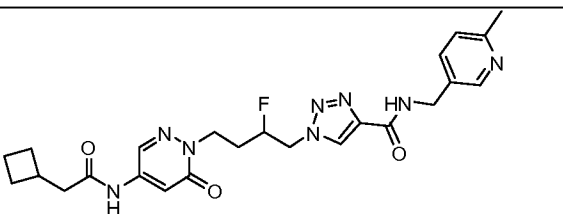
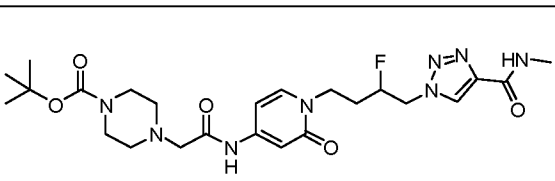
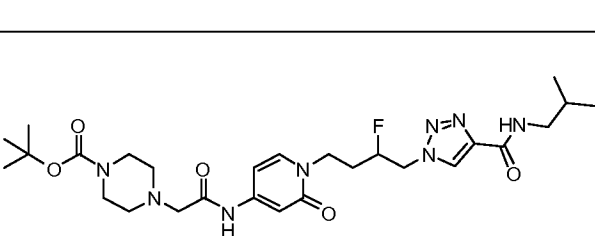
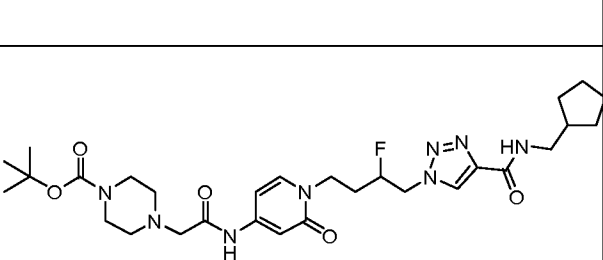
369		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{6-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
370		1-[4-(4-cyclopentaneamido-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N-{{6-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
371		1-(2-fluoro-4-{3-fluoro-4-[2-(2-fluorophenyl)acetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{{6-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
372		1-{2-fluoro-4-[3-fluoro-4-(2-fluoro-2-phenylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{{6-(trifluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
373		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
374		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{{6-(fluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide

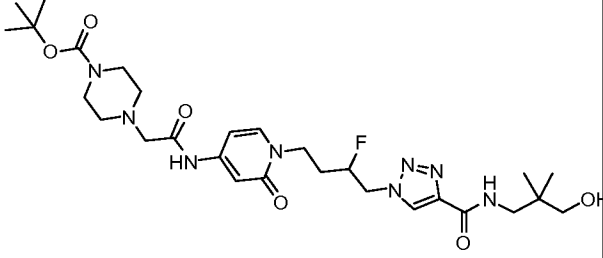
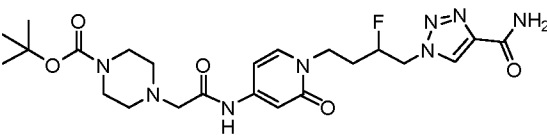
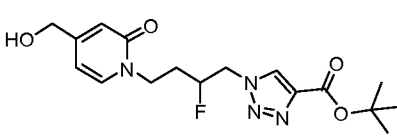
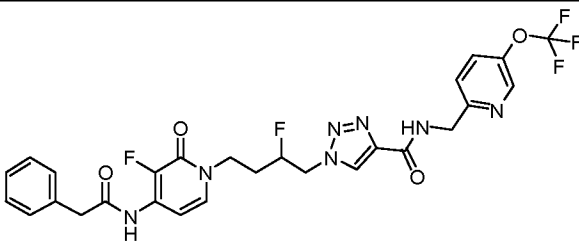
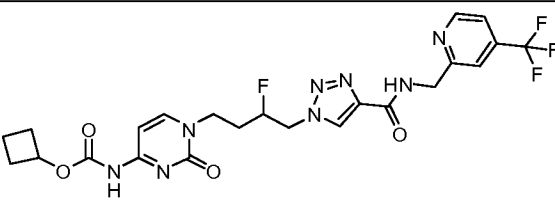
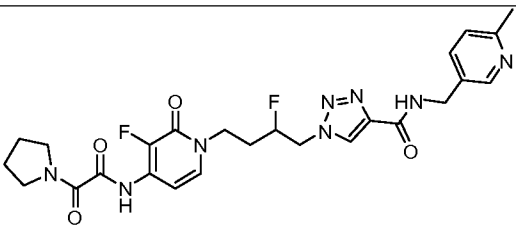
375		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{{6-(fluoromethyl)pyridin-3-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
376		cyclobutyl N-(3-fluoro-1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamate
377		cyclobutyl N-(3-fluoro-1-{3-fluoro-4-[4-({4-(trifluoromethyl)pyridin-2-yl}methyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamate
378		ethyl 1-{4-[4-(2-cyclopentylacetamido)-2-oxo-1,2-dihydropyrimidin-1-yl]-2-fluorobutyl}-1H-1,2,3-triazole-4-carboxylate
379		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{{5-(trifluoromethyl)pyridin-2-yl}methyl}-1H-1,2,3-triazole-4-carboxamide
380		N-[(6-cyanopyridin-3-yl)methyl]-1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
381		N-(cyclopentylmethyl)-1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide

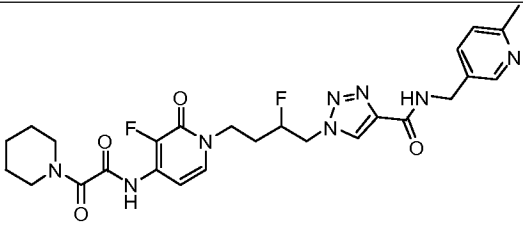
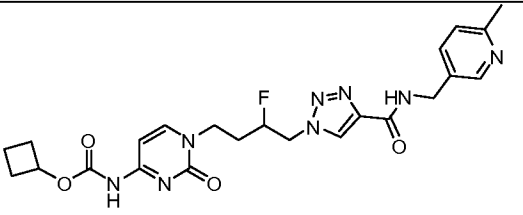
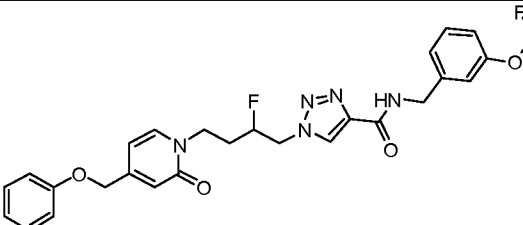
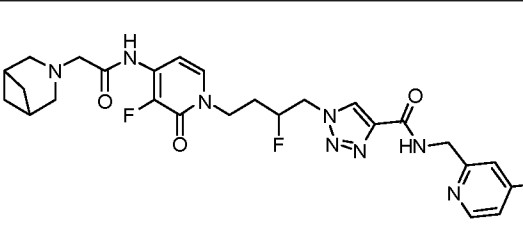
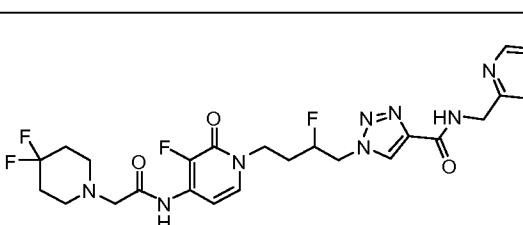
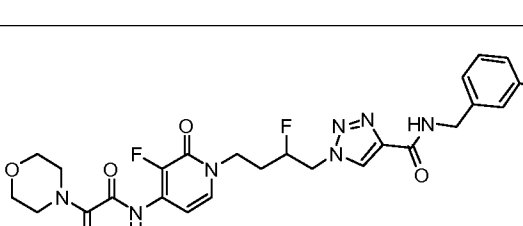
382		1-[4-(4-amino-2-oxo-1,2-dihydropyrimidin-1-yl)-2-fluorobutyl]-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
383		cyclohexyl N-(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
384		propan-2-yl N-(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
385		cyclobutyl N-(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
386		1-{4-[4-(2-cyclopentylacetamido)-6-oxo-1,6-dihydropyridazin-1-yl]-2-fluorobutyl}-N-{{3-(trifluoromethoxy)phenyl}methyl}-1H-1,2,3-triazole-4-carboxamide
387		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-[(3-fluoropyridin-2-yl)methyl]-1H-1,2,3-triazole-4-carboxamide

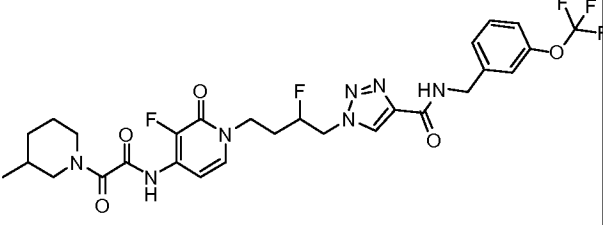
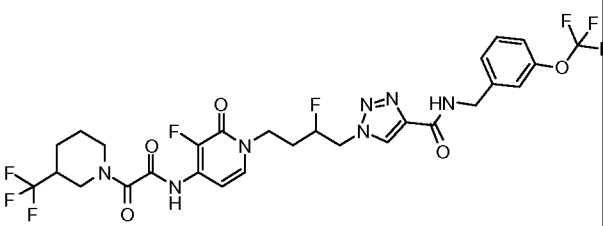
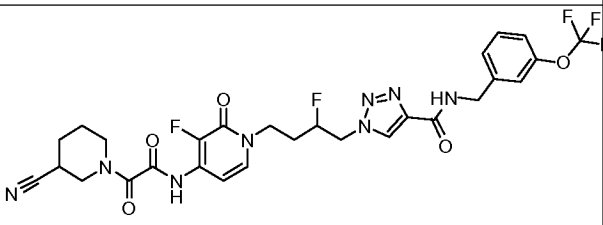
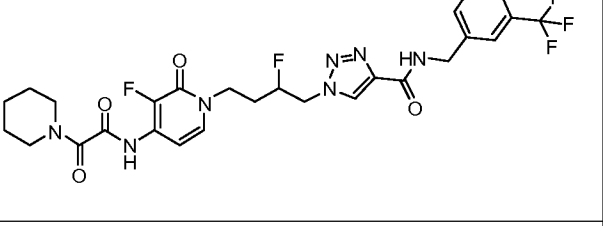
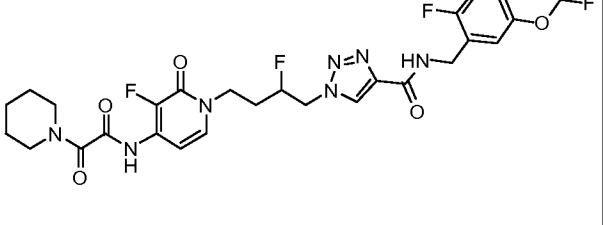
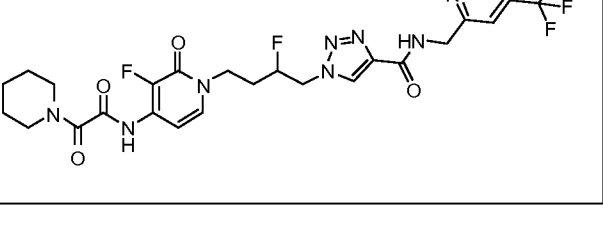
388		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[6-(fluoromethyl)pyridin-3-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
389		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[5-(trifluoromethoxy)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
390		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[5-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
391		1-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-1H-1,2,3-triazole-4-carboxamide
392		N-[(5-chloro-2-fluorophenyl)methyl]-1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxamide
393		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide

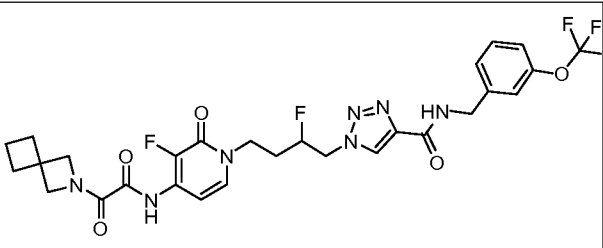
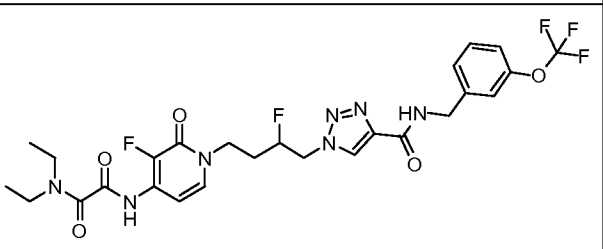
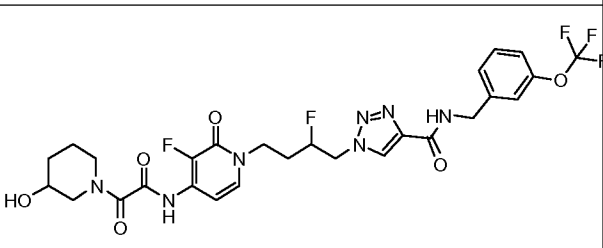
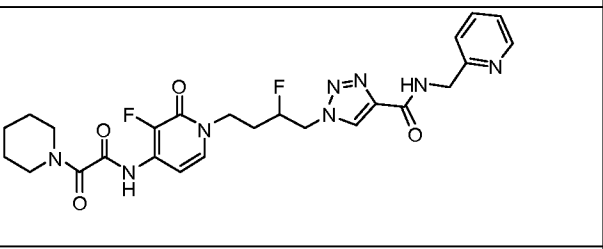
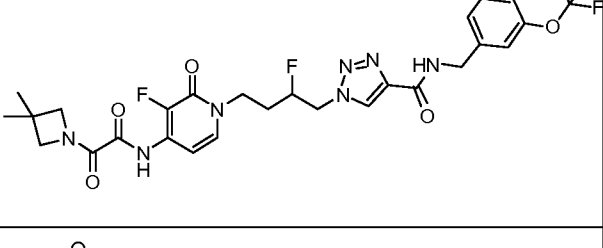
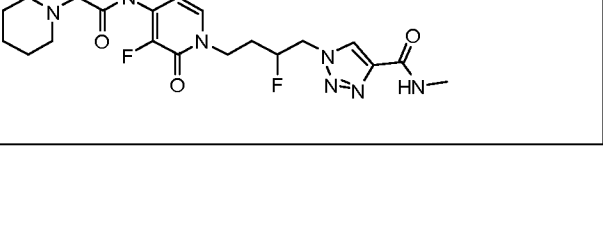
394		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[5-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
395		N-[(5-chloro-2-fluorophenyl)methyl]-1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-1H-1,2,3-triazole-4-carboxamide
396		cyclobutyl N-{3-fluoro-1-[3-fluoro-4-(4-{[(6-methylpyridin-3-yl)methyl]carbamoyl}-1H-1,2,3-triazol-1-yl)butyl]-2-oxo-1,2-dihydropyridin-4-yl} carbamate
397		cyclobutyl N-(3-fluoro-1-{3-fluoro-4-[4-({[6-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl) carbamate
398		cyclobutyl N-(3-fluoro-1-{3-fluoro-4-[4-({[5-(trifluoromethyl)pyridin-3-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl) carbamate
399		cyclobutyl N-(3-fluoro-1-{3-fluoro-4-[4-({[6-(trifluoromethyl)pyridin-3-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl) carbamate

