(54) Title: OXAZOLIDINONE HYDROXAMIC ACID COMPOUNDS FOR THE TREATMENT OF BACTERIAL INFECTIONS

(57) Abstract: This invention pertains generally to treating bacterial infections using organic compounds of Formula I. In certain aspects, the invention pertains to treating infections caused by Gram-negative bacteria. (I) wherein X, Y, R₁, R₂, R₃, R₄ and R₅ are defined herein.

(1) wherein X, Y, R₁, R₂, R₃, R₄ and R₅ are defined herein.
OXAZOLIDINONE HYDROXAMIC ACID COMPOUNDS FOR THE TREATMENT OF BACTERIAL INFECTIONS

FIELD OF THE INVENTION

This invention pertains generally to compounds and compositions for treating bacterial infections. In certain aspects, the invention pertains to treating infections caused by Gram-negative bacteria. More specifically, the invention pertains to treating Gram-negative infections by inhibiting the activity of UDP-3-O-(R-3-hydroxydecanoyl)-N-acetylgalacloseamine deacetylase (LpxC). The invention provides small molecule inhibitors of LpxC, pharmaceutical compositions containing such inhibitors, methods of treating patients with such compounds and pharmaceutical compounds, and methods of preparing such pharmaceutical compositions and inhibitors. The inhibitors can be used to treat Gram-negative infections of patients, either alone or in combination with other antibacterials.

BACKGROUND OF THE INVENTION

Over the past several decades, the frequency of antimicrobial resistance and its association with serious infectious diseases have increased at alarming rates. The increasing prevalence of resistance among nosocomial pathogens is particularly disconcerting. It is currently estimated that, of the over 2 million nosocomial infections occurring each year in the United States, 50 to 60% are caused by antimicrobial-resistant strains of bacteria. The high rate of resistance to commonly used antibacterial agents increases the morbidity, mortality, and costs associated with nosocomial infections. In the United States, nosocomial infections are thought to contribute to or cause more than 77,000 deaths per year while costing approximately $5 to $10 billion dollars. Among Gram-positive organisms, the most important resistant pathogens are methicillin-(oxacillin-) resistant Staphylococcus aureus, β-lactam-resistant and multidrug-resistant pneumococci, and vancomycin-resistant enterococci. Important causes of Gram-negative resistance include extended-spectrum β-lactamases (ESBLs) in Klebsiella pneumoniae, Escherichia coli, and Proteus mirabilis, high-level third-generation cephalosporin (Amp C) β-lactamase resistance among Enterobacter species and Citrobacter freundii, and multidrug-resistance genes observed in Pseudomonas, Acinetobacter, and Stenotrophomonas.

The problem of antibacterial resistance is compounded by the existence of bacterial strains resistant to multiple antibacterials. For example, Pseudomonas aeruginosa isolates resistant to fluoroquinolones are virtually all resistant to additional antibacterial medicines. This makes it increasingly difficult to select a suitable antibiotic for a given infection: frequently an ineffective antibiotic is administered first, which delays effective treatment and increases mortality.
Thus there is therefore a need for new antibactenals, particularly antibactenals that are not cross-resistant with widely-used antibiotics. In particular, there is a need for new Gram-negative antibactenals. Gram-negative bacteria are in general more resistant to a large number of antibactenals and chemotherapeutic agents than are Gram-positive bacteria.

Summary of the Invention

The present invention provides novel compounds, pharmaceutical formulations including the compounds, methods of inhibiting UDP-3-O-(R-3-hydroxydecanoyl)-N-acetylglicosamine deacetylase (LpxC), and methods of treating Gram-negative bacterial infections. Compounds acting on this target site have been reported as antibactenals, see e.g., WO2014/160649. The present invention provides novel inhibitory compounds and compositions, and methods for their use as antibactenals, particularly for Gram-negative bacterial infections.

In one aspect, the invention provides compounds of Formula (I):

![Chemical Structure](image)

(I)

or a pharmaceutically acceptable salt thereof, wherein:

- \( X \) is \( N \) or \( C \), wherein when \( X = N \), \( R^4 \) is absent;
- \( Y \) is \( N \) or \( C \), wherein when \( Y = N \), \( R^5 \) is absent;
- \( R^1, R^2, R^4 \) and \( R^5 \) are independently selected from the group consisting of hydrogen, halogen, \(-CH_3\), and \(-\text{Cihaloalkyl}\);
- \( R^3 \) is \( L\)-\( R \);
- \( L \) is a divalent bond, or \(-CH_2-\);
- \( R \) is selected from group consisting of halogen, \(-C_1-C_4\)-alkyl optionally substituted with one or more groups selected from halogen, \( C_1-C_4\)-alkoxy, \(-CN\) and \(-OH\);
- \(-CN\),
- \(-C_C_4\)-alkoxy optionally substituted with one or more groups selected from halogen, \( C_1-C_4\)-alkoxy, \(-CN\) and \(-OH\);
- \(-S-C_4\)-alkyl wherein the alkyl is optionally substituted with one or more groups...
selected from halogen, CrC₄alkoxy, -CN and -OH;
- C₂-C₅alkenyl optionally substituted with one or more groups selected from halogen, - CN, -OH and C₁-C₄alkoxy;
- C₂-C₅alkynyl optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, -CN and -OH;
- C₃-C₇cycloalkyl optionally substituted with one or more groups selected from halogen, C₁-C₄alkyl, -Cl-C₄alkyl-CrC₄alkoxy, C₁-C₄alkoxy, CrC₄haloalkyl, nitrile, -S(0)₂-C₁-C₄alkyl and -OH;
- C₆-C₁₅aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl and C₁-C₄alkyl;
- CrC₄alkyl-C₆-Cioaryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, CrC₄haloalkyl and C₁-C₄alkyl;
- CrC₄alkyl-C₃-C₇cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more groups selected from halogen, Cl-C₄alkoxy, C₁-C₄haloalkoxy, CrC₄haloalkyl and C₁-C₄alkyl;
- C₅-C₆cycloalkenyl optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl and C₁-C₄alkyl;
- 4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂-CrC₄alkyl and -OH, and said heterocyclyl may contain one unsaturated bond;
- CrC₄alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, Ci-C₄haloalkoxy, CrC₄haloalkyl, Ci-C₄alkyl, nitrile, -S(0)₂-CrC₄alkyl and -OH;
- C₃-C₅cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂-CrC₄alkyl and -OH;
- 5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, Ci-C₄haloalkoxy, Ci-C₄haloalkyl, Ci-C₄alkyl, nitrile, -S(0)₂-CrC₄alkyl and -OH;
- CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂-CrC₄alkyl and -OH; and
-C₃-C₅ cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, CrC₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂C₁-C₄ alkyl and -OH; or

\[ \text{R is selected from group consisting of} \]

-CrC₆alkyl optionally substituted with one or more groups selected from halogen, Cl-C₄ alkoxy, -CN, -OH and a 5-6 membered heterocyclyl containing one or two heteroatoms selected from N, O and S as ring members and optionally substituted with up to two halo, oxo or C₁-C₃ alkyl;

-C₂-C₆ alkenyl optionally substituted with one or more groups selected from halogen, CN, -OH and C₁-C₄ alkoxy;

-C₂-C₆ alkenyl optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, -CN and -OH;

-C₃-C₇ cycloalkyl optionally substituted with one or more groups selected from halogen, C₁-C₄ alkyl, -C₆ alkoxyCrC₄ alkoxy, C₁-C₄ alkoxy, CrC₄ haloalkyl, nitrile, -S(0)₂C₁-C₄ alkyl, -OH, and C₁-C₃ alkyl substituted with a group selected from CN, OH, -S0₂R', -NHC(0)R', and a 5-6 membered heterocyclyl containing one or two heteroatoms selected from N, O and S as ring members and optionally substituted with up to two halo, oxo or R', and wherein R' is C₁-C₃ alkyl;

-C₆-C₇ aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl and C₁-C₄ alkyl;

-C₆-C₇ aryl-C₇ aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, CrC₄ haloalkyl and C₁-C₄ alkyl;

-4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂C₁-C₄ alkyl and -OH;

-CrC₄ alkylnyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂C₁-C₄ alkyl and -OH;

-C₃-C₅ cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or
more groups selected from halogen, \( \text{CrC}_4\text{haloalkoxy} \), \( \text{CrC}_4\text{haloalkoxy} \), \( \text{CrC}_4\text{haloalkyl} \), \( \text{C}_1\text{-C}_4 \text{alkyl} \), nitrile, \( -\text{S}(0)\text{2}\text{C}_1\text{-C}_4\text{alkyl} \) and \( -\text{OH} \);

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, \( \text{C}_1\text{-C}_4\text{alkoxy} \), \( \text{CrC}_4\text{haloalkoxy} \), \( \text{CrC}_4\text{haloalkyl} \), \( \text{C}_1\text{-C}_4 \text{alkyl} \), nitrile, \( -\text{S}(0)\text{2}\text{C}_1\text{-C}_4\text{alkyl} \) and \( -\text{OH} \);

- \( \text{CrC}_4\text{alkyl-5} \) to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, \( \text{C}_1\text{-C}_4\text{alkoxy} \), \( \text{CrC}_4\text{haloalkoxy} \), \( \text{CrC}_4\text{haloalkyl} \), \( \text{C}_1\text{-C}_4 \text{alkyl} \), nitrile, \( -\text{S}(0)\text{2}\text{C}_1\text{-C}_4\text{alkyl} \) and \( -\text{OH} \); and

\[ -\text{C}_3\text{-C}_2\text{cycloalkyl-5} \] to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, \( \text{C}_1\text{-C}_4\text{alkoxy} \), \( \text{CrC}_4\text{haloalkoxy} \), \( \text{CrC}_4\text{haloalkyl} \), \( \text{C}_1\text{-C}_4 \text{alkyl} \), nitrile, \( -\text{S}(0)\text{2}\text{C}_1\text{-C}_4\text{alkyl} \) and \( -\text{OH} \); or

\( R^2 \) and \( R^3 \) taken together form a 4 to 7 membered heteroaryl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, \( \text{C}_1\text{-C}_4\text{alkoxy} \), \( \text{CrC}_4\text{haloalkoxy} \), \( \text{CrC}_4\text{haloalkyl} \), \( \text{C}_1\text{-C}_4 \text{alkyl} \), and \( \text{C}_1\text{-C}_4 \text{alkyl} \).

Various embodiments of these compounds are described herein.

In one aspect, the invention provides a method of inhibiting a deacetylase enzyme in Gram-negative bacteria, thereby affecting bacterial growth, comprising administering to a patient in need of such inhibition a compound of formula I.

In another aspect, the invention provides a method of inhibiting LpxC, thereby modulating the virulence of a bacterial infection, comprising administering to a patient in need of such inhibition a compound of formula I.

In another aspect, the invention provides a method for treating a subject with a Gram-negative bacterial infection, which comprises administering to the subject in need thereof an antibacterial effective amount of a compound of formula I with a pharmaceutically acceptable carrier. In certain embodiments, the subject is a mammal and in some other embodiments, the subject is a human.

In another aspect, the invention provides a method of administering an inhibitory amount of a compound of formula I to fermentative or non-fermentative Gram-negative bacteria. In certain embodiment of the method of administering an inhibitory amount of a compound of formula I to fermentative or non-fermentative Gram-negative bacteria, the Gram-negative bacteria are selected from the group consisting of *Pseudomonas aeruginosa* and other *Pseudomonas* species, *Stenotrophomonas maltophilia*, *Burkholderia cepacia* and other *Burkholderia* species, *Alcaligenes xylosoxidans*, species of *Acinetobacter*,
Enterobacteriaceae, Haemophilus, Moraxella, Bacteroides, Fransicella, Shigella, Proteus, Vibrio, Salmonella, Bordetella, Helicobactor, Legionella, Citrobacter, Serratia, Campylobactor, Yersinia and Neisseria.

In another embodiment, the invention provides a method of administering an inhibitory amount of a compound of formula I to Gram-negative bacteria, such as Enterobacteriaceae which is selected from the group consisting of organisms such as Serratia, Proteus, Klebsiella, Enterobacter, Citrobacter, Salmonella, Providencia, Morganella, Cedecea, Yersina and Edwardsiella species and Escherichia coli.

Another embodiment of the invention provides a pharmaceutical composition comprising an effective amount of a compound of Formula I with a pharmaceutically acceptable carrier thereof.

Pharmaceutical formulations according to the present invention are provided which include any of the compounds described above and a pharmaceutically acceptable carrier.

Other aspects of the invention are discussed infra.

DETAILED DESCRIPTION OF THE INVENTION

For purposes of interpreting this specification, the following definitions will apply unless specified otherwise and whenever appropriate, terms used in the singular will also include the plural and vice versa.

Definitions

Terms used in the specification have the following meanings:

"LpxC" is an abbreviation that stands for UDP-3-0-(R-3-hydroxydecanoyl)-N-acetylg glucosamine deacetylase.

As used herein, the term "subject" refers to an animal. In certain aspects, the animal is a mammal. A subject also refers to for example, primates (e.g., humans), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds and the like. In certain embodiments, the subject is a human.

As used herein, the term "inhibition" or "inhibiting" refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

As used herein, the term "treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, "treating" or "treatment" refers to modulating the disease or disorder,
either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g.,
stabilization of a physical parameter), or both. In yet another embodiment, "treating" or
"treatment" refers to preventing or delaying the onset or development or progression of the
disease or disorder.

As used herein, the term "a," "an," "the" and similar terms used in the context of the
present invention (especially in the context of the claims) are to be construed to cover both
the singular and plural unless otherwise indicated herein or clearly contradicted by the
context.

All methods described herein can be performed in any suitable order unless
otherwise indicated herein or otherwise clearly contradicted by context. The use of any and
all examples, or exemplary language (e.g. "such as") provided herein is intended merely to
better illuminate the invention and does not pose a limitation on the scope of the invention
otherwise claimed.

The term "antibacterial agent" refers to agents synthesized or modified in the
laboratory that have either bactericidal or bacteriostatic activity. An "active" agent in this
context will inhibit the growth of *P. aeruginosa* and/or other Gram-negative bacteria. The
term "inhibiting the growth" indicates that the rate of increase in the numbers of a population
of a particular bacterium is reduced. Thus, the term includes situations in which the bacterial
population increases but at a reduced rate, as well as situations where the growth of the
population is stopped, as well as situations where the numbers of the bacteria in the
population are reduced or the population even eliminated. If an enzyme activity assay is
used to screen for inhibitors, one can make modifications in bacterial uptake/efflux, solubility,
half-life, etc. to compounds in order to correlate enzyme inhibition with growth inhibition.

"Optionally substituted" means the group referred to can be substituted at one or
more positions by any one or any combination of the radicals listed thereafter.

"Halo" or "halogen", as used herein, may be fluorine, chlorine, bromine or iodine.

"CrC 4-Alkyl", as used herein, denotes straight chain or branched alkyl having 1-4
carbon atoms. If a different number of carbon atoms is specified, such as C<sub>6</sub> or C<sub>3</sub>, then the
definition is to be amended accordingly, such as "CrC 4-Alkyl" will represent methyl, ethyl,
propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

"CrC 4-Alkoxy", as used herein, denotes straight chain or branched alkoxy having 1-4
carbon atoms. If a different number of carbon atoms is specified, such as C<sub>6</sub> or C<sub>3</sub>, then the
definition is to be amended accordingly, such as "CrC 4-Alkoxy" will represent methoxy,
ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy.

"CrC 4-Haloalkyl", as used herein, denotes straight chain or branched alkyl having 1-4
carbon atoms with at least one hydrogen substituted with a halogen. If a different number
of carbon atoms is specified, such as C<sub>6</sub> or C<sub>3</sub>, then the definition is to be amended
Accordingly, such as "Cl-C₄-Haloalkyl" will represent methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl that have at least one hydrogen substituted with halogen, such as where the halogen is fluorine: CF₃CF₂-, (CF₃)₂CH-, CH₃-CF₂-, CF₃CF₂-, CF₃, CF₂H-, CF₃CF₂CHCF₃ or CF₃CF₂CF₂CF₂-. 

"C₃-C₇-cycloalkyl" as used herein refers to a saturated monocyclic hydrocarbon ring of 3 to 7 carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. If a different number of carbon atoms is specified, such as C₃-C₆, then the definition is to be amended accordingly.

"4- to 8-Membered heterocyclyl", "5- to 6- membered heterocyclyl", "3- to 10-membered heterocyclyl", "3- to 14-membered heterocyclyl", "4- to 14-membered heterocyclyl" and "5- to 14-membered heterocyclyl", refers, respectively, to 4- to 8-membered, 5- to 6-membered, 3- to 10-membered, 3- to 14-membered, 4- to 14-membered and 5- to 14-membered heterocyclic rings containing 1 to 7, 1 to 5 or 1 to 3 heteroatoms selected from the group consisting of nitrogen, oxygen and sulphur, which may be saturated, or partially saturated. The heterocyclic group can be attached at a heteroatom or a carbon atom. The term "heterocyclyl" includes single ring groups, fused ring groups and bridged groups. Examples of such heterocyclyl include, but are not limited to pyrrolidine, piperidine, piperazine, pyrrolidine, pyrrolidinone, morpholine, tetrahydrofuran, tetrahydrothiophene, tetrahydrothiopyran, tetrahydroxopyran, 1,4-dioxane, 1,4-oxathiane, 8-aza-bicyclo[3.2.1]octane, 3,8-diazabicyclo[3.2.1]octane, 3-Oxa-8-aza-bicyclo[3.2.1]octane, 8-Oxa-3-aza-bicyclo[3.2.1]octane, 2-Oxa-5-aza-bicyclo[2.2.1]heptane, 2,5-Diaza-bicyclo[2.2.1]heptane, azetidine, ethylenedioxy, octane or thiazole.

"Heteroaryl" is a completely unsaturated (aromatic) ring. The term "heteroaryl" refers to a 5-14 membered monocyclic- or bicyclic- or tricyclic-aromatic ring system, having 1 to 8 heteroatoms selected from N, O or S. Typically, the heteroaryl is a 5-10 membered ring system (e.g., 5-7 membered monocycle or an 8-10 membered bicycle) or a 5-7 membered ring system. Typical heteroaryl groups include furan, isothiazole, thiadiazole, oxadiazole, indazole, indazole, indole, quinoline, 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrryl, 2-., 4-., or 5-imidazolyl, 3-., 4-., or 5-pyrazolyl, 2-., 4-., or 5-thiazolyl, 3-., 4-., or 5-isothiazolyl, 2-., 4-., or 5-oxazolyl, 3-., 4-., or 5-isoxazolyl, 3- or 5-(1,2,4-triazolyl), 4- or 5-(1,2,3-triazolyl), tetrazolyl, triazine, pyrimidine, 2-., 3-, or 4-pyridyl, 3- or 4-pyridazine, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, and 2-, 4-, or 5-pyrimidinyl.

The term "hydroxy" or "hydroxyl" includes groups with an -OH.

The term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.
Various embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments.

In one aspect, the invention provides compounds of Formula (I) as described in the following embodiments, including pharmaceutical salts of these compounds, pharmaceutical compositions and combinations containing these compounds and salts, and methods of using these compounds and compositions to inhibit growth of certain bacteria and to treat infections caused by such bacteria. Particular embodiments of the invention include these:

1. A compound of the formula (I):

   ![Chemical Structure](image)

   (I)

or a pharmaceutically acceptable salt thereof, wherein:

- X is N or C, wherein when X is N, R⁴ is absent;
- Y is N or C, wherein when Y is N, R⁵ is absent;
- R¹, R², R⁴ and R⁵ are independently selected from the group consisting of hydrogen, halogen, -CH₃, and -C₄haloalkyl;
- R³ is L-R;
- L is a divalent bond, or -CH₂-;
- R is selected from group consisting of halogen,
  -CrC₄alkyl optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, -CN and -OH;
  -CN,
  -CrC₄alkoxy optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, -CN and -OH;
  -S-CrC₄ alkyl wherein the alkyl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, -CN and -OH;
  -C₂-C₆alkenyl optionally substituted with one or more groups selected from halogen, -CN, -OH and C₁-C₄alkoxy;
  -C₂-C₆alkynyl optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, -CN and -OH;
-C₃-C₇ cycloalkyl optionally substituted with one or more groups selected from halogen, CrC₄ alkyl, -Cl-C₄ alkylCrC₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, CrC₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, CrC₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, and -OH;

-C₆-C₇ aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, and C₁-C₄ alkyl;

-C₆-C₇ alkyl-C₁-C₇ aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, CrC₄ haloalkyl and C₁-C₄ alkyl;

-CrC₄ alkyl-C₆-C₇ aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, CrC₄ haloalkyl and C₁-C₄ alkyl;

-CrC₄ alkyl-C₃-C₇ cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, CrC₄ haloalkyl and C₁-C₄ alkyl;

-C₆-C₇ cycloalkenyl optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, C₁-C₄ haloalkoxy and C₁-C₄ alkyl;

4 to 7 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl and -OH, and said heterocyclyl may contain one unsaturated bond;

-CrC₄ alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, C₁-C₄ haloalkoxy, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl and -OH;

-C₆-C₇ cycloalkenyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, CrC₄ haloalkoxy, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl and -OH;

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl and -OH;

-CrC₄ alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl and -OH; and

-C₆-C₇ cycloalkenyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl and -OH; or
L is or

R is selected from group consisting of

-\(\text{CrC}_6\) alkyl optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_4\) alkoxy, -CN, -OH and a 5-6 membered heterocyclcyl containing one or two heteroatoms selected from N, O and S as ring members and optionally substituted with up to two halo, oxo or c1-c3 alkyl;

-\(\text{C}_2\) alkynyl optionally substituted with one or more groups selected from halogen, -CN, -OH and \(\text{C}_1-\text{C}_2\) alkoxy;

-\(\text{C}_2\) alkynyl optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_4\) alkoxy, -CN and -OH;

-\(\text{C}_3-\text{C}_7\) cycloalkyl optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_2\) alkyl, \(-\text{Cl}\text{-C}_2\) alkyl\(\text{CrC}_1\) alkoxy, \(\text{C}_1-\text{C}_4\) alkoxy, \(\text{CrC}_4\) haloalkyl, nitrile, -\(\text{S(0)}\) \(\text{C}_1-\text{C}_2\) alkyl, -OH, and \(\text{C}_1-\text{C}_3\) alkyl substituted with a group selected from CN, OH, -\(\text{S0}_{2}R'\), -\(\text{NHC(0)}R'\), and a 5-6 membered heterocyclyl containing one or two heteroatoms selected from N, O and S as ring members and optionally substituted with up to two halo, oxo or \(R'\), and wherein \(R'\) is c1-c3 alkyl;

-\(\text{Ce-C}_5\) alkoxy, wherein the aryl is optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_4\) alkoxy, \(\text{CrC}_4\) haloalkoxy, \(\text{CrC}_4\) haloalkyl and \(\text{C}_1-\text{C}_4\) alkyl;

-\(\text{CrC}_4\) alkyl-\(\text{C}_1-\text{C}_2\) alkoxy, wherein the aryl is optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_2\) alkoxy, \(\text{CrC}_2\) haloalkoxy, \(\text{CrC}_4\) haloalkyl and \(\text{C}_1-\text{C}_4\) alkyl;

-\(\text{C}_4\) alkyl-\(\text{C}_2\) alkoxy, wherein the halogen is optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_2\) alkoxy, \(\text{CrC}_4\) haloalkoxy, \(\text{CrC}_4\) haloalkyl and \(\text{C}_1-\text{C}_4\) alkyl; 4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_4\) alkoxy, \(\text{CrC}_4\) haloalkoxy, \(\text{CrC}_4\) haloalkyl, \(\text{C}_1-\text{C}_4\) alkyl, nitrile, -\(\text{S(0)}\) \(\text{C}_1-\text{C}_4\) alkyl and -OH;

-\(\text{CrC}_4\) alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_4\) alkoxy, \(\text{CrC}_4\) haloalkoxy, \(\text{CrC}_4\) haloalkyl, \(\text{C}_1-\text{C}_4\) alkyl, nitrile, -\(\text{S(0)}\) \(\text{C}_1-\text{C}_4\) alkyl and -OH;

-\(\text{C}_3\) cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, \(\text{C}_1-\text{C}_4\) alkoxy, \(\text{CrC}_4\) haloalkoxy, \(\text{CrC}_4\) haloalkyl, \(\text{C}_1-\text{C}_4\) alkyl, nitrile, -\(\text{S(0)}\) \(\text{C}_1-\text{C}_4\) alkyl and -OH;

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from
halogen, CrC₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl and -OH;
-CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl and -OH; and
-C₃-C₅cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl and -OH; or
R² and R³ taken together form a 4 to 7 membered heteroaryl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, Cl-C₄haloalkyl and C₁-C₄alkyl.

An alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, or cycloalkenyl that is described as optionally substituted with one or more groups may be unsubstituted, or it may be substituted with one or more of the designated groups, up to the number of hydrogen atoms on the unsubstituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, or cycloalkenyl. In some substituted embodiments, the alkyl, alkenyl, alkynyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, or cycloalkenyl is substituted with one, two or three of the designated groups, unless otherwise specified.

2. The compound of embodiment 1, wherein X is N and Y is C, and R⁴ is absent.
3. The compound of embodiment 1, wherein X is C and Y is N, and R⁵ is absent.
4. The compound of embodiment 1, wherein X is C and Y is C.
5. The compound of any of the preceding embodiments, wherein L is

\[
\text{L} = \begin{array}{c}
\text{C} \\
\text{C} \\
\text{C} \\
\text{C}
\end{array}
\]

6. The compound of any of embodiments 1-4, wherein L is a bond.

7. The compound of any of embodiments 1-4, wherein L is

8. The compound of any of the preceding embodiments, wherein R is -C₃-C₅cycloalkyl optionally substituted with one to three groups selected from halogen, -OH, C₁-C₄alkyl, -Cl-C₂alkylCrC₄alkoxy, CrC₄alkoxy, CrC₄haloalkyl, nitrile, and -S(0)₂CrC₄alkyl.

9. The compound of any of embodiments 1-7, wherein R is phenyl optionally
substituted with one or more groups selected from halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl and C₁-C₄ alkyl.

In some such embodiments, phenyl is unsubstituted or substituted with up to three groups selected from F, Cl, Br, CrC₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl and C₁-C₄ alkyl.

10. The compound of any of the preceding embodiments, wherein Z is H.

11. The compound of embodiment 1, wherein

X is N or C, wherein when X is N, R⁴ is absent;
Y is N or C, wherein when Y is N, R⁵ is absent;
R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen, halogen, -CH₃, and -C₄ haloalkyl;
R³ is L-R;
L is a divalent bond, or -CH₂⁻;
R is selected from group consisting of halogen,
-CrC₄ alkyl optionally substituted with halogen, C₁-C₄ alkoxy, -CN or -OH,
-CN,
-CrC₄ alkoxy optionally substituted with halogen or C₁-C₄ alkoxy,
-C₂₋₄ alkyl optionally substituted with halogen, -CN, -OH or C₁-C₄ alkoxy,
-C₂₋₄ alkyl optionally substituted with halogen, C₁-C₄ alkoxy, -CN or -OH,
-C₃₋₄ cycloalkyl optionally substituted with halogen, Cr-C₄ alkyl, -CrC₄ alkylCr₄ alkoxy, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, nitrile, -S(0)₂ C₁-C₄ alkyl or -OH,
-C₆₃-C₂ aryl, wherein the aryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl or C₁-C₄ alkyl,
-CrC₄ alkyl-C₂ aryl, wherein the aryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl or C₁-C₄ alkyl,

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂ C₁-C₄ alkyl or -OH,
-CrC₄ alkyl-C₄ to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂ C₁-C₄ alkyl or -OH,
-C₃₋₅ cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂ C₁-C₄ alkyl or -OH,
5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl or -OH,

-CrC₄ alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl or -OH, and

-C₅-C₆ cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂CrC₄ alkyl or -OH; or

\[
\begin{array}{c}
\text{L is } \quad \quad \\
\text{R is selected from group consisting of} \\
\text{-CrC}_4 \text{ alkyl optionally substituted with halogen, } \text{Cl-} \text{C}_4 \text{ alkoxy, } \text{-CN or } \text{-OH}, \\
\text{-C}_2 \text{C}_6 \text{ alkenyl optionally substituted with halogen, } \text{-CN, } \text{-OH or } \text{C}_1 \text{-C}_4 \text{ alkoxy}, \\
\text{-C}_2 \text{C}_6 \text{ alkenyl optionally substituted with halogen, } \text{C}_1 \text{-C}_4 \text{ alkoxy, } \text{-CN or } \text{-OH}, \\
\text{C}_6 \text{CYCLOALKYL optionally substituted with halogen, } \text{CrC}_4 \text{ alkyl, } \text{-C}_1 \text{-C}_4 \text{ alkenylCr} \\
\text{C}_2 \text{alcohol, } \text{C}_1 \text{-C}_4 \text{ alkoxy, } \text{C}_1 \text{-C}_4 \text{ haloalkoxy, nitrile, } \text{-S(0) } \text{C}_1 \text{-C}_4 \text{ alkyl or } \text{-OH}}, \\
\text{C}_6 \text{-Claryl, wherein the aryl is optionally substituted with one or more halogen, } \text{C}_1 \text{-C}_4 \text{ alkoxy, CrC}_4 \text{ haloalkoxy, CrC}_4 \text{ haloalkyl or C}_1 \text{-C}_4 \text{ alkyl}, \\
\text{-CrC}_4 \text{ alkyl-C}_6 \text{-Claryl, wherein the aryl is optionally substituted with one or more halogen, } \text{C}_1 \text{-C}_4 \text{ alkoxy, CrC}_4 \text{ haloalkoxy, CrC}_4 \text{ haloalkyl or C}_1 \text{-C}_4 \text{ alkyl,} \end{array}
\]

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, Ci-C₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂Ci-C₄ alkyl or -OH,

-CrC₄ alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂C₁-C₄ alkyl or -OH,

-C₅-C₆ cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, CrC₄ haloalkyl, Ci-C₄ alkyl, nitrile, -S(0)₂Cr C₄ alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)₂C₁-C₄ alkyl or -OH,
-CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH, and

-C₃-C₅cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl or -OH; or

R² and R³ taken together form a 4 to 7 membered heteroaryl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄haloalkyl or C₁-C₄alkyl.

In additional embodiments of the invention, the compound or a pharmaceutically acceptable salt thereof is represented by formula II:

![Chemical Structure](image)

wherein the substituents are as defined in any of the embodiments above.

In other embodiments of the invention, the compound or a pharmaceutically acceptable salt is represented by formulae I or II of any of the preceding embodiments, wherein

X is N or C, wherein when X is N, R⁴ is absent;
Y is N or C, wherein when Y is N, R⁵ is absent;
R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen, halogen, -CH₃, and Cihaloalkyl;
R³ is L-R;
L is a divalent bond, or -CH₂⁻;
R is selected from group consisting of halogen,
-CrC₄alkyl optionally substituted with halogen, C₁-C₄alkoxy, -CN or -OH,
-CN,
-C₁-C₄alkoxy optionally substituted with halogen or C₁-C₄alkoxy,
-C₂-C₆alkenyl optionally substituted with halogen, -CN, -OH or C₁-C₄alkoxy,
-C$_2$-C$_4$ alkynyl optionally substituted with halogen, CrC$_4$ alkoxy, -CN or -OH,
-C$_3$-C$_7$ cycloalkyl optionally substituted with halogen, C$_1$-C$_4$ alky1, -CrC$_4$ alkoxy
C$_4$ alkoxy, C$_1$-C$_4$ alkoxy, C$_1$-C$_4$ halaoalkyl, nitrile, -S(0)$_2$C$_1$-C$_4$ alkyl or -OH,
-C$_6$-Cl$_3$aryl, wherein the aryl is optionally substituted with one or more halogen, C$_1$-C$_4$
C$_4$ alkoxy, CrC$_4$ haloalkoxy, CrC$_4$ haloalkyl or C$_1$-C$_4$ alky1,
-CrC$_4$ alkyl-C$_5$-Cl$_3$aryl, wherein the aryl is optionally substituted with one or more
halogen, C$_1$-C$_4$ alkoxy, CrC$_4$ haloalkoxy, Ci-C$_4$ haloalkyl or Ci-C$_4$ alkyl,

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heterocyclyl is optionally substituted with one or more halogen, C$_1$-C$_4$
alkoxy, C$_1$-C$_4$ haloalkoxy, C$_1$-C$_4$ haloalkyl, C$_1$-C$_4$ alkyl, nitrile, -S(0)$_2$C$_1$-C$_4$ alkyl or -OH,
-Ci-C$_4$ alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected
from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more
halogen, C$_1$-C$_4$ alkoxy, CrC$_4$ haloalkoxy, CrC$_4$ haloalkyl, C$_1$-C$_4$ alkyl, nitrile, -S(0)$_2$Cr
C$_4$ alkyl or -OH,
-C$_3$-C$_5$ cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms
selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or
more halogen, Ci-C$_4$ alkoxy, C$_1$-C$_4$ haloalkoxy, CrC$_4$ haloalkyl, Ci-C$_4$ alkyl, nitrile, -S(0)$_2$Cr
C$_4$ alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heteroaryl is optionally substituted with one or more halogen, Ci-C$_4$
alkoxy, C$_1$-C$_4$ haloalkoxy, C$_1$-C$_4$ haloalkyl, C$_1$-C$_4$ alkyl, nitrile, -S(0)$_2$C$_1$-C$_4$ alkyl or -OH,
-CrC$_4$ alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from
N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C$_1$-
C$_4$ alkoxy, Ci-C$_4$ haloalkoxy, CrC$_4$ haloalkyl, Ci-C$_4$ alkyl, nitrile, -S(0)$_2$Cr-C$_4$ alkyl or -OH,
-and
-C$_3$-C$_5$ cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected
from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen,
C$_1$-C$_4$ alkoxy, C$_1$-C$_4$ haloalkoxy, C$_1$-C$_4$ haloalkyl, C$_1$-C$_4$ alkyl, nitrile, -S(0)$_2$Cr-C$_4$ alkyl or -OH; or

L is

R is selected from group consisting of
-CrC$_4$ alkyl optionally substituted with halogen, C$_1$-C$_4$ alkoxy, -CN or -OH,
-C$_2$-C$_6$ alkenyl optionally substituted with halogen, -CN, -OH or C$_1$-C$_4$ alkoxy,
-C$_2$-C$_4$ alky1nyl optionally substituted with halogen, C$_1$-C$_4$ alkoxy, -CN or -OH,
-C$_3$-C$_7$ cycloalkyl optionally substituted with halogen, CrC$_4$ alkyl, -Cl-C$_4$ alkyICr
C$_4$ alkoxy, C$_1$-C$_4$ alkoxy, C$_1$-C$_4$ haloalkyl, nitrile, -S(0)$_2$C$_1$-C$_4$ alkyl or -OH,
-C₆-Cl₄aryl, wherein the aryl is optionally substituted with one or more halogen, C₁-
C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or C₁-C₄alkyl,
-CrC₄alkyl-C₆-Cl₄aryl, wherein the aryl is optionally substituted with one or more
halogen, CrC₄alkoxy, CrC₄haloalkoxy, Cr-C₄haloalkyl or Cr-C₄alkyl,

4 to 7 membered heterocycl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heterocycl is optionally substituted with one or more halogen, C₁-C₄alkoxy,
C₁-C₄haloalkoxy, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl or -OH,

-CrC₄alkyl-4 to 7 membered heterocycl containing 1 to 3 heteroatoms selected
from N, S, and O, wherein said heterocycl is optionally substituted with one or more
halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl
or -OH,

-C₃-C₅cycloalkyl-4 to 7 membered heterocycl containing 1 to 3 heteroatoms
selected from N, S, and O, wherein said heterocycl is optionally substituted with one or
more halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, CrC₄haloalkyl, Cr-C₄alkyl, nitrile, -S(0)₂Cr
C₄alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heteroaryl is optionally substituted with one or more halogen, Cr-C₄alkoxy,
C₁-C₄haloalkoxy, C₁-C₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH,

-CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from
N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-
C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH, and

-C₃-C₅cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected
from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen,
C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl or -OH; or

R² and R³ taken together form a 4 to 7 membered heteroaryl containing 1 to 3
heteroatoms selected from N, S, and O, wherein said heterocycl is optionally substituted
with one or more halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄haloalkyl or C₁-C₄alkyl.