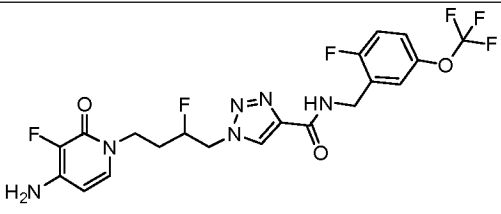
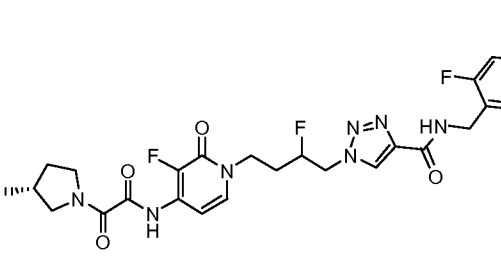
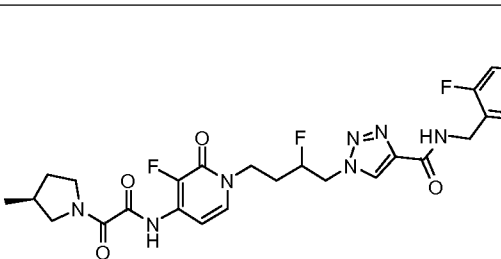
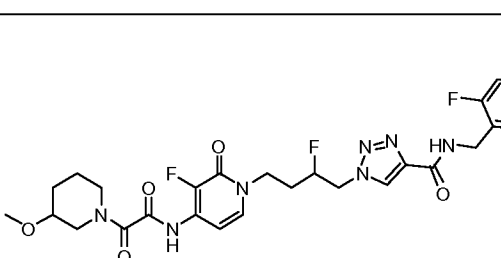
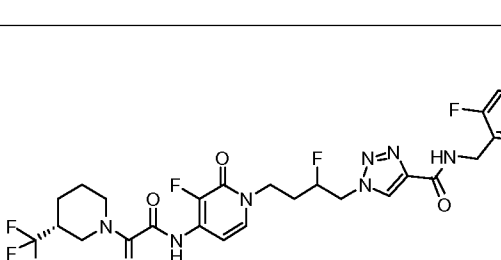
400		1-{4-[4-(2-cyclopentylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[5-(trifluoromethoxy)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
401		1-{4-[4-(2-cyclobutylacetamido)-6-oxo-1,6-dihydropyridazin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
402		1-{4-[4-(2-cyclobutylacetamido)-6-oxo-1,6-dihydropyridazin-1-yl]-2-fluorobutyl}-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
403		tert-butyl 4-{[(1-{3-fluoro-4-[4-(methylcarbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)carbamoyl]methyl}piperazine-1-carboxylate
404		tert-butyl 4-({[1-(3-fluoro-4-{4-[(2-methylpropyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl]carbamoyl}methyl)piperazine-1-carboxylate
405		tert-butyl 4-({[1-(4-{4-[(cyclopentylmethyl)carbamoyl]-1H-1,2,3-triazol-1-yl]-3-fluorobutyl}-2-oxo-1,2-dihydropyridin-4-yl]carbamoyl}methyl)piperazine-1-carboxylate

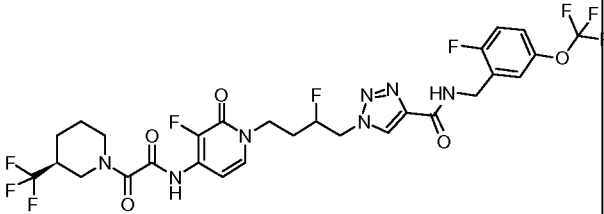
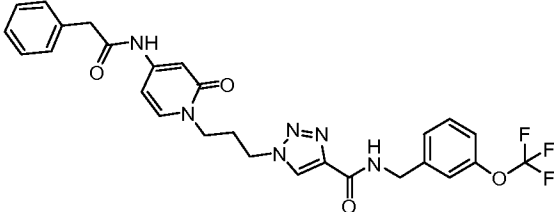
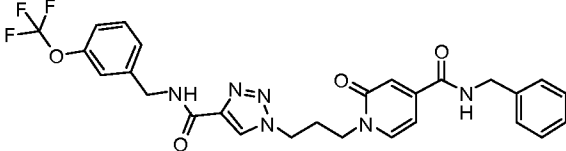
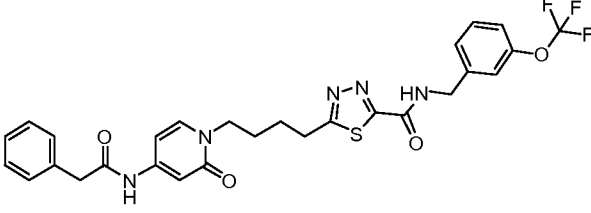
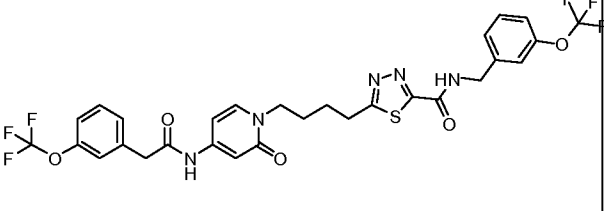
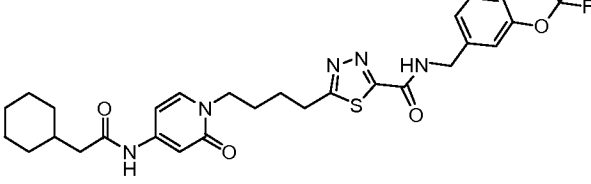
406		tert-butyl 4-({[1-(3-fluoro-4-{4-[(3-hydroxy-2,2-dimethylpropyl)carbamoyl]-1H-1,2,3-triazol-1-yl}butyl)-2-oxo-1,2-dihydropyridin-4-yl]carbamoyl}methyl)piperazine-1-carboxylate
407		tert-butyl 4-[(1-[4-(4-carbamoyl-1H-1,2,3-triazol-1-yl)-3-fluorobutyl]-2-oxo-1,2-dihydropyridin-4-yl]carbamoyl)methyl]piperazine-1-carboxylate
408		tert-butyl 1-{2-fluoro-4-[4-(hydroxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-1H-1,2,3-triazole-4-carboxylate
409		1-{2-fluoro-4-[3-fluoro-2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-[[5-(trifluoromethoxy)pyridin-2-yl]methyl]-1H-1,2,3-triazole-4-carboxamide
410		cyclobutyl N-(1-{3-fluoro-4-[4-({[4-(trifluoromethyl)pyridin-2-yl]methyl}carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
411		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-oxo-2-(pyrrolidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide

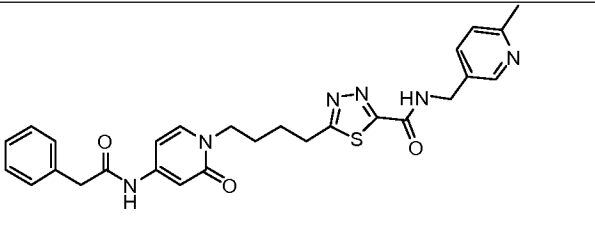
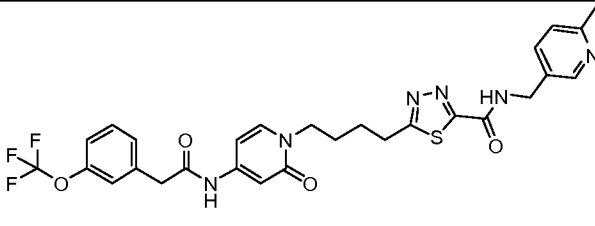
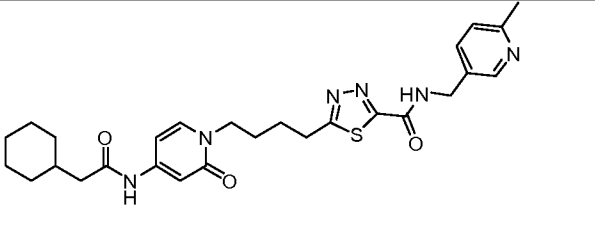
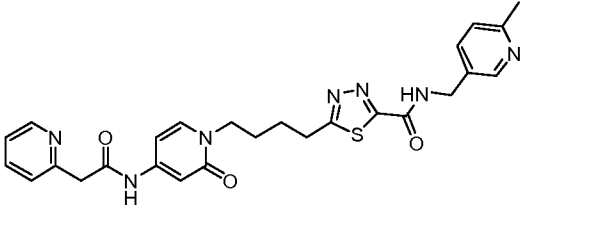
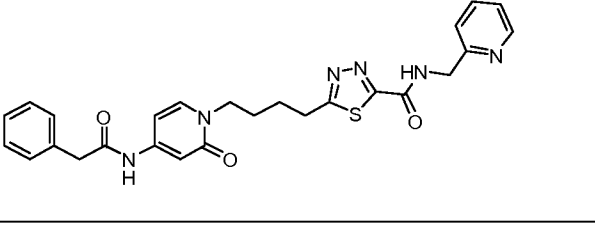
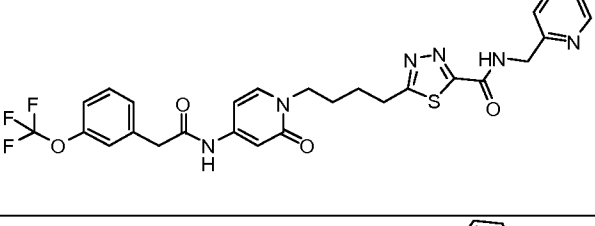
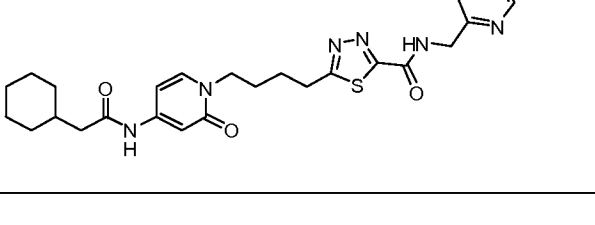
412		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1H-1,2,3-triazole-4-carboxamide
413		cyclobutyl N-{1-[3-fluoro-4-(4-{[(6-methylpyridin-3-yl)methyl]carbamoyl}-1H-1,2,3-triazol-1-yl)butyl]-2-oxo-1,2-dihydropyrimidin-4-yl} carbamate
414		1-{2-fluoro-4-[2-oxo-4-(phenoxyethyl)-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
415		1-{4-[4-(2-{3-azabicyclo[3.1.1]heptan-3-yl}acetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
416		1-(4-{4-[2-(4,4-difluoropiperidin-1-yl)acetamido]-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
417		1-(2-fluoro-4-{3-fluoro-4-[2-(morpholin-4-yl)-2-oxoacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

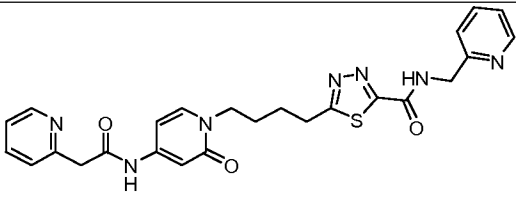
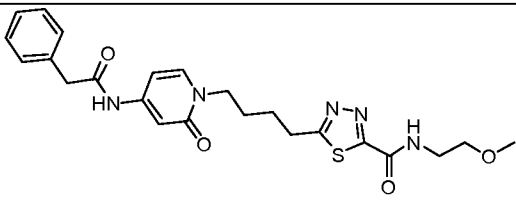
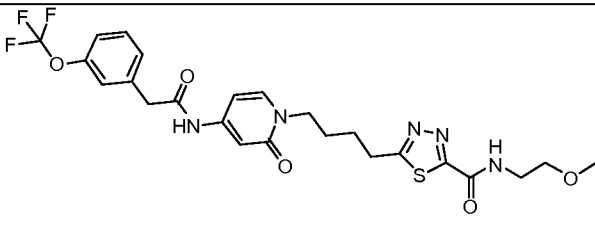
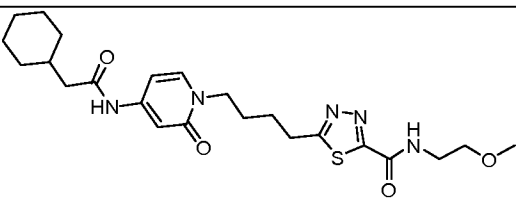
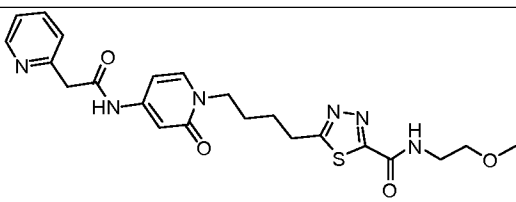
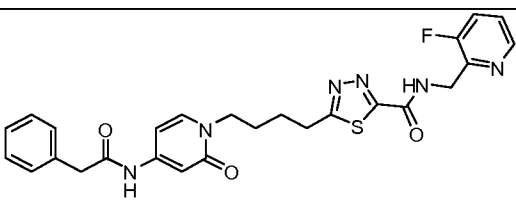
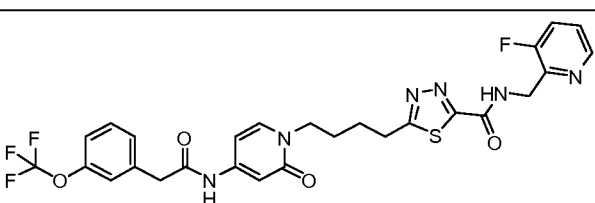
418		1-(2-fluoro-4-{3-fluoro-4-[2-(3-methylpiperidin-1-yl)-2-oxoacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
419		1-[2-fluoro-4-(3-fluoro-2-oxo-4-{2-oxo-2-[3-(trifluoromethyl)piperidin-1-yl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
420		1-(4-{4-[2-(3-cyanopiperidin-1-yl)-2-oxoacetamido]-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
421		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethyl)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
422		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
423		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide

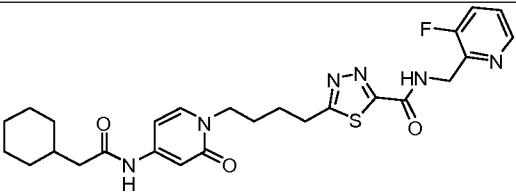
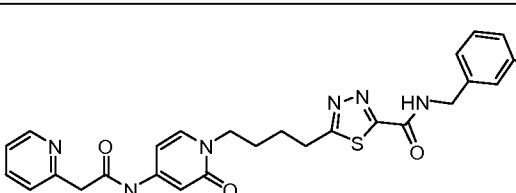
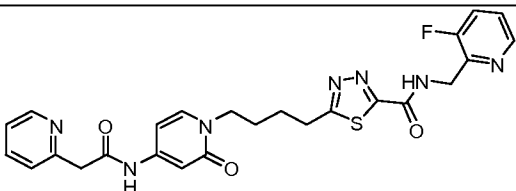
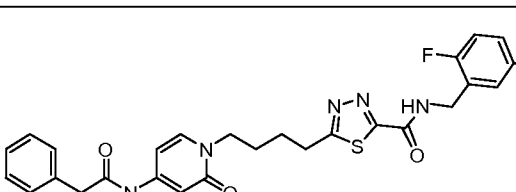
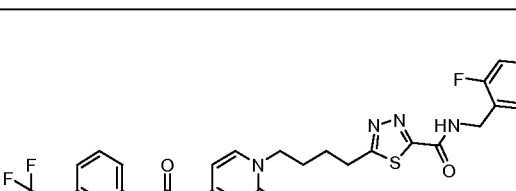
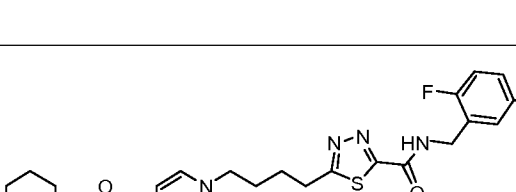
424		1-{4-[4-(2-{2-azaspiro[3.3]heptan-2-yl}-2-oxoacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
425		N,N-diethyl-N'-(3-fluoro-1-{3-fluoro-4-[4-({[3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyridin-4-yl)ethanediamide
426		1-(2-fluoro-4-{3-fluoro-4-[2-(3-hydroxypiperidin-1-yl)-2-oxoacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
427		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-(pyridin-2-ylmethyl)-1H-1,2,3-triazole-4-carboxamide
428		1-(4-{4-[2-(3,3-dimethylazetidin-1-yl)-2-oxoacetamido]-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
429		1-(2-fluoro-4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-methyl-1H-1,2,3-triazole-4-carboxamide

430		1-[4-(4-amino-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl)-2-fluorobutyl]-N- {[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
431		1-[2-fluoro-4-(3-fluoro-4-{2-[(3R)-3-methylpyrrolidin-1-yl]-2-oxoacetamido}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N- {[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
432		1-[2-fluoro-4-(3-fluoro-4-{2-[(3S)-3-methylpyrrolidin-1-yl]-2-oxoacetamido}-2-oxo-1,2-dihydropyridin-1-yl)butyl]-N- {[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
433		1-(2-fluoro-4-{3-fluoro-4-[2-(3-methoxypiperidin-1-yl)-2-oxoacetamido]-2-oxo-1,2-dihydropyridin-1-yl}butyl)-N- {[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
434		1-[2-fluoro-4-(3-fluoro-2-oxo-4-{2-oxo-2-[(3R)-3-(trifluoromethyl)piperidin-1-yl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N- {[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

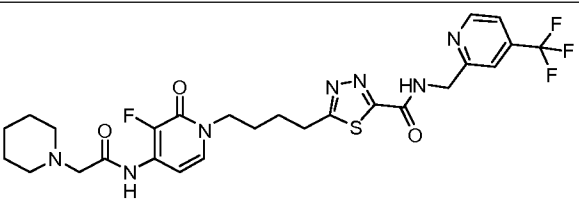
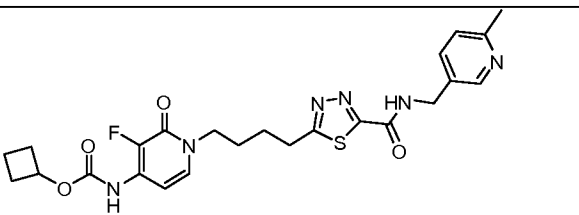
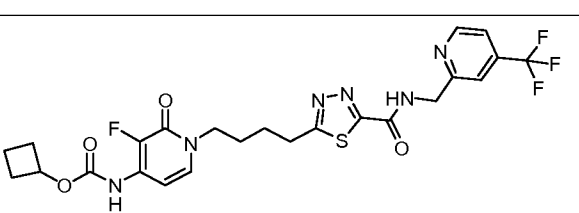
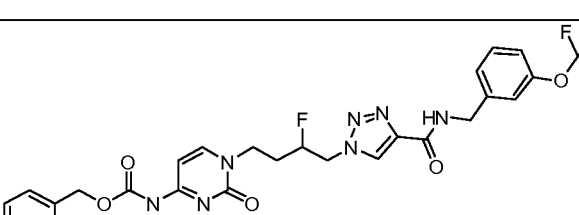
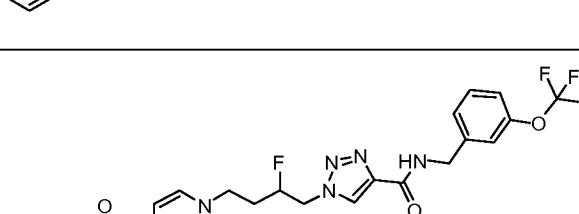
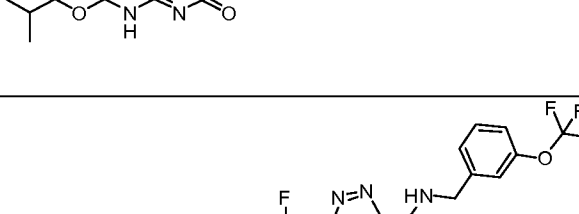
435		1-[2-fluoro-4-(3-fluoro-2-oxo-4-{2-oxo-2-[(3S)-3-(trifluoromethyl)piperidin-1-yl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N-{[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
436		1-{3-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]propyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
437		N-benzyl-2-oxo-1-{3-[4-({[3-(trifluoromethoxy)phenyl]methyl}carbonyl)-1H-1,2,3-triazol-1-yl]propyl}-1,2-dihydropyridine-4-carboxamide
438		5-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1,3,4-thiadiazole-2-carboxamide
439		5-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N-{[3-(trifluoromethoxy)phenyl]methyl}-1,3,4-thiadiazole-2-carboxamide
440		5-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1,3,4-thiadiazole-2-carboxamide

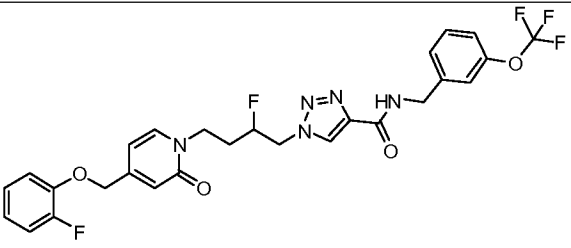
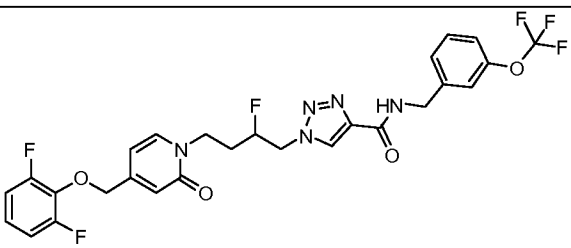
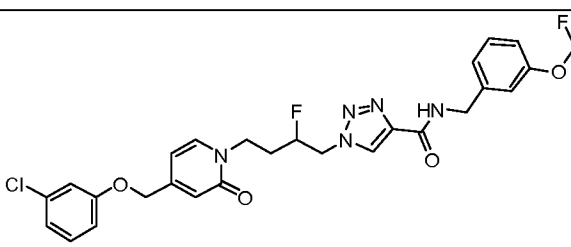
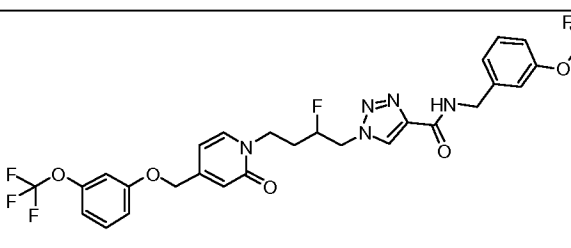
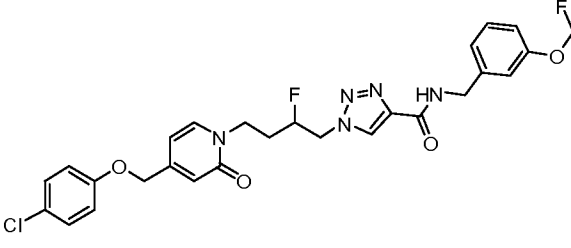
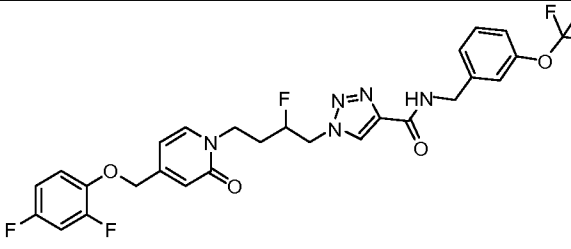
441		N-[(6-methylpyridin-3-yl)methyl]-5-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1,3,4-thiadiazole-2-carboxamide
442		N-[(6-methylpyridin-3-yl)methyl]-5-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1,3,4-thiadiazole-2-carboxamide
443		5-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-[(6-methylpyridin-3-yl)methyl]-1,3,4-thiadiazole-2-carboxamide
444		N-[(6-methylpyridin-3-yl)methyl]-5-(4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-1,3,4-thiadiazole-2-carboxamide
445		5-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-N-(pyridin-2-ylmethyl)-1,3,4-thiadiazole-2-carboxamide
446		5-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-N-(pyridin-2-ylmethyl)-1,3,4-thiadiazole-2-carboxamide
447		5-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-(pyridin-2-ylmethyl)-1,3,4-thiadiazole-2-carboxamide