In other embodiments of the invention, the compound or a pharmaceutically
acceptable salt is represented by formula I or II according to any of the preceding
embodiments, wherein:

X is N or C, wherein when X is N, R⁴ is absent;
Y is N or C, wherein when Y is N, R⁵ is absent;
R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen,
halogen, -CH₃, and Cihaloalkyl;
R³ is L-R;
L is a divalent bond, or \(-\text{CH}_2\)2;
R is selected from group consisting of
halogen,
-C\(_4\)alkyl optionally substituted with halogen, CrC\(_4\)alkoxy, -CN or -OH,
-CN,
-C\(_1\)-C\(_4\)alkoxy optionally substituted with halogen or CrC\(_4\)alkoxy,
-C\(_2\)-C\(_6\)alkenyl optionally substituted with halogen, -CN, -OH or C\(_1\)-C\(_4\)alkoxy,
-C\(_2\)-C\(_4\)alkynyl optionally substituted with halogen, CrC\(_4\)alkoxy, -CN or -OH,
-C\(_3\)-C\(_7\)cycloalkyl optionally substituted with halogen, CrC\(_4\)alkyl, -C\(_1\)-C\(_4\)alkylCrC\(_4\)alkoxy, C\(_1\)-C\(_4\)alkoxy, C\(_1\)-C\(_4\)haloalkyl, nitrile, -S(0)2C\(_1\)-C\(_4\)alkyl or -OH,
-Ce-Ciaryl, wherein the aryl is optionally substituted with one or more halogen, CrC\(_4\)alkoxy, CrC\(_4\)haloalkoxy, CrC\(_4\)haloalkyl or C\(_1\)-C\(_4\)alkyl,
-CrC\(_4\)alkyl-C\(_6\)-Ciaryl, wherein the aryl is optionally substituted with one or more
halogen, C\(_1\)-C\(_4\)alkoxy, CrC\(_4\)haloalkoxy, CrC\(_4\)haloalkyl or Ci-C\(_4\)alkyl,
4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heterocyclyl is optionally substituted with one or more halogen, C\(_1\)-C\(_4\)alkoxy,
C\(_1\)-C\(_4\)haloalkoxy, C\(_1\)-C\(_4\)haloalkyl, C\(_1\)-C\(_4\)alkyl, nitrile, -S(0)2C\(_1\)-C\(_4\)alkyl or -OH,
-CrC\(_4\)alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected
from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more
halogen, C\(_1\)-C\(_4\)alkoxy, CrC\(_4\)haloalkoxy, CrC\(_4\)haloalkyl, C\(_1\)-C\(_4\)alkyl, nitrile, -S(0)2CrC\(_4\)alkyl
or -OH,
-C\(_3\)-C\(_5\)cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms
selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or
more halogen, C\(_1\)-C\(_4\)alkoxy, CrC\(_4\)haloalkoxy, CrC\(_4\)haloalkyl, C\(_1\)-C\(_4\)alkyl, nitrile, -S(0)2Ci-C\(_4\)alkyl or -OH,
5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heteroaryl is optionally substituted with one or more halogen, C\(_1\)-C\(_4\)alkoxy,
C\(_1\)-C\(_4\)haloalkoxy, C\(_1\)-C\(_4\)haloalkyl, C\(_1\)-C\(_4\)alkyl, nitrile, -S(0)2C\(_1\)-C\(_4\)alkyl or -OH,
-CrC\(_4\)alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from
N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C\(_1\)-
C\(_4\)alkoxy, CrC\(_4\)haloalkoxy, CrC\(_4\)haloalkyl, C\(_1\)-C\(_4\)alkyl, nitrile, -S(0)2C\(_1\)-C\(_4\)alkyl or -OH,
-and
-C\(_3\)-C\(_5\)cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected
from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen,
C\(_1\)-C\(_4\)alkoxy, C\(_1\)-C\(_4\)haloalkoxy, C\(_1\)-C\(_4\)haloalkyl, C\(_1\)-C\(_4\)alkyl, nitrile, -S(0)2C\(_1\)-C\(_4\)alkyl or -OH;
or
R\(_2\) and R\(_3\) taken together form a 4 to 7 membered heteroaryl containing 1 to 3
heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted.
with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl or C₁-C₄ alkyl.

In other embodiments of the invention, the compound or a pharmaceutically acceptable salt is any of the preceding embodiments where the compound is represented by formula III:

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III:
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wherein

- X is N or C, wherein when X is N, R⁴ is absent;
- Y is N or C, wherein when Y is N, R⁵ is absent;
- R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen, halogen, -CH₃, and Cihaloalkyl;
- R is selected from group consisting of
  - CrC₄ alkyl optionally substituted with halogen, C₁-C₄ alkoxy, -CN or -OH,
  - C₂⁻C₆ alkenyl optionally substituted with halogen, -CN, -OH or C₁-C₄ alkoxy,
  - C₂⁻C₄ alkynyl optionally substituted with halogen, C₁-C₄ alkoxy, -CN or -OH,
  - C₃⁻C₇ cycloalkyl optionally substituted with halogen, C₁-C₄ alkyl, CrC₂ alkyl or CrC₂ alkyl CrC₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, nitrile, -S(0)=C₁-C₄ alkyl or -OH,
  - C₆⁻C₉ aryl, wherein the aryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, C₁-C₄ haloalkyl or C₁-C₄ alkyl,
  - CrC₄ alkyl-C₆⁻C₉ aryl, wherein the aryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl or CrC₄ alkyl,
- 4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)=C₁-C₄ alkyl or -OH,
- CrC₄ alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)=C₁-C₄ alkyl or -OH,
- C₃⁻C₅ cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁-C₄ alkyl, nitrile, -S(0)=C₁-C₄ alkyl or -OH,
C₄alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl or -OH,

-CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH, and

-C₅cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl or -OH; or

R² and R³ taken together form a 4 to 7 membered heteroaryl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, Ci-C₄alkoxy, Ci-C₄haloalkoxy, Ci-C₄haloalkyl or Ci-C₄alkyl.

In additional embodiments of the invention, the compound or a pharmaceutically acceptable salt represented by formula III as described above, wherein:

X is C,

Y is N or C, wherein when Y is N, R⁵ is absent;
R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen, halogen, -CH₃, and Cihaloalkyl;
R is selected from group consisting of
-CrC₄alkyl optionally substituted with halogen, C₁-C₄alkoxy, -CN or -OH,
-C₂-Cealkene optionally substituted with halogen, Ci-C₄alkoxy, -CN or -OH,
-C₃-C₅cycloalkyl optionally substituted with halogen, Ci-C₄alkyl, -CrC₄alkylCrC₄alkoxy, C₁-C₄alkoxy, C₁-C₄haloalkoxy, nitrile, -S(0)₂C₁-C₄alkyl or -OH,

-C₅-Ci₅aryl, wherein the aryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or C₁-C₄alkyl,

-CrC₄alkyl-C₅-Ci₅aryl, wherein the aryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, Ci-C₄haloalkyl or Ci-C₄alkyl,

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl or -OH,

-CrC₄alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl or -OH,
-C₃₋C₅ cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁₋C₄ alkyl, nitrile, -S(0)₂ Cr C₄ alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, Ci-C₄ haloalkyl or C₁₋C₄ alkyl, and

-CrC₄ alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl or C₁₋C₄ alkyl.

In additional embodiments of the invention, the compound or a pharmaceutically acceptable salt is represented by formula III as described above, wherein:

X is C,

Y is C,

R¹, R², R³ or R⁴ are independently selected from the group consisting of hydrogen and halogen

R is selected from group consisting of

-C₁₋C₄ alkyl optionally substituted with halogen, C₁₋C₄ alkoxy, -CN or -OH,

-C₃₋C₇ cycloalkyl optionally substituted with halogen, Ci-C₄ alkyl, -CrC₄ alkylCr C₄ alkoxy, C₁₋C₄ alkoxy, C₁₋C₄ haloalkyl, nitrile, -S(0)₂ C₁₋C₄ alkyl or -OH,

-C₆₋Ci₃ aryl, wherein the aryl is optionally substituted with one or more halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl or C₁₋C₄ alkyl,

-CrC₄ alkyl-C₆-Cioaryl, wherein the aryl is optionally substituted with one or more halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, Ci-C₄ haloalkyl or Ci-C₄ alkyl,

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁₋C₄ alkoxy, C₁₋C₄ haloalkoxy, C₁₋C₄ haloalkyl, C₁₋C₄ alkyl, nitrile, -S(0)₂ C₁₋C₄ alkyl or -OH,

-CrC₄ alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, C₁₋C₄ alkyl, nitrile, -S(0)₂ CrC₄ alkyl or -OH,

-C₃₋C₅ cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC₄ alkoxy, C₁₋C₄ haloalkoxy, CrC₄ haloalkyl, Ci-C₄ alkyl, nitrile, -S(0)₂ Cr C₄ alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl or CrC₄ alkyl, and
- CrC₄ alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl or CrC₄ alkyl.

In another embodiment of the invention, the compound or a pharmaceutically acceptable salt represented by formula III (above), wherein
X is C,
Y is C,
R₁, R₂, R₄ or R₅ are independently selected from the group consisting of hydrogen and halogen;
R is - CrC₄ alkyl optionally substituted with halogen, C₁-C₄ alkoxy, -CN or -OH.

In additional embodiments of the invention, the compound or a pharmaceutically acceptable salt thereof is any of the preceding embodiments represented by formula III above, wherein:
X is C,
Y is C,
R₁, R₂, R₄ or R₅ are independently selected from the group consisting of hydrogen and halogen;
R is - C₃-C₇ cycloalkyl optionally substituted with halogen, C₁-C₄ alkyl, - CrC₄ alkyl Cr C₂ alkoxy, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, nitrile, - S(0)₂ C₁-C₄ alkyl or -OH.

In an embodiment of the invention, the compound or a pharmaceutically acceptable salt represented by formula III (above), wherein:
X is C,
Y is C,
R₁, R₂, R₄ or R₅ are independently selected from the group consisting of hydrogen and fluorine;
R is - C₃-C₇ cycloalkyl optionally substituted with halogen, C₁-C₄ alkyl, - CrC₄ alkyl Cr C₂ alkoxy, Cl-C₄ alkoxy, C₁-C₄ haloalkyl, nitrile, - S(0)₂ C₁-C₄ alkyl or -OH.

In additional embodiments of the invention, the compound or a pharmaceutically acceptable salt thereof is any of the preceding embodiments represented by formula III, wherein:
X is C,
Y is C,

$R^1$, $R^2$, $R^4$ or $R^5$ are independently selected from the group consisting of hydrogen and halogen;

$R$ is selected from group consisting of

- 4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, $C_1$-$C_4$ alkoxy, $C_1$-$C_4$ haloalkoxy, $C_1$-$C_4$ alkyl, nitrile, $-S(0)_2CrC_4$ alkyl or -OH,

$-C_3$-$C_5$ cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, $C_1$-$C_4$ alkoxy, $CrC_4$ haloalkoxy, $CrC_4$ haloalkyl, $C_1$-$C_4$ alkyl, nitrile, $-S(0)_2CrC_4$ alkyl or -OH,

In additional embodiments of the invention, the compound or a pharmaceutically acceptable salt thereof is any of the preceding embodiments represented by formula III, wherein:

$X$ is C,

$Y$ is C,

$R^1$, $R^2$, $R^4$ or $R^5$ are independently selected from the group consisting of hydrogen, halogen, $-CH_3$, and C haloalkyl;

$R$ is selected from group consisting of
In further embodiments of the invention, the compound or a pharmaceutically acceptable salt of any of the preceding embodiments is represented by formula IV:

wherein,

Y is N or C, wherein when Y is N, R₅ is absent;
R¹, R², R₄ or R₅ are independently selected from the group consisting of hydrogen, halogen, -CH₃, and Cihaloalkyl;
L is a divalent bond;

R is selected from group consisting of , Br, , and

In additional embodiments of the invention, the compound or a pharmaceutically acceptable salt of any of the preceding embodiments is represented by formula I, II or IV, wherein:

X is C;
Y is C;
R₁, R₂, R₄ or R₅ are independently selected from the group consisting of hydrogen, halogen, -CH₃ and Cihaloalkyl;
R³ is L-R;
L is a divalent bond, or-CH₂;
R is halogen,
-CrC₄alkyl optionally substituted with halogen, CrC₄alkoxy, -CN or -OH,
-CN,
-CrC₄alkoxy optionally substituted with halogen or CrC₄alkoxy, or
R² and R³ taken together form a 4 to 7 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocycl is optionally substituted with one or more halogen, Cr-C₄alkoxy, Cr-C₄haloalkoxy, Cr-C₄haloalkyl or Cr-C₄alkyl.

In specific embodiments of the invention, the compound is selected from:

1.1. (R)-3-((S)-3-(4-bromophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
1.2. (R)-3-((S)-3-(4-bromo-2-methylphenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
1.3. (R)-3-((S)-3-(4-bromo-2-fluorophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
1.4. (R)-3-((S)-3-(4-bromo-2,6-difluorophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
2.1. (R)-3-((S)-3-[1,1′-biphenyl]-4-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
2.2. (R)-3-((S)-3-(4-(3-fluoropyridin-4-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
2.3. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-3-(naphthalen-2-yl)-2-oxooxazolidin-5-yl)propanamide
2.4. (R)-3-((S)-3-(benzo[d]thiazol-6-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
2.5. (R)-N-hydroxy-2-methyl-3-((S)-3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide
2.6. (R)-3-((S)-3-(benzo[b]thiophen-6-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
2.7. (2R)-N-hydroxy-3-((5S)-3-(4′-(2-hydroxypropyl)-1,1′-biphenyl)-4-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide
2.8. (R)-N-hydroxy-3-((S)-3-(4′-((R)-2-hydroxypropyl)-[1,1′-biphenyl]-4-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.1. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(prop-1-yn-1-yl)phenyl)oxazolidin-5-yl)propanamide

3.1.2. (R)-3-((S)-3-4-(cyclopropylethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.3. (R)-3-((S)-3-(4-(but-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.4. (R)-N-hydroxy-3-((S)-3-(3-hydroxyprop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.5. (R)-3-((S)-3-(4-(methoxyprop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.6. (R)-N-hydroxy-3-((S)-3-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.7. (2R)-N-hydroxy-3-((5S)-3-(4-(cyclopropylethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.8. (R)-N-hydroxy-3-((S)-3-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.9. N-hydroxy-3-((5S)-3-(4-(3-methoxybut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.10. (R)-N-hydroxy-3-((S)-3-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.11. (R)-N-hydroxy-3-((S)-3-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.12. (2R)-3-((5S)-3-(4-(2-(cyanomethyl)cyclopropyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.13. (2R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((5S)-3-(4-(2-(morpholinomethyl)cyclopropyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)propanamide

3.1.14. (R)-3-((S)-3-(4-(4-cyanobut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.15. N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-3-(4-(4-morpholinobut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)propanamide

3.1.16. (2R)-N-hydroxy-3-((5S)-3-(4-(2-(hydroxymethyl)cyclopropyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.17. (2R)-N-hydroxy-3-((5S)-3-(4-(4-methoxypent-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide
3.1.18. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-((tetrahydro-2H-pyran-4-yl)ethynyl)phenyl)oxazolidin-5-yl)propanamide

3.1.19. (R)-3-((S)-3-((3-ethoxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.20. (R)-3-((S)-3-((4-fluorobut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.21. (R)-3-((S)-3-((3-(cyanomethyl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.22. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-((3-tetrahydro-2H-pyran-4-yl)prop-1-yn-1-yl)phenyl)oxazolidin-5-yl)propanamide

3.1.23. (R)-3-((S)-3-((4,4-difluorobut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.24. (R)-N-hydroxy-3-((S)-3-((4-((3-hydroxy-3-methylcyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.25. (R)-N-hydroxy-3-((S)-3-((4-((3-hydroxy-3-methylcyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.26. (R)-3-((S)-3-((5-fluoropent-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.27. (R)-N-hydroxy-3-((S)-3-((4-(6-methoxyhex-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.28. (R)-N-hydroxy-3-((S)-3-((4-(6-hydroxyhex-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.29. (R)-3-((S)-3-((4-(5,5-difluoropent-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.30. (R)-N-hydroxy-3-((S)-3-((4-(5-methoxypent-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.31. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-3-((3-(methylsulfonyl)methyl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)propanamide

3.1.32. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(4,4,4-trifluorobut-1-yn-1-yl)phenyl)oxazolidin-5-yl)propanamide

3.1.33. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-3-((4-((3-(methylsulfonyl)methyl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)propanamide

3.1.34. (R)-3-((S)-3-((4-(5-(2H-1,2,3-triazol-2-yl)pent-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.35. (2R)-3-((5S)-3-((2,2-difluorocyclopropyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.1.36. (R)-N-hydroxy-3-((S)-3-(4-(((1r,3S)-3-(2-hydroxypropan-2-yl)cyclobutyl)ethynyl)phenyl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.37. (R)-N-hydroxy-3-((S)-3-(4-(5-hydroxypenta-1,3-diyn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.38. (R)-N-hydroxy-3-((S)-3-(4-(5-methoxypenta-1,3-diyn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.39. (2R)-N-hydroxy-3-((5S)-3-(4-(6-hydroxyhept-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.40. (R)-N-hydroxy-3-((S)-3-(4-(6-hydroxy-6-methylhept-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.41. (2R)-N-hydroxy-3-((5S)-3-(4-(5-hydroxyhexa-1,3-diyn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.42. (R)-3-((S)-3-(4-((3-(2-acetamidopropan-2-yl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.43. (R)-3-((S)-3-(4-((3-(2-acetamidopropan-2-yl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

3.1.44. (2R)-N-hydroxy-3-((5S)-3-(4-(4-hydroxypent-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.45. (R)-N-hydroxy-3-((S)-3-(4-((1s,3R)-3-hydroxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.46. (R)-N-hydroxy-3-((S)-3-(4-((1r,3S)-3-hydroxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.47. (R)-N-hydroxy-3-((S)-3-(4-((1s,3R)-3-methoxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.48. (R)-N-hydroxy-3-((S)-3-(4-((1r,3S)-3-methoxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

3.1.49. (R)-N-hydroxy-2-methyl-3-((S)-3-(4-(1-methyl-1H-pyrazol-4-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide

3.1.50. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(pent-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)propanamide

3.1.51. (2R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((5S)-2-oxo-3-(4-(3-(tetrahydrofuran-3-yl)prop-1-yn-1-yl)phenyl)oxazolidin-5-yl)propanamide

3.1.52. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(pyridin-4-yethynyl)phenyl)oxazolidin-5-yl)propanamide

3.1.53. (R)-N-hydroxy-2-methyl-3-((S)-3-(4-(3-methylbut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide
3.1.54. (R)-3-((S)-3-(4-(((1s,3R,4S)-3,4-dimethoxycyclopentyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.1.55. (R)-N-hydroxy-2-methyl-3-((S)-3-((6-methylpyridin-3-yl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide
3.1.56. (2R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-3-(4-((tetrahydrofuran-3-yl)ethynyl)phenyl)oxazolidin-5-yl)propanamide
3.1.57. (R)-N-hydroxy-3-((S)-3-(4-((methoxymethyl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide
3.1.58. (R)-N-hydroxy-3-((S)-3-(4-((methoxymethyl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide
3.1.59. (R)-3-((S)-3-(4-((3-fluorocyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.1.60. (R)-3-((S)-3-(4-((3-fluorocyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.2.1. (R)-N-hydroxy-2-methyl-3-((S)-3-(2-methyl-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide
3.3.1. (R)-3-((S)-3-(2-fluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.3.3. (R)-3-((S)-3-(2-fluoro-4-((1r,3S)-3-methoxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.4.1. (R)-3-((S)-3-(3-fluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.5.1. (R)-N-hydroxy-2-methyl-3-((S)-3-(3-chloro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide
3.6.1. (R)-3-((S)-3-(3-chloro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.7. (R)-3-((S)-3-(2,3-difluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.8. (R)-3-((S)-3-(3,5-difluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.9. (R)-3-((S)-3-(4-(but-1-yn-1-yl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.10. (R)-3-((S)-3-(3-fluoro-4-((1r,3S)-3-methoxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.11. (R)-3-((S)-3-(4-(cyclopropylethynyl)-2-fluorophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
3.12. (R)-3-((S)-3-(4-(cyclopropylethynyl)-3-fluorophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
4.1. (R)-3-((S)-3-(4-(but-2-yn-1-yloxy)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

4.2. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(2,2,2-trifluoroethoxy)phenyl)oxazolidin-5-yl)propanamide

5.1.1. (R)-3-((S)-3-(4-cyclopropylphenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

5.3. (R)-N-hydroxy-3-((S)-3-(4-(methoxymethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

5.4. (R)-3-((S)-3-(4-(cyanomethyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

5.5. (R)-N-hydroxy-3-((S)-3-(4-(2-methoxyethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

5.6. (2R)-N-hydroxy-3-((SS)-3-(4-(2-(2-methoxyethyl)cyclopropyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

5.7. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-propylphenyl)oxazolidin-5-yl)propanamide

5.8. (R)-3-((S)-3-(4-(2-(3-ethoxycyclobutyl)ethyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

5.9. (R)-3-((S)-3-(4-(E)-but-2-en-2-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

5.10. (R)-3-((S)-3-(4-(2-(3-ethoxycyclobutyl)ethyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

5.11. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(E)-prop-1-en-1-yl)phenyl)oxazolidin-5-yl)propanamide

5.12. (R)-N-hydroxy-3-((S)-3-(4-(3-(3-methoxyprop-1-yn-1-yl)cyclobutyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide

5.13. (R)-3-((S)-3-(4-(2-cyclopropylethyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

5.14. (R)-3-((S)-3-(4-(3-fluoropropyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

5.15. (R)-3-((S)-3-(4-(2,2-difluoropropyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

5.16. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(2,2,2-trifluoroethyl)thio)phenyl)oxazolidin-5-yl)propanamide

5.17. (R)-3-((S)-3-(4-(3,3-difluoropropyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
5.18. \((R)-3-((S)-3-(4-(ethylthio)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
5.19. \((R)-3-((S)-3-(4-(3,3-difluorocyclobutyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
5.20. \((R)-3-((S)-3-(4-(1,1-difluoropropyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
5.21. \((R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(pent-3-yn-1-yl)phenyl)oxazolidin-5-yl)propanamide\)
5.22. \((2R)-N-hydroxy-2-methyl-3-((S)-3-(2-methylcyclopropyl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide\)
5.23. \((2R)-3-((S)-3-(4-(4-fluorocyclopent-1-en-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
5.24. \((R)-3-((S)-3-(4-(Z)-1-fluoroprop-1-en-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
5.25. \((R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-3-(4′-(2-morpholinoethyl)-1,1′-biphenyl)-4-yl)-2-oxooxazolidin-5-yl)propanamide\)
5.26. \((R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-3-(4′-(2-morpholinoethoxy)-1,1′-biphenyl)-4-yl)-2-oxooxazolidin-5-yl)propanamide\)
5.27. \((R)-N-hydroxy-3-((S)-3-(4′-(2-hydroxyethyl)-1,1′-biphenyl)-4-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide\)
5.28. \((R)-3-((S)-3-(4-(3,6-dihydro-2H-pyran-4-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
6.1. \((R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-(prop-1-yn-1-yl)pyridin-2-yl)oxazolidin-5-yl)propanamide\)
6.2. \((R)-3-((S)-3-(6-cyclopropylethynyl)pyridin-3-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
6.3. \((R)-3-((S)-3-(5-cyclopentylethynyl)pyridin-2-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
6.4. \((R)-3-((S)-3-(5-cyclobutylethynyl)pyridin-2-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
6.5. \((R)-3-((S)-3-(5-(but-1-yn-1-yl)pyridin-2-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide\)
6.6. \((R)-N-hydroxy-2-methyl-3-((S)-3-(5-(3-methylbut-1-yn-1-yl)pyridin-2-yl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide\)
6.7. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-pentylypyridin-2-yl)oxazolidin-5-yl)propanamide
6.8. (R)-3-((S)-3-(5-bromopyridin-2-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide
6.9. (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-phenylpyridin-2-yl)oxazolidin-5-yl)propanamide
6.10. (R)-3-((S)-3-(5-(cyclopropylethynyl)pyridin-2-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide;
and the pharmaceutically acceptable salts of any of these species.

In another aspect, a compound or pharmaceutically acceptable salt according to any of the above embodiments is combined with a pharmaceutically acceptable carrier to provide a pharmaceutical composition. In some embodiments, a compound or pharmaceutically acceptable salt according to any of the above embodiments is used in combination with a second therapeutic agent. Suitable therapeutic agents for use in such combinations, including immunomodulators, are disclosed herein.

In another aspect, a compound (including pharmaceutically acceptable salts) or pharmaceutical composition according to any of the embodiments described above can be used in a method to treat a bacterial infection. Typically, the infection is caused by a Gram-negative bacterium. The method comprises administering such compound to a subject in need of treatment for a Gram-negative bacterial infection, generally in an amount sufficient to treat the infection. The bacterial infection can suitably be caused by a bacterium selected from the group consisting of Pseudomonas aeruginosa and other Pseudomonas species, Stenotrophomonas maltophilia, Burkholderia cepacia and other Burkholderia species, Alcaligenes xylosoxidans, species of Acinetobacter, Enterobacteriaceae, Haemophilus, Moraxella, Bacteroides, Francisella, Shigella, Proteus, Vibrio, Salmonella, Bordetella, Helicobacter, Legionella, Citrobacter, Serratia, Campylobacter, Yersinia and Neisseria.

The compounds and compositions described herein, including any of the particular embodiments of Formula (I), (III) or (III) described above, can be used or administered in combination with one or more therapeutic agents that act as immunomodulators, e.g., an activator of a costimulatory molecule, or an inhibitor of an immune-inhibitory molecule, or a vaccine. The Programmed Death 1 (PD-1) protein is an inhibitory member of the extended CD28/CTLA4 family of T cell regulators (Okazaki et al. (2002) Curr Opin Immunol 14: 391779-82; Bennett et al. (2003) J. Immunol. 170:71 1-8). PD-1 is expressed on activated B cells, T cells, and monocytes. PD-1 is an immune-inhibitory protein that negatively regulates
TCR signals (Ishida, Y. et al. (1992) EMBO J. 11:3887-3895; Blank, C. et al. (Epub 2006 Dec. 29) Immunol. Immunother. 56(5):739-745), and is up-regulated in chronic infections. The interaction between PD-1 and PD-L1 can act as an immune checkpoint, which can lead to, e.g., a decrease in infiltrating lymphocytes, a decrease in T-cell receptor mediated proliferation, and/or immune evasion by cancerous or infected cells (Dong et al. (2003) J. Mol. Med. 81:281-7; Blank et al. (2005) Cancer Immunol. Immunother. 54:307-314; Konishi et al. (2004) Clin. Cancer Res. 10:5094-100). Immune suppression can be reversed by inhibiting the local interaction of PD-1 with PD-L1 or PD-L2; the effect is additive when the interaction of PD-1 with PD-L2 is blocked as well (Iwai et al. (2002) Proc. Nat'l. Acad. Sci. USA 99:12293-7; Brown et al. (2003) J Immunol. 170:1257-66). Immunomodulation can be achieved by binding to either the immune-inhibitory protein (e.g., PD-1) or to binding proteins that modulate the inhibitory protein (e.g., PD-L1, PD-L2).

In one embodiment, the combination therapies of the invention include an immunomodulator that is an inhibitor or antagonist of an inhibitory molecule of an immune checkpoint molecule. In another embodiment the immunomodulator binds to a protein that naturally inhibits the immuno-inhibitory checkpoint molecule. When used in combination with antibacterial compounds, these immunomodulators can enhance the antimicrobial response, and thus enhance efficacy relative to treatment with the antibacterial compound alone.

The term "immune checkpoints" refers to a group of molecules on the cell surface of CD4 and CD8 T cells. These molecules can effectively serve as "brakes" to down-modulate or inhibit an adaptive immune response. Immune checkpoint molecules include, but are not limited to, Programmed Death 1 (PD-1), Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), B7H1, B7H4, OX-40, CD137, CD40, and LAG3, which directly inhibit immune cells. Immunotherapeutic agents which can act as immune checkpoint inhibitors useful in the methods of the present invention, include, but are not limited to, inhibitors of PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4, and/or TGFR beta. Inhibition of an inhibitory molecule can be performed by inhibition at the DNA, RNA or protein level. In some embodiments, an inhibitory nucleic acid (e.g., a dsRNA, siRNA or shRNA), can be used to inhibit expression of an inhibitory molecule. In other embodiments, the inhibitor of an inhibitory signal is a polypeptide, e.g., a soluble ligand, or an antibody or antigen-binding fragment thereof, that binds to the inhibitory molecule.

By "in combination with," it is not intended to imply that the therapy or the therapeutic agents must be administered at the same time and/or formulated for delivery together, although these methods of delivery are within the scope described herein. The immunomodulator can be administered concurrently with, prior to, or subsequent to, one or more compounds of the invention, and optionally one or more additional therapies or therapeutic agents. The therapeutic agents in the combination can be administered in any
order. In general, each agent will be administered at a dose and/or on a time schedule determined for that agent. It will further be appreciated that the therapeutic agents utilized in this combination may be administered together in a single composition or administered separately in different compositions. In general, it is expected that each of the therapeutic agents utilized in combination be utilized at levels that do not exceed the levels at which they are utilized individually. In some embodiments, the levels utilized in combination will be lower than those utilized individually.

In certain embodiments, the antibacterial compounds described herein are administered in combination with one or more immunomodulators that are inhibitors of PD-1, PD-L1 and/or PD-L2. Each such inhibitor may be an antibody, an antigen binding fragment thereof, an immunoadhesin, a fusion protein, or an oligopeptide. Examples of such immunomodulators are known in the art.

In some embodiments, the immunomodulator is an anti-PD-1 antibody chosen from MDX-1 106, Merck 3475 or CT- 011.

In some embodiments, the immunomodulator is an immunoadhesin (e.g., an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (e.g., an Fc region of an immunoglobulin sequence).

In some embodiments, the immunomodulator is a PD-1 inhibitor such as AMP-224.

In some embodiments, the the immunomodulator is a PD-L1 inhibitor such as anti-PD-L1 antibody.

In some embodiments, the immunomodulator is an anti-PD-L1 binding antagonist chosen from YW243.55.S70, MPDL3280A, MEDI-4736, MSB-001 071 8C, or MDX-1 105. MDX-1 105, also known as BMS-936559, is an anti-PD-L1 antibody described in WO2007/005874. Antibody YW243.55.S70 is an anti-PD-L1 described in WO 201 0/077634.

In some embodiments, the immunomodulator is nivolumab (CAS Registry Number: 946414-94-4). Alternative names for nivolumab include MDX-1 106, MDX-1 106-04, ONO-4538, or BMS-936558. Nivolumab is a fully human IgG4 monoclonal antibody which specifically blocks PD-1. Nivolumab (clone 5C4) and other human monoclonal antibodies that specifically bind to PD-1 are disclosed in US 8,008,449, EP21 61336 and WO2006/1 21168.

In some embodiments, the immunomodulator is an anti-PD-1 antibody Pembrolizumab. Pembrolizumab (also referred to as Lambrolizumab, MK-3475, MK03475, SCH-900475 or KEYTRUDA®; Merck) is a humanized IgG4 monoclonal antibody that binds to PD-1. Pembrolizumab and other humanized anti-PD-1 antibodies are disclosed in Hamid, O. et al. (2013) New England Journal of Medicine 369 (2): 134-44, US 8,354,509, WO2009/1 14335, and WO2013/079174.
In some embodiments, the immunomodulator is Pidilizumab (CT-01 1; Cure Tech), a humanized IgG1k monoclonal antibody that binds to PD1. Pidilizumab and other humanized anti-PD-1 monoclonal antibodies are disclosed in WO2009/101611.

Other anti-PD1 antibodies useful as immunomodulators for use in the methods disclosed herein include AMP 514 (Amplimmune), and anti-PD1 antibodies disclosed in US 8,609,089, US 201 0028330, and/or US 201 014649. In some embodiments, the anti-PD-L1 antibody is MSB001 071 8C. MSB001 071 8C (also referred to as A09-246-2; Merck Serono) is a monoclonal antibody that binds to PD-L1.

In some embodiments, the immunomodulator is MDPL3280A (Genentech / Roche), a human Fc optimized IgG1 monoclonal antibody that binds to PD-L1. MDPL3280A and other human monoclonal antibodies to PD-L1 are disclosed in U.S. Patent No.: 7,943,743 and U.S Publication No.: 201 0039906. Other anti-PD-L1 binding agents useful as immunomodulators for methods of the invention include YW243.55.S70 (see WO201 0/077634), MDX-1 105 (also referred to as BMS-936559), and anti-PD-L1 binding agents disclosed in WO2007/005874.

In some embodiments, the immunomodulator is AMP-224 (B7-DCIg; Amplimmune; e.g., disclosed in WO20 10/027827 and WO201 1/066342), is a PD-L2 Fc fusion soluble receptor that blocks the interaction between PD1 and B7-H1.

In some embodiments, the immunomodulator is an anti-LAG-3 antibody such as BMS-98601 6. BMS-98601 6 (also referred to as BMS98601 6) is a monoclonal antibody that binds to LAG-3. BMS-98601 6 and other humanized anti-LAG-3 antibodies are disclosed in US 201 1/0150829, WO201 0/015970, and WO201 4/008218.

In certain embodiments, the combination therapies disclosed herein include a modulator of a costimulatory molecule or an inhibitory molecule, e.g., a co-inhibitory ligand or receptor.

In one embodiment, the costimulatory modulator, e.g., agonist, of a costimulatory molecule is chosen from an agonist (e.g., an agonistic antibody or antigen-binding fragment thereof, or soluble fusion) of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD1 1a/CD1 8), ICOS (CD278), 4-1 BB (CD1 37), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, NKp80, CD1 60, B7-H3 or CD83 ligand.

In another embodiment, the combination therapies disclosed herein include an immunomodulator that is a costimulatory molecule, e.g., an agonist associated with a positive signal that includes a costimulatory domain of CD28, CD27, ICOS and/or GITR.

Exemplary GITR agonists include, e.g., GITR fusion proteins and anti-GITR antibodies (e.g., bivalent anti-GITR antibodies), such as, a GITR fusion protein described in U.S. Patent No.: 6,111,090, European Patent No.: 090505B 1, U.S Patent No.: 8,586,023, PCT Publication Nos.: WO 201 0/0031 18 and 201 1/090754, or an anti-GITR antibody.

In one embodiment, the immunomodulator used is a soluble ligand (e.g., a CTLA-4-Ig), or an antibody or antibody fragment that binds to PD-L1, PD-L2 or CTLA4. For example, the anti-PD-1 antibody molecule can be administered in combination with an anti-CTLA-4 antibody, e.g., ipilimumab, for example. Exemplary anti-CTLA4 antibodies include Tremelimumab (IgG2 monoclonal antibody available from Pfizer, formerly known as ticilimumab, CP-675,206); and Ipilimumab (CTLA-4 antibody, also known as MDX-010, CAS No. 477202-00-9).

In one embodiment, an anti-PD-1 antibody molecule is administered after treatment with a compound of the invention as described herein.

In another embodiment, an anti-PD-1 or PD-L1 antibody molecule is administered in combination with an anti-LAG-3 antibody or an antigen-binding fragment thereof. In another embodiment, the anti-PD-1 or PD-L1 antibody molecule is administered in combination with an anti-TIM-3 antibody or antigen-binding fragment thereof. In yet other embodiments, the anti-PD-1 or PD-L1 antibody molecule is administered in combination with an anti-LAG-3 antibody and an anti-TIM-3 antibody, or antigen-binding fragments thereof. The combination of antibodies recited herein can be administered separately, e.g., as separate antibodies, or linked, e.g., as a bispecific or trispecific antibody molecule. In one embodiment, a bispecific antibody that includes an anti-PD-1 or PD-L1 antibody molecule and an anti-TIM-3 or anti-LAG-3 antibody, or antigen-binding fragment thereof, is administered. In certain embodiments, the combination of antibodies recited herein is used to treat a cancer, e.g., a cancer as described herein (e.g., a solid tumor). The efficacy of the aforesaid combinations can be tested in animal models known in the art. For example, the animal models to test the synergistic effect of anti-PD-1 and anti-LAG-3 are described, e.g., in Woo et al. (2012) Cancer Res. 72(4):917-27).

Exemplary immunomodulators that can be used in the combination therapies include, but are not limited to, e.g., afutuzumab (available from Roche®); pegfilgrastim (Neulasta®); lenalidomide (CC-5013, Revlimid®); thalidomide (Thalomid®), actimid (CC4047); and cytokines, e.g., IL-21 or IRX-2 (mixture of human cytokines including
interleukin 1, interleukin 2, and interferon γ, CAS 951209-71-5, available from IRX Therapeutics).

Exemplary doses of such immunomodulators that can be used in combination with the antibacterial compounds of the invention include a dose of anti-PD-1 antibody molecule of about 1 to 10 mg/kg, e.g., 3 mg/kg, and a dose of an anti-CTLA-4 antibody, e.g., ipilimumab, of about 3 mg/kg.

Examples of embodiments of the methods of using the antibacterial compounds of the invention in combination with an immunomodulator include these:

1. A method to treat a bacterial infection in a subject, comprising administering to the subject a compound of Formula (I) as described herein, and an immunomodulator.

2. The method of embodiment 1, wherein the immunomodulator is an activator of a costimulatory molecule or an inhibitor of an immune checkpoint molecule.

3. The method of either of embodiments 1 and 2, wherein the activator of the costimulatory molecule is an agonist of one or more of OX40, CD2, CD27, CDS, ICAM-1, LFA-1 (CD11A/CD18), ICOS (CD278), 4-1BB (CD137), GITR, CD30, CD40, BAFFR, HVEM, CD7, LIGHT, NKG2C, SLAMF7, Nkp80, CD160, B7-H3 and CD83 ligand.

4. The method of any of embodiments 1-3 above, wherein the inhibitor of the immune checkpoint molecule is chosen from PD-1, PD-L1, PD-L2, CTLA4, TIM3, LAG3, VISTA, BTLA, TIGIT, LAIR1, CD160, 2B4 and TGFR beta.

5. The method of any of any of embodiments 1-3, wherein the inhibitor of the immune checkpoint molecule is chosen from an inhibitor of PD-1, PD-L1, LAG-3, TIM-3 or CTLA4, or any combination thereof.

6. The method of any of embodiments 1-5, wherein the inhibitor of the immune checkpoint molecule is a soluble ligand or an antibody or antigen-binding fragment thereof, that binds to the immune checkpoint molecule.

7. The method of any of embodiments 1-6, wherein the antibody or antigen-binding fragment thereof is from an IgG1 or IgG4 (e.g., human IgG1 or IgG4).

8. The method of any of embodiments 1-9, wherein the antibody or antigen-binding fragment thereof is altered, e.g., mutated, to increase or decrease one or more of: Fc receptor binding, antibody glycosylation, the number of cysteine residues, effector cell function, or complement function.

9. The method of any of embodiments 1-8, wherein the antibody molecule is a bispecific or multispecific antibody molecule that has a first binding specificity to PD-1 or PD-L1 and a second binding specificity to TIM-3, LAG-3, or PD-L2.

10. The method of any of embodiments 1-9, wherein the immunomodulator is an anti-PD-1 antibody chosen from Nivolumab, Pembrolizumab or Pidilizumab.
11. The method of any of embodiments 1-10, wherein the immunomodulator is an anti-PD-L1 antibody chosen from YW243.55.S70, MPDL3280A, MEDI-4736, MSB-0010718C, or MDX-1405.

12. The method of any of embodiments 1-10, wherein the immunomodulator is an anti-LAG-3 antibody molecule.

13. The method of embodiment 12, wherein the anti-LAG-3 antibody molecule is BMS-986016.

14. The method of any of embodiments 1-10, wherein the immunomodulator is an anti-PD-1 antibody molecule administered by injection (e.g., subcutaneously or intravenously) at a dose of about 1 to 30 mg/kg, e.g., about 5 to 25 mg/kg, about 10 to 20 mg/kg, about 1 to 5 mg/kg, or about 3 mg/kg., e.g., once a week to once every 2, 3, or 4 weeks.

15. The method of embodiment 14, wherein the anti-PD-1 antibody molecule is administered at a dose from about 10 to 20 mg/kg every other week.

16. The method of embodiment 15, wherein the anti-PD-1 antibody molecule, e.g., Nivolumab, is administered intravenously at a dose from about 1 mg/kg to 3 mg/kg, e.g., about 1 mg/kg, 2 mg/kg or 3 mg/kg, every two weeks.

17. The method of claim 15, wherein the anti-PD-1 antibody molecule, e.g., Nivolumab, is administered intravenously at a dose of about 2 mg/kg at 3-week intervals.

The compounds as defined in embodiments may be synthesized by the general synthetic routes below, specific examples of which are described in more detail in the Examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed in situ under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure material.

Compounds of the present invention and intermediates can also be converted into each other according to methods generally known to those skilled in the art.

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J.

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known to those skilled in the art. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, e.g. the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, e.g. by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, e.g. a free carboxy group and a free amino group, may be formed, e.g. by the neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g. with weak bases, or by treatment with ion exchangers.

Salts can be converted into the free compounds in accordance with methods known to those skilled in the art. Metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by e.g. medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.
Intermediates and final products can be worked up and/or purified according to standard methods, e.g. using chromatographic methods, distribution methods, (re-)crystallization, and the like.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known to those skilled in the art, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, e.g. in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190 °C, including, for example, from approximately -80 °C to approximately 150 °C, for example at from -80 to -60 °C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereo isomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereo isomers, for example analogously to the methods described under "Additional process steps".

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanolic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, methycyclohexane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds of the present invention, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.
The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

The term "an optical isomer" or "a stereoisomer" refers to any of the various stereoisomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. The term "chiral" refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn-Ingold-Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-.

Depending on the choice of the starting materials and procedures, the compounds can be present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible stereoisomers, including racemic mixtures, diastereomeric mixtures and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synths or chiral reagents, or resolved using conventional techniques. If the
compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, e.g., by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, e.g., by fractional crystallization of a salt formed with an optically active acid, e.g., tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-0,0-p-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, e.g., high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the present invention may inherently or by design form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The compounds of the present invention, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

As used herein, the terms "salt" or "salts" refers to an acid addition or base addition salt of a compound of the present invention. "Salts" include in particular "pharmaceutically acceptable salts". The term "pharmaceutically acceptable salts" refers to salts that retain the biological effectiveness and properties of the compounds of this invention and, which typically are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids, e.g., acetate, aspartate, benzoate, besylate, bromide/hydrobromide,
bicarbonate/carbonate, bisulfate/sulfate, camphorsulfonate, chloride/hydrochloride, chlortheophyllonate, citrate, ethandisulfonate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hydroiodide/iodide, isethionate, lactate, lactobionate, laurylsulfate, malate, maleate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, nicotinate, nitrate, octadecanoate, oleate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, propionate, stearate, succinate, subsalicylate, tartrate, tosylate and trifluoroacetate salts.

Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like.

Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, toluenesulfonic acid, sulfosalicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases.

Inorganic bases from which salts can be derived include, for example, ammonium salts and metals from columns I to XII of the periodic table. In certain embodiments, the salts are derived from sodium, potassium, ammonium, calcium, magnesium, iron, silver, zinc, and copper; particularly suitable salts include ammonium, potassium, sodium, calcium and magnesium salts.

Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like. Certain organic amines include isopropylamine, benzathine, cholinate, diethanolamine, diethylamine, lysine, meglumine, piperazine and tromethamine.

The pharmaceutically acceptable salts of the present invention can be synthesized from a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable. Additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002).

Any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds of the present invention. Isotopically labeled
compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as $^{2}$H, $^{3}$H, $^{11}$C, $^{13}$C, $^{14}$C, $^{15}$N, $^{16}$F, $^{31}$P, $^{32}$P, $^{35}$S, $^{36}$Cl, $^{125}$I respectively. The invention includes various isotopically labeled compounds of the present invention, for example those into which radioactive isotopes, such as $^{3}$H and $^{14}$C, or those into which non-radioactive isotopes, such as $^{2}$H and $^{13}$C are present. Such isotopically labeled compounds are useful in metabolic studies (with $^{14}$C), reaction kinetic studies (with, for example $^{2}$H or $^{3}$H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an $^{15}$F labeled compound of the present invention may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of the present invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

Further, substitution with heavier isotopes, particularly deuterium (i.e., $^{2}$H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the present invention. The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), or at least 6600 (99% deuterium incorporation).

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, e.g. $^{2}$H$_{2}$O, de-acetone, $^{2}$H$_{5}$DMSO.

Compounds of the present invention that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of the present invention by known co-crystal forming procedures. Such procedures include grinding,
heating, co-subliming, co-melting, or contacting in solution compounds of the invention with
the co-crystal former under crystallization conditions and isolating co-crystals thereby
formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the
invention further provides co-crystals comprising a compound of the present invention.

All methods described herein can be performed in any suitable order unless
otherwise indicated or otherwise clearly contradicted by context. The use of any and all
examples, or exemplary language (e.g. "such as") provided herein is intended merely to
better illuminate the invention and not as a limitation on the scope of the claimed invention.

Substitution with heavier isotopes such as deuterium, i.e. $^2$H, may afford certain
therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo
half-life or reduced dosage requirements, and hence may be preferred in some
circumstances. For example, deuterium substitution at non-exchangeable hydrocarbon
bonds (e.g., C-H) may retard epimerization and/or metabolic oxidation in vivo.

Isotopically-labeled compounds of the invention, i.e. compounds of formula (I), can
generally be prepared by conventional techniques known to those skilled in the art or by
processes analogous to those described in the accompanying Examples and Preparations
Sections using an appropriate isotopically-labeled reagent in place of the non-labeled
reagent previously.

In another aspect, the invention provides a method of inhibiting a deacetylase
enzyme in a Gram-negative bacterium, the method comprising the step of contacting the
Gram-negative bacteria with a compound of the invention, e.g., a compound of Formula I or
salt thereof.

In still another aspect, the invention provides a method for treating a subject with a
Gram-negative bacterial infection, the method comprising the step of administering to the
subject in need thereof an antibacterial effective amount of a compound of the invention,
e.g., a compound of Formula I or salt thereof with a pharmaceutically acceptable carrier.

The compounds of the invention can be used for treating conditions caused by the
bacterial production of endotoxin and, in particular, by Gram-negative bacteria and bacteria
that use LpxC in the biosynthesis of lipopolysaccharide (LPS) or endotoxin.

The compounds of the invention also are useful in the treatment of patients suffering
from or susceptible to pneumonia, sepsis, cystic fibrosis, wound, complicated diabetic foot or
complicated urinary tract infections and sexually transmitted diseases caused by Gram-
negative pathogens. The compounds of the invention also are useful in the conditions that
are caused or exacerbated by the bacterial production of lipid A and LPS or endotoxin, such
as sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive
pulmonary disease (COPD) and acute exacerbations of chronic bronchitis (AECB). For these
conditions, treatment includes the administration of a compound of the invention, or a
combination of compounds of the invention, optionally with a second agent wherein the second agent is a second antibacterial agent or a second non-antibacterial agent.

For sepsis, septic shock, systemic inflammation, localized inflammation, chronic obstructive pulmonary disease (COPD) and acute exacerbations of chronic bronchitis (AECB), preferred second non-antibacterial agents include antiendotoxins including endotoxin receptor-binding antibodies, endotoxin-binding antibodies, antiCD14-binding protein antibodies antiligopolysaccharide-binding protein antibodies and tyrosine kinase inhibitors.

In treatment of serious or chronic respiratory tract infections, the compounds of the present invention may also be used with second non-antibacterial agents administered via inhalation. Preferred non-antibacterial agents used in this treatment include anti-inflammatory steroids, non-steroidal anti-inflammatory agents, bronchodilators, mucolytics, anti-asthma therapeutics and lung fluid surfactants. In particular, the non-antibacterial agent may be selected from a group consisting of albuterol, salbuterol, budesonide, beclomethasone, dexamethasone, nedocromil, beclomethasone, fluticasone, flunisolide, triamcinolone, ibuprofen, rofecoxib, naproxen, celecoxib, nedocromil, ipratropium, metaproterenol, pirbuterol, salmeterol, bronchodilators, mucolytics, calfactant, beractant, poractant alfa, surfaxin and pulmozyme (also called domase alfa).

The compounds of the invention can be used, alone or in combination with a second antibacterial agent for the treatment of a serious or chronic respiratory tract infection including serious lung and nosocomial infections such as those caused by Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Proteus mirabilis, Serratia marcescens, Stenotrophomonas maltophilia, Pseudomonas aeruginosa, Burkholderia cepacia, Acinetobacter baumanii, Alcaligenes xylosoxidans, Flavobacterium meningosepticum, Providencia stuartii and Citrobacter freundii, community lung infections such as those caused by Haemophilus influenzae, Legionella species, Moraxella catarrhalis, Enterobacter species, Acinetobacter species, Klebsiella species, and Proteus species, and infections caused by other bacterial species such as Neisseria species, Shigella species, Salmonella species, Helicobacter pylori, Vibrionaceae and Bordetella species as well as the infections is caused by a Brucella species, Francisella tularensis and/or Yersinia Pestis.

A compound of the present invention may also be used in combination with other agents, e.g., an additional antibiotic agent that is or is not of the formula I, for treatment of a bacterial infection in a subject.

By the term "combination", is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the present invention and a combination partner may be administered independently at the same time or
separately within time intervals that especially allow that the combination partners show a cooperative, e.g., synergistic, effect, or any combination thereof.

When used for treating Gram-negative bacteria, the compounds of the present invention can be used to sensitize Gram-negative bacteria to the effects of a second agent.

An embodiment of the present invention is compounds of the present invention used in combination with a second antibacterial agent, non-limiting examples of antibacterial agents may be selected from the following groups:

1) Macrolides or ketolides such as erythromycin, azithromycin, clarithromycin, and telithromycin;
2) Beta-lactams including penicillin such as penicillin G, penicillin V, methicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, ampicillin, amoxicillin, carbenicillin, ticarcillin, mezlocillin, pipercillin, azlocillin, temocillin, cephalosporin such as cepalothin, cephapirin, cephadrine, cephaloridine, cefazolin, cefamandole, cefuroxime, cephalaxin, cefprozil, cefaclor, loracarbef, cefoxitin, cefinemetazole, cefotaxime, ceftizoxime, ceftriaxone, cefoperazone, ceftazidime, cefixime, cefpodoxime, cefditoren, cefdinir, cefpirome, cefepime, and carbapenems such as carbapenem, imipenem, meropenem and PZ-601;
3) Monobactams such as aztreonam;
4) Quinolones such as nalidixic acid, oxolinic acid, norfloxacin, pefloxacin, enoxacin, ofloxacin, levofl oxacin, ciprofloxacin, temafloxacin, lomefloxacin, grepafloxacin, sparfl oxacin, trovafloxacin, clinafloxacin, gatifloxacin, moxifloxacin, sitafloxacin, ganefloxacin, gemifloxacin and pazufloxacin;
5) Antibacterial sulfonamides and antibacterial sulphanilamides, including paraaminobenzoic acid, sulfadiazine, sulfisoxazole, sulfamethoxazole and sulfathalidone;
6) Aminoglycosides such as streptomycin, neomycin, kanamycin, paromycin, gentamicin, tobramycin, amikacin, netilmicin, spectinomycin, sisomicin, dibekalin and isepamicin;
7) Tetracyclines such as tetracycline, chiortetracycline, demeclocycline, minocycline, oxytetracycline, methacycline, doxycycline, tetracycline;
8) Rifamycins such as rifampicin (also called rifampin), rifampente, rifabutin, bezoxazinorifamycin and rifaximin;
9) Lincosamides such as lincomycin and clindamycin;
10) Glycopeptides such as vancomycin and teicoplanin;
11) Streptogramins such as quinupristin and daflopristin;
12) Oxazolidinones such as linezolid;
13) Polymyxin, colistin and colymycin;
14) Trimethoprim and bacitracin.
15) Efflux pump inhibitors.
The second antibacterial agent may be administered in combination with the compounds of the present inventions wherein the second antibacterial agent is administered prior to, simultaneously, or after the compound or compounds of the present invention. When simultaneous administration of a compound of the invention with a second agent is desired and the route of administration is the same, then a compound of the invention may be formulated with a second agent into the same dosage form. An example of a dosage form containing a compound of the invention and a second agent is a tablet or a capsule.

When used for treating serious or chronic respiratory tract infections, the compounds of the invention may be used alone or in combination with a second antibacterial agent administered via inhalation. In the case of inhalation, a preferred second antibacterial agent is selected from a group consisting of tobramycin, gentamicin, aztreonam, ciprofloxacin, polymyxin, colistin, colymycin, azithromycin and clarithromycin.

While the compounds of the invention are often less susceptible to beta-lactamases that confer resistance to other monobactams in drug-resistant bacteria, their activity may be enhanced in some resistant strains by use in combination with a beta-lactamase inhibitor (BLI). Suitable BLI’s include clavulanic acid, sulbactam, tazobactam, avibactam, and various BLIs disclosed in WO2014/152996, WO2013/149136, and US2013/02813459. Accordingly, the invention also provides compositions comprising a compound of Formula I, II or III as described herein, in combination with a beta-lactamase inhibitor such as those named above, and methods of using a compound of Formula I, II or III in combination with a beta-lactamase inhibitor to treat drug-resistant bacterial infections.

The language "effective amount" of the compound is that amount necessary or sufficient to treat or prevent a bacterial infection and/or a disease or condition described herein. In an example, an effective amount of the LpxC inhibitor is the amount sufficient to treat bacterial infection in a subject. In another example, an effective amount of the LpxC inhibitor is an amount sufficient to treat a bacterial infection, such as, but not limited to Pseudomonas aeruginosa and the like in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound of the invention. For example, the choice of the compound of the invention can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds of the invention without undue experimentation.

The regimen of administration can affect what constitutes an effective amount. The compound of the invention can be administered to the subject either prior to or after the onset of a bacterial infection. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) of the invention can be
proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

Compounds of the invention may be used in the treatment of states, disorders or diseases as described herein, or for the manufacture of pharmaceutical compositions for use in the treatment of these diseases. The invention provides methods of use of compounds of the present invention in the treatment of these diseases or pharmaceutical preparations having compounds of the present invention for the treatment of these diseases.

The language "pharmaceutical composition" includes preparations suitable for administration to mammals, e.g., humans. When the compounds of the present invention are administered as pharmaceuticals to mammals, e.g., humans, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The phrase "pharmaceutically acceptable carrier" is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfate and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, \(\alpha\)-
tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine
tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal,
inhalation, topical, transdermal, buccal, sublingual, rectal, vaginal and/or parenteral
administration. The formulations may conveniently be presented in unit dosage form and
may be prepared by any methods well known in the art of pharmacy. The amount of active
ingredient that can be combined with a carrier material to produce a single dosage form will
generally be that amount of the compound that produces a therapeutic effect. Generally, out
of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine
percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most
preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing
into association a compound of the present invention with the carrier and, optionally, one or
more accessory ingredients. In general, the formulations are prepared by uniformly and
intimately bringing into association a compound of the present invention with liquid carriers,
or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of
capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and
acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or
non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or
syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and
acacia) and/or as mouth washes and the like, each containing a predetermined amount of a
compound of the present invention as an active ingredient. A compound of the present
invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills,
drages, powders, granules and the like), the active ingredient is mixed with one or more
pharmacologically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or
any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose,
mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose,
alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as
glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca
starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such
as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting
agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as
kaolin and bentonite clay; lubricants, such as talc, calcium stearate, magnesium stearate,
solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents.
In the case of capsules, tablets and pills, the pharmaceutical compositions may also
comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluent commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

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

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile...
injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

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

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenteral-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, etc., administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used
herein means modes of administration other than enteral and topical administration, usually
by injection, and includes, without limitation, intravenous, intramuscular, intra-arterial,
intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal,
subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and
intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral
administration" and "administered peripherally" as used herein mean the administration of a
compound, drug or other material other than directly into the central nervous system, such
that it enters the patient's system and, thus, is subject to metabolism and other like
processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by
any suitable route of administration, including orally, nasally, as by, for example, a spray,
rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments
or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present
invention, which may be used in a suitable hydrated form, and/or the pharmaceutical
compositions of the present invention, are formulated into pharmaceutically acceptable
dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of
this invention may be varied so as to obtain an amount of the active ingredient which is
effective to achieve the desired therapeutic response for a particular patient, composition,
and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity
of the particular compound of the present invention employed, or the ester, salt or amide
thereof, the route of administration, the time of administration, the rate of excretion of the
particular compound being employed, the duration of the treatment, other drugs, compounds
and/or materials used in combination with the particular compound employed, the age, sex,
weight, condition, general health and prior medical history of the patient being treated, and
like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and
prescribe the effective amount of the pharmaceutical composition required. For example, the
physician or veterinarian could start doses of the compounds of the invention employed in
the pharmaceutical composition at levels lower than that required in order to achieve the
desired therapeutic effect and gradually increase the dosage until the desired effect is
achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of
the compound that is the lowest dose effective to produce a therapeutic effect. Such an
effective dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 1.0 to about 100 mg per kg per day. An effective amount is that amount treats a bacterial infection.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition.

The compounds as defined in embodiments may be synthesized by the general synthetic routes below, specific examples of which are described in more detail in the Examples.

**General Synthetic Schemes**

One method for synthesizing compounds with formula (I) was described in **Scheme A**. The synthesis started with protecting 4-bromoanaline A-1 as benzyl carbamate A-2. Deprotonation of compound A-2 followed by reacting with (R)-glycidyl butyrate yielded the oxazolidinone alcohol A-3, which was then converted to iodide A-4. Compound A-4 was coupled with ethyl 2-(methylsulfonyl)propanoate under basic condition to provide compound A-5. Various fragment R3 could be coupled with aryl bromide A-5 to give ester A-6. Ester A-6 was converted to hydroxamic acid I via saponification of the ethyl ester, amidation of the free acid with 0-(tetrahydro-2Hpyran-2-yl)hydroxylamine (THPONH₂) and THP deprotection under acid condition.

**Scheme A**
The intermediate **A-4** could also be synthesized by the general method described in Scheme B. Reaction between amine **A-1** and epichlorohydrin under heating condition provided epoxide opening product **B-1**. Cyclization of aminoalcohol **B-1** by treating with CDI provide oxazolidinone **B-2**. The chloride **B-2** was then displaced with iodide to provide compound **A-4**.

**Scheme B**
Scheme C described another general method for the synthesis of intermediate A-6. Amine C-1 could be converted to C-2 using methods described in either Scheme A or Scheme B. Intermediate A-6 could be prepared from compound C-2 via deprotecting PMB group and then coupling with various aryl groups.

Scheme C

Compounds of the invention are prepared from commonly available compounds using procedures known to those skilled in the art, including any one or more of the following conditions without limitation:

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group," unless the context indicates otherwise. The protection of
functional groups by such protecting groups, the protecting groups themselves, and their
cleavage reactions are described for example in standard reference works, such as e.g.,
(Electronic Version, 48 Volumes)); J. F. W. McOmie, "Protective Groups in Organic
Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and
New York 1981, in "Methoden der organischen Chemie" (Methods of Organic Chemistry),
Houben Weyl, 4th edition, Volume 15/1, Georg Thieme Verlag, Stuttgart 1974, in H.-D.
Jakubke and H. Jeschkeit, "Aminosauren, Peptide, Proteine" (Amino acids, Peptides,
Proteins), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen
Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (Chemistry of
Carbohydrates: Monosaccharides and Derivatives), Georg Thieme Verlag, Stuttgart 1974. A
characteristic of protecting groups is that they can be removed readily (i.e., without the
occurrence of undesired secondary reactions) for example by solvolysis, reduction,
photolysis or alternatively under physiological conditions (e.g., by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group
may be prepared in a manner known per se. For example, salts of compounds of the
present invention having acid groups may be formed, for example, by treating the
compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic
acids, e.g., the sodium salt of 2-ethyl hexanoic acid, with organic alkali metal or alkaline
earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen
carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with
the corresponding calcium compounds or with ammonia or a suitable organic amine,
stoichiometric amounts or only a small excess of the salt-forming agent preferably being
used. Acid addition salts of compounds of the present invention are obtained in customary
manner, e.g., by treating the compounds with an acid or a suitable anion exchange reagent.
Internal salts of compounds of the present invention containing acid and basic salt-forming
groups, e.g., a free carboxy group and a free amino group, may be formed, e.g., by the
neutralisation of salts, such as acid addition salts, to the isoelectric point, e.g., with weak
bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and
ammonium salts can be converted, for example, by treatment with suitable acids, and acid
addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a
manner known per se into the individual isomers; diastereoisomers can be separated, for

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example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by, e.g., medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, e.g., using chromatographic methods, distribution methods, (re-)crystallization, and the like.

The process steps to synthesize the compounds of the invention can be carried out under reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, e.g., in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190°C, including, for example, from approximately -80°C to approximately 150°C, for example at from -80 to -60°C, at room temperature, at from -20 to 40°C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described in Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag, Stuttgart, Germany, 2005.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise
indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

The present invention also relates to pro-drugs of a compound of the present invention that are converted in vivo to the compounds of the present invention as described herein. Any reference to a compound of the present invention is therefore to be understood as referring also to the corresponding pro-drugs of the compound of the present invention, as appropriate and expedient.

In accordance with the foregoing the invention provides in a yet further aspect:

• A pharmaceutical combination comprising a) a first agent which is a compound of the invention, e.g. a compound of formula I or any subformulae thereof, and b) a co-agent, e.g. a second drug agent as defined above, or a beta-lactamase inhibitor.
• A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention, e.g. a compound of formula I or any subformulae thereof, and a co-agent, e.g. a second drug agent as defined above, or a beta-lactamase inhibitor.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. Fixed combinations are also within the scope of the present invention. The administration of a pharmaceutical combination of the invention results in a beneficial effect, e.g. a synergistic therapeutic effect, compared to a monotherapy applying only one of its pharmaceutically active ingredients.

Each component of a combination according to this invention may be administered separately, together, or in any combination thereof.

The compound of the invention and any additional agent may be formulated in separate dosage forms. Alternatively, to decrease the number of dosage forms
administered to a patient, the compound of the invention and any additional agent may be formulated together in any combination. For example, the compound of the invention inhibitor may be formulated in one dosage form and the additional agent may be formulated together in another dosage form. Any separate dosage forms may be administered at the same time or different times.

Alternatively, a composition of this invention comprises an additional agent as described herein. Each component may be present in individual compositions, combination compositions, or in a single composition.

The invention is further illustrated by the following examples, which should not be construed as further limiting. The assays used throughout the Examples are accepted in the art as being predictive of efficacy for treating subjects.

**GENERAL SYNTHESIS METHODS**

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

**LIST OF ABBREVIATIONS**

- **Ac**  
  acetyl
- **ACN**  
  Acetonitrile
- **AcOEt / EtOAc**  
  Ethyl acetate
- **AcOH**  
  acetic acid
- **aq**  
  aqueous
- **Ar**  
  aryl
- **Bn**  
  benzyl
- **Bu**  
  butyl (nBu = n-butyl, tBu = tert-butyl)
- **CDI**  
  Carbonyldiimidazole
- **CH₃CN**  
  Acetonitrile
- **DBU**  
  1,8-Diazabicyclo[5.4.0]-undec-7-ene
- **Boc₂O**  
  di-tert-butyl dicarbonate
- **DCE**  
  1,2-Dichloroethane
- **DCM**  
  Dichloromethane
- **DiBAI-H**  
  Diisobutylaluminum Hydride
DIPEA  N-Ethyldiisopropylamine
DMAP  Dimethylaminopyridine
DMF  N,N'-Dimethylformamide
DMSO  Dimethylsulfoxide
EI  Electrospray ionisation
Et\_2O  Diethylether
Et\_3N  Triethylamine
Ether  Diethylether
EtOAc  Ethylacetate
EtOH  Ethanol
FC  Flash Chromatography
h  hour(s)
HATU  0-(7-Azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HBTU  0-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HCl  Hydrochloric acid
HMPA  Hexamethylphosphoramide
HOBt  1-Hydroxybenzotriazole
HPLC  High Performance Liquid Chromatography
H\_2O  Water
L  liter(s)
LC-MS  Liquid Chromatography Mass Spectrometry
LiHMDS  Lithium bis(trimethylsilyl)amide
MgSO\_4  Magnesium Sulfate
Me  methyl
Mel  Iodomethane
MeOH  Methanol
mg  milligram
min  minute(s)
mL  milliliter
MS  Mass Spectrometry
NaHCO\_3  Sodium Bicarbonate
Na\_2SO\_4  Sodium Sulfate
NH\_2OH  hydroxylamine
Pd/C  palladium on charcoal
Pd(OH)\_2  palladium hydroxide
**Synthesis of compound 1.1**

Reagents: Step 1: CBZ-Cl, NaHCO₃, Acetone, Water, 5 °C to room temperature. Step 2: n-BuLi, THF, -75 °C to room temperature. Step 3: Iodine, triphenylphosphine, imidazole, rt. Step 4: NaH (60%), N,N-dimethylformamide, 0 °C to room temperature. Step 5: LiOH, THF, MeOH, Water, room temperature. Step 6: NH₂OTHP, EDC.HCl, HOBt, TEA, dichloromethane, room temperature. Step 7: 35.5% aq. HCl, EtOH, room temperature.
Step 1. Synthesis of benzyl (4-bromophenyl) carbamate [1.1a] 4- Bromoaniline (5.0 g, 29.1 mmol, 1.0 equiv) was dissolved in acetone: water (2:1, 45 ml) mixture. The solution was cooled to 5 °C and NaHCO₃ (5.13 g, 61.1 mmol, 2.1 equiv), CBZ-Cl (4.96 g, 29.1 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 3 hours, then quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a crude residue. The residue was purified by silica gel column chromatography (8-10 % EtOAc/Hexane) to afford product 1.1a (8.0 g, 90 % yield). LCMS (m/z): 306.3 [M+H]. ¹H NMR (400 MHz, CDCl₃) δ 7.45 - 7.38 (m, 7H), 7.31 (d, J = 8.6 Hz, 2H), 6.70 (s, 1H), 5.21 (d, J = 8.7 Hz, 2H).

Step 2. Synthesis of (R)-3-(4-bromophenyl)-5-(hydroxymethyl) oxazolidin-2-one [1.1b] 1.1a (6.0 g, 19.6 mmol, 1.0 equiv) was dissolved in THF (60 ml) and cooled to -75 °C. n-BuLi (1.51 g, 23.5 mmol, 1.2 equiv) was gradually added and the reaction mixture was stirred at -75 °C for 1 hour. (R)-oxiran-2-ylmethyl butyrate (2.82 g, 19.6 mmol, 1.0 equiv) was added, the reaction mixture was stirred at -75 °C for 1 hour, allowed to attain room temperature, and stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (50-60 % EtOAc/Hexane) to afford product 1.1b (3.5 g, 65.6 % yield). LCMS (m/z): 274.1 [M+H]. ¹H NMR(400 MHz, DMSO-d₆) δ 7.64 - 7.49 (m, 4H), 5.23 (t, J = 5.7 Hz, 1H), 4.71 (td, J = 9.4, 3.7 Hz, 1H), 4.08 (t, J = 9.0 Hz, 1H), 3.82 (dd, J = 8.8, 6.2 Hz, 1H), 3.68 (ddd, J = 12.3, 5.5, 3.4 Hz, 1H), 3.56 (ddd, J = 12.3, 5.8, 4.1 Hz, 1H).

Step 3. Synthesis of (R)-3-(4-bromophenyl)-5-(iodomethyl) oxazolidin-2-one [1.1c] Triphenylphosphine (2.5 g, 95.6 mmol, 1.3 equiv) and imidazole (0.70 g, 10.3 mmol, 1.4 equiv) were dissolved in dichloromethane (20 ml). Iodine (2.42 g, 9.5 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 15 minutes. 1.1b (2.0 g, 73.5 mmol, 1.0 equiv) was added portion wise. The reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a residue. The residue was purified by silica gel column chromatography (20-30 % EtOAc/Hexane) to afford product 1.1c (1.5 g, 53.4 % yield). LCMS (m/z): 382.1 [M+H]. ¹H NMR (400 MHz, DMSO-d₆) δ 7.69 - 7.48 (m, 4H), 4.75 (td, J = 10.8, 5.1 Hz, 1H), 4.27 - 4.13 (m, 1H), 3.72 - 3.53 (m, 3H).

Step 4. Synthesis of ethyl 3-((S)-3-(4-bromophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonfyl) propanoate [1.1d] Ethyl 2-(methylsulfonfyl) propanoate (0.95 g, 5.2 mmol, 2.0 equiv) dissolved in N,N-dimethylformamide (6 mL) and cooled to 0-5 °C. NaH (60 %) (0.157 g, 3.9 mmol, 1.5 equiv)
was added in portion wise and the reaction mixture was stirred at room temperature for 1.5 hours. A solution of 1.1c (1.0 g, 26.2 mmol, 1.0 equiv) in N,N-dimethylformamide (4 ml) was added drop wise at 5 °C. The reaction mixture was stirred at 5 °C for 30 minutes. The reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (20-25 % EtOAc/Hexane) to afford product 1.1d (0.165 g, 14.5 % yield). In some cases, 1.1d was obtained as a mixture of diastereomers (R)-ethyl 3-((S)-3-(4-bromophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate and (S)-ethyl 3-((S)-3-(4-bromophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate. The mixture of diastereomers was carried through the following steps and the separation of diastereomers was conducted at the hydroxamic acid stage. LCMS (m/z): 436.3 [M+H]. 1H NMR (400 MHz, DMSO d-6) δ 7.64 - 7.56 (m, 2H), 7.54 - 7.48 (m, 2H), 4.96 - 4.75 (m, 1H), 4.31 - 4.16 (m, 2H), 3.85 - 3.73 (m, 1H), 3.22 - 3.10 (m, 4H), 2.68 (dd, J = 14.9, 2.5 Hz, 1H), 2.36 (dd, J = 14.7, 8.9 Hz, 1H), 1.61 (d, J = 27.1 Hz, 3H), 1.26 (dd, J = 8.5, 5.7 Hz, 3H).