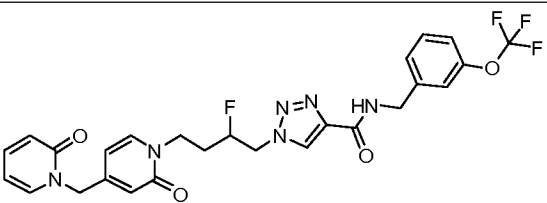
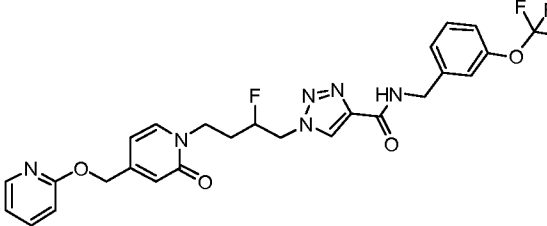
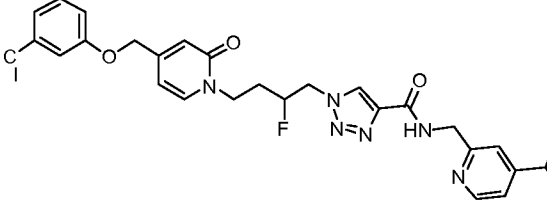
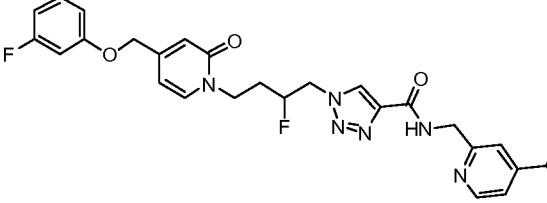
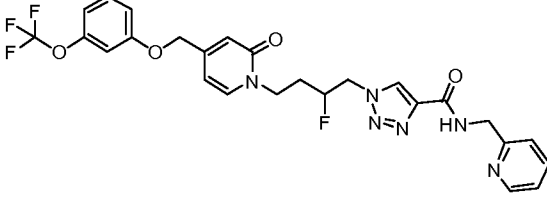
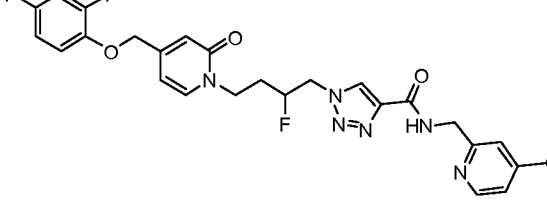
448		5-(4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-(pyridin-2-ylmethyl)-1,3,4-thiadiazole-2-carboxamide
449		N-(2-methoxyethyl)-5-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1,3,4-thiadiazole-2-carboxamide
450		N-(2-methoxyethyl)-5-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1,3,4-thiadiazole-2-carboxamide
451		5-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-(2-methoxyethyl)-1,3,4-thiadiazole-2-carboxamide
452		N-(2-methoxyethyl)-5-(4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-1,3,4-thiadiazole-2-carboxamide
453		N-[(3-fluoropyridin-2-yl)methyl]-5-{4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl}-1,3,4-thiadiazole-2-carboxamide
454		N-[(3-fluoropyridin-2-yl)methyl]-5-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1,3,4-thiadiazole-2-carboxamide

455		5-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-[(3-fluoropyridin-2-yl)methyl]-1,3,4-thiadiazole-2-carboxamide
456		5-(4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1,3,4-thiadiazole-2-carboxamide
457		N-[(3-fluoropyridin-2-yl)methyl]-5-(4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-1,3,4-thiadiazole-2-carboxamide
458		N-{[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-5-(4-[2-oxo-4-(2-phenylacetamido)-1,2-dihydropyridin-1-yl]butyl)-1,3,4-thiadiazole-2-carboxamide
459		N-{[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-5-[4-(2-oxo-4-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,2-dihydropyridin-1-yl)butyl]-1,3,4-thiadiazole-2-carboxamide
460		5-{4-[4-(2-cyclohexylacetamido)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-1,3,4-thiadiazole-2-carboxamide

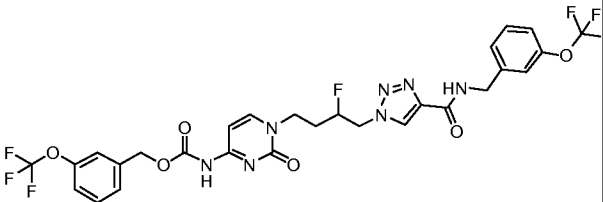
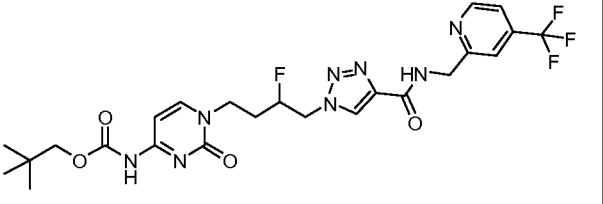
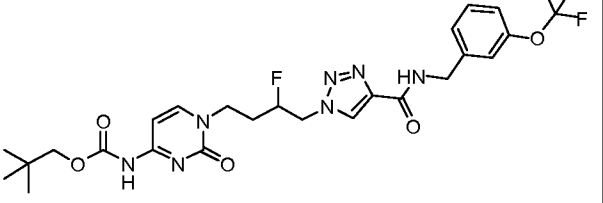
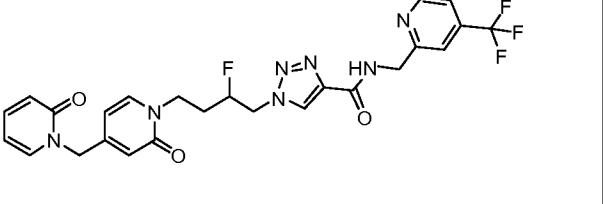
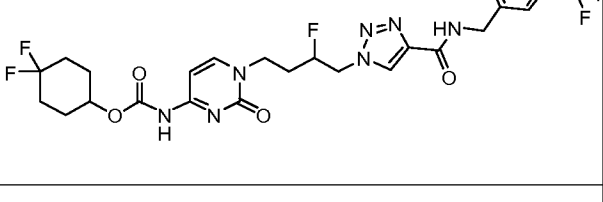
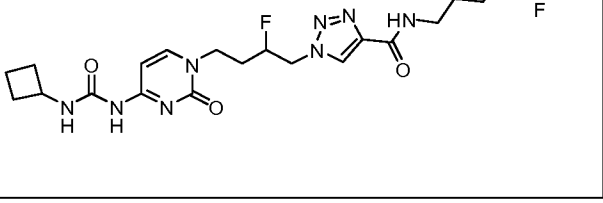
461		N-{[2-fluoro-5-(trifluoromethoxy)phenyl]methyl}-5-(4-{2-oxo-4-[2-(pyridin-2-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-1,3,4-thiadiazole-2-carboxamide
462		5-(4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1,3,4-thiadiazole-2-carboxamide
463		5-(4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-[(6-methylpyridin-3-yl)methyl]-1,3,4-thiadiazole-2-carboxamide
464		5-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-[(6-methylpyridin-3-yl)methyl]-1,3,4-thiadiazole-2-carboxamide
465		5-{4-[4-(2-cyclobutylacetamido)-3-fluoro-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1,3,4-thiadiazole-2-carboxamide
466		5-(4-{3-fluoro-2-oxo-4-[2-oxo-2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1,3,4-thiadiazole-2-carboxamide

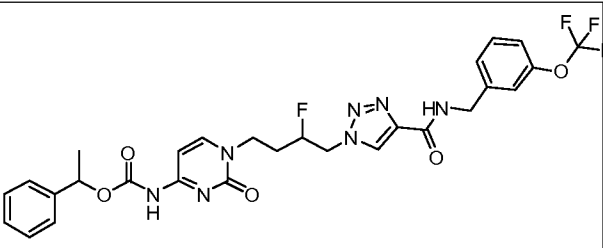
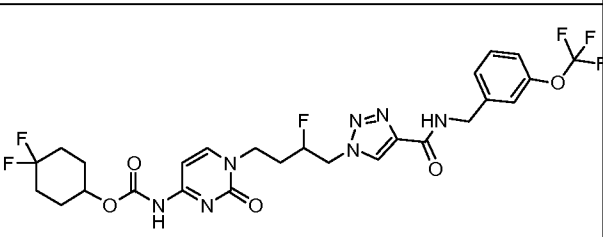
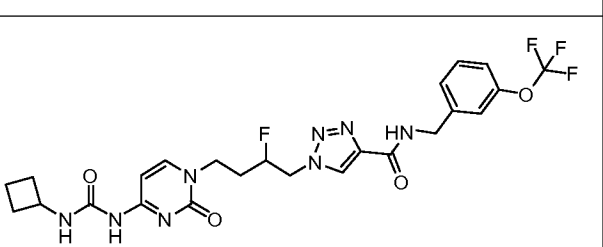
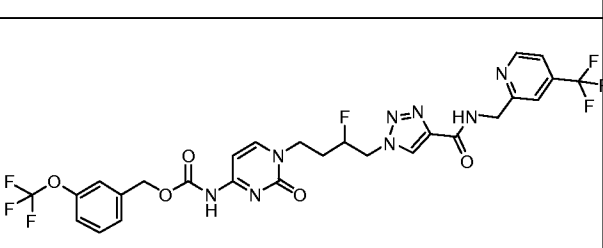
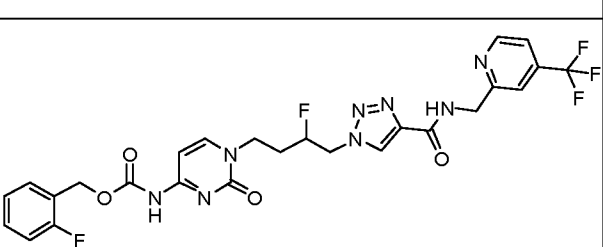
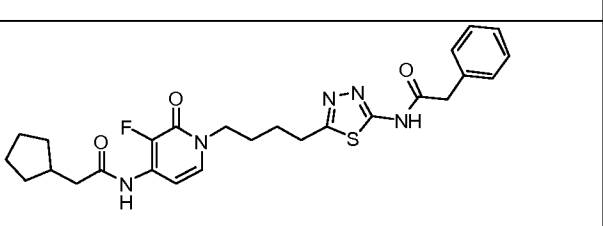
467		5-(4-{3-fluoro-2-oxo-4-[2-(piperidin-1-yl)acetamido]-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1,3,4-thiadiazole-2-carboxamide
468		cyclobutyl N-{3-fluoro-1-[4-(5-{{(6-methylpyridin-3-yl)methyl}carbonyl}-1,3,4-thiadiazol-2-yl)butyl]-2-oxo-1,2-dihydropyridin-4-yl} carbamate
469		cyclobutyl N-(3-fluoro-2-oxo-1-{4-[5-{{(4-(trifluoromethyl)pyridin-2-yl)methyl}carbonyl}-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyridin-4-yl) carbamate
470		benzyl N-(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl}carbonyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl) carbamate
471		2-methylpropyl N-(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl}methyl}carbonyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl) carbamate
472		1-{2-fluoro-4-[4-(3-fluorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

473		1-{2-fluoro-4-[4-(2-fluorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
474		1-{4-[4-(2,6-difluorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
475		1-{4-[4-(3-chlorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
476		1-(2-fluoro-4-{2-oxo-4-[3-(trifluoromethoxy)phenoxy]methyl}-1,2-dihydropyridin-1-yl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
477		1-{4-[4-(4-chlorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
478		1-{4-[4-(2,4-difluorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide

479		1-(2-fluoro-4-{2-oxo-4-[(2-oxo-1,2-dihydropyridin-1-yl)methyl]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
480		1-(2-fluoro-4-{2-oxo-4-[(pyridin-2-yloxy)methyl]-1,2-dihydropyridin-1-yl}butyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
481		1-{4-[4-(3-chlorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
482		1-{2-fluoro-4-[4-(3-fluorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
483		1-(2-fluoro-4-{2-oxo-4-[3-(trifluoromethoxy)phenoxymethyl]-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
484		1-{4-[4-(2,4-difluorophenoxymethyl)-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide

485		1-{4-[4-(2,6-difluorophenoxy)methyl]-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
486		1-{4-[4-(4-chlorophenoxy)methyl]-2-oxo-1,2-dihydropyridin-1-yl]-2-fluorobutyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
487		1-{2-fluoro-4-[4-(2-fluorophenoxy)methyl]-2-oxo-1,2-dihydropyridin-1-yl]butyl}-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
488		benzyl N-(1-{3-fluoro-4-[4-({4-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
489		(2-fluorophenyl)methyl N-(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
490		2-methylpropyl N-(1-{3-fluoro-4-[4-({4-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate

491		[3-(trifluoromethoxy)phenyl]methyl N-(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
492		2,2-dimethylpropyl N-(1-{3-fluoro-4-[4-({4-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
493		2,2-dimethylpropyl N-(1-{3-fluoro-4-[4-({3-(trifluoromethoxy)phenyl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
494		1-(2-fluoro-4-{2-oxo-4-[(2-oxo-1,2-dihydropyridin-1-yl)methyl]-1,2-dihydropyridin-1-yl}butyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide
495		4,4-difluorocyclohexyl N-(1-{3-fluoro-4-[4-({4-(trifluoromethyl)pyridin-2-yl]methyl} carbamoyl)-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
496		1-(4-{4-[(cyclobutylcarbamoyl)amino]-2-oxo-1,2-dihydropyrimidin-1-yl}-2-fluorobutyl)-N-{[4-(trifluoromethyl)pyridin-2-yl]methyl}-1H-1,2,3-triazole-4-carboxamide

497		1-phenylethyl N-(1-{3-fluoro-4-[4-((3-(trifluoromethoxy)phenyl)methyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
498		4,4-difluorocyclohexyl N-(1-{3-fluoro-4-[4-((3-(trifluoromethoxy)phenyl)methyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
499		1-(4-{4-[(cyclobutylcarbamoyl)amino]-2-oxo-1,2-dihydropyrimidin-1-yl}-2-fluorobutyl)-N-{[3-(trifluoromethoxy)phenyl]methyl}-1H-1,2,3-triazole-4-carboxamide
500		[3-(trifluoromethoxy)phenyl]methyl N-(1-{3-fluoro-4-[4-((4-(trifluoromethyl)pyridin-2-yl)methyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
501		(2-fluorophenyl)methyl N-(1-{3-fluoro-4-[4-((4-(trifluoromethyl)pyridin-2-yl)methyl)carbamoyl]-1H-1,2,3-triazol-1-yl]butyl}-2-oxo-1,2-dihydropyrimidin-4-yl)carbamate
502		2-cyclopentyl-N-(3-fluoro-2-oxo-1-{4-[5-(2-phenylacetamido)-1,3,4-thiadiazol-2-yl]butyl}-1,2-dihydropyridin-4-yl)acetamide

503		2-cyclopentyl-N-{3-fluoro-2-oxo-1-[4-(5-{2-[3-(trifluoromethoxy)phenyl]acetamido}-1,3,4-thiadiazol-2-yl)butyl]-1,2-dihydropyridin-4-yl}acetamide
504		2-cyclopentyl-N-[3-fluoro-2-oxo-1-(4-{5-[2-(pyridin-2-yl)acetamido]-1,3,4-thiadiazol-2-yl}butyl)-1,2-dihydropyridin-4-yl]acetamide
505		2-cyclopentyl-N-{1-[4-(5-acetamido-1,3,4-thiadiazol-2-yl)butyl]-3-fluoro-2-oxo-1,2-dihydropyridin-4-yl}acetamide

[0323] Table 2 below reports the observed molecular ion (ES⁺) (Mass Spec) [M+H]⁺ of each Example, as well as the method by which each compound may be made by reference to each Example whose synthesis is substantially similar that one skilled in the art could produce the compound using, if necessary, variations known in the art.