**Step 5. Synthesis of 3-((S)-3-(4-bromophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methyl sulfonyl) propanoic acid [1.1e]**

1.1d (0.15 g, 0.34 mmol, 1.0 equiv) was dissolved in THF (2.0 ml), MeOH (1.0 ml), LiOH (0.025 g, 1.04 mmol, 3.0 equiv) in water (1 ml) was added. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness and the residue was diluted with water, acidified by 1.0 N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford compound 1.1e (0.11 g, 78.3 % yield). The crude material was used in the next step with no further purification. LCMS (m/z): 408.2 [M+H]. 1H NMR (400 MHz, DMSO d-6) δ 7.57 (d, J = 8.9 Hz, 2H), 7.49 (d, J = 9.1 Hz, 2H), 4.78 (d, J = 7.9 Hz, 1H), 4.19 (d, J = 8.9 Hz, 1H), 3.79 (t, J = 8.1 Hz, 1H), 3.13 (s, 3H), 2.70 - 2.57 (m, 1H), 2.30 (dd, J = 14.3, 9.0 Hz, 1H), 1.59 (s, 3H).


1.1e (0.11 g, 0.27 mmol, 1.0 equiv) was dissolved in dichloromethane (4 ml). Et3N (0.137 g, 1.35 mmol, 5.0 equiv), EDC.HCl (0.078 g, 0.41 mmol, 1.5 equiv), HOBT (0.066 g, 0.49 mmol, 1.8 equiv) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.064 g, 0.54 mmol, 2.0 equiv) were added to the solution. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (70-75% EtOAc/Hexane) to afford product 1.1f which was used as such for next step (0.075 g, 54.7 % yield). LCMS (m/z): 522.4 [M+18]. 1H NMR (400 MHz, DMSO) δ 7.58 (t, J = 6.0 Hz, 2H), 7.51 (dd, J = 8.0, 6.7 Hz, 2H),...
4.67 (d, J = 8.1 Hz, 1H), 4.17 (t, J = 8.8 Hz, 1H), 4.04 (s, 1H), 3.78 (t, J = 8.2 Hz, 1H), 3.07 (t, J = 8.2 Hz, 3H), 2.78 (d, J = 12.2 Hz, 1H), 2.23 (dd, J = 13.4, 8.2 Hz, 1H), 1.59 - 1.41 (m, 6H).

Step 7. Synthesis of (R)-3-((S)-3-(4-bromophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [1.1]

1.1f (0.07 g, 0.14 mmol, 1.0 equiv) was dissolved in ethanol (2.0 ml), 35.5% aqueous HCl (0.5 ml) was added and reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure and residue was triturated with n-pentane. The solvent was decanted and the crude product was further purified by preparative HPLC purification to afford the product 1.1 as desired diastereomer (0.023 g, 39.5% yield). LCMS (m/z): 423.2 [M+H].

H NMR (400 MHz, CD3CN) δ 9.56 (s, 1H), 7.53 (dd, J = 24.8, 9.1 Hz, 4H), 4.76 - 4.62 (m, 1H), 4.16 (t, J = 8.7 Hz, 1H), 3.76 (t, J = 8.3 Hz, 1H), 3.00 (d, J = 23.6 Hz, 3H), 2.83 - 2.70 (m, 1H), 2.33 (dd, J = 14.4, 9.0 Hz, 1H), 2.18 (s, 3H), 1.66 (d, J = 21.6 Hz, 3H).

1-2. Synthesis of compound 1.2

Reagents: Step 1: CBZ-Cl, NaHCO3, Acetone:Water, 0°C to room temperature. Step 2: n-BuLi(2.5M in hexane), THF, -78°C to room temperature. Step 3: Iodine, triphenylphosphine, imidazole, rt. Step 4: NaH (60%), N,N-dimethylformamide, 0°C to room temperature. Step 5: LiOH, THF, MeOH, Water, room temperature. Step 6: NH2OTHP, EDC.HCI, HOBt, TEA, DCM, room temperature. Step 7: Methanolic-HCl (8%w/w), MeOH, room temperature.

Step 1. Synthesis of benzyl (4-bromo-2-methylphenyl)carbamate [1.2a]

4-Bromo-2-methylaniline (3.0 g, 16.1 mmol, 1.0 equiv) was dissolved in acetone: water (2:1, 27 ml) and the solution was cooled to 0°C. NaHCO3 (2.84 g, 33.8 mmol, 2.1 equiv), CBZ-Cl (2.75 g, 16.1 mmol, 1.0 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water
and extracted with EtOAc. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated to obtain a crude residue. The residue was purified by silica gel column chromatography (5-8 % EtOAc in Hexane) to afford product 1.2a (4.8 g, 92.9 % yield). LCMS (m/z): 320.2 [M-H]. 1H NMR (400 MHz, DMSO) δ 9.08 (s, 1H), 7.82 - 7.06 (m, 8H), 5.14 (s, 2H), 2.27 (d, J = 54.4 Hz, 3H).

**Step 2. Synthesis of (R)-3-(4-bromo-2-methylphenyl)-5-(hydroxymethyl)oxazolidin-2-one [1.2b].** 1. **2a** (2.0 g, 6.2 mmol, 1.0 equiv) was dissolved in THF (60 mL) and cooled to -78°C. n-BuLi (2.5M in hexane) (0.40 g, 6.3 mmol, 1.01 equiv) was added and the reaction mixture was stirred at -78° for 45 minutes. (R)-oxiran-2-ylmethyl butyrate (0.91 g, 6.3 mmol, 1.01 equiv) was added, the reaction mixture was stirred at -78° for 15 minutes and allowed to attain room temperature for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (10-35 % EtOAc in Hexane) to afford product 1.2b (1.30 g, 73.0 % yield). LCMS (m/z): 286.2 [M-H]. 1H NMR (400 MHz, DMSO) δ 7.64 - 7.40 (m, 2H), 7.29 (d, J = 8.4 Hz, 1H), 5.26 (t, J = 5.7 Hz, 1H), 4.71 (td, J = 9.3, 3.8 Hz, 1H), 4.03 - 3.89 (m, 1H), 3.77 - 3.63 (m, 2H), 3.61 - 3.48 (m, 1H), 2.22 (s, 3H).

**Step 3. Synthesis of (R)-3-(4-bromo-2-methylphenyl)-5-(iodomethyl)oxazolidin-2-one [1.2c].** Triphenylphosphine (1.54 g, 5.9 mmol, 1.3 equiv) and imidazole (0.40 g, 5.9 mmol, 1.3 equiv) were dissolved in dichloromethane (15 mL). Iodine (1.49 g, 5.9 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 15 min. 1.2b (1.3 g, 4.5 mmol, 1.0 equiv) was dissolved in dichloromethane (10 mL) and added dropwise. The reaction mixture was stirred at room temperature for 10 hours. The reaction mixture was quenched with water, and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (10-25 % EtOAc in Hexane) to afford product 1.2c (1.28 g, 74.4 % yield). LCMS (m/z): 396.1 [M-H]. 1H NMR (400 MHz, DMSO) δ 7.65 - 7.43 (m, 2H), 7.33 (d, J = 8.4 Hz, 1H), 4.76 (td, J = 10.8, 5.1 Hz, 1H), 4.16 - 3.95 (m, 1H), 3.72 - 3.51 (m, 3H), 2.26 (s, 3H).

**Step 4. Synthesis of ethyl (R)-3-((S)-3-(4-bromo-2-methylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [1.2d].** Ethyl 2-(methylsulfonyl)propanoate (1.91 g, 10.6 mmol, 4.0 equiv) was dissolved in N,N-dimethylformamide (14 mL) and cooled to 0-5°C. NaH (60 %) (0.13 g, 5.3 mmol, 2.0 equiv) was added and the reaction mixture was stirred at the same temperature for 1 hour. A solution of 1.2c (1.05 g, 2.7 mmol, 1.0 equiv) in N,N-dimethylformamide (4 mL) was added drop wise at 0-5°C and the reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed
with brine, dried over sodium sulfate and concentrated to obtain a crude residue. The residue was purified by silica gel column chromatography (10-30 % EtOAc in Hexane) to afford product 1.2d as mixture of diastereomers. The product was further purified by preparative HPLC to afford 1.2d as the desired diastereomer (0.64 g, 53.4 % yield). LCMS (m/z): 448.3 [M-H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.62 - 7.42 (m, 2H), 7.33 (d, \(J = 8.5\) Hz, 1H), 5.01 - 4.75 (m, 1H), 4.39 - 4.19 (m, 2H), 4.11 (dd, \(J = 26.7, 6.7, 4.2\) Hz, 1H), 3.69 (dd, \(J = 27.8, 19.3\) Hz, 1H), 3.28 - 3.06 (m, 3H), 2.68 (d, \(J = 14.8\) Hz, 1H), 2.39 (dd, \(J = 14.6, 8.9\) Hz, 1H), 2.30 - 2.13 (s, 3H), 1.74 - 1.51 (m, 3H), 1.27 - 1.22 (m, 3H).

**Step 5. Synthesis of (R)-3-((S)-3-(4-bromo-2-methylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid** [1.2e]. 1.2d (0.2 g, 0.44 mmol, 1.0 equiv) was dissolved in THF (4 mL) and MeOH (2 mL). LiOH (0.037 g, 0.89 mmol, 2.0 equiv) in water (1 mL) was added and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness, the residue was diluted with water, acidified by 1N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 1.2e (0.175 mg, 93.3 % yield). The crude material was used in the next step with no further purification. LCMS (m/z): 422.1 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 4.19 (s, 2H), 3.72 (t, \(J = 8.1\) Hz, 1H), 3.16 (s, 3H), 2.64 (d, \(J = 14.7\) Hz, 1H), 2.36 (dd, \(J = 14.6, 8.7\) Hz, 1H), 2.22 (s, 3H), 1.62 (s, 3H).

**Step 6. Synthesis of (2R)-3-((S)-3-(4-bromo-2-methylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide** [1.2f] 1.2e (0.20 g, 0.44 mmol, 1.0 equiv) was dissolved in THF (6 mL). Et\(_3\)N (0.26 g, 2.2 mmol, 5.0 equiv), EDC.HCl (0.16 g, 0.8 mmol, 1.8 equiv), HOBT (0.09 g, 0.7 mmol, 1.5 equiv) and 0-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.11 g, 0.9 mmol, 2.0 equiv) were added to the solution. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (10-40 % EtOAc in Hexane) to afford product 1.2f which was used as such for next step (0.15 g, 71.4 % yield). LCMS (m/z): 538.3 [M+18].

**Step 7. Synthesis of (R)-3-((S)-3-(4-bromo-2-methylphenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide** [1.2] 1.2f (0.15 g, 0.28 mmol, 1.0 equiv) was dissolved in methanol (2.0 mL). Methanolic HCl solution (8% w/w, 2.0 mL) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to dryness and the crude product was purified by preparative HPLC to afford product 1.2 as desired diastereomer (0.08 g, 56.1 % yield). LCMS (m/z): 452.3 [M+18]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.08 (s,
1H), 9.29 (s, 1H), 7.62 - 7.44 (m, 2H), 7.33 (d, J = 8.5 Hz, 1H), 4.68 (d, J = 6.2 Hz, 1H), 3.99 (t, J = 8.5 Hz, 1H), 3.69 (t, J = 8.2 Hz, 1H), 3.09 (s, 3H), 2.77 (d, J = 16.3 Hz, 1H), 2.35 - 2.15 (m, 4H), 1.61 (s, 3H).

**I-3. Synthesis of compound 1.3**

![Chemical diagram](https://example.com/chemical-diagram.png)

**Reagents:** Step 1: CBZ-Cl, NaHCO₃. Acetone: Water, 5 °C to room temperature. Step 2: n-BuLi (23 % in hexane), THF, -75 °C to room temperature. Step 3: Iodine, triphenylphosphine, imidazole, THF, room temperature. Step 4: NaH (60%), N,N-dimethylformamide, 0 °C to room temperature. Step 5: LiOH.H₂O, THF, MeOH, Water, room temperature. Step 6: NH₂OTHP, EDC.HCl, HOBT, NMM, THF, room temperature. Step 7: 35.5% aq. HCl, EtOH, room temperature.

**Step 1. Synthesis of benzyl (4-bromo-2-fluorophenyl)carbamate [1.3a]**

4-bromo-2-fluoroaniline (5.0 g, 26.3 mmol, 1.0 equiv) was dissolved in acetone: water (2:1, 100 mL) mixture. The solution was cooled to 5 °C and NaHCO₃ (4.42 g, 52.6 mmol, 2.0 equiv), CBZ-Cl (6.73 g, 39.5 mmol, 1.0 equiv) were added. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 1.3a (7.80 g, 91.8% yield). LCMS (m/z): 321.9 [M-H]. ¹H NMR (400 MHz, DMSO) δ 9.63 (s, 1H), 7.66 (t, J = 8.5 Hz, 1H), 7.57 (dd, J = 10.4, 2.2 Hz, 1H), 7.37 (ddt, J = 9.7, 7.9, 6.6 Hz, 6H), 5.16 (s, 2H).

**Step 2. Synthesis of (R)-3-(4-bromo-2-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one [1.3b]**

1. 3a (3.0 g, 9.3 mmol, 1.0 equiv) was dissolved in THF (50 mL) and cooled to -75 °C. n-BuLi (23 % in hexane) (1.19 g, 18.6 mmol, 2.0 equiv) was gradually added and the reaction mixture was stirred at -75 °C for 1 hour. (R)-oxiran-2-ylmethyl butyrate (1.61 g, 11.15 mmol, 1.2 equiv) was added, the reaction mixture was stirred at -75 °C for 1 hour,
allowed to attain room temperature and stirred at room temperature overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (50-60 % EtOAc in Hexane) to afford product 1.3b (1.6 g, 59.7% yield). LCMS (m/z): 290.2 [M+] ¹H NMR (400 MHz, DMSO) δ 7.70 (dd, J = 10.7, 2.0 Hz, 0.5H), 7.58 - 7.46 (m, 1.5H), 7.39 - 7.23 (m, 1H), 5.31 (d, J = 53.6 Hz, 1H), 4.73 (ddd, J = 13.0, 6.4, 4.0 Hz, 1H), 4.09 - 3.97 (m, 1H), 3.80 (t, J = 7.4 Hz, 1H), 3.73 - 3.64 (m, 1H), 3.63 - 3.53 (m, 1H).

**Step 3. Synthesis of (R)-3-((4-bromo-2-fluorophenyl)-5-(iodomethyl)oxazolidin-2-one [1.3c].** Triphenylphosphine (1.88 g, 7.2 mmol, 1.3 equiv) and imidazole (0.49 g, 7.2 mmol, 1.3 equiv) were dissolved in THF (25 mL). Iodine (1.83 g, 7.2 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 10 minutes. A solution of 1.3b (1.60 g, 5.5 mmol, 1.0 equiv) in THF (5 mL) was added dropwise. The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (15-20% EtOAc in Hexane) to afford product 1.3c (1.4 g, 63.6 % yield). LCMS (m/z): 401.99 [M+2], ¹H NMR (400 MHz, DMSO) δ 7.72 (dd, J = 10.7, 2.0 Hz, 0.5H), 7.61 - 7.47 (m, 1.5H), 7.39 - 7.24 (m, 1H), 4.78 (td, J = 9.8, 4.9 Hz, 1H), 4.15 (td, J = 8.8, 1.6 Hz, 1H), 3.71 - 3.52 (m, 3H).

**Step 4. Synthesis of (R)-ethyl 3-((S)-3-((4-bromo-2-fluorophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [1.3d].** Ethyl 2-(methylsulfonyl)propanoate (2.53 g, 14.0 mmol, 4.0 equiv) dissolved in N,N-dimethylformamide (25 mL) and cooled to 0-5 ºC. NaH (60%) (0.17 g, 7.0 mmol, 2.0 equiv) was added in portion wise and the reaction mixture was stirred at room temperature for 2 hours. A solution of 1.3c (1.4 g, 3.51 mmol, 1.0 equiv) in N,N-dimethylformamide (5 mL) was added drop wise. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (50-60 % EtOAc in Hexane) to afford 1.3d as mixture of diastereomers. The product was further purified by preparative HPLC to afford product 1.3d as desired diastereomer (0.35 g, 22.2% yield). LCMS (m/z): 471.3 [M+18], ¹H NMR (400 MHz, DMSO) δ 7.78 - 7.68 (m, 1H), 7.60 - 7.47 (m, 2H), 4.94 - 4.76 (m, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.11 (t, J = 8.4 Hz, 1H), 3.80 (t, J = 8.2 Hz, 1H), 3.17 (s, 3H), 2.75 - 2.64 (m, 1H), 2.37 (dd, J = 14.8, 8.7 Hz, 1H), 1.64 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).

**Step 5. Synthesis of (R)-3-((S)-3-((4-bromo-2-fluorophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [1.3e].** 1.3d (0.13 g, 0.29 mmol, 1.0 equiv) was dissolved in THF (3.0 mL), MeOH (1.0 mL). LiOH (0.036 g, 0.86 mmol, 3.0 equiv) in water
(1 ml_) was added. The resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated to dryness and the residue was diluted with water, acidified by 1N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford compound 1.3e (0.1 1g, 90.2% yield). The crude material was used in the next step with no further purification. LCMS (m/z): 426.2 [M+2]. 1H NMR (400 MHz, DMSO) δ 7.71 (dd, J = 10.6, 1.9 Hz, 1H), 7.52 (dt, J = 8.8, 7.7 Hz, 2H), 4.85 (d, J = 5.8 Hz, 1H), 4.13 (t, J = 8.4 Hz, 1H), 3.80 (t, J = 8.1 Hz, 1H), 3.14 (d, J = 11.6 Hz, 3H), 2.65 (d, J = 17.3 Hz, 1H), 2.34 (dd, J = 14.7, 8.6 Hz, 1H), 1.62 (d, J = 8.3 Hz, 3H).


1.3e (0.11 g, 0.26 mmol, 1.0 equiv) was dissolved in THF (13 ml). N-methyl morpholine (0.13 g, 1.3 mmol, 5.0 equiv), HOBT (0.042 g, 0.31 mmol, 1.2 equiv) and O-(tetrahydro-2H-pyran-2-y1) hydroxylamine (0.061 g, 0.52 mmol, 2.0 equiv) were added. The reaction mixture was stirred at room temperature for 10 minutes and EDC.HCl (0.074 g, 0.39 mmol, 1.5 equiv) was added. The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated up to dryness. The residue was purified by silica gel column chromatography (2-3 % MeOH in dichloromethane) to afford product 1.3f which was used as such for next step (0.09 g, 66.2% yield). LCMS (m/z): 540.4 [M+18]. 1H NMR (400 MHz, DMSO) δ 11.48 (s, 1H), 7.71 (d, J = 10.7 Hz, 1H), 7.52 (dd, J = 15.4, 6.0 Hz, 2H), 4.73 (s, 1H), 4.07 (d, J = 8.3 Hz, 1H), 3.80 - 3.72 (m, 2H), 3.10 (t, J = 11.3 Hz, 3H), 2.79 (d, J = 13.8 Hz, 1H), 2.24 (s, 1H). 1.48 (d, J = 27.7 Hz, 6H).

Step 7. Synthesis of (R)-3-((S)-3-(4-bromo-2-fluorophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [1.3]. 1.3f (0.09 g, 0.17 mmol, 1.0 equiv) was dissolved in ethanol (3 ml), 35.5 % aqueous HCl (0.5 ml) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched in to water, neutralized with sodium bicarbonate and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain the crude product. The crude product was purified by preparative HPLC to afford 1.3 as desired diastereomer (0.042 g, 55.2% yield). LCMS (m/z): 458.3 [M+18]. 1H NMR (400 MHz, CD3CN) δ 9.66 (s, 1H), 7.61 - 7.37 (m, 3H), 7.25 (s, 1H), 4.75 (dt, J = 8.2, 5.7 Hz, 1H), 4.11 (t, J = 8.6 Hz, 1H), 3.77 (t, J = 8.2 Hz, 1H), 2.99 (d, J = 32.5 Hz, 3H), 2.75 (dd, J = 14.4, 2.5 Hz, 1H), 2.36 (dd, J = 14.4, 8.9 Hz, 1H), 1.69 (s, 3H).

I-4. Synthesis of compound 1.4
Reagents: Step 1: CBZ-CI, NaHCO₃, Acetone:Water, 0°C to room temperature. Step 2: n-BuLi (23 % in hexane), THF, -78°C to room temperature. Step 3: Iodine, triphenylphosphine, imidazole, THF, room temperature. Step 4: NaH (60%), N,N-dimethylformamide, 0°C to room temperature. Step 5: LiOH.H₂O, THF, MeOH, Water, rt. Step 6: NH₂THP, EDC.HCl, HOBT, N-methyl morpholine, THF, rt. Step 7: 35.5% aq. HCl, EtOH, room temperature.

Step 1. Synthesis of benzyl (4-bromo-2,6-difluorophenyl)carbamate [1.4a]

4-bromo-2,6-difluorobenzylamine (1.0 g, 4.81 mmol, 1.0 equiv) was dissolved in acetone:water (2:1, 9 mL) and cooled to 0°C. NaHCO₃ (0.89 g, 10.58 mmol, 2.2 equiv), CBZ-CI (1.07 g, 6.25 mmol, 1.3 equiv) were added and the reaction mixture was stirred at room temperature for 7 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the residue. The residue was purified by silica gel chromatography (2:5 % EtOAc in Hexane) to afford product 1.4a (1.23 g, 75% yield). ¹H NMR (400 MHz, DMSO) δ 9.40 (s, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.50 - 7.26 (m, 5H), 5.14 (s, 2H).

Step 2. Synthesis of (R)-3-(4-bromo-2,6-difluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one [1.4b]. 1. 4a (1.23 g, 3.66 mmol, 1.0 equiv) was dissolved in THF (35 mL) and cooled to -78°C. n-BuLi (23% in hexane) (0.34 g, 5.39 mmol, 1.5 equiv) was gradually added and the reaction mixture was stirred at -78°C for 1 hour. (R)-oxiran-2-ylmethyl butyrate (0.62 g, 4.32 mmol, 1.2 equiv) in THF (5 mL) was added drop wise and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (55-60 % EtOAc in Hexane) to afford product 1.4b (0.72 g, 65% yield). LCMS (m/z): 308.1 [M-H]. ¹H NMR (400 MHz, DMSO) δ 7.73 - 7.22 (m, 2H), 5.28 (t, J = 5.7 Hz, 1H), 4.81 (dd, J = 8.9, 6.3 Hz, 1H), 3.99 - 3.88 (m, 1H), 3.75 - 3.65 (m, 2H), 3.60 - 3.52 (m, 1H).
Step 3. Synthesis of (R)-3-(4-bromo-2,6-difluorophenyl)-5-(iodomethyl)oxazolidin-2-one [1.4c]. Triphenylphosphine (0.80 g, 3.04 mmol, 1.3 equiv) was dissolved in THF (10 mL), imidazole (0.21 g, 3.04 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 5 minutes. Iodine (0.77 g, 3.04 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 10 minutes. 1.4b (0.72 g, 2.34 mmol, 1.0 equiv) in THF (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (10-15 % EtOAc in Hexane) to afford product 1.4c (0.70 g, 72% yield). \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.91 - 7.18 (m, 2H), 4.85 (dt, \(J = 10.8, 4.7\) Hz, 1H), 4.18 - 3.96 (m, 1H), 3.69 - 3.54 (m, 2H), 3.47 - 3.25 (m, 1H).

Step 4. Synthesis of ethyl 3-((S)-3-(4-bromo-2,6-difluorophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [1.4d]. Ethyl 2-(methylsulfonyl)propanoate (1.21 g, 6.7 mmol, 4.0 equiv) was dissolved in N,N-dimethylformamide (15 mL) and cooled to 0-5 °C. NaH (60%) (0.08 g, 3.35 mmol, 2.0 equiv) was added portion wise and the reaction mixture was stirred at room temperature for 2 hours. A solution of 1.4c (0.70 g, 1.67 mmol, 1.0 equiv) in DMF (6 mL) was added drop wise at 0-5°C. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a crude residue. The residue was purified by silica gel column chromatography (28-32 % EtOAc in Hexane) to afford product 1.4d (0.39 g, 50% yield). LCMS (m/z): 472.1 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.70 - 7.29 (m, 2H), 5.06 - 4.89 (m, 1H), 4.34 - 4.17 (m, 2H), 4.15 - 4.00 (m, 1H), 3.78 - 3.60 (m, 1H), 3.20 - 3.08 (m, 3H), 2.70 (d, \(J = 2.8\) Hz, 1H), 2.39 - 2.27 (m, 1H), 1.71 - 1.53 (m, 3H), 1.28 - 1.21 (m, 3H).

Step 5. Synthesis of 3-((S)-3-(4-bromo-2,6-difluorophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [1.4e]. 1.4d (0.39 g, 0.84 mmol, 1.0 equiv) was dissolved in THF (7 mL), MeOH (1.8 mL). LiOH.H\(_2\)O (0.112 g, 2.57 mmol, 3.0 equiv) in water (1.8 mL) was added and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness, diluted with water, acidified by 1N HCl aqueous solution to the pH 2 to 3 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford compound 1.4e (0.259 g, 70% yield). The crude material was used in the next step with no further purification. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 14.24 - 13.75 (m, 1H), 7.70 - 7.28 (m, 2H), 5.10 - 4.88 (m, 1H), 4.13 - 4.04 (m, 1H), 3.76 - 3.62 (m, 1H), 3.19 - 3.09 (m, 3H), 2.77 - 2.58 (m, 1H), 2.30 (dd, \(J = 14.8, 8.5\) Hz, 1H), 1.60 (dd, \(J = 18.5, 15.0\) Hz, 3H).

1.4e (0.16 g, 0.36 mmol, 1.0 equiv) was dissolved in THF (10 ml_). N-methyl morpholine (0.183 g, 1.81 mmol, 5.0 equiv), HOBT (0.058 g, 0.43 mmol, 1.2 equiv) and EDC.HCl (0.104 g, 0.54 mmol, 1.5 equiv) were added to the solution and the reaction mixture was stirred at rt for 5 minutes. 0-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.085 g, 0.72 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a crude residue. The residue was purified by silica gel chromatography (2% MeOH in dichloromethane) to afford product 1.4f which was used as such for next step (0.16 g, 81.6% yield). LCMS (m/z): 560.4 [M+18]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.66 (d, \(J = 8.2\) Hz, 1H), 7.27 (d, \(J = 8.4\) Hz, 1H), 4.95 (d, \(J = 10.2\) Hz, 1H), 4.79 (s, 1H), 4.03 (d, \(J = 6.1\) Hz, 2H), 3.78 - 3.65 (m, 2H), 3.46 (d, \(J = 31.5\) Hz, 2H), 3.08 (d, \(J = 10.1\) Hz, 3H), 2.79 (d, \(J = 14.1\) Hz, 1H), 2.20 (dd, \(J = 14.7, 8.7\) Hz, 1H), 1.87 - 1.70 (m, 3H), 1.52 (s, 6H).

Step 7. Synthesis of (R)-3-((S)-3-(4-bromo-2,6-difluorophenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [1.4]. 1.4f (0.160 g, 0.29 mmol, 1.0 equiv) was dissolved in ethanol (6 ml_), 35.5% aq. HCl (0.16 ml_) was added and reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water, neutralized by saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a residue. The residue was purified by preparative HPLC to afford 1.4 as desired diastereomer (0.1 g, 74 % yield). LCMS (m/z): 476.3 [M+18]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.07 (s, 1H), 9.28 (s, 1H), 7.70 (d, \(J = 7.5\) Hz, 2H), 4.76 (tt, \(J = 8.2, 3.9\) Hz, 1H), 4.04 (t, \(J = 8.5\) Hz, 1H), 3.68 (t, \(J = 8.3\) Hz, 1H), 3.09 (s, 3H), 2.94 - 2.69 (m, 1H), 2.20 (dd, \(J = 14.5, 8.7\) Hz, 1H), 1.60 (s, 3H).

II-1 Synthesis of compound 2.1

![Synthesis Diagram](image-url)
Reagents: Step 1: CH3COOK, PdCl2(dppe), 1,4-dioxane, 110°C. Step 2: LiOH·H2O, THF, MeOH, Water, room temperature. Step 3: NH2OTHP, EDC·HCl, HOBT, TEA, dichloromethane, room temperature. Step 4: Conc. HCl, EtOH, room temperature.

Step 1. Synthesis of (R)-ethyl 3-((S)-3-(biphenyl-4-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [2.1a]. 1.1d (0.25 g, 0.6 mmol, 1.0 equiv), phenylboronic acid (0.084 g, 0.7 mmol, 1.2 equiv), potassium acetate (0.17 g, 1.7 mmol, 3.0 equiv) were dissolved in 1,4-dioxane (5 mL) and degassed for 10 minutes. PdCl2(dppe) (0.042 g, 0.06 mmol, 0.1 eq) was added and the resulting reaction mixture was stirred at 110°C for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (5-10% EtOAc in Hexane) to afford product 2.1a (0.23 g, 91.6% yield). LCMS (m/z): 449.4 [M+18]. 1H NMR (400 MHz, DMSO) δ 7.73 (d, J = 8.9 Hz, 2H), 7.70 - 7.61 (m, 4H), 7.47 (t, J = 7.7 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 4.82 (dd, J = 14.9, 7.1 Hz, 1H), 4.27 (q, J = 6.9 Hz, 3H), 3.92 - 3.83 (m, 1H), 3.18 (s, 3H), 2.71 (dt, J = 10.0, 5.0 Hz, 1H), 2.44 - 2.33 (m, 1H), 1.66 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).

Step 2. Synthesis of (R)-3-((S)-3-(biphenyl-4-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [2.1b]. 2.1a (0.23 g, 0.5 mmol, 1.0 equiv) was dissolved in THF (4 mL), MeOH (1 mL) and water (1 mL). LiOH·H2O (0.067 g, 1.6 mmol, 3.0 equiv) was added and the resulting mixture was stirred at rt for 3 hours. The reaction mixture was concentrated to dryness, the residue was diluted with water, acidified by 1N aqueous HCl to the pH 4 to 5, the precipitated solid was filtered and dried to afford product 2.1b (0.19 g, 88.8% yield). LCMS (m/z): 404.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 14.14 (s, 1H), 7.72 (d, J = 8.6 Hz, 2H), 7.65 (dd, J = 17.4, 8.1 Hz, 3H), 7.46 (t, J = 7.4 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 4.82 (d, J = 7.5 Hz, 1H), 4.28 (t, J = 8.7 Hz, 1H), 3.87 (t, J = 8.2 Hz, 1H), 3.16 (s, 3H), 2.67 (d, J = 14.3 Hz, 1H), 2.34 (ddd, J = 14.3, 8.8 Hz, 1H), 1.64 (d, J = 10.2 Hz, 3H).

Step 3. Synthesis of (2R)-3-((S)-3-(biphenyl-4-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methyl sulfonfonyl)-N-(tetrahydro-2H-pyran-2-yl)propanamide [2.1c]. 2.1b (0.19 g, 0.5 mmol, 1.0 equiv) was dissolved in dichloromethane (10 mL), Et3N (0.24 g, 2.4 mmol, 5.0 equiv) was added dropwise and stirred for 10 minutes. EDC·HCl (0.14 g, 0.7 mmol, 1.5 equiv), HOBT (0.12 g, 0.8 mmol, 1.8 equiv), 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.11 g, 0.9 mmol, 2.0 equiv) were added and the reaction mixture was stirred at rt for 24 hours. The reaction mixture was concentrated to afford a residue. The residue was purified by silica gel chromatography (0.5-2 % MeOH in dichloromethane) to afford product 2.1c which was used as such for next step (0.165 g, 69.6% yield). LCMS (m/z): 520.2 [M+23]. 1H NMR (400 MHz, DMSO) δ 7.78 - 7.59 (m, 6H), 7.47 (t, J = 7.7 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 4.99 (d, J = 9.5 Hz, 1H), 4.69 (s, 1H), 4.24 (t, J = 8.4 Hz, 1H), 4.05 (d, J = 6.9 Hz, 1H).
1H), 3.52 (s, 1H), 3.48 - 3.41 (m, 2H), 3.10 (d, J = 9.3 Hz, 3H), 2.82 (d, J = 16.6 Hz, 1H), 2.25 (dd, J = 14.7, 9.1 Hz, 1H), 1.83 (d, J = 9.1 Hz, 5H), 1.52 (dd, J = 28.4, 6.9 Hz, 6H).

**Step 4. Synthesis of (R)-3-((S)-3-(biphenyl-4-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [2.1].** 2.1c (0.165 g, 0.3 mmol, 1.0 equiv) was dissolved in ethanol (5 ml). 35.5% aq. HCl (1 ml) was added and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure to dryness to afford a residue. The residue was co-distilled with diethyl ether and purified by preparative HPLC purification to afford product 2.1 (0.07 g, 50.7% yield). LCMS (m/z): 419.4 [M+H].

**II-2. Synthesis of compound 2.2**

![Diagram of compound synthesis](image)

**Reagents:** Step 1: K$_2$CO$_3$, PdCl$_2$(dppf), N, N-dimethylformamide, 80°C. Step 2: LiOH.H$_2$O, THF, MeOH, Water, room temperature. Step 3: NH$_2$OTHP, EDC.HCl, HOBt, TEA, dichloromethane, room temperature. Step 4: 35.5% aq. HCl, EtOH, room temperature.

**Step 1. Synthesis of ethyl 3-((S)-3-(4-(3-fluoropyridin-4-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [2.2a].** 1.1d (0.2 g, 0.46 mmol, 1.0 eq) and K$_2$CC>3 (0.19 g, 1.4 mmol, 3.0 equiv) were dissolved in N, N-dimethylformamide (5 ml). 3-fluoro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) pyridine (0.17 g, 0.78 mmol, 1.7 equiv) was added and the reaction mixture was degassed for 10 minutes. PdCl$_2$(dppf)$_2$ (0.023 g, 0.032 mmol, 0.07 equiv) was added and the reaction mixture was stirred at 80°C under microwave irradiation for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water and brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column
chromatography (80-90% EtOAc in Hexane) to afford product 2.2a which was used as such for next step (0.15 g, 72% yield). LCMS (m/z): 451.3 [M+H].

Step 2. Synthesis of 3-((S)-3-(4-(3-fluoropyridin-4-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [2.2b]. 2.2a (0.15 g, 0.33 mmol, 1.0 equiv) was dissolved in THF (8 mL), methanol (1 mL). LiOH.H$_2$O (0.04 g, 0.99 mmol, 3.0 equiv) in water (1 mL) was added. The resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness and the residue was diluted in water, acidified by 1N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 2.2b (0.1 g, 71% yield). LCMS (m/z): 423.3 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 14.45 - 13.91 (m, 1H), 8.79 - 8.25 (m, 2H), 8.08 - 7.44 (m, 4H), 6.94 - 6.51 (m, 1H), 4.83 (s, 1H), 4.29 (t, $J$ = 8.7 Hz, 1H), 4.01 - 3.80 (m, 1H), 3.14 (dd, $J$ = 19.6, 11.8 Hz, 3H), 2.67 (d, $J$ = 14.8 Hz, 1H), 2.37 (d, $J$ = 8.7 Hz, 1H), 1.75 - 1.34 (m, 3H).

Step 3. Synthesis of 3-((S)-3-(4-(3-fluoropyridin-4-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [2.2c]

2.2b (0.1 g, 0.23 mmol, 1.0 equiv) was dissolved in THF (10 mL). Et$_3$N (0.11 g, 1.18 mmol, 5.0 equiv), HOBT (0.057 g, 0.42 mmol, 1.8 equiv) and EDC.HCl (0.067 g, 0.35 mmol, 1.5 equiv) were added. 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.055 g, 0.47 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 2.2c which was used as such for next step (0.1 g, 81% yield). LCMS (m/z): 522.4 [M+H].

Step 4. Synthesis of (R)-3-((S)-3-(4-(3-fluoropyridin-4-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [2.2]. 2.2c (0.1 g, 0.191 mmol, 1.0 equiv) was dissolved in ethanol (5 mL). 35.5% aq. HCl (0.5 mL) was added and reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude product. The crude product was purified by preparative HPLC to afford 2.2 as desired diastereomer (0.01 g, 12% yield). LCMS (m/z): 438.5 [M+H]. $^1$H NMR (400 MHz, CD$_3$CN) $\delta$ 9.75 - 9.46 (m, 1H), 8.56 (s, 1H), 8.48 (d, $J$ = 4.8 Hz, 1H), 7.71 (d, $J$ = 9.1 Hz, 4H), 7.62 - 7.51 (m, 1H), 4.73 (d, $J$ = 5.9 Hz, 1H), 4.25 (t, $J$ = 8.7 Hz, 1H), 3.89 - 3.81 (m, 1H), 3.04 (s, 3H), 2.79 (d, $J$ = 14.1 Hz, 1H), 2.36 (dd, $J$ = 13.6, 8.1 Hz, 1H), 1.71 (s, 3H).

†3. Synthesis of compound 2.3

Step 1. Synthesis of benzyl naphthalen-2-ylcarbamate [2.3a]
Naphthalen-2-amine (2.5 g, 17.4 mmol, 1.0 equiv) was dissolved in acetone: water (2:1, 30 ml). NaHCO₃ (3.07 g, 36.6 mmol, 2.1 equiv) was added and the reaction mixture was cooled to 0 °C. CBZ-Cl (3.12 g, 18.3 mmol, 1.05 equiv) was added and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (0-40 % EtOAc in Hexane) to afford product 2.3a (3.7 g, 76.4 % yield). LCMS (m/z): 278.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 10.02 (s, 1H), 8.09 (s, 1H), 7.88 - 7.74 (m, 3H), 7.51 - 7.30 (m, 8H), 5.20 (s, 2H).

Step 2. Synthesis of (R)-5-(hydroxymethyl)-3-(naphthalen-2-yl)oxazolidin-2-one [2.3b]
2.3a (1 g, 3.6 mmol, 1.0 equiv) was dissolved in THF (8 ml) and cooled to -78 °C. n-BuLi (1.5M in hexane) (0.46 g, 7.22 mmol, 2.0 equiv) was added and the reaction mixture was stirred at -78 °C for 1 hour. (R)-oxiran-2-ylmethyl butyrate (0.62 g, 4.3 mmol, 1.2 equiv) was added and the reaction mixture was allowed to attain room temperature for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0-60 % EtOAc in Hexane) to afford product 2.3b (0.4 g, 40.7 % yield). LCMS (m/z): 274.9 [M+H]. ¹H NMR (400 MHz, DMSO) δ 8.04 (dd, J = 9.0, 2.3 Hz, 1H), 7.95 (d, J = 9.1 Hz, 1H), 7.87 (dd, J = 10.7, 5.5 Hz, 3H), 7.55 - 7.41 (m, 2H), 5.26 (t, J = 5.7 Hz, 1H), 4.77 (dt, J = 9.7, 3.8 Hz, 1H), 4.28 - 4.17 (m, 1H), 3.98 (dd, J = 8.8, 6.3 Hz, 1H), 3.72 (ddd, J = 12.3, 5.5, 3.5 Hz, 1H), 3.67 - 3.54 (m, 1H).

Step 3. Synthesis of (R)-5-(iodomethyl)-3-(naphthalen-2-yl)oxazolidin-2-one [2.3c].
Triphenylphosphine (0.56 g, 2.13 mmol, 1.3 equiv) and imidazole (0.156 g, 2.3 mmol, 1.4 equiv) were dissolved in dichloromethane (10 ml) and the reaction mixture was stirred at room temperature for 10 minutes. Iodine (0.54 g, 2.13 mmol, 1.3 equiv) and 2.3b (0.4 g, 1.64 mmol, 1.0 equiv) were added and the reaction mixture was stirred at rt for 3 hours. The mixture was concentrated and the residue was purified by silica gel chromatography (0-40% EtOAc in Hexane) to afford product 2.3c (0.4 g, 68.6 % yield). LCMS (m/z): 354.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 8.06 - 7.84 (m, 5H), 7.58 - 7.41 (m, 2H), 4.81 (td, J = 10.8, 5.4 Hz, 1H), 4.41 - 4.25 (m, 1H), 3.82 (dd, J = 9.3, 6.0 Hz, 1H), 3.64 (qd, J = 10.7, 5.0 Hz, 2H).

Step 4. Synthesis of ethyl 2-methyl-2-(methylsulfonyl)-3-((S)-3-(naphthalen-2-yl)-2-oxooxazolidin-5-yl)propanoate [2.3d].
Ethyl 2-(methylsulfonyl)propanoate (0.61 g, 3.4 mmol, 3.0 equiv) was dissolved in N,N-dimethylformamide (6 mL) and cooled the reaction mixture to 0-5 °C. NaH(60 %) (0.07 g, 2.8 mmol, 2.5 equiv) was added and the reaction mixture was stirred at room temperature for 1 hour. 2.3c (0.4 g, 1.1 mmol, 1.0 equiv) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was
quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (0-60 % EtOAc in Hexane) to afford 2.3d (0.18 g, 39.2 % yield). LCMS (m/z): 406.3 [M+H]. \textsuperscript{1}H NMR (400 MHz, DMSO) δ 7.96 (s, 2H), 7.88 (dd, J = 15.2, 10.5 Hz, 3H), 7.49 (dt, J = 14.9, 6.8 Hz, 2H), 4.85 (d, J = 7.8 Hz, 1H), 4.40 - 4.18 (m, 3H), 4.08 - 3.92 (m, 1H), 3.18 (s, 3H), 2.77 - 2.67 (m, 1H), 2.41 (dd, J = 14.9, 8.9 Hz, 1H), 1.68 (s, 3H), 1.25 (dd, J = 7.9, 3.2 Hz, 3H).

Step 5. Synthesis of 2-methyl-2-(methylsulfonfonyl)-3-((S)-3-(naphthalen-2-yl)-2-oxo oxazolidin-5-yl)propanoic acid [2.3e]. 2.3d (0.18 mg, 0.4 mmol, 1.0 equiv) was dissolved in MeOH (2 mL) and water (1 mL). LiOH.H\textsubscript{2}O (0.037 g, 0.8 mmol, 2.0 equiv) was added and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated to dryness, the residue was diluted with water, acidified by 1N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford compound 2.3e (0.15 g, 90.1 % yield). The crude product was used in the next step with no further purification. LCMS (m/z): 378.3 [M+H]. \textsuperscript{1}H NMR (400 MHz, DMSO) δ 14.22 - 13.76 (m, 1H), 7.96 (s, 2H), 7.88 (dd, J = 16.6, 9.4 Hz, 2H), 7.68 - 7.57 (m, 1H), 7.56 - 7.49 (m, 1H), 7.49 - 7.40 (m, 1H), 4.86 (s, 1H), 4.36 (t, J = 8.8 Hz, 1H), 4.03 (dd, J = 14.3, 7.1 Hz, 1H), 3.16 (d, J = 9.7 Hz, 3H), 2.69 (d, J = 13.4 Hz, 1H), 2.37 (dd, J = 14.7, 8.9 Hz, 1H), 1.65 (d, J = 6.3 Hz, 3H).

Step 6. Synthesis of 2-methyl-2-(methylsulfonfonyl)-3-((S)-3-(naphthalen-2-yl)-2-oxo oxazolidin-5-yl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [2.3f]. 2.3e (0.15 g, 0.4 mmol, 1.0 equiv), Et\textsubscript{3}N (0.20 g, 2.0 mmol, 5.0 equiv), EDC.HCl (0.11 g, 0.6 mmol, 1.5 equiv), HOBT (0.09 g, 0.7 mmol, 1.8 equiv) and 0-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.09 g, 0.8 mmol, 2.0 equiv) were dissolved in dichloromethane. The reaction mixture was stirred at rt for 24 hours. The reaction mixture was concentrated to afford a residue. The residue was purified by silica gel column chromatography (0-5 % MeOH in dichloromethane) to afford product 2.3f which was used as such for next step (0.15 g, 79.7 % yield). LCMS (m/z): 494.4 [M+H]. \textsuperscript{1}H NMR (400 MHz, DMSO) δ 8.17 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.97 (d, J = 2.0 Hz, 1H), 7.92 - 7.82 (m, 2H), 7.78 - 7.72 (m, 1H), 7.60 - 7.50 (m, 2H), 4.73 (s, 1H), 4.33 (d, J = 8.6 Hz, 1H), 3.92 (d, J = 8.8 Hz, 1H), 3.77 - 3.73 (m, 3H), 3.45 - 3.43 (m, 2H), 3.16 - 3.07 (m, 3H), 2.83 (m, 1H), 2.29 (m, 1H), 1.67 - 1.60 (m, 9H).

Step 7. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonfonyl)-3-((S)-3-(naphthalen-2-yl)-2-oxooxazolidin-5-yl)propanamide [2.3]. 2.3f (0.15 g, 0.3 mmol, 1.0 equiv) was dissolved in ethanol (1 mL). 35.5% aq. HCl (0.5 mL) was added to the solution and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to afford a crude product. The crude product was purified by preparative HPLC purification to afford 2.3 as desired diastereomer (0.016 g, 13 % yield). LCMS (m/z):
400 [M+18]. ¹H NMR (400 MHz, DMSO) δ 9.36 (s, 1H), 8.20 - 7.78 (m, 5H), 7.49 (d, J = 27.3 Hz, 2H), 4.71 (m, 1H), 4.32 (m, 1H), 3.93 (m, 1H), 3.10 (s, 3H), 2.83 (d, J = 14.1 Hz, 1H), 2.34 - 2.20 (m, 1H), 1.63 (s, 3H), 1.24 (s, 3H).

II-4. Synthesis of compound 2.4

Reagents: Step 1: Cul, Cs₂C₂O₃, trans-cyclohexane-1,2-diamine, 1,4-dioxane, 125 °C. Step 2: LiOH.H₂O, THF, MeOH, Water, room temperature. Step 3: NH₂THP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 4: HCl (in IPA), dichloromethane, MeOH, room temperature.

Step 1. Synthesis of ethyl 3-((S)-3-(benzo[d]thiazol-6-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [2.4a]. 6.1e mix diastereomers (0.3 g, 1.07 mmol, 1.0 equiv), 6-bromobenzoc[d]thiazole (0.25 g, 1.1 mmol, 1.1 equiv) were dissolved in 1,4-dioxane (8 mL). Cul (0.25 g, 1.3 mmol, 1.2 equiv), trans-cyclohexane-1,2-diamine (0.17 g, 1.5 mmol, 1.4 equiv), Cs₂C₂O₃ (0.52 g, 1.6 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 125 °C for 5 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (20-30 % EtOAc in Hexane) to afford product 2.4a (0.32 g, 48.5 % yield). LCMS (m/z): 413.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 9.33 (s, 1H), 8.28 (d, J = 2.1 Hz, 1H), 8.11 (dd, J = 8.9, 3.0 Hz, 1H), 7.93 - 7.78 (m, 1H), 4.84 (d, J = 7.5 Hz, 1H), 4.38 - 4.17 (m, 3H), 3.91 (dd, J = 17.1, 8.3 Hz, 1H), 3.18 (s, 3H), 2.75 - 2.64 (m, 1H), 2.40 (dd, J = 14.8, 8.9 Hz, 1H), 1.70 - 1.57 (m, 3H), 1.30 - 1.25 (m, 3H).

Step 2. Synthesis of 3-((S)-3-(benzo[d]thiazol-6-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [2.4b]. 2.4a (0.35 g, 0.84 mmol, 1.0 equiv) was dissolved in THF (5 mL), MeOH (2 mL). LiOH.H₂O (0.071 g, 1.69 mmol, 2.0 equiv) in water (2mL) was added and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated to dryness; the residue was diluted with water, acidified by 1N HCl aqueous solution to pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 2.4b (0.19 g, 60 % yield).
LCMS (m/z): 385.3 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 14.27 - 14.02 (m, 1H), 9.33 (s, 1H), 8.28 (d, $J = 2.2$ Hz, 1H), 8.11 (d, $J = 8.9$ Hz, 1H), 7.88 - 7.77 (m, 1H), 4.85 (d, $J = 5.5$ Hz, 1H), 4.32 (t, $J = 8.6$ Hz, 1H), 3.98 - 3.85 (m, 1H), 3.17 (s, 3H), 2.66 (d, $J = 14.6$ Hz, 1H), 2.36 (dd, $J = 14.8$, 8.9 Hz, 1H), 1.71 - 1.54 (m, 3H).

**Step 3. Synthesis of 3-((S)-3-(benzo[d]thiazol-6-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methyl sulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [2.4c].** $2.4b$ (0.19 g, 0.49 mmol, 1.0 equiv), N-methyl morpholine (0.25 g, 2.4 mmol, 5.0 equiv), EDC.HCl (0.14 g, 0.74 mmol, 1.5 equiv), HOBT (0.080 g, 0.6 mmol, 1.2 equiv) and 0-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.11 g, 0.98 mmol, 2.0 equiv) were added in THF (6 ml). The reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (3-5 % MeOH in dichloromethane) to afford product $2.4c$ which was used for next step (0.16 g, 67 % yield). LCMS (m/z): 484.4 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 9.29 (s, 1H), 8.24 (d, $J = 9.8$ Hz, 1H), 8.09 (d, $J = 9.1$ Hz, 1H), 7.80 (d, $J = 8.0$ Hz, 1H), 4.70 (s, 1H), 4.26 (t, $J = 8.7$ Hz, 1H), 4.02 (s, 1H), 3.88 (t, $J = 8.1$ Hz, 1H), 3.49 (s, 1H), 3.10 - 3.01 (m, 3H), 2.79 (d, $J = 14.3$ Hz, 1H), 2.32 - 2.21 (m, 1H), 1.72 - 1.47 (m, 9H).

**Step 4. Synthesis of (R)-3-((S)-3-(benzo[d]thiazol-6-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [2.4].** $2.4c$ (0.16 g, 0.33 mmol, 1.0 equiv) was dissolved in methanol (2 ml) and dichloromethane (4 ml). HCl (in IPA) (1 ml) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to afford a crude product. The crude product was purified by preparative HPLC purification to afford $2.4$ as desired diastereomer (0.042 g, 32 % yield). LCMS (m/z): 399.3 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 9.29 (s, 1H), 8.24 (d, $J = 2.2$ Hz, 1H), 8.09 (d, $J = 9.0$ Hz, 1H), 7.79 (dd, $J = 9.0$, 2.2 Hz, 1H), 4.67 (d, $J = 7.6$ Hz, 1H), 4.25 (t, $J = 8.7$ Hz, 1H), 3.93 - 3.84 (m, 1H), 3.07 (s, 3H), 2.79 (d, $J = 14.6$ Hz, 1H), 2.23 (dd, $J = 14.5$, 9.0 Hz, 1H), 1.63 (d, $J = 19.8$ Hz, 3H).

**II-5. Synthesis of compound 2.5**
Reagents: Step 1: CBZ-CI, NaHC0 3, Acetone: Water, 0 °C to room temperature. Step 2: n-BuLi (2.5M in hexane), THF, -70°C to room temperature. Step 3: Iodine, triphenylphosphine, imidazole, dichloromethane, room temperature. Step 4: NaH (60%), N,N-dimethylformamide, 0 °C to room temperature. Step 5: LiOH.H2O, THF, MeOH, Water, room temperature. Step 6: NH2OTHP, EDC.HCI, HOBt, N-methyl morpholine, THF, room temperature. Step 7: 35.5% aq. HCl, EtOH, room temperature.

Step 1. Synthesis of benzyl (1-methyl-1H-indazol-5-yl)carbamate [2.5a]

1-methyl-1H-indazol-5-amine (2.0 g, 13.6 mmol, 1.0 equiv) was dissolved in acetone: water (2:1, 15 ml), NaHC0 3 (2.39 g, 28.5 mmol, 2.1 equiv) was added and the reaction mixture was stirred at room temperature for 10 minutes. The reaction mixture was cooled to 0 °C, CBZ-CI (3.01 g, 17.7 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude product was triturated with n-pentane, decanted the solvent and dried to afford product 2.5a (3.18 g, 83.2 % yield). LCMS (m/z): 282.2 [M-H]. 1H NMR (400 MHz, DMSO) δ 9.78 (s, 1H), 7.97 (d, J = 0.6 Hz, 1H), 7.91 (s, 1H), 7.56 (d, J = 9.0 Hz, 1H), 7.52 - 7.31 (m, 6H), 5.17 (s, 2H), 4.01 (s, 3H).

Step 2. Synthesis of (R)-5-(hydroxymethyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one [2.5b]. 2.5a (3 g, 10.66 mmol, 1.0 equiv) was dissolved in THF (16 ml) and cooled to -70 °C. n-BuLi (2.5M in hexane) (1.36 g, 21.32 mmol, 2.0 equiv) was gradually added and the reaction mixture was stirred at -70 °C for 1 hour. (R)-oxiran-2-ylmethyl butyrate (1.46 g, 12.79 mmol, 1.2 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel
column chromatography (0-2 % MeOH in dichloromethane) to afford product 2.5b (2.1 g, 79.6 % yield). LCMS (m/z): 248.3 [M+H]. \( ^1H \) NMR (400 MHz, DMSO) \( \delta \) 8.05 (dd, \( J = 8.2, 0.8 \) Hz, 1H), 7.83 - 7.77 (m, 2H), 7.71 - 7.65 (m, 1H), 5.21 (d, \( J = 29.6 \) Hz, 1H), 4.76 - 4.67 (m, 1H), 4.15 (t, \( J = 8.9 \) Hz, 1H), 4.05 (d, \( J = 3.2 \) Hz, 3H), 3.90 (dt, \( J = 12.0, 6.0 \) Hz, 1H), 3.70 (dd, \( J = 12.2, 3.1 \) Hz, 1H), 3.59 (dd, \( J = 12.2, 3.9 \) Hz, 1H).

**Step 3. Synthesis of (R)-5-(iodomethyl)-3-(1-methyl-1H-indazol-5-yl)oxazolidin-2-one [2.5c].** Triphenylphosphine (2.75 g, 10.5 mmol, 1.3 equiv) was dissolved in dichloromethane (10 mL). imidazole (0.71 g, 10.5 mmol, 1.3 equiv) and iodine (2.66 g, 10.5 mmol, 1.3 equiv) were added and the reaction mixture was stirred at room temperature for 15 minutes. A solution of 2.5b (2.0 g, 8.08 mmol, 1.0 equiv) in dichloromethane (5 mL) was drop wise added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (0-5 % MeOH in dichloromethane) to afford product 2.5c (2.1 g, 72.7 % yield). LCMS (m/z): 358.2 [M+H]. \( ^1H \) NMR (400 MHz, DMSO) \( \delta \) 8.05 (dd, \( J = 8.2, 0.8 \) Hz, 1H), 7.83 - 7.77 (m, 2H), 7.71 - 7.65 (m, 1H), 4.75 (td, \( J = 10.7, 5.2 \) Hz, 1H), 4.27 (t, \( J = 9.0 \) Hz, 1H), 4.11 - 4.01 (m, 3H), 3.73 (dd, \( J = 9.1, 6.0 \) Hz, 1H), 3.62 (qd, \( J = 10.7, 4.9 \) Hz, 2H).

**Step 4. Synthesis of ethyl-2-methyl-3-((S)-3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanoate [2.5d].** Ethyl 2-(methylsulfonyl) propanoate (4.03 g, 22.4 mmol, 4.0 equiv) was dissolved in N,N-dimethylformamide (8 mL) and cooled to 0-5 °C. NaH (60%) (0.45 g, 11.20 mmol, 2.0 equiv) was added in portions and the reaction mixture was stirred at rt for 1.5 hours. A solution of 2.5c (2 g, 5.6 mmol, 1.0 equiv) in DMF (4 mL) was added drop wise at 0-5 °C and the reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (0-20 % EtOAc in Hexane) to afford product 2.5d which was used for next step (1.8 g, 78.5 % yield). LCMS (m/z): 410.4 [M+H].

**Step 5. Synthesis of 2-methyl-3-((S)-3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanoic acid [2.5e].** 2.5d (1.8 g, 4.39 mmol, 1.0 equiv) was dissolved in THF (5 mL), MeOH (2.5 mL). LiOH.H\(_2\)O (0.55 g, 13.2 mmol, 3.0 equiv) in water (2.5 mL) was added and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water, acidified by 1N HCl aqueous solution to the pH 3 to 4 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford 2.5e (0.95 g, 56.7 % yield). The crude product was used in the next step with no further purification. LCMS (m/z): 382.3 [M+H]. \( ^1H \) NMR (400 MHz,
DMSO) δ 14.07 (s, 1H), 8.08 (d, J = 24.4 Hz, 1H), 7.82 - 7.64 (m, 3H), 4.96 - 4.76 (m, 1H),
4.27 (dd, J = 10.5, 6.8 Hz, 1H), 4.07 (d, J = 20.5 Hz, 3H), 3.98 - 3.84 (m, 1H), 3.15 (d, J =
11.4 Hz, 3H), 2.66 (dd, J = 14.6, 2.6 Hz, 1H), 2.39 - 2.28 (m, 1H), 1.69 - 1.49 (m, 3H).

Step 6. Synthesis of 2-methyl-3-((S)-3-(1-methyl-1H-indazol-5-yl)-2-oxooxazolidin-5-yl)-
2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [2.5f]. 2.5e (0.8 g,
2.09 mmol, 1.0 equiv) was dissolved in THF (12 mL), N-methyl morpholine (1.06 g, 10.48
mmol, 5.0 equiv) was added and the reaction mixture was stirred at rt for 5 minutes.
EDC.HCl (0.6 g, 3.14 mmol, 1.5 equiv), HOBT (0.34 g, 2.52 mmol, 1.2 equiv), 0-(tetrahydro-
2H-pyran-2-yl)hydroxylamine (0.49 g, 4.19 mmol, 2.0 equiv) were added and the reaction
mixture was stirred at rt for 14 hours. The reaction mixture was diluted with water and
extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate
and concentrated to afford a crude residue. The residue was purified by silica gel column
chromatography (0-5 % MeOH in dichloromethane) to afford product 2.5f which was used for
next step immediately (0.41 g, 40.7 % yield). LCMS (m/z): 397.3 [M+18]. 1H NMR (400
MHz, DMSO) δ 11.57 - 11.47 (m, 1H), 8.05 (s, 1H), 7.79 - 7.65 (m, 3H), 5.06 - 4.94 (m,
1H), 4.69 (d, J = 7.6 Hz, 1H), 4.23 (t, J = 8.8 Hz, 1H), 3.86 (t, J = 7.5 Hz, 1H), 3.49 (dd, J =
24.5, 12.9 Hz, 2H), 3.09 (t, J = 7.6 Hz, 3H), 2.81 (m, 1H), 2.30 - 2.20 (m, 1H), 1.60 (m, 9H).

Step 7. Synthesis of (R)-N-hydroxy-2-methyl-3-((S)-3-(1-methyl-1H-indazol-5-yl)-2-
oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide [2.5]. 2.5f (0.41 g, 0.85 mmol, 1.0
equiv) was dissolved in ethanol (7 mL). 35.5% aq. HCl (0.82 mL) was added and reaction
mixture was stirred at rt for 1 hour. The reaction mixture was diluted with water, neutralized
by saturated sodium bicarbonate solution and extracted with dichloromethane. The organic
layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude
product. The crude product was purified by preparative HPLC purification to afford 2.5 as
desired diastereomer (0.065 g, 19.2 % yield). LCMS (m/z): 397.4 [M+H]. 1H NMR (400
MHz, DMSO) δ 11.09 (s, 1H), 9.31 (s, 1H), 8.05 (s, 1H), 7.72 (dd, J = 17.6, 11.6, 5.2 Hz,
3H), 4.66 (d, J = 6.1 Hz, 1H), 4.23 (t, J = 8.6 Hz, 1H), 4.07 (d, J = 20.2 Hz, 3H), 3.91 - 3.82
(m, 1H), 3.10 (s, 3H), 2.79 (d, J = 14.6 Hz, 1H), 2.24 (dd, J = 14.4, 8.8 Hz, 1H), 1.62 (s, 3H).

#6. Synthesis of compound 2.6
**Reagents:**

Step 1: Cul, Cs₂CO₃, trans-cyclohexane-1,2-diamine, 1,4-dioxane, 125 °C. Step 2: LiOH.H₂O, THF, MeOH, Water, room temperature. Step 3: NH₂OTHP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 4: 35.5% aq. HCl, EtOH, room temperature.

**Step 1. Synthesis of (R)-ethyl-3-((S)-3-(benzo[b]thiophen-6-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [2.6a].** 6.1e (0.25 g, 0.9 mmol, 1.0 equiv), 6-bromobenzo[0]thiophene (0.23 g, 1.0 mmol, 1.1 equiv) were dissolved in 1,4-dioxane (5 ml). Cul (0.20 g, 1.1 mmol, 1.2 equiv), trans-cyclohexane-1,2-diamine (0.14 g, 1.2 mmol, 1.4 equiv) and Cs₂CO₃ (0.44 g, 1.3 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 125 °C for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (20-30 % EtOAc in Hexane) to afford product 2.6a which was used for next step (0.35 g, 79 % yield). LCMS (m/z): 412.3 [M+H].

**Step 2. Synthesis of (R)-3-((S)-3-(benzo[b]thiophen-6-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [2.6b].** 2.6a (0.35 g, 0.8 mmol, 1.0 equiv) was dissolved in THF (4 ml), MeOH (1 ml). LiOH.H₂O (0.11 g, 2.5 mmol, 3.0 equiv) in water (1 ml) was added and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water, acidified by 1N HCl aqueous solution to the pH 3 to 4 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the product 2.6b which was used for next step (0.29 g, 89.2 % yield). LCMS (m/z): 384.4 [M+H].

**Step 3. Synthesis of (R)-3-((S)-3-(benzo[b]thiophen-6-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [2.6c] 2.6b (0.23 g, 0.6 mmol, 1.0 equiv) was dissolved in THF (5 ml). N-methyl morpholine (0.30 g, 3.0 mmol, 5.0 equiv), EDC.HCl (0.17 g, 0.9 mmol, 1.5 equiv), HOBT (0.15 g, 1.1 mmol, 1.8 equiv), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.14 g, 1.2 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated and purified by silica gel column.
chromatography (1-2 % MeOH in dichloromethane) to afford product 2.6c which was used for next step (0.2 g, 54.8 % yield). LCMS (m/z): 481.6 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 8.14 - 8.08 (m, 1H), 7.89 (d, \(J = 8.8\) Hz, 1H), 7.72 - 7.66 (m, 2H), 7.43 (d, \(J = 5.4\) Hz, 1H), 4.72 (d, \(J = 7.8\) Hz, 1H), 4.26 (t, \(J = 8.7\) Hz, 1H), 3.93 - 3.83 (m, 2H), 3.76 (d, \(J = 15.4\) Hz, 1H), 3.50 (dd, \(J = 23.6\), 12.0 Hz, 3H), 3.08 (dd, \(J = 9.5\), 7.5 Hz, 3H), 2.81 (d, \(J = 16.5\) Hz, 1H), 2.32 - 2.23 (m, 1H), 1.64 (s, 3H), 1.52 (m, 6H).

Step 4. Synthesis of (R)-3-((S)-3-(benzo[b]thiophen-6-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [2.6]. 2.6c (0.2 g, 0.4 mmol, 1.0 equiv) was dissolved in ethanol (5 mL). 35.5% aq. HCl (0.2 mL) was added to the solution and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was quenched with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was purified by preparative HPLC purification to afford 2.6 as desired diastereomer (0.083 g, 50.3 % yield). LCMS (m/z): 399.4 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.11 (s, 1H), 9.33 (s, 1H), 8.11 (s, 1H), 7.90 (d, \(J = 8.8\) Hz, 1H), 7.76 - 7.63 (m, 2H), 7.43 (d, \(J = 5.4\) Hz, 1H), 4.80 - 4.58 (m, 1H), 4.26 (t, \(J = 8.7\) Hz, 1H), 3.94 - 3.81 (m, 1H), 3.18 - 3.04 (m, 3H), 2.80 (dd, \(J = 14.4\), 2.7 Hz, 1H), 2.24 (dd, \(J = 14.4\), 8.8 Hz, 1H), 1.62 (s, 3H).

II-7. Synthesis of 2.7 and 2.8 Compounds 2.7 and 2.8 were synthesized by the process of example 2.1. Compound 2.7: LCMS (m/z): 477.4 [M+H]. Compound 2.8: LCMS (m/z): 477.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO-d6) \(\delta\) 11.08 (s, 1H), 9.30 (br s, 1H), 7.69 (d, \(J = 8.4\) Hz, 2H), 7.60 (d, \(J = 8.4\) Hz, 2H), 7.57 (d, \(J = 7.7\) Hz, 2H), 7.27 (d, \(J = 7.8\) Hz, 2H), 4.65 (q, \(J = 9.1\), 8.6 Hz, 1H), 4.22 (t, \(J = 8.7\) Hz, 1H), 3.84 (q, \(J = 9.2\), 7.9 Hz, 2H), 3.09 (s, 3H), 2.80 (d, \(J = 15.0\) Hz, 1H), 2.70 (dt, \(J = 15.1\), 7.9 Hz, 1H), 2.60 (dd, \(J = 13.3\), 6.0 Hz, 1H), 2.22 (dd, \(J = 14.7\), 9.1 Hz, 1H), 1.61 (s, 3H), 1.06 (d, \(J = 5.9\) Hz, 3H).

II.1.1. Synthesis of compound 3.1.1

\[ \text{Br} \quad 1.1d \quad + \quad \text{ac} \quad \rightarrow \quad \text{Step 1} \quad \text{3.1.1a} \quad \text{Step 2} \quad \text{3.1.1b} \]

\[ \text{Step 3} \quad \text{3.1.1c} \quad \text{Step 4} \quad \text{3.1.1} \]
**Reagents:** Step 1: DBU, dppb, PdCl₂ (PPh₃)₂, DMSO, 100°C. Step 2: LiOH.H₂O, THF, MeOH, Water, room temperature. Step 3: N-methyl morpholine, NH₂OTH, EDC.HCl, HOBT, THF, room temperature. Step 4: 35.5% aq. HCl HCl, EtOH, room temperature.

**Step 1. Synthesis of ethyl 2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(prop-1-ynyl)phenyl) oxazolidin-5-yl)propanoate [3.1.1a].**  
1.1d (4.0 g, 9.22 mmol, 1.0 equiv) (mixture of diastereomer), but-2-ynoic acid (1.16 g, 13.83 mmol, 1.5 equiv), PdCl₂(PPh₃)₂ (0.072 g, 0.10 mmol, 0.01 equiv), 1,4-bis (diphenylphosphino) butane (0.09 g, 0.20 mmol, 0.02 equiv) and DBU (2.80 g, 18.43 mmol, 2.0 equiv) were added in DMSO (40 mL) in sealed tube. The reaction mixture was stirred at 100°C for 5 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain crude residue. The residue was purified by silica gel column chromatography. 40-50 % EtOAc in Hexane was used as gradient to afford 3.1.1a (2.71 g, 74.8 % yield). LCMS (m/z): 394.4 [M+H], 1H NMR (400 MHz, DMSO) δ 7.51 (d, J = 8.8 Hz, 2H), 7.41 (dd, J = 8.7, 3.3 Hz, 2H), 4.79 (dd, J = 14.5, 7.8 Hz, 1H), 4.34 - 4.13 (m, 3H), 3.90 - 3.73 (m, 1H), 3.23 - 3.08 (m, 3H), 2.86 - 2.64 (m, 1H), 2.31 (ddd, J = 17.1, 14.5, 6.0 Hz, 1H), 2.01 (d, J = 15.4 Hz, 3H), 1.61 (d, J = 27.7 Hz, 3H), 1.25 (q, J = 6.9 Hz, 3H).

**Step 2. Synthesis of 2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(prop-1-ynyl)phenyl) oxazolidin-5-yl)propanoic acid [3.1.1b].**  
3.1.1a (2.71 g, 6.91 mmol, 1.0 equiv) was dissolved in THF (25 mL), MeOH (12 mL). LiOH.H₂O (0.85 g, 20.72 mmol, 3.0 equiv) solution in water (1 mL) was added to the reaction mixture. The resulting mixture was stirred at rt for 2 hours. The reaction mixture was concentrated to dryness and the residue was diluted with water, acidified by 1N HCl aqueous solution to pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.1.1b (2.30 g, 91.3 % yield). The crude material was used in the next step with no further purification. LCMS (m/z): 366.4 [M+H], 1H NMR (400 MHz, DMSO) δ 7.50 (d, J = 8.9 Hz, 2H), 7.43 - 7.37 (m, 2H), 4.84 - 4.73 (m, 1H), 4.20 (t, J = 8.7 Hz, 1H), 3.84 - 3.76 (m, 1H), 3.13 (s, 3H), 2.63 (d, J = 14.8 Hz, 1H), 2.30 (dd, J = 14.9, 8.9 Hz, 1H), 2.01 (s, 3H), 1.60 (s, 3H).

**Step 3. Synthesis of 2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(prop-1-ynyl)phenyl) oxazolidin-5-yl)-N-(tetrahydro-2H-pyran-2-yl)propanamide [3.1.1g].**  
3.1.1b (2.3 g, 6.30 mmol, 1.0 equiv) was dissolved in to THF (50 mL), N-methyl morpholine (3.18 g, 31.51 mmol, 5.0 equiv), EDC.HCl (1.12 g, 9.45 mmol, 1.5 equiv), HOBT (1.02 g, 7.56 mmol, 1.2 equiv) and 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (1.47 g, 12.61 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain crude residue. The residue was purified by silica gel column chromatography.
chromatography. 2-3 % MeOH in dichloromethane was used as gradient for elution to afford product 3.1.1c and carry for next step. (2.5 g, 85.5 % yield). LCMS (m/z): 482.6 [M+18]. 1H NMR (400 MHz, DMSO) δ 7.58 - 7.48 (m, 2H), 7.41 (d, J = 8.7 Hz, 2H), 4.67 (d, J = 8.3 Hz, 1H), 4.18 (t, J = 8.7 Hz, 1H), 4.13 - 3.96 (m, 1H), 3.84 - 3.71 (m, 2H), 3.51 (s, 1H), 3.46 - 3.37 (m, 1H), 3.15 - 2.96 (m, 3H), 2.78 (d, J = 13.3 Hz, 1H), 2.23 (dd, J = 14.5, 9.0 Hz, 1H), 2.10 - 1.95 (m, 3H), 1.64 - 1.51 (m, 6H).

**Step 4. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(prop-1-ynyl)phenyl)oxazolidin-5-yl)propanamide [3.1.1]**. 3.1.1c (2.5 g, 5.39 mmol, 1.0 equiv) was dissolved in ethanol (30 ml) and 35.5% aq. HCl (1 ml) was added. The reaction mixture was stirred at rt for 4 hours. The reaction was quenched with water, neutralized by saturated aqueous sodium bicarbonate solution, and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to afford crude product 3.1.1. The crude product was purified by preparative HPLC purification to afford 3.1.1 as desired diastereomer (0.70 g, 34.0 % yield). LCMS (m/z): 379.3 [M-H].