Table 2: Observed Molecular Weight and Synthesis for Examples

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
30	383	384	1
31	501	502	1
32	409	409	2
33	569	569	2
34	485	486	2
35	450	451	2
36	490	491	2
37	451	452	2

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
38	451	452	2
39	456	457	2
40	492	493	10
41	574	575	10
42	584	585	7
43	536	537	7
44	576	577	7
45	574	575	6

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
46	572	573	6
47	562	563	5
48	576	577	5
49	569	570	8
50	492	493	5
51	568	569	10
52	652	653	10
53	646	647	10
54	520	521	5
55	586	587	5
56	576	577	5
57	501	502	7
58	492	493	8
59	652	653	8
60	569	570	8
61	628	629	8
62	534	535	8
63	574	575	8
64	668	669	7
65	598	599	10
66	586	587	10
67	598	599	10

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
68	646	647	10
69	569	570	10
70	583	584	10
71	526	527	15
72	384	385	16
73	504	503	16
74	516	517	16
75	580	581	20
76	504	505	20
77	462	463	21
78	596	597	20
79	468	469	16
80	602	603	19
81	587	588	19
82	503	504	19
83	518	519	19
84	518	519	19
85	631	632	19
86	449	450	23
87	463	464	23
88	503	504	23
89	525	526	23

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
90	525	526	23
91	680	681	15
92	420	421	15
93	436	437	24
94	464	465	24
95	504	505	24
96	512	513	24
97	498	499	24
98	478	479	24
99	580	581	22
100	512	513	22
101	596	597	22
102	548	549	24
103	588	589	24
104	562	563	24
105	590	591	24
106	547	548	23
107	587	588	23
108	586	587	22
109	587	588	22
110	596	597	22
111	546	547	22

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
112	564	565	24
113	520	521	22
114	584	585	22
115	569	570	10
116	581	582	22
117	534	535	22
118	581	582	22
119	472	473	28
120	519	520	28
120	519	520	28
121	486	487	28
122	518	519	28
124	535	536	127
125	589	590	127
126	589	590	127
127	Exemplified		
128	492	493	1
129	519	520	1
130	526	527	1
131	527	528	1
132	450	451	1
133	594	595	1

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
134	586	587	12
135	515	516	7
136	535	536	6
137	549	550	8
138	549	550	8
139	534	535	180
140	434	435	4
141	558	559	5
142	476	477	5
143	481	482	10
144	586	587	13
145	505	506	10
146	509	510	10
147	503	504	2
148	517	518	13
149	521	522	13
150	517	518	12
151	521	522	12
152	544	545	10
153	544	545	10
154	516	517	10
155	559	560	10

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
156	587	588	10
157	569	570	10
158	499	500	7
159	477	478	7
160	581	582	13
161	571	572	3
162	517	518	13
163	581	582	12
164	571	572	12
165	517	518	12
166	610	611	10
167	586	587	10
168	568	569	10
169	592	593	10
170	604	605	10
171	626	627	10
172	569	570	386
173	586	587	180
174	612	613	7
175	592	593	12
176	610	611	12
177	523	524	12

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
178	577	578	12
179	624	625	10
180	Exemplified		
181	542	543	10
182	605	606	12
183	571	572	12
184	616	617	12
185	660	661	12
186	616	617	12
187	594	595	12
188	535	536	12
189	590	591	12
190	491	492	10
191	491	492	10
192	520	521	10
193	588	589	10
194	559	560	10
195	525	526	12
196	525	526	12
197	525	526	12
198	541	542	12
199	509	510	12

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
200	511	512	12
201	546	547	10
202	574	575	10
203	574	575	10
204	588	589	10
205	675	676	10
206	576	577	10
207	603	604	10
208	590	591	10
209	603	604	10
210	560	561	10
211	675	676	10
212	610	611	180
213	595	596	337
214	532	533	12
215	562	563	12
216	554	555	12
217	564	565	12
218	621	622	12
219	693	694	12
220	578	579	12
221	679	680	12

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
222	715	716	12
223	602	603	12
224	602	603	12
225	465	466	180
226	586	587	180
227	597	598	337
228	611	612	337
229	636	637	337
230	608	609	337
231	643	644	337
232	601	602	337
233	536	537	337
234	568	569	12
235	611	612	12
236	621	622	12
237	671	672	12
238	621	622	12
239	707	708	12
240	617	618	12
241	707	708	12
242	657	658	12
243	639	640	12

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
244	635	636	12
245	693	694	12
246	587	588	12
247	593	594	12
248	601	602	12
249	693	694	12
250	587	588	12
251	617	618	12
252	593	594	12
253	637	638	12
254	608	609	337
255	666	667	12
256	618	619	337
257	623	624	337
258	595	596	180
259	595	596	180
260	595	596	180
261	595	596	180
262	595	596	180
263	587	588	386
264	594	595	180
265	578	579	180

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
266	541	542	180
267	527	528	180
268	585	586	180
269	593	594	337
270	579	580	337
271	694	695	337
272	637	638	12
273	651	652	12
274	629	630	337
275	611	612	337
276	623	624	337
277	665	666	337
278	609	610	337
279	672	673	337
280	593	594	337
281	665	666	12
282	486	487	180
283	611	612	365
284	634	635	180
285	634	635	180
286	620	621	180
287	620	621	180

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
288	611	612	337
289	711	712	180
290	647	648	337
291	629	630	337
292	684	685	337
293	597	598	337
294	641	642	337
295	647	648	337
296	712	713	337
297	724	725	337
298	517	518	180
299	611	612	180
300	683	684	180
301	721	722	180
302	689	690	180
303	527	528	180
304	Exemplified		
305	662	663	180
306	662	663	180
307	535	536	180
308	722	723	337
309	634	635	365

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
310	634	635	365
311	441	442	180
312	565	566	180
313	565	566	180
314	Exemplified		
315	618	619	180
316	618	619	180
317	589	589	180
318	581	582	180
319	571	572	180
320	571	572	180
321	471	472	180
322	471	472	180
323	589	590	180
324	668	669	180
325	647	648	180
326	605	606	180
327	622	623	180
328	622	623	180
329	581	582	180
330	571	572	180
331	471	472	180

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
332	567	568	180
333	603	604	180
334	640	641	180
335	640	641	180
336	567	568	180
337	Exemplified		
338	596	597	337
339	582	583	180
340	584	585	180
341	596	597	180
342	582	583	180
343	603	604	180
344	596	597	180
345	610	611	180
346	612	613	180
347	586	587	358
348	589	590	180
349	603	604	180
350	567	568	180
351	596	597	337
352	610	611	337
353	590	591	180

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
354	572	573	180
355	596	597	180
356	517	518	180
357	567	568	180
358	Exemplified		
359	558	559	358
360	581	582	180
361	607	608	180
362	607	608	180
363	668	669	180
364	567	568	180
365	Exemplified		
366	471	472	180
367	589	590	180
368	603	604	180
369	581	582	180
370	567	568	180
371	607	608	180
372	607	608	180
373	539	540	180
374	531	532	180
375	553	554	180

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
376	584	585	180
377	569	570	180
379	589	590	180
380	546	547	180
381	512	513	180
382	469	470	491
383	595	596	491
384	555	556	491
385	567	568	491
386	Exemplified		
387	531	532	180
388	545	546	180
389	583	584	180
390	567	568	180
391	408	409	180
392	572	573	180
393	513	514	180
394	581	582	180
395	564	565	180
396	515	516	180
397	569	570	180
398	569	570	180

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
399	569	570	180
400	597	598	180
401	550	551	386
402	496	497	386
403	534	535	337
404	576	577	10
405	602	603	10
406	606	607	10
407	520	521	337
408	366	367	414
409	605	606	180
410	552	553	491
411	542	543	358
412	556	557	358
413	498	499	491
414			
415	608	609	337
416	632	633	337
417	627	628	422
418	639	640	435
419	693	694	435
420	650	651	435

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
421	609	610	422
422	Exemplified		
423	610	611	422
424	637	638	435
425	613	614	435
426	641	642	435
427	542	543	422
428	625	626	358
429	465	466	422
430	504	505	180
431	643	644	435
432	643	644	435
433	673	674	435
434	711	712	435
435	Exemplified		
436	554	555	8
437	554	555	8
438	585	586	464
439	669	670	464
440	591	592	464
441	516	517	464
442	600	601	464

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
443	522	523	464
444	517	518	464
445	502	503	464
446	586	587	464
447	508	509	464
448	503	504	464
449	469	470	464
450	553	554	464
451	475	476	464
452	470	471	464
453	520	521	464
454	604	605	464
455	526	527	464
456	586	587	464
457	521	522	464
458	603	604	464
459	687	688	464
460	609	610	464
461	604	605	464
462	541	542	464
463	555	556	464
464	Exemplified		

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
465	566	567	464
466	609	610	464
467	595	596	464
468	Exemplified		
469	568	569	468
470	603	604	491
471	569	570	491
472	577	578	414
473	577	578	414
474	595	596	414
475	593	594	414
476	643	644	414
477	593	594	414
478	595	596	414
479	560	561	414
480	560	561	414
481	578	579	414
482	562	563	414
483	628	629	414
484	580	581	414
485	580	581	414
486	578	579	414

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
487	562	563	414
488	588	589	491
489	621	622	491
490	554	555	491
491	Exemplified		
492	568	569	491
493	583	584	491
494	545	546	414
495	616	617	491
496	551	552	491

Ex. No.	Exact mass	Obs. mass	Synthesis, as in Ex.
497	617	618	491
498	631	632	491
499	566	567	491
500	672	673	491
501	606	607	491
502	511	512	1
503	595	596	1
504	512	513	1
505	435	436	1

Biological Activity Assays

[0324] The following are assays that may be used to evaluate the biological efficacy of compounds of Formula (I).

GLS1 Enzymatic Activity Assay

[0325] The inhibition of purified recombinant human GAC by varying concentrations of inhibitors is assessed via a dual-coupled enzymatic assay. The glutamate produced by the glutaminase reaction is used by glutamate oxidase to produce α -ketoglutarate, ammonia, and hydrogen peroxide, with this hydrogen peroxide subsequently being used by horseradish peroxidase to produce resorufin in the presence of Amplex UltraRed. The assay buffer consisted of 50 mM Hepes (pH 7.4), 0.25 mM EDTA and 0.1 mM Triton X-100. GAC was incubated with potassium phosphate (10 minutes at room temperature) prior to incubation with inhibitor (10 minutes at room temperature). The final reaction conditions were as follows: 2 nM GAC, 50 mM potassium phosphate, 100 mU/mL glutamate oxidase (Sigma), 1 mM glutamine (Sigma), 100 mU/mL horseradish peroxidase (Sigma), 75 μ M Amplex UltraRed (Life Technologies), and

1% (v/v) DMSO. The production of resorufin was monitored on a Perkin Elmer Envision plate reader (excitation 530nm, emission 590nm) either in a kinetics or endpoint mode (at 20 minutes). IC₅₀ values were calculated using a four-parameter logistic curve fit.

Proliferation Assay

[0326] A549 cells were routinely maintained in RPMI 1640 media (Gibco catalog number 11875-093) supplemented with 10% dialyzed fetal bovine serum using a humidified incubator (37°C, 5% CO₂ and ambient O₂). In preparation for the viability assay, cells were inoculated into 384-well black CulturPlates (Perkin Elmer) at a density of 1000 cells/well in a volume of 40uL. Following a 24-hour incubation at 37°C, 5% CO₂ and ambient O₂, cells were treated with compound (10uL) in a final DMSO concentration of 0.5% (v/v). The microplates were then incubated for 72 hours (37°C, 5% CO₂ and ambient O₂). Cell Titer Fluor (Promega) was subsequently added (10uL of 6x reagent) and mixed for 15 minutes at room temperature. The plates were then incubated for 30 minutes (37°C, 5% CO₂ and ambient O₂) and fluorescence was subsequently read on the Perkin Elmer Envision plate reader. EC₅₀ values were calculated using a four-parameter logistic curve fit.

[0327] Non-limiting examples include the following compounds and pharmaceutically acceptable salts thereof.

[0328] Table 3 below reports the IC₅₀ against GLS1 and the EC₅₀ against A549 cell proliferation, both in nanomolar, and both wherein A = < 100 nM, B = 100-500 nM, C > 500 - 5000 nM, and D > 5000 nM. "ND" indicates no data.

Table 3: GLS1 IC₅₀ Data and A549 EC₅₀ Data

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
1	A	C
2	B	C
3	A	B
4	C	D

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
5	A	B
6	A	C
7	A	B
8	A	B

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
9	C	N.D.
10	A	C
11	C	D
12	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
13	A	A
14	A	A
15	A	D
16	A	C
17	A	D
18	B	D
19	A	B
20	A	A
21	C	N.D.
22	A	C
23	A	C
24	A	A
25	C	N.D.
26	C	N.D.
27	C	N.D.
28	A	B
29	A	D
30	C	N.D.
31	A	C
32	C	D
33	A	B
34	B	D

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
35	C	D
36	B	C
37	C	D
38	C	D
39	B	C
40	B	C
41	A	C
42	A	B
43	A	B
44	A	A
45	A	A
46	B	D
47	A	C
48	A	C
49	B	C
50	C	D
51	A	C
52	A	B
53	A	C
54	B	C
55	A	B
56	A	C

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
57	B	C
58	C	D
59	A	B
60	B	D
61	B	C
62	B	C
63	A	B
64	A	B
65	A	C
66	A	C
67	A	C
68	A	D
69	A	C
70	A	C
71	C	D
72	C	D
73	A	C
74	C	D
75	A	A
76	A	B
77	C	D
78	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
79	C	C
80	A	B
81	A	C
82	A	D
83	A	D
84	A	D
85	A	B
86	C	D
87	C	D
88	B	C
89	B	D
90	B	D
91	A	B
92	A	C
93	B	C
94	A	B
95	A	A
96	A	B
97	B	D
98	A	B
99	A	A
100	A	C

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
101	A	B
102	A	B
103	A	A
104	A	A
105	A	B
106	B	C
107	A	C
108	A	A
109	B	C
110	A	B
111	A	A
112	A	B
113	A	C
114	A	A
115	C	N.D.
116	A	A
117	A	C
118	A	A
119	C	D
120	C	C
120	B	C
121	C	D

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
122	B	B
124	B	C
125	A	A
126	A	B
127	A	A
128	B	D
129	A	C
130	A	C
131	A	C
132	B	D
133	A	B
134	A	A
135	B	C
136	B	D
137	C	N.D.
138	C	N.D.
139	A	B
140	C	N.D.
141	A	A
142	C	N.D.
143	B	C
144	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
145	A	B
146	A	B
147	B	D
148	A	C
149	B	C
150	B	D
151	B	C
152	A	B
153	A	A
154	A	C
155	B	D
156	B	C
157	C	D
158	A	C
159	B	C
160	A	C
161	A	B
162	A	C
163	A	B
164	A	B
165	A	C
166	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
167	A	A
168	A	C
169	A	B
170	A	B
171	A	B
172	B	C
173	A	A
174	A	B
175	A	A
176	A	A
177	A	A
178	A	A
179	A	C
180	A	A
181	A	B
182	A	B
183	A	C
184	A	A
185	A	C
186	A	A
187	A	A
188	C	D

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
189	B	D
190	A	C
191	A	B
192	B	D
193	B	C
194	A	A
195	B	C
196	A	C
197	A	C
198	A	B
199	A	A
200	B	C
201	A	B
202	A	B
203	A	B
204	A	C
205	A	A
206	A	A
207	C	N.D.
208	A	C
209	A	C
210	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
211	A	B
212	A	A
213	B	C
214	A	B
215	A	B
216	A	B
217	A	A
218	B	N.D.
219	A	A
220	A	A
221	A	A
222	A	B
223	A	A
224	A	A
225	C	N.D.
226	A	A
227	A	B
228	A	A
229	B	C
230	B	N.D.
231	B	D
232	A	B

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
233	A	C
234	A	B
235	A	C
236	A	C
237	A	B
238	A	B
239	A	A
240	A	C
241	A	A
242	A	B
243	A	B
244	A	C
245	A	A
246	A	C
247	A	C
248	A	C
249	A	A
250	A	B
251	A	B
252	A	B
253	A	C
254	B	N.D.

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
255	A	A
256	A	C
257	A	C
258	A	A
259	A	A
260	A	A
261	A	A
262	A	A
263	A	B
264	A	A
265	A	A
266	A	A
267	A	A
268	A	B
269	A	A
270	B	C
271	A	A
272	A	B
273	A	C
274	A	A
275	A	A
276	A	B

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
277	A	B
278	A	B
279	A	D
280	B	C
281	A	A
282	C	D
283	A	A
284	A	A
285	A	A
286	A	A
287	A	A
288	A	A
289	A	A
290	A	A
291	A	A
292	A	A
293	A	B
294	A	A
295	A	A
296	A	A
297	A	A
298	B	C

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
299	B	C
300	A	A
301	A	A
302	A	B
303	A	A
304	A	A
305	A	A
306	A	A
307	A	B
308	A	B
309	C	C
310	C	C
311	C	D
312	A	B
313	A	B
314	C	B
315	A	A
316	A	A
317	A	A
318	A	A
319	B	N.D.
320	B	B

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
321	D	N.D.
322	D	N.D.
323	A	A
324	A	A
325	A	A
326	A	A
327	A	A
328	A	A
329	A	A
330	A	B
331	C	D
332	A	A
333	A	A
334	A	A
335	A	B
336	A	A
337	A	A
338	B	B
339	A	A
340	A	A
341	A	A
342	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
343	A	A
344	B	A
345	B	A
346	A	A
347	B	D
348	A	A
349	A	A
350	A	A
351	A	A
352	A	A
353	A	B
354	A	A
355	A	A
356	B	B
357	A	B
358	A	A
359	B	C
360	A	A
361	A	A
362	A	A
363	A	A
364	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
365	C	B
366	D	D
367	A	B
368	A	A
369	A	A
370	B	B
371	A	B
372	A	B
373	B	C
374	A	B
375	B	C
376	A	A
377	A	A
379	A	B
380	B	C
381	B	C
382	C	D
383	A	A
384	A	B
385	A	B
386	A	B
387	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
388	A	A
389	A	A
390	B	A
391	C	D
392	A	A
393	A	A
394	A	A
395	A	A
396	B	A
397	B	B
398	A	A
399	B	B
400	A	A
401	A	B
402	B	C
403	B	C
404	B	C
405	B	B
406	C	D
407	C	D
408	D	D
409	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
410	B	C
411	C	C
412	B	C
413	B	C
414	A	C
415	A	A
416	A	A
417	B	C
418	A	A
419	A	A
420	A	C
421	A	A
422	A	A
423	A	B
424	A	B
425	A	B
426	A	C
427	C	C
428	A	A
429	C	C
430	C	D
431	A	A

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
432	A	A
433	A	B
434	A	A
435	A	A
436	D	N.D.
437	D	N.D.
438	A	A
439	A	A
440	A	A
441	A	C
442	A	A
443	A	A
444	B	N.D.
445	B	C
446	A	B
447	A	A
448	C	N.D.
449	C	N.D.
450	B	C
451	A	B
452	C	N.D.
453	B	C

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
454	A	B
455	A	A
456	A	B
457	C	N.D.
458	A	A
459	A	A
460	A	A
461	A	C
462	B	B
463	B	B
464	A	A
465	A	A
466	A	B
467	A	B
468	B	B
469	A	B
470	A	A
471	A	A
472	A	B
473	A	B
474	A	B
475	A	C

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
476	A	C
477	A	B
478	A	B
479	C	C
480	B	C
481	A	B
482	A	B
483	A	B
484	A	B
485	B	B

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
486	A	A
487	B	B
488	A	A
489	A	A
490	A	B
491	A	A
492	A	A
493	A	A
494	C	D
495	A	C

Ex.	GLS1 IC ₅₀	A549 EC ₅₀
496	C	D
497	A	B
498	A	A
499	C	D
500	A	A
501	A	B
502	A	B
503	A	A
504	A	B
505	A	C

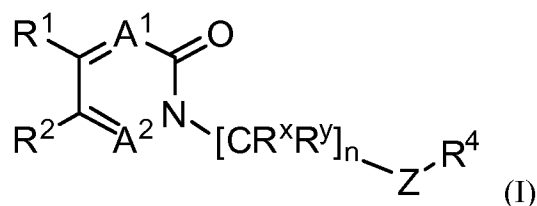
Other Embodiments

[0329] The detailed description set-forth above is provided to aid those skilled in the art in practicing the present disclosure. However, the disclosure described and claimed herein is not to be limited in scope by the specific embodiments herein disclosed because these embodiments are intended as illustration of several aspects of the disclosure. Any equivalent embodiments are intended to be within the scope of this disclosure. Indeed, various modifications of the disclosure in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description, which do not depart from the spirit or scope of the present inventive discovery. Such modifications are also intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

1. A compound of structural Formula I



or a salt thereof, wherein:

n is chosen from 3, 4, and 5;

each R^x and R^y is independently chosen from alkyl, cyano, H, and halo, wherein two R^x groups together with the atoms to which they are attached optionally form a cycloalkyl ring;

A¹ and A² are independently chosen from C-H, C-F, and N;

R¹ and R⁴ are independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, hydroxyl, C(R³)₂C(O)R³, C(R³)₂C(O)N(R³)₂, C(R³)₂N(R³)₂, C(R³)₂NR³C(O)R³, C(R³)₂NR³C(O)OR³, C(R³)₂NR³C(O)N(R³)₂, C(R³)₂NR³S(O)R³, C(R³)₂NR³S(O)₂R³, N(R³)₂, NR³C(O)R³, NR³C(O)OR³, NR³C(O)N(R³)₂, NR³S(O)R³, NR³S(O)₂R³, C(O)N(R³)₂, S(O)N(R³)₂, S(O)₂N(R³)₂, C(O)R³, SR³, S(O)R³, and S(O)₂R³, wherein each R¹ and R⁴ may be optionally substituted with between 0 and 3 R^z groups;

R² is chosen from alkyl, heterocycloalkyl, cyano, cycloalkyl, H, halo, and haloalkyl, wherein R¹ and R² together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^z groups;

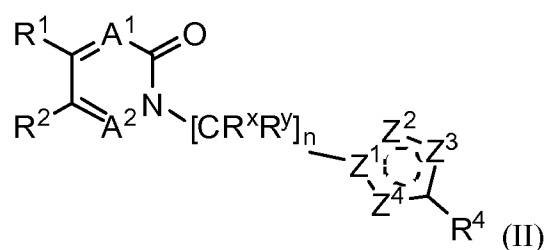
each R³ is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein each R³ may be optionally substituted with between 0 and 3 R^z groups, wherein two R³ groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^z groups;

each R^Z group is independently chosen from alkenyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyarylalkyl, alkoxycycloalkyl, alkoxycycloalkylalkyl, alkoxyhaloalkyl, alkoxyheteroaryl, alkoxyheteroarylalkyl, alkoxyheterocycloalkyl, alkoxyheterocycloalkylalkyl, alkyl, alkylaryl, alkylarylalkyl, alkylcycloalkyl, alkylcycloalkylalkyl, alkylheteroaryl, alkylheteroarylalkyl, alkylheterocycloalkyl, alkylheterocycloalkylalkyl, aryl, arylalkyl, arylalkyloxy, arylhaloalkyl, aryloxy, cyano, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, cycloalkylhaloalkyl, cycloalkyloxy, H, halo, haloalkoxy, haloalkoxyalkyl, haloalkoxyaryl, haloalkoxyarylalkyl, haloalkoxycycloalkyl, haloalkoxycycloalkylalkyl, haloalkoxyheteroaryl, haloalkoxyheteroarylalkyl, haloalkoxyheterocycloalkyl, haloalkoxyheterocycloalkylalkyl, haloalkyl, haloalkylaryl, haloalkylarylalkyl, haloalkylcycloalkyl, haloalkylcycloalkylalkyl, haloalkylheteroaryl, haloalkylheteroarylalkyl, haloalkylheterocycloalkyl, haloalkylheterocycloalkylalkyl, haloaryl, haloarylalkyl, haloarylalkyloxy, haloaryloxy, halocycloalkyl, halocycloalkylalkyl, halocycloalkylalkyloxy, halocycloalkyloxy, haloheteroaryl, haloheteroarylalkyl, haloheteroarylalkyloxy, haloheteroaryloxy, haloheterocycloalkyl, haloheterocycloalkylalkyl, haloheterocycloalkylalkyloxy, haloheterocycloalkyloxy, heteroaryl, heteroarylalkyl, heteroarylalkyloxy, heteroarylhaloalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkylalkyloxy, heterocycloalkylhaloalkyl, heterocycloalkyloxy, hydroxyl, oxo, $N(R^6)_2$, $NR^6C(O)C(R^6)_3$, $NR^6C(O)OC(R^6)_3$, $NR^6C(O)N(R^6)_2$, $NR^6S(O)C(R^6)_3$, $NR^6S(O)_2C(R^6)_3$, $C(O)N(R^6)_2$, $S(O)N(R^6)_2$, $S(O)_2N(R^6)_2$, $C(O)C(R^6)_3$, $SC(R^6)_3$, $S(O)C(R^6)_3$, and $S(O)_2C(R^6)_3$;

each R^6 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein two R^6 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^x groups; and

Z is heteroaryl, which may be optionally substituted.