**III.1.2. Synthesis of compound 3.1.2**

<table>
<thead>
<tr>
<th>Step</th>
<th>Reagents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DBU, dppb, PdCl₂(PPh₃)₂, DMSO, 90°C</td>
</tr>
<tr>
<td>2</td>
<td>LiOH.H₂O, THF, MeOH, Water, room temperature</td>
</tr>
<tr>
<td>3</td>
<td>NH₂OTHP, EDC.HCl, HOBt, TEA, dichloromethane, room temperature</td>
</tr>
<tr>
<td>4</td>
<td>Conc.HCl, EtOH, room temperature</td>
</tr>
</tbody>
</table>

**Step 1. Synthesis of ethyl 3-((S)-3-(4-(cyclopropylethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.2a]**. 1.1d (0.50 g, 1.15 mmol, 1.0 equiv), 3-cyclopropylpropioic acid (0.13 g, 1.15 mmol, 1.0 equiv), PdCl₂(PPh₃)₂ (0.008 g, 0.012 mmol, 0.01 equiv), 1,4-bis(diphenylphosphino)butane (0.01 g, 0.026 mmol, 0.02 equiv) and DBU (0.35 g, 2.30 mmol, 2.0 equiv) were added in DMSO (5 mL) in sealed tube. The
reaction mixture was stirred at 90°C for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain crude residue. The residue was purified by silica gel column chromatography (20-30 % EtOAc in Hexane) to afford product **3.1.2a** (0.33 g, 68.3 % yield). LCMS (m/z): 437.3 [M+18]. $^1$H NMR (400 MHz, DMSO) δ 7.50 (d, J = 8.9 Hz, 2H), 7.44 - 7.32 (m, 2H), 4.97 - 4.71 (m, 1H), 3.80 (dd, J = 15.3, 7.6 Hz, 3H), 3.15 (d, J = 6.5 Hz, 3H), 2.74 - 2.63 (m, 1H), 2.35 (dd, J = 14.8, 8.9 Hz, 1H), 1.64 (s, 3H), 1.26 (dd, J = 9.0, 5.1 Hz, 3H), 0.96 - 0.81 (m, 2H), 0.78 - 0.66 (m, 2H).

**Step 2. Synthesis of 3-((S)-3-(4-(cyclopropylethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [3.1.2b]**. **3.1.2a** (0.33 g, 0.79 mmol, 1.0 equiv) dissolved in THF (6 mL), MeOH (2 mL). LiOH.H$_2$O (0.099 g, 2.36 mmol, 3.0 equiv) in water (1 mL) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated to dryness, diluted with water, acidified by 1.0N HCl aqueous solution to pH 4 to 5 and extracted with EtOAc. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated to obtain product **3.1.2b** (0.25 g, 81.4 % yield). LCMS (m/z): 392.2 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 14.18 - 14.04 (m, 1H), 7.56 - 7.47 (m, 1H), 7.43 - 7.35 (m, 1H), 4.79 (d, J = 7.5 Hz, 1H), 4.21 (t, J = 8.7 Hz, 1H), 3.84 - 3.77 (m, 1H), 3.19 - 3.13 (m, 2H), 2.70 - 2.62 (m, 1H), 2.36 - 2.29 (m, 1H), 1.62 (d, J = 10.1 Hz, 2H), 1.18 (t, J = 7.1 Hz, 1H), 0.88 (dt, J = 6.3, 4.0 Hz, 1H), 0.72 (dt, J = 6.7, 3.9 Hz, 1H).


**3.1.2b** (0.13 g, 0.34 mmol, 1.0 equiv) was dissolved in dichloromethane (7 mL). Et$_3$N (0.32 g, 3.20 mmol, 5.0 equiv) was added to obtain clear solution. EDC.HCl (0.19 g, 0.96 mmol, 1.5 equiv), HOBT (0.16 g, 1.15 mmol, 1.8 equiv) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.15 g, 1.28 mmol, 2.0 equiv) were added to the reaction mixture and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated to afford the residue. The residue was purified by silica gel column chromatography (2-4 % MeOH in dichloromethane) to afford product **3.1.2c** which was used as such for next step (0.25 g, 79.6 % yield). LCMS (m/z): 489.3 [M-H]. $^1$H NMR (400 MHz, DMSO) δ 11.51 (s, 1H), 7.62 - 7.46 (m, 2H), 7.38 (d, J = 8.8 Hz, 2H), 4.67 (d, J = 8.0 Hz, 1H), 4.03 (dd, J = 14.2, 7.1 Hz, 1H), 3.84 - 3.66 (m, 2H), 3.54 - 3.42 (m, 2H), 3.07 (t, J = 8.4 Hz, 3H), 2.76 (t, J = 11.3 Hz, 1H), 2.28 - 2.19 (m, 1H), 1.81 (t, J = 13.5 Hz, 3H), 1.77 - 1.62 (m, 6H), 0.92 - 0.79 (m, 2H), 0.76 - 0.60 (m, 2H).

**Step 4. Synthesis of (R)-3-((S)-3-(4-(cyclopropylethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [3.1.2]**. **3.1.2c** (0.25 g, 0.51 mmol, 1.0 equiv) was dissolved in ethanol (5 mL). 35.5% aq. HCl (0.5 mL) was added to the
solution and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to dryness to afford the residue. The residue was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude product. The crude product was purified by preparative HPLC to afford 3.1.2 as the desired diastereomer (0.020 g, 9.7 % yield). LCMS (m/z): 407.3 [M+H]. 

\[ \text{H NMR (400 MHz, DMSO)} \delta 11.08 \text{ (s, 1H)}, 9.31 \text{ (s, 1H)}, 7.50 \text{ (d, J = 8.9 Hz, 2H)}, 7.39 \text{ (d, J = 8.9 Hz, 2H)}, 4.64 \text{ (d, J = 8.3 Hz, 1H)}, 4.17 \text{ (t, J = 8.8 Hz, 1H)}, 3.83 - 3.73 \text{ (m, 1H)}, 3.08 \text{ (s, 3H)}, 2.77 \text{ (d, J = 12.0 Hz, 1H)}, 2.21 \text{ (dd, J = 14.4, 8.8 Hz, 1H)}, 1.60 \text{ (s, 3H)}, 1.53 \text{ (td, J = 8.2, 4.1 Hz, 1H)}, 0.92 - 0.84 \text{ (m, 2H)}, 0.77 - 0.69 \text{ (m, 2H)}. \]

II.1.3. Synthesis of compound 3.1.3

**Reagents:** Step 1: DBU, dppb, PdCl\(_2\)(PPh\(_3\))\(_2\), DMSO, 100°C. Step 2: LiOH.H\(_2\)O, THF, MeOH, Water, room temperature. Step 3: NH\(_2\)OTH, EDC.HCl, HOBt, N-methyl morpholine, THF, room temperature. Step 4: 35.5 % aq. HCl, EtOH, room temperature.

**Step 1. Synthesis of ethyl (R)-3-\((S)-3-(4-(but-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.3a]**

1.1d (desired diastereomer) (0.2 g, 0.46 mmol, 1.0 equiv), pent-2-ynoic acid (0.068 g, 0.69 mmol, 1.5 equiv), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.005 g, 0.007 mmol, 0.012 equiv), 1,4-bis (diphenylphosphino)butane (0.005 g, 0.013 mmol, 0.023 equiv) and DBU (0.142 g, 0.93 mmol, 2.0 equiv) was added in DMSO (7 ml) in sealed tube. The reaction mixture was stirred at 100°C for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (30-40 % EtOAc in Hexane) to afford product 3.1.3a (0.15 g, 80 % yield). LCMS (m/z): 408.3 [M+H]. 

\[ \text{H NMR (400 MHz, DMSO)} \delta 7.52 \text{ (d, J = 8.8 Hz, 2H)}, 7.41 \text{ (d, J = 8.7 Hz, 2H)}, 4.79 \text{ (dd, J = \ldots} \]
14.3, 7.8 Hz, 1H), 4.24 (dt, J = 18.1, 7.8 Hz, 3H), 3.88 - 3.76 (m, 1H), 3.16 (s, 3H), 2.76 - 2.63 (m, 1H), 2.47 - 2.31 (m, 3H), 1.64 (s, 3H), 1.21 - 1.13 (m, 3H).

**Step 2. Synthesis of (R)-3-((S)-3-(4-(but-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [3.1.3b]**

3.1.3a (0.15 g, 0.37 mmol, 1.0 equiv) was dissolved in THF (2.0 ml_). MeOH (1.0 ml_). LiOH.H_2O (0.046 g, 1.1 mmol, 3.0 equiv) in water (1 ml_) was added. The resulting mixture was stirred at rt for 2 hours. The reaction mixture was concentrated to dryness and the residue was diluted with water, acidified by 1N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford compound 3.1.3b (0.110 mg, 78.5 % yield). The crude material was used in the next step with no further purification. LCMS (m/z): 380.3 [M+H]. ^1H NMR (400 MHz, DMSO) δ 14.10 (s, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.79 (d, J = 7.5 Hz, 1H), 4.22 (t, J = 8.8 Hz, 1H), 3.81 (dd, J = 10.5, 6.1 Hz, 1H), 3.16 (d, J = 5.2 Hz, 3H), 2.64 (dd, J = 14.8, 2.7 Hz, 1H), 2.42 (q, J = 7.5 Hz, 2H), 2.32 (dd, J = 14.7, 8.8 Hz, 1H), 1.61 (s, 3H), 1.16 (t, J = 7.5 Hz, 3H).

**Step 3. Synthesis of (2R)-3-((S)-3-(4-(but-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [3.1.3c]**

3.1.3b (0.11 g, 0.29 mmol, 1.0 equiv) was dissolved in THF (5 ml_). N-methyl morpholine (0.15 g, 1.45 mmol, 5.0 equiv), HOBT (0.05 g, 0.35 mmol, 1.2 equiv) and O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.07 g, 0.58 mmol, 2.0 equiv) were added and stirred for 5 minutes. EDC.HCl (0.05 g, 0.44 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (1-2 % MeOH in dichloromethane) to afford product 3.1.3c which was carry forwarded for next step. (0.11 g, 79.1 % yield). LCMS (m/z): 477.4 [M-H]. ^1H NMR (400 MHz, DMSO) δ 7.51 (dd, J = 8.6, 2.9 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.67 (d, J = 7.8 Hz, 1H), 4.19 (q, J = 8.9 Hz, 1H), 4.12 - 4.01 (m, 1H), 3.83 - 3.75 (m, 2H), 3.52 - 3.39 (m, 2H), 3.18 - 3.04 (m, 3H), 2.78 (d, J = 14.1 Hz, 1H), 2.42 (q, J = 7.5 Hz, 2H), 2.23 (dd, J = 13.8, 9.8 Hz, 1H), 1.45 (m, 6H), 1.16 (t, J = 7.5 Hz, 3H).

**Step 4. Synthesis of (R)-3-((S)-3-(4-(but-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy -2-methyl-2-(methylsulfonyl)propanamide [3.1.3]**

3.1.3c (0.11 g, 0.23 mmol, 1.0 equiv) was dissolved in ethanol (5.0 ml_). 35.5 % aqueous HCl (1 ml_) was added and the reaction mixture was stirred at rt for 2 hours. The reaction mixture was quenched with water, neutralized by sodium bicarbonate and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC to afford 3.1.3 as desired diastereomer (0.065 g, 72 % yield). LCMS (m/z): 395.3 [M+H]. ^1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (d, J = 1.5 Hz,
1H), 7.51 (d, J = 8.8 Hz, 2H), 7.42 (t, J = 8.8 Hz, 2H), 4.63 (d, J = 6.5 Hz, 1H), 4.18 (t, J =
8.8 Hz, 1H), 3.84 - 3.71 (m, 1H), 3.08 (s, 3H), 2.77 (d, J = 11.8 Hz, 1H), 2.42 (q, J = 7.5 Hz,
2H), 2.21 (dd, J = 14.4, 8.9 Hz, 1H), 1.60 (s, 3H), 1.16 (t, J = 7.5 Hz, 3H).

III.1.4. Synthesis of compound 3.1.4

Reagents: Step A: But-3-yn-2-ol, n-BuLi (23 % in hexane), C0₂, THF, -40 °C. Step 1: DBU,
dppb, PdCl₂(PPh₃)₂, DMSO, 90 °C. Step 2: LiOH.H₂O, THF, MeOH, Water, room
temperature. Step 3: NH₂OTH, EDC.HCl, HOBt, N-methyl morpholine, THF, room
temperature. Step 4: 35.5% aq. HCl, EtOH, room temperature.

Step A. Synthesis of 4-hydroxypent-2-ynoic acid. But-3-yn-2-ol (0.5 g, 7.13 mmol, 1.0
equiv) was dissolved in THF (15 ml) and the reaction mixture was cooled at -40 °C. n-BuLi
(23% in hexane) (0.91 g, 14.27 mmol, 2.0 equiv) was added dropwise and the mixture was
stirred at -40 °C for 1 hour. The CO₂ gas was purged into reaction mixture for 40 minutes.
The reaction mixture was diluted with water and extracted with EtOAc. The aqueous layer
was acidified by 35.5% aq. HCl to pH 3 to 4 and extracted with EtOAc. The organic layer
was washed with brine, dried over sodium sulfate and concentrated to afford product (0.5 g,
61.4% yield). The crude material was used in the next step without further purification. ¹H
NMR (400 MHz, DMSO) δ 5.69 (s, 1H), 4.52 (q, J = 6.5 Hz, 1H), 1.33 (d, J = 6.7 Hz, 3H).

Step 1. Synthesis of ethyl 3-((5S)-3-(4-(3-hydroxybut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.4a]

1.1d (0.73 g, 1.68 mmol, 1.0 equiv), 4-hydroxypent-2-ynoic acid (0.38 g, 3.37 mmol, 2.0 equiv),
PdCl₂(PPh₃)₂ (0.012 g, 0.017 mmol, 0.01 equiv), 1,4-bis(diphenylphosphino)
butane (0.016 g, 0.039 mmol, 0.02 equiv) and DBU (0.51 g, 3.36 mmol, 2.0 equiv) were
dissolved in DMSO (23 ml) in sealed tube. The reaction mixture was stirred at 90 °C for 8
hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic
layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude
residue. The residue was purified by silica gel column chromatography (40-60 % EtOAc in Hexane) to afford product 3.1.4a (0.36 g, 50.6 % yield). LCMS (m/z): 424.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.55 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 4.79 (d, J = 7.4 Hz, 1H), 4.58 (q, J = 6.5 Hz, 1H), 4.32 - 4.17 (m, 3H), 3.88 - 3.76 (m, 1H), 3.15 (d, J = 13.9 Hz, 3H), 2.68 (d, J = 12.7 Hz, 1H), 2.36 (dd, J = 14.8, 8.9 Hz, 1H), 1.61 (d, J = 27.7 Hz, 3H), 1.38 (d, J = 6.6 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 2. Synthesis of 3-((5S)-3-((3-hydroxybut-1-yn-1-yl)phenyl)-2-methyl-2-(methylsulfonyl)propanoic acid [3.1.4b]. 3.1.4a (0.13 g, 0.31 mmol, 1.0 equiv) was dissolved in THF (4 ml_), MeOH (1.5 ml_). LiOH.H₂O (0.039 g, 0.92 mmol, 3.0 equiv) in water (1.5 ml_) was added and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water, acidified by 1N HCl aqueous solution to pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.1.4b (0.10 g, 82.6 % yield). 1H NMR (400 MHz, DMSO) δ 14.09 - 13.98 (m, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.9 Hz, 2H), 5.46 (s, 3H), 4.83 - 4.76 (m, 1H), 4.62 - 4.55 (m, 1H), 4.23 (s, 1H), 3.82 (s, 1H), 3.15 (s, 3H), 2.68 - 2.65 (m, 1H), 2.33 (m, 1H), 1.61 (s, 3H), 1.38 (d, J = 6.6 Hz, 3H).

Step 3. Synthesis of 3-((5S)-3-((3-hydroxybut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [3.1.4c]. 3.1.4b (0.08 g, 0.20 mmol, 1.0 equiv) was dissolved in THF (8 ml_). N-methyl morpholine (0.10 g, 1.01 mmol, 5.0 equiv), HOBT (0.033 g, 0.24 mmol, 1.2 equiv), O-(tetrahydro -2H-pyran-2-yl) hydroxylamine (0.048 g, 0.41 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 10 minutes. EDC.HCl (0.058 g, 0.30 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated under reduced pressure to afford a residue. The residue was purified by silica gel column chromatography (2-3 % MeOH in dichloromethane) to afford product 3.1.4c which was used as such for next step (0.10 g, 80% yield). LCMS (m/z): 512.6 [M+18]. 1H NMR (400 MHz, DMSO) δ 7.55 (dd, J = 8.3, 5.9 Hz, 2H), 7.43 (d, J = 8.8 Hz, 2H), 4.67 (m, 1H), 4.19 (m, 1H), 3.76 (dd, J = 7.3, 4.1 Hz, 2H), 3.60 (m, 1H), 3.51 (m, 1H), 3.47 - 3.43 (m, 2H), 3.14 - 3.02 (m, 3H), 2.78 (m, 1H), 2.27 (m, 1H), 1.62 (s, 3H), 1.44 (m, 6H), 1.38 (d, J = 6.6 Hz, 3H).

Step 4. Synthesis of (2R)-N-hydroxy-3-((5S)-3-((3-hydroxybut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [3.1.4]. 3.1.4c (0.10 g, 0.20 mmol, 1.0 equiv) was dissolved in ethanol (3 ml_), 35.5% aq. HCl (0.1 ml_) was added to the solution and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the crude product. The crude product was purified
by preparative HPLC purification to afford product 3.1.4 (0.02 g, 24.1% yield). LCMS (m/z): 408.9 [M-H]. 1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.54 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 5.46 (d, J = 5.4 Hz, 1H), 4.71 - 4.54 (m, 1H), 4.19 (t, J = 8.8 Hz, 1H), 3.86 - 3.72 (m, 1H), 3.08 (s, 3H), 2.78 (d, J = 14.5 Hz, 1H), 2.21 (dd, J = 14.4, 8.9 Hz, 1H), 1.60 (s, 3H), 1.38 (d, J = 6.6 Hz, 3H).

III.1.5. Synthesis of compound 3.1.5

Reagents: Step A: 3-methoxyprop-1-yn-1-yl, n-BuLi (2.5M in hexane), CO₂, THF, -40°C. Step v. DBU, dppb, PdCl₂(PPh₃)₂, DMSO, 90°C. Step 2: LiOH.H₂O, THF, MeOH, Water, room temperature. Step 3: NH₂OTHP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 4: 35.5% aq. HCl, EtOH, room temperature.

Step A. Synthesis of 4-methoxybut-2-ynoic acid.

3-methoxyprop-1-yn-1-yl (1.0 g, 14.2 mmol, 1.0 equiv) was dissolved in THF (25 mL) and the solution was cooled at -40°C. n-BuLi (2.5M in hexane) (1.80 g, 28.5 mmol, 2.0 equiv) was added drop wise and the reaction mixture was stirred at -40°C for 1 hour. The CO₂ gas was purged into the reaction mixture for 30 minutes. The reaction mixture was diluted with water and extracted with EtOAc. The aqueous layer was acidified with 35.5% aq. HCl solution to pH 3 to 4 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product (1.10 g, 67.6% yield). 1H NMR (400 MHz, DMSO) δ 13.74 (s, 1H), 4.29 (s, 2H), 3.29 (s, 3H).

Step 1. Synthesis of ethyl 3-((S)-3-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.5a]. 1.1d (0.26 g, 0.59 mmol, 1.0 equiv), 4-methoxybut-2-ynoic acid (0.082 g, 0.72 mmol, 1.2 equiv), PdCl₂(PPh₃)₂ (0.004 g, 0.006 mmol, 0.01 equiv), 1,4-bis(diphenylphosphino)butane (0.006 g, 0.014 mmol, 0.023 equiv) and DBU (0.18 g, 1.20 mmol, 2.0 equiv) were dissolved in DMSO (15.0 mL) in sealed tube and the reaction mixture was stirred at 90°C for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was
purified by silica gel column chromatography (50 % EtOAc in Hexane) to afford product 3.1.5a (0.19 g , 75 % yield). LCMS (m/z): 424.5 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.67 - 7.42 (m, 4H), 4.80 (dd, $J = 15.5, 9.4$ Hz, 1H), 4.35 (d, $J = 20.0$ Hz, 2H), 4.28 - 4.20 (m, 2H), 3.88 - 3.77 (m, 1H), 3.33 (s, 2H), 3.23 - 3.10 (m, 3H), 2.79 - 2.65 (m, 1H), 2.37 (dd, $J = 14.9, 8.9$ Hz, 1H), 1.68 - 1.53 (m, 3H), 1.28 - 1.23 (m, 3H).

**Step 2. Synthesis of 3-((S)-3-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [3.1.5b]**

3.1.5a (0.19 g, 0.45 mmol, 1.0 equiv) was dissolved in THF (1.5 mL). MeOH (0.9 mL), LiOH.H$_2$O (0.057 g, 1.35 mmol, 3.0 equiv) in water (0.9 mL) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness; the residue was dissolved with water, acidified by 1N HCl aqueous solution to pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was triturated with n-pentane, the solvent was decanted and dried to afford product 3.1.5b (0.17 g, 93.2 % yield). LCMS (m/z): 396.3 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 14.18 - 13.86 (m, 1H), 7.56 (dd, $J = 9.6, 2.7$ Hz, 2H), 7.49 (d, $J = 8.9$ Hz, 2H), 4.81 (d, $J = 5.3$ Hz, 1H), 4.30 (d, $J = 17.8$ Hz, 2H), 4.22 (t, $J = 8.8$ Hz, 1H), 3.86 - 3.80 (m, 1H), 3.33 (s, 3H), 3.14 (s, 3H), 2.67 - 2.60 (m, 1H), 2.32 - 2.26 (m, 1H), 1.59 (s, 3H).

**Step 3. Synthesis of 3-((S)-3-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yl)oxy)propanamide [3.1.5c]**

3.1.5b (0.14 g, 0.36 mmol, 1.0 equiv) was dissolved in THF (12 mL). N-methyl morpholine (0.18 g, 1.77 mmol, 5.0 equiv), HOBT (0.057 g, 0.42 mmol, 1.2 equiv), O-(tetrahydro -2H-pyran-2-yl)hydroxylamine (0.084 g, 0.71 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 5 minutes. EDC.HCl (0.10 g, 0.53 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (2 % MeOH in dichloromethane) to afford product 3.1.5c which was used for next step (0.14 g, 82 % yield). LCMS (m/z): 493.5 [M-H]. AA27-sttep-3> $^1$H NMR (400 MHz, DMSO) $\delta$ 7.66 - 7.46 (m, 4H), 4.67 (m, 1H), 4.57 (d, $J = 4.9$ Hz, 10H), 4.21 (m, 1H), 4.05 (m, 1H), 3.77 (m, 2H), 3.51 (m, 1H), 3.46 - 3.39 (m, 2H), 3.33 (s, 3H), 3.15 - 3.02 (m, 3H), 2.85 - 2.70 (m, 1H), 2.24 (m, 1H), 1.62 (m, 3H), 1.50 - 1.40 (m, 6H).

**Step 4. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [3.1.5]**

3.1.5c (0.14 g, 0.29 mmol, 1.0 equiv) was dissolved in ethanol (5 mL), 35.5% aq. HCl (1 mL) was added and the reaction mixture was stirred at room temperature for 1 hour. The
reaction mixture was quenched with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was purified by preparative HPLC purification to afford 3.1.5 as desired diastereomer (0.033 g, 27.7 % yield). LCMS (m/z): 411.4 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 11.08 (s, 1H), 9.31 (s, 1H), 7.56 (d, $J = 8.9$ Hz, 2H), 7.50 (d, $J = 8.9$ Hz, 2H), 4.71 - 4.59 (m, 1H), 4.32 (s, 2H), 4.20 (t, $J = 8.8$ Hz, 1H), 3.84 - 3.76 (m, 1H), 3.33 (s, 3H), 3.08 (s, 3H), 2.84 - 2.73 (m, 1H), 2.22 (dd, $J = 14.4$, 8.9 Hz, 1H), 1.60 (s, 3H).

III.1.6. Synthesis of compound 3.1.6

![Chemical structure](image)

Reagents: Step A: 2-methylbut-3-yn-2-ol, n-BuLi (2.5M in hexane), C0$_2$, THF, -40 °C. Step v: DBU, dppb, PdCl$_2$(PPh$_3$)$_2$, DMSO, 90 °C. Step 2: LiOH.H$_2$O, THF, MeOH, Water, room temperature. Step 3: NH$_2$OTHP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 4: 35.5% aq. HCl, EtOH, 0 °C to room temperature.

Step A. Synthesis of 4-hydroxy-4-methylpent-2-ynoic acid.

2-methylbut-3-yn-2-ol (1.0 g, 11.89 mmol, 1.0 equiv) was dissolved in THF (40 mL) and the reaction mixture was cooled at -40°C. n-BuLi (2.5M in hexane) (1.52 g, 23.7 mmol, 2.0 equiv) was added drop wise and the reaction mixture was stirred at -40°C for 1 hour. The C0$_2$ gas was purged into reaction mixture for 1 hour. The reaction mixture was quenched with saturated ammonium chloride solution, acidified by 35.5% aq. HCl solution to pH 3 to 4 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product (0.75 g, 49.2 % yield). The crude material was used in the next step with no further purification. LCMS (m/z): 127.1 [M-H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 13.59 (s, 1H), 5.73 (s, 1H), 1.40 (s, 6H).

Step 1. Synthesis of ethyl 3-((S)-3-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)-2-oxo oxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.6a]. 1.1d (0.5 g, 1.15 mmol, 1.0 equiv), 4-hydroxy-4-methylpent-2-ynoic acid (0.18 g, 1.38 mmol, 1.2 equiv),
PdCl$_2$(PPh$_3$)$_2$ (0.008 g, 0.011 mmol, 0.01 equiv), 1,4-bis(diphenylphosphino)butane (0.011 g, 0.026 mmol, 0.02 equiv) and DBU (0.35 g, 2.3 mmol, 2.0 equiv) were dissolved in DMSO (10 ml) in sealed tube. The reaction mixture was stirred at 90 °C for 5 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (0-10% MeOH in dichloromethane) to afford product 3.1.6a (0.44 g, 87.3% yield). LCMS (m/z): 438.3 [M+H]. 

$^1$H NMR (400 MHz, DMSO) $\delta$ 7.53 (s, 2H), 7.42 (t, $J = 6.1$ Hz, 2H), 4.79 (d, $J = 9.9$ Hz, 1H), 4.32 - 4.21 (m, 3H), 3.85 - 3.79 (m, 1H), 3.15 (d, $J = 10.6$ Hz, 3H), 2.68 (d, $J = 12.8$ Hz, 1H), 2.40 - 2.34 (m, 1H), 1.64 (s, 3H), 1.46 (s, 6H), 1.26 (t, $J = 7.1$ Hz, 3H).

**Step 2. Synthesis of 3-((S)-3-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [3.1.6b].**

3.1.6a (0.22 g, 0.50 mmol, 1.0 equiv) was dissolved in THF (3 ml), MeOH (1.5 ml), LiOH.H$_2$O (0.063 g, 1.51 mmol, 3.0 equiv) in water (1.5 ml) was added to the reaction mixture and the resulting mixture was stirred at rt for 2 hours. The reaction mixture was diluted with water, acidified by 1N HCl aqueous solution to pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The product was triturated with n-pentane to afford product 3.1.6b (0.195 g, 94.7% yield). 

$^1$H NMR (400 MHz, DMSO) $\delta$ 14.25 - 13.99 (m, 3H), 7.54 (d, $J = 8.9$ Hz, 2H), 7.41 (d, $J = 8.9$ Hz, 2H), 4.79 (s, 1H), 4.22 (t, $J = 8.8$ Hz, 1H), 3.81 (d, $J = 8.4$ Hz, 1H), 3.14 (d, $J = 3.7$ Hz, 3H), 2.64 (d, $J = 14.9$ Hz, 1H), 2.35 - 2.28 (m, 1H), 1.60 (s, 3H), 1.47 (d, $J = 5.6$ Hz, 6H).


3.1.6b (0.18 g, 0.44 mmol, 1.0 equiv) was dissolved in THF (7 ml). N-methyl morpholine (0.22 g, 2.20 mmol, 5.0 equiv), EDC.HCl (0.13 g, 0.66 mmol, 1.5 equiv), HOBT (0.071 g, 0.53 mmol, 1.2 equiv), 0-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.103 g, 0.88 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0-5 % MeOH in dichloromethane) to afford product 3.1.6c (0.14 g, 62.7% yield) which was used as such for next step. LCMS (m/z): 507.5 [M-H]. 

$^1$H NMR (400 MHz, DMSO) $\delta$ 7.70 - 7.36 (m, 4H), 5.71 (s, 1H), 4.66 (m, 1H), 4.17 (m, 1H), 4.03 (m, 1H), 3.73 (m, 4H), 3.12 - 3.02 (m, 3H), 2.77 (m, 1H), 2.17 (m, 1H), 1.67 - 1.37 (m, 15H).

**Step 4. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-(3-hydroxy-3-methylbut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [3.1.6]**
3.1.6c (0.14 g, 0.28 mmol, 1.0 equiv) dissolved in ethanol (5 mL) and cooled the solution at 0 °C. 35.5% aq. HCl (0.21 mL) was added and stirred the reaction mixture at room temperature for 1 hour. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC purification to afford 3.1.6 (0.045 g, 38.5% yield).

LCMS (m/z): 423.4 [M-H]. \( ^1H \) NMR (400 MHz, DMSO) \( \delta \) 11.09 (s, 1H), 9.30 (s, 1H), 7.54 (d, \( J = 8.9 \) Hz, 2H), 7.42 (d, \( J = 8.9 \) Hz, 2H), 5.47 (s, 1H), 4.65 (d, \( J = 7.2 \) Hz, 1H), 4.19 (t, \( J = 8.7 \) Hz, 1H), 3.84 - 3.74 (m, 1H), 3.08 (s, 3H), 2.76 (d, \( J = 14.2 \) Hz, 1H), 2.21 (dd, \( J = 14.5, 8.9 \) Hz, 1H), 1.59 (s, 3H), 1.46 (s, 6H).

111.1.8. Synthesis of compound 3.1.8

Compound 3.1.8 was synthesized by the process of example 3.1.1. LCMS (m/z): 437.4 [M-1]. \( ^1H \) NMR (400 MHz, DMSO) \( \delta \) 11.08 (s, 1H), 9.21 (s, 1H), 7.55 (d, \( J = 8.6 \) Hz, 2H), 7.46 (d, \( J = 8.6 \) Hz, 2H), 4.67 (s, 1H), 4.18 (t, \( J = 8.9 \) Hz, 1H), 3.85 - 3.73 (m, 1H), 3.30 (d, \( J = 5.6 \) Hz, 3H), 3.16 - 2.98 (m, 3H), 2.76 (d, \( J = 14.3 \) Hz, 1H), 2.20 (dd, \( J = 14.2, 8.4 \) Hz, 1H), 1.65 - 1.51 (m, 3H), 1.45 (d, \( J = 19.9 \) Hz, 6H).

111.1.9. Synthesis of compound 3.1.9

Compound 3.1.9 was synthesized by the process of example 3.1.1. LCMS (m/z): 442.4 [M+18]. \( ^1H \) NMR (400 MHz, DMSO) \( \delta \) 11.01 (s, 1H), 9.24 (s, 1H), 7.52 (d, \( J = 22.6 \) Hz, 4H), 4.67 (m, 1H), 4.35 (m, 1H), 4.18 (m, 1H), 3.80 (m, 1H), 3.08 (s, 3H), 2.75 (d, \( J = 13.7 \) Hz, 1H), 2.19 (m, 1H), 1.57 (s, 3H), 1.41 (d, \( J = 5.0 \) Hz, 3H).

111.1.10. Synthesis of compound 3.1.10

Compound 3.1.10 was synthesized by the process of example 3.1.1. LCMS (m/z): 411.3 [M+H]. \( ^1H \) NMR (400 MHz, DMSO) \( \delta \) 11.06 (s, 1H), 9.32 (s, 1H), 7.52 (d, \( J = 8.8 \) Hz, 2H), 7.46 - 7.36 (m, 2H), 4.91 (t, \( J = 5.5 \) Hz, 1H), 4.63 (d, \( J = 6.5 \) Hz, 1H), 4.18 (t, \( J = 8.9 \) Hz, 1H), 3.81 - 3.72 (m, 1H), 3.58 (dd, \( J = 12.5, 6.7 \) Hz, 2H), 3.16 - 3.01 (m, 3H), 2.77 (d, \( J = 14.9 \) Hz, 1H), 2.55 (t, \( J = 6.8 \) Hz, 2H), 2.21 (dd, \( J = 14.4, 8.9 \) Hz, 1H), 1.66 - 1.52 (m, 3H).

111.1.11. Synthesis of compound 3.1.11

Step 1. Synthesis of ethyl (R)-3-((S)-3-(4-(4-methoxybut-1 -yn-1 -yl)phenyl)-2-oxooxazolidin -5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.11 b]  

3.1.11a (which was synthesized by the process of example 3.1.1) (0.31 g, 0.73 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide (10 mL). Ag\(_2\)O (0.50 g, 2.19 mmol, 3.0 equiv), iodomethane (1.03 g, 7.3 mmol, 10.0 equiv) were added and the reaction
mixture was stirred at 80 °C for 48 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0-40 % EtOAc in Hexane) to afford product 3.1.11b (0.21 g, 66.6 % yield). LCMS (m/z): 435.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.58 - 7.50 (m, 2H), 7.44 (dd, J = 16.2, 12.9 Hz, 2H), 4.94 - 4.74 (m, 1H), 4.35 - 4.12 (m, 3H), 3.81 (dd, J = 11.1, 5.5 Hz, 1H), 3.51 (t, J = 6.7 Hz, 1H), 3.28 (d, J = 12.1 Hz, 3H), 3.28 - 3.20 (m, 1H), 3.17 (d, J = 3.9 Hz, 3H), 2.88 - 2.59 (m, 3H), 2.36 (dd, J = 14.8, 8.9 Hz, 1H), 1.71 - 1.54 (m, 3H), 1.30 - 1.20 (m, 3H).

Step 2. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-(4-methoxybut-1-yl)phenyl)-2-oxo oxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [3.1.11]

3.1.11 was synthesized by the process of example 3.1.1. LCMS (m/z): 425.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.11 (s, 1H), 9.31 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 4.64 (d, J = 7.3 Hz, 1H), 4.18 (t, J = 8.9 Hz, 1H), 3.78 (t, J = 8.0 Hz, 1H), 3.51 (t, J = 6.6 Hz, 2H), 3.29 (s, 3H), 3.11 (d, J = 20.7 Hz, 3H), 2.77 (d, J = 16.1 Hz, 1H), 2.66 (t, J = 6.6 Hz, 2H), 2.21 (dd, J = 14.3, 8.9 Hz, 1H), 1.62 (d, J = 20.3 Hz, 3H).


Step 1. Synthesis of pent-4-ynenitrile [3.1.14b]

But-3-yn-1-yl 4-methylbenzenesulfonate 3.1.14a (5 g, 21.0 mmol, 1.0 equiv) was dissolved in dimethyl sulfoxide (40 mL). NaN₃ (5.23 g, 106.0 mmol, 5 equiv) was added and the reaction mixture was stirred at 70 °C for 30 minutes. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (2-3 % MeOH in dichloromethane) to afford product 3.1.14b (1 g, 55 % yield). 1H NMR (400 MHz, DMSO) δ 4.13 (q, J = 5.3 Hz, 1H), 3.17 (d, J = 5.2 Hz, 2H), 2.51 (dd, J = 3.6, 1.8 Hz, 2H).