2. The compound as recited in claim 1, wherein the compound has structural Formula II:



or a salt thereof, wherein:

n is chosen from 3, 4, and 5;

each R^x and R^y is independently chosen from alkyl, cyano, H, and halo, wherein two R^x groups together with the atoms to which they are attached optionally form a cycloalkyl ring;

A^1 and A^2 are independently chosen from C-H, C-F, and N;

Z^1 is chosen from C and N;

Z^2 , Z^3 , and Z^4 are independently chosen from N, O, S, and CH, wherein at least one of Z^1 , Z^2 , Z^3 , and Z^4 is chosen from N, O, and S;

R^1 and R^4 are independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, hydroxyl, $C(R^3)_2C(O)R^3$, $C(R^3)_2C(O)N(R^3)_2$, $C(R^3)_2N(R^3)_2$, $C(R^3)_2NR^3C(O)R^3$, $C(R^3)_2NR^3C(O)OR^3$, $C(R^3)_2NR^3C(O)N(R^3)_2$, $C(R^3)_2NR^3S(O)R^3$, $C(R^3)_2NR^3S(O)_2R^3$, $N(R^3)_2$, $NR^3C(O)R^3$, $NR^3C(O)OR^3$, $NR^3C(O)N(R^3)_2$, $NR^3S(O)R^3$, $NR^3S(O)_2R^3$, $C(O)N(R^3)_2$, $S(O)N(R^3)_2$, $S(O)_2N(R^3)_2$, $C(O)R^3$, SR^3 , $S(O)R^3$, and $S(O)_2R^3$, wherein each R^1 and R^4 may be optionally substituted with between 0 and 3 R^z groups;

R^2 is chosen from alkyl, heterocycloalkyl, cyano, cycloalkyl, H, halo, and haloalkyl, wherein R^1 and R^2 together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^z groups;

each R^3 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein each R^3 may be optionally substituted with between 0 and 3 R^z groups, wherein two R^3 groups together with the atoms to which they are

attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups;

each R^Z group is independently chosen from alkenyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyarylalkyl, alkoxycycloalkyl, alkoxycycloalkylalkyl, alkoxyhaloalkyl, alkoxyheteroaryl, alkoxyheteroarylalkyl, alkoxyheterocycloalkyl, alkoxyheterocycloalkylalkyl, alkyl, alkylaryl, alkylarylalkyl, alkylcycloalkyl, alkylcycloalkylalkyl, alkylheteroaryl, alkylheteroarylalkyl, alkylheterocycloalkyl, alkylheterocycloalkylalkyl, aryl, arylalkyl, arylalkyloxy, arylhaloalkyl, aryloxy, cyano, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, cycloalkylhaloalkyl, cycloalkyloxy, H, halo, haloalkoxy, haloalkoxyalkyl, haloalkoxyaryl, haloalkoxyarylalkyl, haloalkoxycycloalkyl, haloalkoxycycloalkylalkyl, haloalkoxyheteroaryl, haloalkoxyheteroarylalkyl, haloalkoxyheterocycloalkyl, haloalkoxyheterocycloalkylalkyl, haloalkyl, haloalkylaryl, haloalkylarylalkyl, haloalkylcycloalkyl, haloalkylcycloalkylalkyl, haloalkylheteroaryl, haloalkylheteroarylalkyl, haloalkylheterocycloalkyl, haloalkylheterocycloalkylalkyl, haloaryl, haloarylalkyl, haloarylalkyloxy, haloaryloxy, halocycloalkyl, halocycloalkylalkyl, halocycloalkylalkyloxy, halocycloalkyloxy, haloheteroaryl, haloheteroarylalkyl, haloheteroarylalkyloxy, haloheteroaryloxy, haloheterocycloalkyl, haloheterocycloalkylalkyl, haloheterocycloalkylalkyloxy, haloheterocycloalkyloxy, heteroaryl, heteroarylalkyl, heteroarylalkyloxy, heteroarylhaloalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkylalkyloxy, heterocycloalkylhaloalkyl, heterocycloalkyloxy, hydroxyl, oxo,, NR^6 , $NR^6C(O)C(R^6)_3$, $NR^6C(O)OC(R^6)_3$, $NR^6C(O)N(R^6)_2$, $NR^6S(O)C(R^6)_3$, $NR^6S(O)_2C(R^6)_3$, $C(O)N(R^6)_2$, $S(O)N(R^6)_2$, $S(O)_2N(R^6)_2$, $C(O)C(R^6)_3$, $SC(R^6)_3$, $S(O)C(R^6)_3$, and $S(O)_2C(R^6)_3$; and

each R^6 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein two R^6 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^X groups.

3. The compound as recited in claim 2, wherein:

n is 4; and

A¹ and A² are CH.

4. The compound as recited in claim 2, wherein:

n is 4;

A¹ is N; and

A² is CH.

5. The compound as recited in claim 2, wherein:

Z¹ is C;

Z² and Z³ are N;

Z⁴ is S; and

R⁴ is chosen from N(R³)₂, NR³C(O)C(R³)₃, NR³C(O)OC(R³)₃, and NR³C(O)N(R³)₂.

6. The compound as recited in claim 2, wherein:

n is 4;

A¹ and A² are CH;

Z¹ is C;

Z² and Z³ are N;

Z⁴ is S; and

R⁴ is chosen from N(R³)₂, NR³C(O)C(R³)₃, NR³C(O)OC(R³)₃, and NR³C(O)N(R³)₂.

7. The compound as recited in claim 2, wherein:

Z¹ is C;

Z² and Z³ are N;

Z⁴ is S; and

R⁴ is C(O)N(R³)₂.

8. The compound as recited in claim 2, wherein:

n is 4;

A¹ and A² are CH;

Z¹ is C;

Z² and Z³ are N;

Z⁴ is S; and

R⁴ is C(O)N(R³)₂.

9. The compound as recited in claim 2, wherein:

Z¹, Z², and Z³ are N;

Z⁴ is CH; and

R⁴ is chosen from N(R³)₂, NR³C(O)C(R³)₃, NR³C(O)OC(R³)₃, and NR³C(O)N(R³)₂.

10. The compound as recited in claim 2, wherein:

n is 4;

A¹ and A² are CH;

Z¹, Z², and Z³ are N;

Z⁴ is CH; and

R⁴ is chosen from N(R³)₂, NR³C(O)C(R³)₃, NR³C(O)OC(R³)₃, and NR³C(O)N(R³)₂.

11. The compound as recited in claim 2, wherein:

Z¹, Z², and Z³ are N;

Z⁴ is CH; and

R⁴ is C(O)N(R³)₂.

12. The compound as recited in claim 2, wherein:

n is 4;

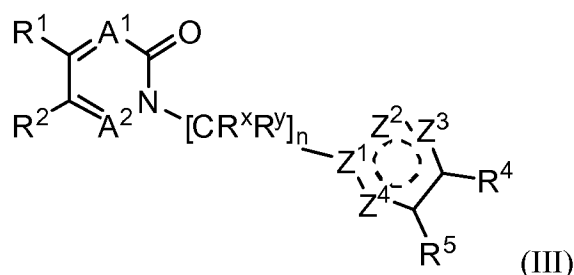
A¹ and A² are CH;

Z¹, Z², and Z³ are N;

Z^4 is CH; and

R^4 is $C(O)N(R^3)_2$.

13. The compound as recited in claim 1, wherein the compound has structural Formula III:



or a salt thereof, wherein:

n is chosen from 3, 4, and 5;

each R^x and R^y is independently chosen from alkyl, cyano, H, and halo, wherein two R^x groups together with the atoms to which they are attached optionally form a cycloalkyl ring;

A^1 and A^2 are independently chosen from C-H, C-F, and N;

Z^1 is chosen from C and N;

Z^2 is chosen from N, CH, and C(O);

Z^3 , and Z^4 are independently chosen from N and CH, wherein at least one of Z^1 , Z^2 , Z^3 , and Z^4 is N;

R^1 and R^4 are independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, hydroxyl, $C(R^3)_2C(O)R^3$, $C(R^3)_2C(O)N(R^3)_2$, $C(R^3)_2N(R^3)_2$, $C(R^3)_2NR^3C(O)R^3$, $C(R^3)_2NR^3C(O)OR^3$, $C(R^3)_2NR^3C(O)N(R^3)_2$, $C(R^3)_2NR^3S(O)R^3$, $C(R^3)_2NR^3S(O)_2R^3$, $N(R^3)_2$, $NR^3C(O)R^3$, $NR^3C(O)OR^3$, $NR^3C(O)N(R^3)_2$, $NR^3S(O)R^3$, $NR^3S(O)_2R^3$, $C(O)N(R^3)_2$, $S(O)N(R^3)_2$, $S(O)_2N(R^3)_2$, $C(O)R^3$, SR^3 , $S(O)R^3$, and $S(O)_2R^3$, wherein each R^1 and R^4 may be optionally substituted with between 0 and 3 R^z groups;

R^2 and R^5 are chosen from alkyl, heterocycloalkyl, cyano, cycloalkyl, H, halo, and haloalkyl, wherein R^1 and R^2 together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally

substituted with between 0 and 3 R^Z groups, wherein R^4 and R^5 together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups;

each R^3 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein each R^3 may be optionally substituted with between 0 and 3 R^Z groups, wherein two R^3 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^Z groups;

each R^Z group is independently chosen from alkenyl, alkoxy, alkoxyalkyl, alkoxyaryl, alkoxyarylalkyl, alkoxycycloalkyl, alkoxycycloalkylalkyl, alkoxyhaloalkyl, alkoxyheteroaryl, alkoxyheteroarylalkyl, alkoxyheterocycloalkyl, alkoxyheterocycloalkylalkyl, alkyl, alkylaryl, alkylarylalkyl, alkylcycloalkyl, alkylcycloalkylalkyl, alkylheteroaryl, alkylheteroarylalkyl, alkylheterocycloalkyl, alkylheterocycloalkylalkyl, aryl, arylalkyl, arylalkyloxy, arylhaloalkyl, aryloxy, cyano, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, cycloalkylhaloalkyl, cycloalkyloxy, H, halo, haloalkoxy, haloalkoxyalkyl, haloalkoxyaryl, haloalkoxyarylalkyl, haloalkoxycycloalkyl, haloalkoxycycloalkylalkyl, haloalkoxyheteroaryl, haloalkoxyheteroarylalkyl, haloalkoxyheterocycloalkyl, haloalkoxyheterocycloalkylalkyl, haloalkyl, haloalkylaryl, haloalkylarylalkyl, haloalkylcycloalkyl, haloalkylcycloalkylalkyl, haloalkylheteroaryl, haloalkylheteroarylalkyl, haloalkylheterocycloalkyl, haloalkylheterocycloalkylalkyl, haloaryl, haloarylalkyl, haloarylalkyloxy, haloaryloxy, halocycloalkyl, halocycloalkylalkyl, halocycloalkylalkyloxy, halocycloalkyloxy, haloheteroaryl, haloheteroarylalkyl, haloheteroarylalkyloxy, haloheteroaryloxy, haloheterocycloalkyl, haloheterocycloalkylalkyl, haloheterocycloalkylalkyloxy, haloheterocycloalkyloxy, heteroaryl, heteroarylalkyl, heteroarylalkyloxy, heteroarylhaloalkyl, heteroaryloxy, heterocycloalkyl, heterocycloalkylalkyl, heterocycloalkylalkyloxy, heterocycloalkylhaloalkyl, heterocycloalkyloxy, hydroxyl, oxo, $N(R^6)_2$, $NR^6C(O)C(R^6)_3$, $NR^6C(O)OC(R^6)_3$, $NR^6C(O)N(R^6)_2$, $NR^6S(O)C(R^6)_3$, $NR^6S(O)_2C(R^6)_3$, $C(O)N(R^6)_2$, $S(O)N(R^6)_2$, $S(O)_2N(R^6)_2$, $C(O)C(R^6)_3$, $SC(R^6)_3$, $S(O)C(R^6)_3$, and $S(O)_2C(R^6)_3$; and

each R^6 is independently chosen from alkenyl, alkoxy, alkyl, aryl, arylalkyl, cyano, cycloalkyl, cycloalkylalkyl, H, halo, haloalkyl, heteroaryl, heteroarylalkyl, heterocycloalkyl, heterocycloalkylalkyl, and hydroxyl, wherein two R^6 groups together with the atoms to which they are attached optionally form an aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring, which may be optionally substituted with between 0 and 3 R^x groups.

14. The compound as recited in claim 13, wherein:

n is 4; and

A^1 and A^2 is are CH.

15. The compound as recited in claim 13, wherein:

n is 4;

A^1 is N;

and A^2 is CH.

16. The compound as recited in claim 13, wherein:

Z^1 is C;

Z^2 and Z^3 are N;

Z^4 is CH;

R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$; and

R^5 is H.

17. The compound as recited in claim 13, wherein:

n is 4;

A^1 and A^2 is are CH;

Z^1 is C;

Z^2 and Z^3 are N;

Z^4 is CH;

R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$; and

R^5 is H.

18. The compound as recited in claim 13, wherein:

Z^1 is C;

Z^2 and Z^3 are N;

Z^4 is CH;

R^4 is $C(O)N(R^3)_2$; and

R^5 is H.

19. The compound as recited in claim 13, wherein:

n is 4;

A^1 and A^2 is are CH;

Z^1 is C;

Z^2 and Z^3 are N;

Z^4 is CH;

R^4 is $C(O)N(R^3)_2$; and

R^5 is H.

20. The compound as recited in claim 13, wherein:

Z^1 is N;

Z^2 is $C(O)$;

Z^4 is CH;

R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$; and

R^5 is H.

21. The compound as recited in claim 13, wherein:

n is 4;

A^1 and A^2 is are CH;

Z^1 is N;

Z^2 is C(O);

Z^4 is CH;

R^4 is chosen from $N(R^3)_2$, $NR^3C(O)C(R^3)_3$, $NR^3C(O)OC(R^3)_3$, and $NR^3C(O)N(R^3)_2$; and

R^5 is H.

22. The compound as recited in claim 13, wherein:

Z^1 is N;

Z^2 is C(O);

Z^4 is CH;

R^4 is C(O) $N(R^3)_2$; and

R^5 is H.

23. The compound as recited in claim 13, wherein:

n is 4;

A^1 and A^2 is are CH;

Z^1 is N;

Z^2 is C(O);

Z^4 is CH;

R^4 is C(O) $N(R^3)_2$; and

R^5 is H.

24. The compound as recited in claim 1, or a salt thereof, wherein the compound is chosen from Examples 1-505.

25. A pharmaceutical composition comprising a compound as recited in claim 1 and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

26. A method of inhibiting GLS1 activity in a biological sample comprising contacting the biological sample with a compound as recited in claim 1.