Step 2. Synthesis of ethyl 2-methyl-2-(methylsulfonyl)-3-((S)-3-(4-(4-morpholinobut-1-yn-1-yl) phenyl)-2-oxoazolidin-5-yl)propanoate [3.1.14c]. 1.1d (0.5 g, 0.11 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide (0.5 mL). PdCl₂(PPh₃)₂ (0.04 g, 0.06 mmol, 0.05 equiv), Cul (0.010 g, 0.06 mmol, 0.05 equiv), triphenyl phosphine (0.06 g, 0.23 mmol, 0.2 equiv), diethyl amine (2.5 mL) were added and the reaction mixture was degassed for 5 minutes. Pent-4-ynenitrile (0.18 g, 2.3 mmol, 2.0 equiv) was added and the reaction mixture was stirred at 130 °C for 15 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (40-50 % EtOAc in Hexane) to afford product 3.1.14c (0.35 g, 70 % yield). LCMS (m/z): 433.1 [M+H].

3.1.14 was synthesized by the process of example 3.1.1. LCMS (m/z): 418.6 [M-1].

\[ ^1H \text{NMR (400 MHz, DMSO)} \delta 11.09 (s, 1H), 9.32 (s, 1H), 7.55 (d, \ J = 8.8 \text{ Hz}, 2H), 7.50 - 7.38 (m, 2H), 4.64 (d, \ J = 8.0 \text{ Hz}, 1H), 4.19 (t, \ J = 8.7 \text{ Hz}, 1H), 3.85 - 3.73 (m, 1H), 3.15 - 2.99 (m, 3H), 2.88 - 2.67 (m, 5H), 2.22 (dd, \ J = 14.4, 9.0 \text{ Hz}, 1H), 1.57 (d, \ J = 19.5 \text{ Hz}, 3H). \]

III. 1.15. Synthesis of compound 3.1.15

Compound 3.1.15 was synthesized by the process of 3.1.14. LCMS (m/z): 479.5 [M+H]. \[^1H \text{NMR (400 MHz, CD}_2\text{CN)} \delta 8.12 (s, 1H), 7.50 (d, \ J = 7.6 \text{ Hz}, 2H), 7.40 (d, \ J = 7.8 \text{ Hz}, 2H), 4.68 (m, 1H), 4.16 (m, 1H), 3.78 (d, \ J = 16.5 \text{ Hz}, 1H), 3.66 (m, 4H), 3.11 - 2.86 (m, 3H), 2.76 (d, \ J = 14.2 \text{ Hz}, 1H), 2.63 (s, 3H), 2.54 (s, 4H), 2.33 (dd, \ J = 13.9, 8.5 \text{ Hz}, 1H), 1.69 (s, 3H). \]

III. 1.17. Synthesis of compound 3.1.17

Compound 3.1.17 was synthesized by the process of example 3.1.1. LCMS (m/z): 437.7 [M-1]. \[^1H \text{NMR (400 MHz, DMSO)} \delta 11.09 (s, 1H), 9.32 (s, 1H), 7.55 (d, \ J = 8.8 \text{ Hz}, 2H), 7.52 - 7.38 (m, 2H), 4.64 (d, \ J = 8.0 \text{ Hz}, 1H), 4.19 (t, \ J = 8.7 \text{ Hz}, 1H), 3.84 - 3.75 (m, 1H), 3.17 - 2.99 (m, 3H), 2.89 - 2.67 (m, 5H), 2.22 (dd, \ J = 14.4, 9.0 \text{ Hz}, 1H), 1.57 (d, \ J = 19.5 \text{ Hz}, 3H). \]

III. 1.18. Synthesis of compound 3.1.18

Compound 3.1.18 was synthesized by example 3.1.1. LCMS (m/z): 449.6 [M-1]. \[^1H \text{NMR (400 MHz, DMSO)} \delta 11.08 (s, 1H), 9.32 (s, 1H), 7.60 - 7.50 (m, 2H), 7.43 (d, \ J = 8.8 \text{ Hz}, 2H), 4.64 (d, \ J = 6.1 \text{ Hz}, 1H), 4.19 (t, \ J = 8.8 \text{ Hz}, 1H), 3.80 (ddd, \ J = 16.4, 10.5, 6.2 \text{ Hz}, 3H), 3.50 - 3.38 (m, 2H), 3.06 (d, \ J = 19.8 \text{ Hz}, 3H), 2.94 - 2.84 (m, 1H), 2.77 (d, \ J = 11.9 \text{ Hz}, 1H), 2.22 (dd, \ J = 14.4, 8.9 \text{ Hz}, 1H), 1.84 (d, \ J = 9.6 \text{ Hz}, 2H), 1.69 - 1.46 (m, 5H). \]

III. 1.19. Synthesis of compound 3.1.19

Step 1. Synthesis of ethyl 3-(4-methoxybenzyl)oxy)cyclobutane-1-carboxylate [3.1.19a]. Ethyl 3-hydroxycyclobutane-1-carboxylate (4 g, 27.4 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide and cooled to 0 °C. NaH (60 %) (1.66 g, 41.6 mmol, 1.5 equiv) was added portion wise and the reaction mixture was stirred at 0 °C for 24 hours. 1-(chloromethyl)-4-methoxybenzene (5.24 g, 33.3 mmol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EIOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column
chromatography (0-30 % EtOAc in Hexane) to afford product 3.1.19a (4.82 g, 65.8 % yield).

LCMS (m/z): 265.5 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.27 - 7.21 (m, 2H), 6.94 - 6.84 (m, 2H), 4.29 (s, 2H), 4.12 - 3.99 (m, 2H), 3.99 - 3.83 (m, 1H), 3.74 (s, 3H), 2.66 (tt, \(J = 9.7, 8.0\) Hz, 1H), 2.44 - 2.32 (m, 2H), 2.22 - 1.96 (m, 2H), 1.21 - 1.14 (m, 3H).

**Step 2. Synthesis of (3-((4-methoxybenzyl)oxy)cyclobutyl)methanol [3.1.19b]**

3.1.19a (4.8 g, 18.18 mmol, 1.0 equiv) was dissolved in THF (48 mL). Lithium borohydride (2.0 M in THF) (18.18 mL, 36.36 mmol, 2.0 equiv) was added drop wise and the resulting mixture was stirred at room temperature for 6 hours. The reaction mixture was diluted with saturated aqueous sodium sulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0-40 % EtOAc in Hexane) to afford product 3.1.19b (3.87 g, 95.9 % yield). LCMS (m/z): 223.2 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.31 - 7.16 (m, 2H), 6.98 - 6.83 (m, 2H), 4.52 (dt, \(J = 28.6, 5.2\) Hz, 1H), 4.33 - 4.20 (m, 2H), 3.93 - 3.76 (m, 1H), 3.76 - 3.60 (m, 3H), 2.29 - 2.03 (m, 2H), 2.04 - 1.66 (m, 2H).

**Step 3. Synthesis of 3-((4-methoxybenzyl)oxy)cyclobutane-1-carbaldehyde [3.1.19c]**

3.1.19b (3.85 g, 17.34 mmol, 1.0 equiv) was dissolved in dichloromethane (40 mL) and cooled to 10 °C. Dess-Martin periodinane (14.7 g, 34.68 mmol, 2.0 equiv) was added portion wise and the reaction mixture was stirred at room temperature for 10 hours. The reaction mixture was filtered through celite bed. Filtrate was diluted with water, neutralized by aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (0-20 % EtOAc in Hexane) to afford product 3.1.19c (3.65 g, 95.5 % yield). LCMS (m/z): 239.5 [M+18]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 9.67 (dd, \(J = 79.4, 30.1\) Hz, 1H), 7.22 (d, \(J = 8.5\) Hz, 2H), 6.88 (d, \(J = 8.6\) Hz, 2H), 4.31 - 4.23 (m, 2H), 3.97 (dq, \(J = 15.6, 7.7\) Hz, 1H), 3.72 (s, 3H), 2.83 (dd, \(J = 66.9, 58.8\) Hz, 1H), 2.47 - 2.23 (m, 2H), 2.19 - 1.69 (m, 3H).

**Step 4. Synthesis of 1-((3-ethynylcyclobutoxy)methyl)-4-methoxybenzene [3.1.19d]**

3.1.19c (3.6 g, 16.36 mmol, 1.0 equiv) was dissolved in MeOH (36 mL). Ohira-Bestmann reagent (3.86 g, 49.09 mmol, 1.2 equiv) was added. \(\text{K}_2\text{CO}_3\) (4.65 g, 32.72 mmol, 2.0 equiv) and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (0-20 % EtOAc in Hexane) to afford product 3.1.19d (1.99 g, 56.2 % yield). LCMS (m/z): 234.3 [M+18]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.31 - 7.14 (m, 2H), 6.97 - 6.80 (m, 2H), 4.35 - 4.22 (m, 2H), 3.91 - 3.60 (m, 4H), 3.05 - 2.90 (m, 1H), 2.59 - 2.51 (m, 2H), 2.29 - 2.09 (m, 1H), 1.90 - 1.82 (m, 1H).
**Step 5. Synthesis of ethyl (R)-3-((S)-3-(4-((3-((4-methoxybenzyl)oxy)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoaten [3.1.19e]**

1.1d (0.5 g, 1.16 mmol, 1.0 equiv) and 3.1.19d (0.5 g, 2.31 mmol, 2.0 equiv) were mixed with diethyl amine (10 mL) and N,N-dimethylformamide (2 mL). Cul (0.011 g, 0.058 mmol, 0.05 equiv), triphenyl phosphine (0.06 g, 0.23 mmol, 0.2 equiv) were added and the reaction mixture was degassed for 10 minutes. PdCl$_2$(p-ph)$_2$ (0.040 g, 0.058 mmol, 0.05 equiv) was added and the reaction mixture was stirred at 125 °C for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (30-35 % EtOAc in Hexane) to afford product 3.1.19e (0.8 g, 61 % yield). LCMS (m/z): 570.6 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.56 - 7.49 (m, 2H), 7.41 (d, J = 8.7 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 4.79 (d, J = 8.0 Hz, 1H), 4.34 - 4.19 (m, 4H), 4.12 (q, J = 5.2 Hz, 1H), 3.87 (ddd, J = 28.5, 15.6, 7.9 Hz, 2H), 3.23 - 3.11 (m, 5H), 2.69 - 2.58 (m, 2H), 2.42 - 2.22 (m, 2H), 1.98 (dd, J = 18.7, 10.4 Hz, 1H), 1.64 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

**Step 6. Synthesis of ethyl (R)-3-((S)-3-(4-((3-hydroxcyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.19f]**

3.1.19e (0.8 g, 1.40 mmol, 1.0 equiv) was dissolved in dichloromethane (20 mL) and cooled to 0 °C. TFA (1.07 mL, 14.0 mmol, 10.0 equiv) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude residue. The residue was purified by silica gel column chromatography (80 % EtOAc in Hexane) to afford product 3.1.19f (0.55 g, 87 % yield). LCMS (m/z): 450.5 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.57 - 7.49 (m, 2H), 7.40 (d, J = 8.7 Hz, 2H), 4.79 (d, J = 7.4 Hz, 1H), 4.24 (dt, J = 18.3, 8.0 Hz, 3H), 3.85 (dd, J = 34.9, 27.1 Hz, 2H), 3.72 (d, J = 15.0 Hz, 1H), 3.28 - 3.09 (m, 3H), 2.75 - 2.56 (m, 3H), 2.40 - 2.14 (m, 2H), 2.01 - 1.89 (m, 1H), 1.77 - 1.55 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H).

**Step 7. Synthesis of ethyl (R)-3-((S)-3-(4-((3-ethoxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.19g]**

3.1.19f (0.5 g, 1.11 mmol, 1.0 equiv) was added in chloroform (15 mL). DIPEA (0.57 g, 3.33 mmol, 3.0 equiv), Meerwein's reagent (0.63 g, 3.33 mmol, 3.0 equiv) in dichloromethane (3 mL) were added and the reaction mixture was stirred at 5 °C for 15 minutes. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain crude residue. The residue was purified by silica gel column chromatography (40 % EtOAc in Hexane) to afford product 3.1.19g (0.26 g, 49 %
yield). LCMS (m/z): 478.7 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.55 - 7.49 (m, 2H), 7.41 (d, J = 8.7 Hz, 2H), 4.79 (d, J = 7.8 Hz, 1H), 4.24 (dt, J = 17.5, 7.9 Hz, 3H), 3.83 (dd, J = 15.5, 7.6 Hz, 2H), 3.17 (d, J = 5.5 Hz, 4H), 2.79 (d, J = 8.2 Hz, 1H), 2.65 (dd, J = 21.6, 12.3 Hz, 2H), 2.39 - 2.31 (m, 1H), 2.10 - 1.83 (m, 2H), 1.64 (s, 3H), 1.30 - 1.18 (m, 4H).

**Step 8. Synthesis of (R)-3-((S)-3-(4-(3-ethoxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide** [3.1.19]

3.1.19 was synthesized by the process of 3.1.1. 3.1.19-1: LCMS (m/z): 465.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 8.37 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.3 Hz, 2H), 4.66 (s, 1H), 4.17 (s, 1H), 3.82 (dd, J = 16.2, 8.7 Hz, 2H), 3.31 - 3.23 (m, 2H), 3.10 (d, J = 19.2 Hz, 3H), 2.78 (dd, J = 19.8, 11.5 Hz, 2H), 2.70 - 2.56 (m, 2H), 2.19 (s, 2H), 1.99 - 1.91 (m, 2H), 1.57 (s, 3H), 1.09 (t, J = 7.0 Hz, 4H). 3.1.19-11: LCMS (m/z): 465.2 [M+H].

**III.1.20. Synthesis of compound 3.1.20**

![Synthesis Diagram](image)

**Reagents:** Step 1: Diethyl amine, triphenyl phosphine, Cul, PdCl₂(pph₃)₂, N,N-dimethyl formamide, 110 °C. Step 2: DAST, dichloromethane, -70 °C to room temperature. Step 3: LiOH.H₂O, THF, MeOH, water, room temperature. Step 4: NH₂OTHP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 5: HCl (in IPA), room temperature.

**Step 1. Synthesis of ethyl (R)-3-((S)-3-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate** [3.1.20a].

1.1d (0.3 g, 0.7 mmol, 1.0 equiv), but-3-yn-1-ol (0.053 g, 0.8 mmol, 1.1 equiv), triphenyl phosphine (0.036 g, 0.1 mmol, 0.2 equiv) were added in diethyl amine (5 mL), N, N-dimethylformamide (1 mL) and the reaction mixture was degassed for 10 minutes. PdCl₂(pph₃)₂ (0.024 g, 0.03 mmol, 0.05 equiv), Cul (0.013 g, 0.07 mmol, 0.1 equiv) were added and the reaction mixture was stirred at 110 °C for 1 hour. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (1 % MeOH/dichloromethane) to afford the...
desired product 3.1.20a (0.25 g, 85.6 % yield). LCMS (m/z): 424.3 [M+H]. \(^1^H\) NMR (400 MHz, DMSO) \(\delta\) 7.52 (d, \(J = 8.9\) Hz, 2H), 7.42 (d, \(J = 8.9\) Hz, 2H), 4.93 - 4.87 (m, 1H), 4.79 (d, \(J = 7.5\) Hz, 1H), 4.32 - 4.18 (m, 3H), 3.86 - 3.78 (m, 1H), 3.58 (dd, \(J = 12.5, 6.8\) Hz, 2H), 3.16 (s, 3H), 2.69 (d, \(J = 15.0\) Hz, 1H), 2.55 (t, \(J = 6.8\) Hz, 2H), 2.40 - 2.33 (m, 1H), 1.65 (s, 3H), 1.26 (t, \(J = 7.1\) Hz, 3H).

**Step 2. Synthesis of ethyl (R)-3-((S)-3-(4-(4-fluorobut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.20b].** 3.1.20a (0.2 g, 0.5 mmol, 1.0 equiv) was dissolved in dichloromethane (10 ml) and cooled to -70 °C. DAST (0.15 g, 1.0 mmol, 2.0 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (25 % EtOAc/Hexane) to afford the desired product 3.1.20b (0.13 g, 52 % yield). LCMS (m/z): 426.3 [M+H]. \(^1^H\) NMR (400 MHz, DMSO) \(\delta\) 7.54 (d, \(J = 8.8\) Hz, 2H), 7.44 (d, \(J = 8.8\) Hz, 2H), 4.83 - 4.75 (m, 1H), 4.64 (t, \(J = 6.1\) Hz, 1H), 4.52 (t, \(J = 6.1\) Hz, 1H), 4.24 (dt, \(J = 16.4, 7.6\) Hz, 3H), 3.86 - 3.78 (m, 1H), 3.16 (s, 3H), 2.89 (t, \(J = 6.1\) Hz, 1H), 2.84 (t, \(J = 6.1\) Hz, 1H), 2.69 (d, \(J = 15.0\) Hz, 1H), 2.36 (dd, \(J = 14.8, 8.9\) Hz, 1H), 1.65 (s, 3H), 1.26 (t, \(J = 7.1\) Hz, 3H).

**Step 3. Synthesis of (R)-3-((S)-3-(4-(4-fluorobut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoic acid [3.1.20c].**

3.1.20b (0.13 g, 0.3 mmol, 1.0 equiv) was dissolved in THF (4 ml), MeOH (1 ml) and water (1 ml). LiOH.H\(_2\)O (0.026 g, 0.6 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with water, acidified by 1.0 N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.20c (0.1 g, 82.6 % yield). LCMS (m/z): 398.3 [M+H]. \(^1^H\) NMR (400 MHz, DMSO) \(\delta\) 14.12 (s, 1H), 7.54 (d, \(J = 8.8\) Hz, 2H), 7.46 (t, \(J = 11.7\) Hz, 2H), 4.80 (d, \(J = 8.1\) Hz, 1H), 4.64 (t, \(J = 6.1\) Hz, 1H), 4.52 (t, \(J = 6.1\) Hz, 1H), 4.22 (t, \(J = 8.8\) Hz, 1H), 3.87 - 3.78 (m, 1H), 3.15 (s, 3H), 2.89 (t, \(J = 6.0\) Hz, 1H), 2.83 (t, \(J = 6.0\) Hz, 1H), 2.64 (d, \(J = 14.7\) Hz, 1H), 2.32 (dd, \(J = 14.6, 8.5\) Hz, 1H), 1.61 (s, 3H).

**Step 4. Synthesis of (2R)-3-((S)-3-(4-(4-fluorobut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl) oxy) propanamide [3.1.20d].** 3.1.20c (0.1 g, 0.2 mmol, 1.0 equiv) was dissolved in THF (5 ml). N-methyl morpholine (0.13 g, 1.2 mmol, 5.0 equiv), EDC.HCl (0.072 g, 0.4 mmol, 1.5 equiv), HOBT (0.061 g, 0.4 mmol, 1.8 equiv), O-((tetrahydro-2H-pyran-2-yl) hydroxylamine (0.059 g, 0.5 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The
organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (52 % EtOAc/Hexane) to afford the desired product **3.1.20d** (0.09 g, 72.6 % yield). LCMS (m/z): 496.4 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.50 (s, 1H), 7.53 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 4.97 (d, J = 8.5 Hz, 1H), 4.64 (dd, J = 12.0, 5.9 Hz, 2H), 4.52 (t, J = 6.1 Hz, 1H), 4.19 (t, J = 8.8 Hz, 1H), 4.07 - 4.00 (m, 1H), 3.80 (t, J = 8.2 Hz, 1H), 3.51 (d, J = 13.8 Hz, 1H), 3.07 (d, J = 9.4 Hz, 3H), 2.86 (dt, J = 24.0, 6.0 Hz, 2H), 2.79 (d, J = 13.8 Hz, 1H), 2.27 - 2.20 (m, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.54 (s, 3H).

**Step 5. Synthesis of (R)-3-((S)-3-(4-(4-fluorobut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [3.1.20]**

**3.1.20d** (0.09 g, 0.2 mmol, 1.0 equiv) was dissolved in IPA (2 ml). HCl (in IPA) (0.5 ml) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was quenched with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was purified by preparative HPLC purification to afford the desired product **3.1.20** (0.04 g, 53.3 % yield). LCMS (m/z): 413.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 9.31 (s, 1H), 7.54 (d, J = 8.6 Hz, 2H), 7.44 (d, J = 8.6 Hz, 2H), 4.64 (t, J = 6.0 Hz, 2H), 4.52 (t, J = 6.0 Hz, 1H), 4.19 (s, 1H), 3.84 - 3.74 (m, 1H), 3.08 (s, 3H), 2.89 (t, J = 5.8 Hz, 1H), 2.83 (t, J = 5.9 Hz, 1H), 2.77 (d, J = 12.7 Hz, 1H), 2.21 (dd, J = 14.3, 9.1 Hz, 1H), 1.60 (s, 3H).

**III. 1.21. Synthesis of compound 3.1.21**
Reagents: Step 1: Diethyl amine, triphenylphosphine, Cul, PdCl₂(pph₃)₂, N,N-dimethylformamide, 100 °C. Step 2: TFA, dichloromethane, 0 °C to room temperature. Step 3: PTS-Cl, TEA, DMAP, dichloromethane, 0 °C. Step 4: NaCN, DMSO, 80 °C. Step 5: LiOH·H₂O, THF, MeOH, water, room temperature. Step 6: NH₂OTHP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 7: HCl (in IPA), MeOH, dichloromethane, room temperature.

Step 1. Synthesis of ethyl (R)-3-[(S)-3-(4-(((3-ethynylcyclobutyl)methoxy)methyl)-4-methoxybenzyl)oxy]methyl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.21a]. (1.1d) (1.74 g, 4.01 mmol, 1.0 equiv) was suspended in diethyl amine (15 ml) and N,N-dimethylformamide (3 ml) in sealed tube. Cul (0.076 g, 0.40 mmol, 0.1 equiv), triphenylphosphine (0.21 g, 0.08 mmol, 0.2 equiv) were added and the reaction mixture was degassed for 15 minutes. PdCl₂(pph₃)₂ (0.14 g, 0.20 mmol, 0.05 equiv), 1-(((3-ethynylcyclobutyl)methoxy)methyl)-4-methoxybenzene (1.2 g, 5.2 mmol, 1.3 equiv) were added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel chromatography (60-65 % EtOAc/Hexane) to afford the desired product 3.1.21a (2 g, 65.7 % yield). LCMS (m/z): 584.4 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.67 - 7.47 (m, 4H), 7.40 (t, J = 9.4 Hz, 1H), 7.25 (dd, J = 8.7, 2.8 Hz, 1H), 7.03 - 6.88 (m, 2H), 4.83 - 4.74 (m, 1H), 4.40 (d, J = 8.8 Hz, 1H), 4.31 - 4.20 (m, 3H), 3.88 - 3.81 (m, 1H), 3.81 - 3.70 (m,
3H), 3.45 (d, J = 6.8 Hz, 1H), 3.37 (d, J = 6.0 Hz, 2H), 3.32 - 3.21 (m, 1H), 3.16 (t, J = 6.4 Hz, 3H), 2.67 (d, J = 3.9 Hz, 1H), 2.57 (s, 1H), 2.44 - 2.29 (m, 2H), 2.17 (dd, J = 16.2, 7.9 Hz, 1H), 1.87 (d, J = 11.1 Hz, 1H), 1.65 (d, J = 3.8 Hz, 3H), 1.27 (dt, J = 7.2, 3.6 Hz, 3H).

Step 2. Synthesis of ethyl (R)-3-((S)-3-((4-((3-(hydroxymethyl) propanoate [3.1.21b]

3.1.21a (2 g, 3.43 mmol, 1.0 equiv) was suspended in dichloromethane (60 ml) and cooled to 0 °C. TFA (2.6 ml, 34.3 mmol, 10 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with water, basified by solid sodium bicarbonate and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (1.6 % MeOH/dichloromethane) to afford the desired product 3.1.21b (0.9 g, 56.7 % yield). LCMS (m/z): 464.5 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.52 (dd, J = 8.9, 2.1 Hz, 2H), 7.44 - 7.38 (m, 2H), 4.84 - 4.74 (m, 1H), 4.69 - 4.44 (m, 1H), 4.32 - 4.17 (m, 3H), 3.85 - 3.68 (m, 2H), 3.55 - 3.34 (m, 2H), 3.31 - 3.04 (m, 4H), 2.68 (d, J = 12.9 Hz, 1H), 2.48 - 2.21 (m, 3H), 2.14 (dd, J = 9.3, 5.4 Hz, 1H), 1.94 - 1.78 (m, 1H), 1.65 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 3. Synthesis of ethyl (R)-2-methyl-2-(methyllsulfonyl)-3-((S)-2-oxo-3-((4-((3-((tosyloxy) methyl) propanoate [3.1.21c]

3.1.21b (0.45 g, 0.97 mmol, 1.0 equiv) was suspended in dichloromethane (80 ml). TEA (0.49 g, 4.9 mmol, 5.0 equiv), DMAP (0.024 g, 0.2 mmol, 0.2 equiv) were added and the reaction mixture was cooled to 0 °C. 4-methylbenzenesulfonyl chloride (0.28 g, 1.45 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (50-55 % EtOAc/Hexane) to afford the desired product 3.1.21c (0.4 g, 66.8 % yield). LCMS (m/z): 618.9 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.87 - 7.73 (m, 2H), 7.50 (dt, J = 17.9, 8.1 Hz, 4H), 7.39 (t, J = 8.1 Hz, 2H), 4.79 (d, J = 7.8 Hz, 1H), 4.24 (dt, J = 17.9, 8.1 Hz, 3H), 4.17 - 4.08 (m, 1H), 4.04 - 4.00 (m, 1H), 3.85 - 3.78 (m, 1H), 3.76 - 3.62 (m, 1H), 3.32 - 3.03 (m, 4H), 2.67 (s, 1H), 2.43 (d, J = 6.2 Hz, 2H), 2.41 - 2.29 (m, 2H), 2.21 - 2.03 (m, 2H), 1.81 (dd, J = 20.7, 9.1 Hz, 1H), 1.64 (s, 3H), 1.28 - 1.23 (m, 3H).

Step 4. Synthesis of ethyl (R)-3-((S)-3-((4-(cyanoethyl) cyclobutyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methyllsulfonyl) propanoate [3.1.21d]

3.1.21c (0.3 g, 0.48 mmol, 1.0 equiv) was suspended in dimethylsulfoxide (12 ml). NaCN (0.06 g, 1.21 mmol, 2.5 equiv) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was stirred at 80 °C for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed
with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (55 % EtOAc/Hexane) to afford product 3.1.21d (0.14 g, 45.8 % yield). LCMS (m/z): 473.4 [M+H].

Step 5. Synthesis of (R)-3-((S)-3-((3-(cyanomethyl) cyclobutyl) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoic acid [3.1.21e].

3.1.21d (0.14 g, 0.29 mmol, 1.0 equiv) was suspended in THF (2.6 mL), MeOH (0.6 mL) and water (0.6 mL). LiOH.H₂O (0.016 g, 0.35 mmol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to dryness. The residue was diluted with water and washed with EtOAc. The aqueous layer was acidified by 1.0 N HCl aqueous solution to the pH 2 to 3 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.21e (0.1 g, 83.9 % yield). LCMS (m/z): 445.4 [M+H].

Step 6. Synthesis of (2R)-3-((S)-3-((3-(cyanomethyl) cyclobutyl) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl) oxy) propanamide [3.1.21†]. 3.1.21e (0.09 g, 0.2 mmol, 1.0 equiv) was suspended in THF (10 mL). N-methyl morpholine (0.1 g, 1.0 mmol, 5.0 equiv), HOBT (0.033 g, 0.24 mmol, 1.2 equiv), 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.048 g, 0.4 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 5 minutes. EDC.HCl (0.058 g, 0.3 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude residue. The crude residue was purified by silica gel column chromatography (1.6 % MeOH/dichloromethane) to afford the desired product 3.1.21† (0.1 g, 90.9 % yield). LCMS (m/z): 543.5 [M+H].

Step 7. Synthesis of (R)-3-((S)-3-((3-(cyanomethyl) cyclobutyl) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [3.1.21].

3.1.21† (0.1 g, 0.2 mmol, 1.0 equiv) was suspended in methanol (2 mL) and dichloromethane (2 mL). HCl (in IPA) (0.1 mL) was added and the reaction mixture was stirred at rt for 10 minutes. The reaction mixture was concentrated to dryness and co-distilled with dichloromethane to afford a crude residue. The crude residue was purified by preparative HPLC purification to afford the desired product 3.1.21 (0.018 g, 2.14 % yield). LCMS (m/z): 477.3 [M+18]. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.52 (dd, J = 8.9, 2.0 Hz, 2H), 7.42 (dd, J = 8.7, 6.3 Hz, 2H), 4.62 (dd, J = 14.4, 6.9 Hz, 1H), 4.18 (t, J = 8.4 Hz, 1H), 3.78 (t, J = 8.0 Hz, 1H), 3.46 (ddd, J = 27.4, 10.3, 5.2 Hz, 1H), 3.24 - 3.12 (m, 1H), 3.08 (s, 3H), 2.81 - 2.71 (m, 2H), 2.67 (d, J = 6.2 Hz, 1H), 2.49 - 2.42 (m, 1H), 2.23 (dddd, J = 23.5, 16.1, 11.6, 4.8 Hz, 3H), 1.92 (dd, J = 11.0, 4.7 Hz, 1H), 1.62 (d, J = 16.2 Hz, 3H).
III.1.22. Synthesis of compound 3.1.22

Step 1. Synthesis of (tetrahydro-2H-pyran-4-yl) methanol [3.1.22].
Methyl tetrahydro-2H-pyran-4-carboxylate (5 g, 34.68 mmol, 1.0 equiv) was dissolved in THF (60 ml) and methanol (10 ml). Sodium borohydride (2.62 g, 69.36 mmol, 2.0 equiv) was added in portions and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.22a (3.2 g, 80 % yield). 1H NMR (400 MHz, DMSO) δ 3.96 - 3.75 (m, 2H), 3.66 - 3.58 (m, 2H), 3.36 (dd, J = 6.9, 4.7 Hz, 2H), 3.33 - 3.17 (m, 2H), 1.81 - 1.70 (m, 2H), 1.63 - 1.48 (m, 2H).

Step 2. Synthesis of (tetrahydro-2H-pyran-4-yl) methyl 4-methylbenzenesulfonate [3.1.22b]. 3.1.22a (1 g, 8.62 mmol, 1.0 equiv) was dissolved in dichloromethane (20 ml), TEA (4.36 g, 43.11 mmol, 5.0 equiv), DMAP (0.21 g, 1.72 mmol, 0.2 equiv) were added and cooled to 0 °C. 4-methylbenzenesulfonyl chloride (2.46 g, 12.9 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (30-35 % EtOAc/Hexane) to afford the desired product 3.1.22b (0.8 g, 35 % yield). LCMS (m/z): 271.1 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.80 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 3.89 (dd, J = 11.9, 6.4 Hz, 2H), 3.80 (dd, J = 14.4, 6.9 Hz, 2H), 3.24 (dd, J = 22.0, 12.0 Hz, 2H), 2.43 (s, 3H), 1.90 - 1.71 (m, 2H), 1.51 (dd, J = 31.2, 12.6 Hz, 3H).

Step 3. Synthesis of 4-(prop-2-yn-1-yl) tetrahydro-2H-pyran [3.1.22c]. 3.1.22b (0.5 g, 1.85 mmol, 1.0 equiv) was dissolved in dimethylsulfoxide (10 ml). Lithium acetylide ethylene diamine (0.51 g, 5.56 mmol, 3.0 equiv) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (15-20 % diethyl ether/n-pentane) to afford the desired product 3.1.22c (0.16 g, 69 % yield). 1H NMR (400 MHz, DMSO) δ 3.84 (dd, J = 11.2, 4.2 Hz, 2H), 3.27 (td, J = 11.9, 1.9 Hz, 2H), 2.83 (t, J = 2.7 Hz, 1H), 2.13 (dd, J = 6.2, 2.7 Hz, 2H), 1.70 - 1.57 (m, 3H), 1.24 (dd, J = 11.9, 4.3 Hz, 2H).

Step 4. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(tetrahydro-2H-pyran-4-yl) prop-1-yn-1-yl) phenyl) oxazolidin-5-yl) propanamide [3.1.22]. 3.1.22c was converted to compound 3.1.22 by the process of example 3.1.20. LCMS (m/z): 465.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 9.31 (s, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.6 Hz, 2H), 4.64 (d, J = 7.9 Hz, 1H), 4.18 (t, J = 8.6 Hz, 1H),
3.87 (d, J = 8.1 Hz, 2H), 3.84 - 3.74 (m, 1 H), 3.29 (d, J = 11.5 Hz, 2H), 3.08 (s, 3H), 2.77 (d, J = 12.8 Hz, 1H), 2.39 (d, J = 6.2 Hz, 2H), 2.21 (dd, J = 14.5, 8.9 Hz, 1H), 1.69 (d, J = 12.8 Hz, 3H), 1.60 (s, 3H), 1.38 - 1.26 (m, 2H).

III.1.23. Synthesis of compound 3.1.23

Step 1. Synthesis of ethyl (R)-3-((S)-3-(4-(4-hydroxybut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.23a]. 1.1d (0.25 g, 0.6 mmol, 1.0 equiv) was added to diethyl amine (5 ml) and N,N-dimethylformamide (1 ml). Cul (0.011 g, 0.06 mmol, 0.1 equiv), triphenylphosphate (0.03 g, 0.1 mmol, 0.2 equiv) were added and the reaction mixture was degassed for 10 minutes. But-3-yn-1-ol (0.048 g, 0.7 mmol, 1.2 equiv), PdCl₂(pph₃)₂ (0.02 g, 0.03 mmol, 0.05 equiv) were added and the mixture was stirred at 110 °C for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel column chromatography (40-50 % EtOAc/Hexane) to afford the desired product 3.1.23a (0.2 g, 83.3 % yield). LCMS (m/z): 424.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.52 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 4.90 (t, J = 5.6 Hz, 1H), 4.79 (d, J = 6.5 Hz, 1H), 4.32 - 4.16 (m, 3H), 3.87 - 3.77 (m, 1H), 3.58 (dd, J = 12.4, 6.7 Hz, 2H), 3.16 (s, 3H), 2.68 (d, J = 12.6 Hz, 1H), 2.55 (t, J = 6.9 Hz, 2H), 2.37 - 2.31 (m, 1H), 1.64 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 2. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-oxobut-1-yn-1-yl) phenyl) oxazolidin-5-yl) propanoate [3.1.23b]. 3.1.23a (0.2 g, 0.5 mmol, 1.0 equiv) was dissolved in dichloromethane (5 ml). Dess-Martlin periodinane (0.3 g, 0.7 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with mixture of saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with sodium thiosulphate solution, brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.23b (3.5 ml solution in dichloromethane due to we have observed degradation observed during drying). LCMS (m/z): 422.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.63 (dd, J = 11.9, 7.1 Hz, 4H), 4.80 (s, 1H), 4.26 (s, 3H), 3.83 (s, 1H), 3.17 (s, 3H), 2.68 (s, 1H), 2.52 (s, 2H), 2.41 - 2.33 (m, 1H), 2.09 (s, 3H), 1.65 (s, 3H), 1.25 (d, J = 9.2 Hz, 3H).

Step 3. Synthesis of ethyl (R)-3-((S)-3-(4-(4, 4-difluorobut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.23c]. 3.1.23b (3.5 ml, 1.0 equiv) was dissolved in dichloromethane (5 ml) and cooled to -70 °C. DAST (0.36 g, 2.2 mmol, 4.0 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was added to saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue
was purified by silica gel chromatography (30-32 % EtOAc/Hexane) to afford the desired product 3.1.23c (0.13 g, yield). LCMS (m/z): 444.2 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.62 (dd, $J = 5.8$, 4.8 Hz, 2H), 7.59 - 7.54 (m, 2H), 6.47 - 6.06 (m, 1H), 4.79 (d, $J = 9.8$ Hz, 1H), 4.30 - 4.22 (m, 2H), 4.14 (dd, $J = 5.6$, 3.5 Hz, 1H), 3.87 - 3.77 (m, 1H), 3.24 - 3.09 (m, 4H), 2.68 (d, $J = 12.7$ Hz, 1H), 2.38 - 2.33 (m, 1H), 1.64 (s, 3H), 1.28 - 1.23 (m, 3H).