27. A method of treating a GLS1-mediated disorder in a subject in need thereof, comprising the step of administering to the subject a compound as recited in claim 1.
28. The method as recited in claim 27, wherein the subject is a human.
29. The method as recited in claim 27, wherein the GLS1-mediated disorder is chosen from cancer, immunological disorders, and neurological disorders.
30. The method as recited in claim 29, wherein the GLS1-mediated disorder is cancer.
31. The method as recited in claim 30, wherein the cancer is chosen from Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Adrenocortical Carcinoma, AIDS-Related Cancers (Kaposi Sarcoma and Lymphoma), Anal Cancer, Appendix Cancer, Atypical Teratoid/Rhabdoid Tumor, Basal Cell Carcinoma, Bile Duct Cancer (including Extrahepatic), Bladder Cancer, Bone Cancer (including Osteosarcoma and Malignant Fibrous Histiocytoma), Brain Tumor (such as Astrocytomas, Brain and Spinal Cord Tumors, Brain Stem Glioma, Central Nervous System Atypical Teratoid/Rhabdoid Tumor, Central Nervous System Embryonal Tumors, Craniopharyngioma, Ependymoblastoma, Ependymoma, Medulloblastoma, Medulloepithelioma, Pineal Parenchymal Tumors of Intermediate Differentiation, Supratentorial Primitive Neuroectodermal Tumors and Pineoblastoma), Breast Cancer, Bronchial Tumors, Burkitt Lymphoma, Basal Cell Carcinoma, Bile Duct Cancer (including Extrahepatic), Bladder Cancer, Bone Cancer (including Osteosarcoma and Malignant Fibrous Histiocytoma), Carcinoid Tumor, Carcinoma of Unknown Primary, Central Nervous System (such as Atypical Teratoid/Rhabdoid Tumor, Embryonal Tumors and Lymphoma), Cervical Cancer, Childhood Cancers, Chordoma, Chronic Lymphocytic Leukemia (CLL), Chronic Myelogenous Leukemia (CML), Chronic Myeloproliferative Disorders, Colon Cancer, Colorectal Cancer, Craniopharyngioma, Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome), Duct, Bile (Extrahepatic), Ductal Carcinoma In Situ (DCIS), Embryonal Tumors (Central Nervous System), Endometrial Cancer, Ependymoblastoma, Ependymoma, Esophageal Cancer, Esthesioneuroblastoma, Ewing Sarcoma Family of Tumors, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer (like Intraocular Melanoma, Retinoblastoma), Fibrous Histiocytoma of Bone (including Malignant and Osteosarcoma) Gallbladder Cancer, Gastric

(Stomach) Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Stromal Tumors (GIST), Germ Cell Tumor (Extracranial, Extragonadal, Ovarian), Gestational Trophoblastic Tumor, Glioma, Hairy Cell Leukemia, Head and Neck Cancer, Heart Cancer, Hepatocellular (Liver) Cancer, Histiocytosis, Langerhans Cell, Hodgkin Lymphoma, Hypopharyngeal Cancer, Intraocular Melanoma, Islet Cell Tumors (Endocrine, Pancreas), Kaposi Sarcoma, Kidney (including Renal Cell), Langerhans Cell Histiocytosis, Laryngeal Cancer, Leukemia (including Acute Lymphoblastic (ALL), Acute Myeloid (AML), Chronic Lymphocytic (CLL), Chronic Myelogenous (CML), Hairy Cell), Lip and Oral Cavity Cancer, Liver Cancer (Primary), Lobular Carcinoma In Situ (LCIS), Lung Cancer (Non-Small Cell and Small Cell), Lymphoma (AIDS-Related, Burkitt, Cutaneous T-Cell (Mycosis Fungoides and Sézary Syndrome), Hodgkin, Non-Hodgkin, Primary Central Nervous System (CNS), Macroglobulinemia, Waldenström, Male Breast Cancer, Malignant Fibrous Histiocytoma of Bone and Osteosarcoma, Medulloblastoma, Medulloepithelioma, Melanoma (including Intraocular (Eye)), Merkel Cell Carcinoma, Mesothelioma (Malignant), Metastatic Squamous Neck Cancer with Occult Primary, Midline Tract Carcinoma Involving NUT Gene, Mouth Cancer, Multiple Endocrine Neoplasia Syndromes, Multiple Myeloma/Plasma Cell Neoplasm, Mycosis Fungoides, Myelodysplastic Syndromes, Myelodysplastic/Myeloproliferative Neoplasms, Myelogenous Leukemia, Chronic (CML), Myeloid Leukemia, Acute (AML), Myeloma and Multiple Myeloma, Myeloproliferative Disorders (Chronic), Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin Lymphoma, Non-Small Cell Lung Cancer, Oral Cancer, Oral Cavity Cancer, Lip and, Oropharyngeal Cancer, Osteosarcoma and Malignant Fibrous Histiocytoma of Bone, Ovarian Cancer (such as Epithelial, Germ Cell Tumor, and Low Malignant Potential Tumor), Pancreatic Cancer (including Islet Cell Tumors), Papillomatosis, Paraganglioma, Paranasal Sinus and Nasal Cavity Cancer, Parathyroid Cancer, Penile Cancer, Pharyngeal Cancer, Pheochromocytoma, Pineal Parenchymal Tumors of Intermediate Differentiation, Pineoblastoma and Supratentorial Primitive Neuroectodermal Tumors, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Pleuropulmonary Blastoma, Pregnancy and Breast Cancer, Primary Central Nervous System (CNS) Lymphoma, Prostate Cancer, Rectal Cancer, Renal Cell (Kidney) Cancer, Renal Pelvis and Ureter, Transitional Cell Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary

Gland Cancer, Sarcoma (like Ewing Sarcoma Family of Tumors, Kaposi, Soft Tissue, Uterine), Sézary Syndrome, Skin Cancer (such as Melanoma, Merkel Cell Carcinoma, Nonmelanoma), Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Cell Carcinoma, Squamous Neck Cancer with Occult Primary, Metastatic, Stomach (Gastric) Cancer, Supratentorial Primitive Neuroectodermal Tumors, T-Cell Lymphoma (Cutaneous, Mycosis Fungoides and Sézary Syndrome), Testicular Cancer, Throat Cancer, Thymoma and Thymic Carcinoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Trophoblastic Tumor (Gestational), Unknown Primary, Unusual Cancers of Childhood, Ureter and Renal Pelvis, Transitional Cell Cancer, Urethral Cancer, Uterine Cancer, Endometrial, Uterine Sarcoma, Waldenström Macroglobulinemia and Wilms Tumor, or a variant thereof.

32. A method of treating a GLS1-mediated disorder in a subject in need thereof, comprising the sequential or co-administration of a compound as recited in claim 1 or a pharmaceutically acceptable salt thereof, and another therapeutic agent.
33. The method as recited in claim 32, wherein the therapeutic agent is chosen from a taxane, inhibitor of bcr-abl, inhibitor of EGFR, DNA damaging agent, and antimetabolite.
34. The method as recited in claim 32, wherein the therapeutic agent is chosen from aminoglutethimide, amsacrine, anastrozole, asparaginase, bcg, bicalutamide, bleomycin, buserelin, busulfan, camptothecin, capecitabine, carboplatin, carmustine, chlorambucil, chloroquine, cisplatin, cladribine, clodronate, colchicine, cyclophosphamide, cyproterone, cytarabine, dacarbazine, dactinomycin, daunorubicin, demethoxyviridin, dichloroacetate, dienestrol, diethylstilbestrol, docetaxel, doxorubicin, epirubicin, estradiol, estramustine, etoposide, everolimus, exemestane, filgrastim, fludarabine, fludrocortisone, fluorouracil, fluoxymesterone, flutamide, gemcitabine, genistein, goserelin, hydroxyurea, idarubicin, ifosfamide, imatinib, interferon, irinotecan, ironotecan, letrozole, leucovorin, leuprolide, levamisole, lomustine, lonidamine, mechlorethamine, medroxyprogesterone, megestrol, melphalan, mercaptopurine, mesna, metformin, methotrexate, mitomycin, mitotane, mitoxantrone, nilutamide, nocodazole, octreotide, oxaliplatin, paclitaxel, pamidronate, pentostatin, perifosine, plicamycin, porfimer, procarbazine, raltitrexed, rituximab, sorafenib, streptozocin, sunitinib, suramin, tamoxifen, temozolomide, temsirolimus, teniposide,

testosterone, thioguanine, thiotepa, titanocene dichloride, topotecan, trastuzumab, tretinoin, vinblastine, vincristine, vindesine, and vinorelbine.

35. The method as recited in claim 30, wherein the method further comprises administering non-chemical methods of cancer treatment.
36. The method as recited in claim 35, wherein the method further comprises administering radiation therapy.
37. The method as recited in claim 36, wherein the method further comprises administering surgery, thermoablation, focused ultrasound therapy, cryotherapy, or any combination thereof.
38. A compound of any as recited in claim 1 for use in human therapy.
39. A compound of any as recited in claim 1 for use in treating a GLS1-mediated disease.
40. Use of a compound as recited in claim 1 for the manufacture of a medicament to treat a GLS1-mediated disease.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/039150

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 401/06 (2015.01)

CPC - A61K 31/4412 (2015.10)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8) - A61K 31/4412; C07D 401/06, 417/06 (2015.01)

CPC - A61K 31/4412; C07D 401/06, 417/06 (2015.10)

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

USPC - 514/252.05, 333, 363; IPC(8) - A61K 31/4412; C07D 401/06, 417/06 (2015.01); CPC - A61K 31/4412; C07D 401/06, 417/06 (2015.10) (keyword delimited)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, STN, Google Scholar, PubChem

Search terms used: triazole linked pyridone, propyl, GLS1 inhibitor, Glutaminase, vinyl, alkenyl

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4,720,447 A (DE KEYZER et al) 19 January 1988 (19.01.1988) entire document	1, 2, 25, 38, 39
A	US 7,956,070 B2 (ALCARAZ et al) 07 June 2011 (07.06.2011) entire document	1, 2, 25, 38, 39
A	US 2013/0157998 A1 (CALITHERA BIOSCIENCES INC) 20 June 2013 (20.06.2013) entire document	1, 2, 25, 38, 39
A	WO 2014/089048 A1 (CALITHERA BIOSCIENCES INC) 12 June 2014 (12.06.2014) entire document	1, 2, 25, 38, 39
A	US 4,399,140 A (GACEK et al) 16 August 1983 (16.08.1983) entire document	1, 2, 25, 38, 39



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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

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

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

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

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

"T"

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

"X"

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

"Y"

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

"&"

document member of the same patent family

Date of the actual completion of the international search

30 October 2015

Date of mailing of the international search report

04 DEC 2015

Name and mailing address of the ISA/

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

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Authorized officer

Blaine Copenheaver

PCT Helpdesk: 571-272-4300

PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/039150

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Extra Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1, 2, 25, 38, 39

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2015/039150

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-25, 38 and 39 are drawn to compounds of structural Formula I: or a salt thereof, and pharmaceutical compositions thereof.

Group II: claims 26-37 and 40 are drawn to methods thereof and uses thereof.

The first invention of Group I+ is restricted to a compound of structural Formula I, or a salt thereof, wherein n is 3; Rx and Ry are independently alkyl; A1 and A2 are independently C-H; R1 and R4 are independently unsubstituted alkenyl; R2 is alkyl, wherein R1 and R2 together with the atoms to which they are attached do not form a ring; and Z is unsubstituted heteroaryl, where the unsubstituted heteroaryl is the 5-membered ring containing Z1, Z2, Z3, and Z4 as shown in Formula II of the instant invention, where Z1 is C; Z2, Z3, and Z4 are independently N; and pharmaceutical compositions thereof. It is believed that claims 1, 2, 25, 38 and 39 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional formula(e) for each additional compound to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a compound of structural Formula I, or a salt thereof, wherein n is 4; Rx and Ry are independently alkyl; A1 and A2 are independently C-H; R1 and R4 are independently unsubstituted alkenyl; R2 is alkyl, wherein R1 and R2 together with the atoms to which they are attached do not form a ring; and Z is unsubstituted heteroaryl, where the unsubstituted heteroaryl is the 5-membered ring containing Z1, Z2, Z3, and Z4 as shown in Formula II of the instant invention, where Z1 is C; Z2, Z3, and Z4 are independently N; and pharmaceutical compositions thereof. Additional formula(e) will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+ and II do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, compounds of structural Formula I or a salt thereof, pharmaceutical compositions thereof, are not present in Group II; and the special technical features of Group II, methods of inhibiting GLS1 activity, methods of treating GLS1-mediated disorders, and uses thereof, are not present in Group I+.

The Groups I+ and II formulae do not share a significant structural element requiring the selection of alternatives for the compound variables R1, R2, A1, A2, Rx, Ry, Z, n, and R4.

The Groups I+ and II share the technical features of a compound of structural Formula I or a salt thereof; and a pharmaceutical composition comprising a compound and a pharmaceutically acceptable carrier, adjuvant, or vehicle. However, these shared technical features do not represent a contribution over the prior art.

Specifically, US 4,399,140 A to Gacek et al. teach a compound of structural Formula I or a salt thereof, wherein: n is 4; each Rx and Ry are independently selected as H; A1 is independently selected as N; A2 is independently selected as C-H; R1 and R4 are independently selected as H; R2 is chosen as halo; and Z is unsubstituted heteroaryl (Col. 17, Lns. 35-37, 5-Chloro-1-[4-(2-thienyl)butyl]pyrimidine-2-one); and a pharmaceutical composition comprising a compound and a pharmaceutically acceptable carrier, adjuvant, or vehicle (Col. 6, Ln. 58 through Col. 7, Ln. 10).

The inventions listed in Groups I+ and II therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.