Step 4. Synthesis of (R)-3-((S)-3-(4-(4-difluorobut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoic acid [3.1.23d]. 3.1.23c (0.13 g, 0.3 mmol, 1.0 equiv) was dissolved in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL). LiOH.H$_2$O (0.018 g, 0.4 mmol, 1.5 equiv) was added and the reaction mixture was stirred at r.t for 30 minutes. The reaction mixture was quenched with water and the aqueous layer was acidified by 1.0 N HCl to pH 2 to 3 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.23d (0.11 g, 91.7 % yield). The product was used in the next step with no further purification.

LCMS (m/z): 416.2 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 14.13 (s, 1H), 7.55 (d, $J = 8.8$ Hz, 2H), 7.47 (d, $J = 8.8$ Hz, 2H), 6.26 (tt, $J = 55.9$ Hz, 1H), 4.81 (m, 1H), 4.23 (t, $J = 8.8$ Hz, 1H), 3.84 (d, $J = 7.5$ Hz, 1H), 3.23 - 3.06 (m, 5H), 2.67 (m, 1H), 2.33 (m, 1H), 1.61 (s, 3H).

Step 5. Synthesis of (2R)-3-((S)-3-(4-(4, 4-difluorobut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy) propanamide [3.1.23e]. 3.1.23d (0.11 g, 0.3 mmol, 1.0 equiv) was dissolved in THF (5 mL). N-methyl morpholine (0.13 mL, 1.3 mmol, 5.0 equiv), HOBT (0.043 g, 0.3 mmol, 1.2 equiv), 0-((tetrahydro-2H-pyran-2-yl) hydroxylamine (0.062 g, 0.5 mmol, 2.0 equiv), EDC.HCl (0.076 g, 0.4 mmol, 1.5 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (60-70 % EtOAc/Hexane) to afford the desired product 3.1.23e (0.1 g, 73.5 % yield). LCMS (m/z): 514.2 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 11.51 (s, 1H), 7.55 (d, $J = 8.3$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H), 6.26 (tt, $J = 56.0$ Hz, 1H), 4.97 (d, $J = 8.6$ Hz, 1H), 4.69 (s, 1H), 4.20 (d, $J = 8.9$ Hz, 1H), 4.17 - 4.12 (m, 2H), 3.81 (d, $J = 8.8$ Hz, 1H), 3.51 (s, 1H), 3.16 (td, $J = 17.2$, 4.0 Hz, 2H), 3.08 (d, $J = 9.2$ Hz, 3H), 2.79 (d, $J = 13.9$ Hz, 1H), 2.22 (s, 1H), 1.69 (s, 3H), 1.62 (s, 3H), 1.54 (s, 3H).

Step 6. Synthesis of (R)-3-((S)-3-(4-(4, 4-difluorobut-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [3.1.23]. 3.1.23e (0.1 g, 0.2 mmol, 1.0 equiv) was dissolved in DCM (2 mL) and methanol (1 mL). HCl (in IPA) (2 mL) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate
and concentrated to afford a crude residue. The crude product was purified by preparative HPLC purification to afford the desired product **3.1.23** (0.023 g, 27.7 % yield). LCMS (m/z): 429.1 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.31 (s, 1H), 7.55 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 8.8 Hz, 2H), 6.26 (tt, J = 56.0, 3.8 Hz, 1H), 4.65 (d, J = 7.8 Hz, 1H), 4.19 (t, J = 8.7 Hz, 1H), 3.83 - 3.76 (m, 1H), 3.16 (td, J = 17.2, 3.9 Hz, 2H), 3.08 (s, 3H), 2.78 (d, J = 14.3 Hz, 1H), 2.22 (dd, J = 14.5, 8.9 Hz, 1H), 1.60 (s, 3H).


**Step 1. Synthesis of methyl 3-hydroxy-3-methylcyclobutane-1-carboxylate [3.1.24a]**

Methyl 3-oxocyclobutane-1-carboxylate (5 g, 39.02 mmol, 1.0 equiv) was dissolved in diethyl ether (75 mL) and cooled to -78 °C. Methyl magnesium bromide (13 mL, 39.02 mmol, 1.0 equiv) was added and the reaction mixture was stirred at -10 °C for 2 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (10-20 % EtOAc/Hexane) to afford the desired product **3.1.24a** (2.2 g, 40 % yield). ¹H NMR (400 MHz, DMSO) δ 5.07 (d, J = 36.9 Hz, 1H), 3.59 (d, J = 3.5 Hz, 3H), 2.80 - 2.57 (m, 1H), 2.26 - 2.04 (m, 4H), 1.21 (d, J = 14.2 Hz, 3H).

**Step 2. Synthesis of methyl 3-((4-methoxybenzyl) oxy)-3-methylcyclobutane-1-carboxylate [3.1.24b]. 3.1.24a (2.1 g, 14.57 mmol, 1.0 equiv), DIPEA (5.6 g, 43.7 mmol, 3.0 equiv) were dissolved in Dichloromethane (20 mL). 1-(Chloromethyl)-4-methoxybenzene (4.5 g, 29.2 mmol, 2.0 equiv) was added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was concentrated to afford a crude residue, which was purified by silica gel chromatography (5 % EtOAc/Hexane) to afford **3.1.24b** (2.5 g, 75% yield). LCMS (m/z): 282.2 [M+18]. ¹H NMR (400 MHz, DMSO) δ 7.24 (t, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.45 - 4.24 (m, 2H), 3.83 - 3.69 (m, 3H), 3.62 (d, J = 7.0 Hz, 3H), 2.95 - 2.77 (m, 1H), 2.41 - 2.20 (m, 2H), 2.19 - 2.02 (m, 2H), 1.36 (d, J = 19.2 Hz, 3H).

**Step 3. Synthesis of (3-((4-methoxybenzyl) oxy)-3-methylcyclobutyl) methanol [3.1.24c]. 3.1.24b (5.2 g, 19.2 mmol, 1.0 equiv) was dissolved in THF (40 mL) and methanol (4 mL). Sodium borohydride (1.42 g, 38.58 mmol, 2.0 equiv) was added in portions and the reaction mixture was stirred at rt for 24 hours. The reaction mixture was poured in to water and extracted by EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (10-20 % EtOAc/Hexane) to afford the desired product **3.1.24c** (2.6 g, 57 % yield). LCMS (m/z): 237.1 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.24 (t, J = 8.6 Hz, 2H), 6.93 - 6.84 (m, 2H), 4.52 - 4.39 (m, 1H), 4.25 (d, J = 6.6 Hz, 2H), 3.74 (s, 3H), 3.39 (dt, J = 11.1, 5.6 Hz, 2H), 2.05 - 1.69 (m, 4H), 1.33 (d, J = 17.1 Hz, 3H).
Step 4. Synthesis of 3-((4-methoxybenzyl) oxy)-3-methylcyclobutane-1-carbaldehyde [3.1.24d]. 3.1.24c (1.3 g, 5.5 mmol, 1.0 equiv) was dissolved in dichloromethane (20 ml). PCC (2.3 g, 11.0 mmol, 2.0 equiv) was added in portions and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with diethyl ether and filtered. The filtrate was concentrated to afford the desired product 3.1.24d (1.2 g, 100 % yield). The product was used in the next step with no further purification. \(^1\)H NMR (400 MHz, DMSO) δ 9.69 (t, J = 18.9 Hz, 1H), 7.25 (dd, J = 12.3, 8.6 Hz, 2H), 6.89 (dd, J = 8.6, 3.6 Hz, 2H), 4.28 (d, J = 10.0 Hz, 2H), 3.73 (t, J = 5.7 Hz, 3H), 2.99 - 2.80 (m, 1H), 2.33 - 2.01 (m, 4H), 1.44 - 1.20 (m, 3H).

Step 5. Synthesis of 1-((3-ethynyl-1-methylcyclobutoxy) methyl)-4-methoxybenzene [3.1.24e]. 3.1.24d (1.2 g, 5.12 mmol, 1.0 equiv) was dissolved in MeOH (20 ml). K$_2$CO$_3$ (1.4 g, 10.3 mmol, 2.0 equiv), Ohira-Bestmann reagent (1.2 g, 6.15 mmol, 1.2 equiv) was added and the reaction mixture was stirred at rt for 24 hours. The reaction mixture was concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (5 % EtOAc/Hexane) to afford the desired product 3.1.24e (0.7 g, 63 % yield). LCMS (m/z): 248.2 [M+18]. \(^1\)H NMR (400 MHz, DMSO) δ 7.24 (d, J = 8.6 Hz, 2H), 6.93 - 6.82 (m, 2H), 4.25 (s, 2H), 3.75 (d, J = 6.6 Hz, 3H), 3.02 (dd, J = 11.8, 2.4 Hz, 1H), 2.71 (dd, J = 17.5, 8.0 Hz, 1H), 2.30 - 2.19 (m, 2H), 2.12 (t, J = 10.2 Hz, 2H), 1.33 (s, 3H).

Step 6. Synthesis of ethyl (R)-3-((S)-3-(4-((3-methoxybenzyl) oxy)-3-methylcyclobutyl) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.2.24f]. 1.1d (0.88 g, 2.0 mmol, 1.0 equiv) was added to diethyl amine (10 ml) and N, N-dimethylformamide (2 ml). Cul (0.038 g, 0.2 mmol, 0.1 equiv) and triphenylphosphine (0.1 g, 0.4 mmol, 0.2 equiv) were added and the reaction mixture was degassed for 5 minutes. 3.1.24e (0.7 g, 3.03 mmol, 1.5 equiv), PdCl$_2$(PPh$_3$)$_2$ (0.07 g, 0.1 mmol, 0.05 equiv) were added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel chromatography (10 % EtOAc/Hexane) to afford the desired product 3.1.24f (0.9 g, 81 % yield). LCMS (m/z): 584.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) δ 7.52 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.79 (d, J = 7.1 Hz, 1H), 4.37 - 4.17 (m, 5H), 3.83 (d, J = 7.4 Hz, 1H), 3.74 (s, 3H), 3.25 (dd, J = 11.6, 7.1 Hz, 1H), 3.16 (s, 3H), 3.03 - 2.93 (m, 1H), 2.68 (d, J = 15.3 Hz, 2H), 2.39 - 2.21 (m, 4H), 1.64 (s, 3H), 1.44 (d, J = 52.2 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 7. Synthesis of ethyl (R)-3-((S)-3-(4-((3-hydroxy-3-methylcyclobutyl) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1-24g] 3.1.24f (0.8 g, 1.37 mmol, 1.0 equiv) was dissolved in dichloromethane (20 ml) and cooled to 0 °C. TFA (0.8 ml) in dichloromethane (10 ml) was added and the reaction mixture was
stirred at room temperature for 2 hours. The reaction mixture was concentrated, quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was purified by silica gel column chromatography (10 % EtOAc/Hexane) to afford the desired product 3.1.24g (0.5 g, 78 % yield). LCMS (m/z): 464.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.52 (d, \(J = 8.7\) Hz, 2H), 7.40 (d, \(J = 8.7\) Hz, 2H), 4.79 (d, \(J = 8.3\) Hz, 1H), 4.24 (dt, \(J = 18.2, 8.0\) Hz, 3H), 3.86 - 3.77 (m, 1H), 3.16 (s, 3H), 2.85 - 2.74 (m, 1H), 2.68 (d, \(J = 14.1\) Hz, 1H), 2.42 - 2.25 (m, 3H), 2.17 (d, \(J = 9.6\) Hz, 1H), 1.64 (s, 3H), 1.27 - 1.20 (m, 3H).

**Step 8. Synthesis of (R)-3-((S)-3-(4-(3-hydroxy-3-methylcyclobuty1) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoic acid [3.1.24h].**

3.1.24g (0.5 g, 1.08 mmol, 1.0 equiv) was dissolved in THF (6 mL) and MeOH (2 mL). LiOH (0.068 g, 1.61 mmol, 1.5 equiv) in water (2 mL) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated, quenched with water, acidified by 1.0 N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.24h (0.4 g, 85 % yield). LCMS (m/z): 436.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 14.10 (s, 1H), 7.51 (d, \(J = 8.9\) Hz, 2H), 7.40 (d, \(J = 8.8\) Hz, 2H), 4.80 (d, \(J = 6.2\) Hz, 1H), 4.22 (t, \(J = 8.7\) Hz, 1H), 3.85 - 3.78 (m, 1H), 3.15 (s, 3H), 2.79 (t, \(J = 8.1\) Hz, 1H), 2.64 (d, \(J = 14.4\) Hz, 2H), 2.36 - 2.28 (m, 3H), 2.16 (t, \(J = 10.1\) Hz, 2H), 1.62 (d, \(J = 11.2\) Hz, 3H), 1.23 (d, \(J = 5.6\) Hz, 3H).

**Step 9. Synthesis of (2R)-3-((S)-3-(4-((3-hydroxy-3-methylcyclobutyl) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy) propanamide [3.1.24i].** 3.1.24h (0.3 g, 0.68 mmol, 1.0 equiv) was dissolved in THF (6 mL). EDC.HCl (0.24 g, 1.23 mmol, 1.8 equiv), HOBT (0.14 g, 1.03 mmol, 1.5 equiv), N-methyl morpholine (0.39 g, 3.44 mmol, 5.0 equiv), 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.14 g, 1.17 mmol, 1.7 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (40 % EtOAc/Hexane) to afford the desired product 3.1.24i (0.33 g, 88 % yield). LCMS (m/z): 533.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.48 (d, \(J = 3.2\) Hz, 1H), 7.51 (d, \(J = 8.7\) Hz, 2H), 7.40 (d, \(J = 8.7\) Hz, 2H), 5.03 - 4.95 (m, 1H), 4.66 (s, 1H), 4.18 (t, \(J = 8.6\) Hz, 1H), 3.84 - 3.73 (m, 1H), 3.51 (s, 1H), 3.10 (t, \(J = 13.9\) Hz, 3H), 2.75 (t, \(J = 23.7\) Hz, 2H), 2.42 - 2.27 (m, 3H), 2.27 - 2.11 (m, 3H), 1.70 (s, 3H), 1.62 (s, 3H), 1.54 (s, 3H).

**Step 10. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-((3-hydroxy-3-methylcyclobutyl) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanamide [3.1.24 & 3.1.25].** 3.1.24i (0.3 g, 0.56 mmol, 1.0 equiv) was dissolved in methanol (5 mL).
PTSA.H₂O (0.13 g, 0.56 mmol, 1.0 equiv) was added and the reaction mixture was stirred at rt for 2 hours. The reaction mixture was diluted with water, precipitated solid was filtered and dried to afford a crude product. The crude product was purified by preparative HPLC purification to afford the desired product 3.1.24 as isomer-A (0.015 g, 6 % yield). LCMS (m/z): 451.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 5.02 (s, 1H), 4.65 (s, 1H), 4.18 (t, J = 8.7 Hz, 1H), 3.79 (d, J = 7.8 Hz, 1H), 3.20 (s, 1H), 3.08 (s, 3H), 2.77 (d, J = 15.8 Hz, 2H), 2.44 - 2.32 (m, 3H), 2.23 (d, J = 8.2 Hz, 1H), 2.11 - 1.97 (m, 2H), 1.60 (s, 3H), 1.38 (s, 3H). 3.1.25 as isomer-B (0.040 g, 15.8 % yield). LCMS (m/z): 451.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.33 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 5.17 (s, 1H), 4.63 (d, J = 6.6 Hz, 1H), 4.18 (t, J = 8.8 Hz, 1H), 3.85 - 3.68 (m, 1H), 3.08 (s, 3H), 2.78 (dd, J = 16.8, 8.7 Hz, 2H), 2.35 - 2.26 (m, 2H), 2.19 (dt, J = 21.1, 9.8 Hz, 3H), 1.60 (s, 3H), 1.22 (s, 3H).

III.1.26. Synthesis of compound 3.1.26
Step 1. Synthesis of 5-(4-bromophenyl) pent-4-yn-1-ol [3.1.26a].
1-Bromo-4-iodobenzene (1 g, 3.5 mmol, 1.0 equiv) was dissolved in diethyl amine (5 ml) and N, N-dimethylformamide (2 ml). Cul (0.067 g, 0.35 mmol, 0.1 equiv), triphenylphosphine (0.18 g, 0.7 mmol, 0.2 equiv) were added and the reaction mixture was degassed for 15 minutes. Pent-4-yn-1-ol (0.36 g, 4.2 mmol, 1.2 equiv), PdCl₂(pph₃)₂ (0.12 g, 0.17 mmol, 0.05 equiv) were added and the reaction mixture was stirred at 120 °C for 6 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (25-30 % EtOAc/Hexane) to afford the desired product 3.1.26a (0.65 g, 76.47 % yield). ¹H NMR (400 MHz, CDCl₃) δ 7.47 - 7.40 (m, 2H), 7.27 (d, J = 8.5 Hz, 2H), 3.84 (t, J = 5.9 Hz, 2H), 2.55 (t, J = 7.0 Hz, 2H), 1.94 - 1.80 (m, 2H), 1.65 (s, 1H).

Step 2. Synthesis of 1-bromo-4-(5-fluoropent-1-yn-1-yl) benzene [3.1.26b]. 3.1.26a (0.25 g, 1.05 mmol, 1.0 equiv) was dissolved in dichloromethane (10 ml) and cooled to -78 °C. DAST (0.25 g, 1.56 mmol, 1.5 equiv) was added drop wise and the reaction mixture was stirred at -78 °C for 10 minutes. The reaction mixture was stirred at rt for 1 hour. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue that was purified by silica gel chromatography (10 % EtOAc/Hexane) to afford 3.1.26b (0.13 g, 51.6% yield). ¹H NMR (400 MHz, DMSO) δ 7.56 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H), 4.63 (t, J = 5.8 Hz, 1H), 4.51 (t, J = 5.8 Hz, 1H), 2.54 (m, 2H), 1.93 (ddd, J = 25.7, 12.4, 6.0 Hz, 2H).
Step 3. Synthesis of \( (R) \cdot 3 - ((S) \cdot 3 - (4 - ((5\text{-fluorophenyl})-2-oxooxazolidin-5-yl) - N\text{-hydroxy}-2\text{-methyl}-2\text{-methylsulfonyl})\text{propanamide} \) [3.1.26].

3.1.26b was converted to 3.1.26 by the process described in the synthesis of 2.4.

LCMS (m/z): 427.2 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \( \delta 11.09 \) (s, 1H), 9.32 (s, 1H), 7.52 (d, \( J = 8.9 \) Hz, 2H), 7.43 (d, \( J = 8.8 \) Hz, 2H), 4.63 (t, \( J = 5.8 \) Hz, 2H), 4.51 (t, \( J = 5.8 \) Hz, 1H), 4.18 (t, \( J = 8.8 \) Hz, 1H), 3.83 - 3.75 (m, 1H), 3.08 (s, 3H), 2.77 (d, \( J = 12.0 \) Hz, 1H), 2.54 (d, \( J = 7.1 \) Hz, 2H), 2.26 - 2.20 (m, 1H), 1.98 - 1.87 (m, 2H), 1.60 (s, 3H).

111.27. Synthesis of compound 3.1.27

Step 1. Synthesis of ethyl \( (R) \cdot 3 - ((S) \cdot 3 - (4 - (6\text{-methoxyhex-1-yn-1-yl})\text{-phenyl}-2-oxooxazolidin-5-yl)-2\text{-methyl}-2\text{-methylsulfonyl})\text{propanoate} \) 3.1.27b. (R)-ethyl 3-((S)-3-((4-(6-hydroxyhex-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl))propanoate (0.23 g, 0.5 mmol, 1.0 equiv) was suspended in acetonitrile (2.3 mL) in sealed tube. \( \text{Ag}_2\text{O} \) (0.47 g, 2.04 mmol, 4.0 equiv), iodomethane (0.65 g, 10.2 mmol, 20.0 equiv) were added and the reaction mixture was stirred at reflux for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product, which was purified by silica gel column chromatography (48-55 % EtOAc/Hexane) to afford product 3.1.27b (0.18 g, 76 % yield). LCMS (m/z): 466.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \( \delta 7.52 \) (d, \( J = 8.8 \) Hz, 2H), 7.41 (d, \( J = 8.7 \) Hz, 2H), 4.79 (d, \( J = 7.9 \) Hz, 1H), 4.20 (t, \( J = 8.6 \) Hz, 1H), 3.80 (d, \( J = 2.2 \) Hz, 4H), 3.37 (d, \( J = 6.1 \) Hz, 2H), 3.23 (s, 3H), 3.16 (s, 3H), 2.69 (d, \( J = 15.0 \) Hz, 1H), 2.43 (t, \( J = 6.8 \) Hz, 2H), 2.36 (dd, \( J = 14.9, 9.0 \) Hz, 1H), 1.71 - 1.54 (m, 7H).

Step 4. Synthesis of \( (R) \cdot N\text{-hydroxy}-3 - ((S) \cdot 3 - (4 - (6\text{-methoxyhex-1-yn-1-yl})\text{-phenyl}-2-oxooxazolidin-5-yl)-2\text{-methyl}-2\text{-methylsulfonyl})\text{propanamide} \) 3.1.27b was converted to 3.1.27 using the process described in the synthesis of 3.1.20. LCMS (m/z): 470.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \( \delta 11.07 \) (s, 1H), 9.31 (s, 1H), 7.51 (d, \( J = 8.7 \) Hz, 2H), 7.41 (d, \( J = 8.6 \) Hz, 2H), 4.64 (d, \( J = 7.5 \) Hz, 1H), 4.18 (t, \( J = 8.5 \) Hz, 1H), 3.83 - 3.75 (m, 1H), 3.37 (d, \( J = 6.0 \) Hz, 2H), 3.23 (s, 3H), 3.08 (s, 3H), 2.77 (d, \( J = 13.1 \) Hz, 1H), 2.43 (t, \( J = 6.7 \) Hz, 2H), 2.21 (dd, \( J = 14.0, 8.8 \) Hz, 1H), 1.70 - 1.51 (m, 7H).

111.128. Synthesis of compound 3.1.28

Step 1. Synthesis of ethyl \( (R) \cdot 3 - ((S) \cdot 3 - (4 - (6\text{-hydroxyhex-1-yn-1-yl})\text{-phenyl}-2-oxooxazolidin-5-yl)-2\text{-methyl}-2\text{-methylsulfonyl})\text{propanoate} \) [3.1.28a]. 1.1d (0.6 g, 1.38 mmol, 1.0 equiv) was dissolved in diethyl amine (15 mL) and N, N-dimethylformamide (3 mL). Triphenylphosphine (0.073 g, 0.27 mmol, 0.2 equiv), Cul (0.27 g, 0.13 mmol, 0.1 equiv) were added and the reaction mixture was degassed for 15 minutes. \( \text{PdCl}_2(\text{pph}_3)_2 \) (0.049 g, 0.07 mmol, 0.05 equiv), hex-5-yn-1-ol (0.18 g, 1.79 mmol, 1.3 equiv) were added
and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (65-70 % EtOAc/Hexane) to afford the desired product 3.1.29a (0.53 g, 85.1 % yield). LCMS (m/z): 452.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.54 - 7.49 (m, 2H), 7.43 - 7.35 (m, 2H), 4.83 - 4.74 (m, 1H), 4.46 - 4.41 (m, 1H), 4.30 - 4.18 (m, 3H), 3.82 (dd, J = 9.0, 7.6 Hz, 1H), 3.44 (dd, J = 6.7, 4.6 Hz, 2H), 3.16 (s, 3H), 2.68 (dd, J = 14.9, 2.5 Hz, 1H), 2.42 (t, J = 6.6 Hz, 2H), 2.34 (dd, J = 15.2, 6.3 Hz, 1H), 1.64 (s, 3H), 1.57 (dt, J = 6.5, 3.3 Hz, 4H), 1.26 (dd, J = 8.7, 5.5 Hz, 3H).  

**Step 2. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-(6-hydroxyhex-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanamide [3.1.28]**

3.1.28b was converted to 3.1.28 using the precess described in the synthesis of 3.1.20. LCMS (m/z): 437.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.32 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.64 (d, J = 7.2 Hz, 1H), 4.44 (t, J = 5.2 Hz, 1H), 4.18 (t, J = 8.9 Hz, 1H), 3.82 - 3.74 (m, 1H), 3.44 (d, J = 5.2 Hz, 2H), 3.08 (s, 3H), 2.78 (d, J = 14.2 Hz, 1H), 2.42 (s, 2H), 2.25 - 2.18 (m, 1H), 1.60 (s, 3H), 1.57 (d, J = 2.9 Hz, 4H).  

III 1.29. Synthesis of compound 3.1.29

**Step 1. Synthesis of 5-(4-bromophenyl) pent-4-ynal [3.1.29a]**

5-(4-bromophenyl)pent-4-yn-1-ol (0.6 g, 2.49 mmol, 1.0 equiv) was dissolved in dichloromethane (10 ml) and cooled to 0 °C. Dess-Martin periodinane (1.79 g, 4.23 mmol, 1.7 equiv) was added in portion wise and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, sodium thiosulphate solution and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (10-15 % EtOAc/Hexane) to afford the desired product 3.1.29a (0.25 g, 42 % yield). 1H NMR (400 MHz, DMSO) δ 9.71 (s, 1H), 7.60 - 7.51 (m, 2H), 7.36 - 7.29 (m, 2H), 2.77 (t, J = 6.9 Hz, 2H), 2.67 (t, J = 6.8 Hz, 2H).

**Step 2. Synthesis of 1-bromo-4-(5, 5-difluoropent-1-yn-1-yl) benzene [3.1.29b].**

3.1.29a (0.25 g, 1.05 mmol, 1.0 equiv) was dissolved in dichloromethane (10 ml) and cooled to -78 °C. DAST (0.67 g, 4.18 mmol, 4.0 equiv) was added drop wise and the reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was diluted with water, neutralized with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (3-5 % EtOAc/Hexane) to afford the desired product 3.1.29b (0.13 g, 47.6
% yield). $^1$H NMR (400 MHz, DMSO) $\delta$ 7.62 - 7.53 (m, 2H), 7.40 - 7.31 (m, 2H), 6.19 (tt, $J =$ 56.4, 4.5 Hz, 1H), 2.58 (t, $J =$ 7.3 Hz, 2H), 2.20 - 2.06 (m, 2H).

**Step 3. Synthesis of (R)-3-((S)-3-(4-(5-difluoropent-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [3.1.29]**

3.1.29b was converted to 3.1.29 using the process described for the synthesis of 2.4. LCMS (m/z): 445.2 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 11.07 (s, 1H), 9.28 (s, 1H), 7.53 (d, $J =$ 8.8 Hz, 2H), 7.44 (d, $J =$ 8.7 Hz, 2H), 6.19 (tt, $J =$ 56.5, 4.5 Hz, 1H), 4.64 (d, $J =$ 7.0 Hz, 1H), 4.18 (t, $J =$ 8.8 Hz, 1H), 3.79 (t, $J =$ 8.1 Hz, 1H), 3.08 (s, 3H), 2.77 (d, $J =$ 14.1 Hz, 1H), 2.58 (t, $J =$ 7.3 Hz, 2H), 2.24 - 2.18 (m, 1H), 2.17 - 2.05 (m, 2H), 1.60 (s, 3H).

111. **Synthesis of compound 3.1.30**

3.1.30 was prepared using the process described for the synthesis of 3.1.27. LCMS (m/z): 456.0 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 11.07 (s, 1H), 9.28 (s, 1H), 7.52 (d, $J =$ 8.4 Hz, 2H), 7.41 (d, $J =$ 8.4 Hz, 2H), 4.63 (s, 1H), 4.18 (s, 1H), 3.78 (s, 1H), 3.44 (t, $J =$ 6.0 Hz, 2H), 3.26 (s, 3H), 3.08 (s, 3H), 2.77 (d, $J =$ 13.9 Hz, 1H), 2.44 (d, $J =$ 7.1 Hz, 2H), 2.25 - 2.17 (m, 1H), 1.80 - 1.71 (m, 2H), 1.59 (s, 3H).

111. **Synthesis of compound 3.1.31**

3.1.31 was prepared using the process described for the synthesis of 3.1.28. LCMS (m/z): 425.2 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 11.08 (s, 1H), 9.16 (s, 1H), 7.51 (d, $J =$ 8.8 Hz, 2H), 7.41 (d, $J =$ 8.8 Hz, 2H), 4.66 (s, 1H), 4.54 (t, $J =$ 5.2 Hz, 1H), 4.17 (t, $J =$ 8.6 Hz, 1H), 3.82 - 3.75 (m, 1H), 3.52 (dd, $J =$ 11.5, 6.0 Hz, 2H), 3.08 (s, 3H), 2.75 (d, $J =$ 11.5 Hz, 1H), 2.45 (t, $J =$ 7.2 Hz, 2H), 2.23 - 2.16 (m, 1H), 1.72 - 1.64 (m, 2H), 1.58 (s, 3H).

111. **Synthesis of compound 3.1.32**

Step 1. **Synthesis of ethyl (R)-3-((S)-3-(4-ethylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.32a]**

1.1d (0.8 g, 1.8 mmol, 1.0 equiv), propionic acid (0.19 g, 2.7 mmol, 1.5 equiv), 1,4-bis(diphenylphosphino)butane (0.017 g, 0.04 mmol, 0.02 equiv), DBU(0.54 g, 3.7 mmol, 2.0 equiv) were added in DMSO (10 mL) and degassed for 10 minutes. PdCl$_2$(PPh$_3$)$_2$ (0.012 g, 0.02 mmol, 0.01 equiv) was added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (35-40 % EtOAc/Hexane) to afford the desired product 3.1.32a (0.44 g, 62.8 % yield). LCMS (m/z): 380.1 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.58 (dd, $J =$ 11.2, 9.0 Hz, 2H), 7.51 (d, $J =$ 9.0 Hz, 2H), 4.80 (d, $J =$ 8.3 Hz, 1H),...
4.25 (dt, J = 13.4, 7.8 Hz, 3H), 4.15 (s, 1H), 3.87 - 3.79 (m, 1H), 3.16 (s, 3H), 2.69 (d, J = 12.5 Hz, 1H), 2.42 - 2.35 (m, 1H), 1.65 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

**Step 2. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(4,4,4-trifluorobut-1-yn-1-yl)phenyl)oxazolidin-5-yl) propanoate [3.1.32b]**. Mixture of Pd$_3$(dba)$_3$ (0.036 g, 0.04 mmol, 0.05 equiv), DEP-phos (0.085 g, 0.2 mmol, 0.2 equiv), DABCO (0.18 g, 1.6 mmol, 2.0 equiv) were added in sealed tube and the sealed tube was evacuated and backfilled with argon thrice. 1, 1, 1-Trifluoro-2-iodoethane (0.33 g, 1.6 mmol, 2.0 equiv), 3.1.32a (0.3 g, 0.8 mmol, 1.0 equiv) in toluene (10 mL) was added and the reaction mixture was stirred at 80 °C for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel chromatography (30-40 % EtOAc/Hexane) to afford the desired product 3.1.32b (0.29 g, 59.2 % yield). LCMS (m/z): 462.2 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.57 (d, $J = 8.8$ Hz, 2H), 7.51 (t, $J = 7.2$ Hz, 2H), 4.83 - 4.76 (m, 1H), 4.30 - 4.19 (m, 3H), 3.80 (dt, $J = 21.0$, 9.2 Hz, 3H), 3.16 (s, 3H), 2.69 (d, $J = 12.2$ Hz, 1H), 2.40 - 2.35 (m, 1H), 1.65 (s, 3H), 1.26 (t, $J = 7.1$ Hz, 3H).

**Step 3. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(4,4,4-trifluorobut-1-yn-1-yl)phenyl)oxazolidin-5-yl) propanamide [3.1.32]**. 3.1.32b was converted to 3.1.32 using the process described for the synthesis of 3.1.20. LCMS (m/z): 449.2 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 11.09 (s, 1H), 9.32 (s, 1H), 7.57 (d, $J = 8.9$ Hz, 2H), 7.50 (d, $J = 8.9$ Hz, 2H), 4.65 (d, $J = 7.2$ Hz, 1H), 4.20 (t, $J = 8.9$ Hz, 1H), 3.86 - 3.70 (m, 3H), 3.08 (s, 3H), 2.77 (d, $J = 12.4$ Hz, 1H), 2.22 (dd, $J = 14.6$, 9.1 Hz, 1H), 1.60 (s, 3H).

**III.1.33. Synthesis of compound 3.1.33**

**Step 1. Synthesis of 3-methylenecyclobutane-1-carboxylic acid [3.1.33a]**

3-Methylenecyclobutane-1-carbonitrile (24 g, 258.0 mmol, 1.0 equiv) was dissolved in ethanol (160 mL). KOH (72.3 g, 1290.3 mmol, 5.0 equiv) in water (160 mL) was added and the reaction mixture was stirred at 80 °C for 2 hours. The reaction mixture was concentrated, acidified by 1.0 N HCl aqueous solution to the pH 2 to 3 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.33a (26.2 g, 91 % yield). $^1$H NMR (400 MHz, DMSO) $\delta$ 12.22 (s, 1H), 4.89 - 4.66 (m, 2H), 3.13 - 2.98 (m, 1H), 2.95 - 2.73 (m, 4H).

**Step 2. Synthesis of methyl 3-methylenecyclobutane-1-carboxylate [3.1.33b]**

3.1.33a (26.2 g, 233.9 mmol, 1.0 equiv) was dissolved in acetone (200 mL). K$_2$CO$_3$ (64.6 g, 467.8 mmol, 2.0 equiv) was added and cooled to 0 °C. Me$_3$SO$_4$ (35.4 g, 280.7 mmol, 1.2 equiv) was added drop wise and the reaction mixture was stirred at 50 °C for 2 hours. The reaction mixture was quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude
residue. The crude residue was purified by silica gel chromatography (30-35 % diethyl ether/n-pentane) to afford the desired product 3.1.33b (25.3 g, 86 % yield). $^1$H NMR (400 MHz, DMSO) δ 4.85 - 4.76 (m, 2H), 3.62 (s, 3H), 3.23 - 3.12 (m, 1H), 2.91 - 2.83 (m, 4H).

Step 3. Synthesis of methyl 3-(hydroxymethyl) cyclobutane-1-carboxylate [3.1.33c]
3.1.33b (25.3 g, 200.8 mmol, 1.0 equiv) was dissolved in THF (150 mL) and cooled to -20 °C. BH$_3$Me$_2$S (2.0 M) (100 mL, 200.8 mmol, 1.0 equiv) was added dropwise and the reaction mixture was stirred at rt for 4 hours. The reaction mixture was cooled to -10 °C. Methanol (20 mL) was added within 10 minutes. H$_2$O$_2$ (30 %) (13.7 g, 200.8 mmol, 1.0 equiv) and NaOH (3.0 M) (30 mL) were added dropwise and the reaction mixture was stirred at rt for 2 hours. The reaction mixture was quenched with saturated aqueous sodium hydrogen sulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (35-40 % EtOAc/Hexane) to afford the desired product 3.1.33c (17.3 g, 60 % yield). $^1$H NMR (400 MHz, DMSO) δ 4.62 - 4.39 (m, 1H), 3.58 (t, J = 6.9 Hz, 3H), 3.36 (d, J = 46.0 Hz, 2H), 3.16 - 2.96 (m, 1H), 2.35 - 2.26 (m, 1H), 2.14 (ddd, J = 18.0, 10.2, 5.6 Hz, 2H), 1.92 (ddd, J = 18.7, 11.7, 9.7, 3.6 Hz, 2H).

Step 4. Synthesis of methyl 3-(((methylsulfonyl) oxy) methyl) cyclobutane-1-carboxylate [3.1.33d]
3.1.33c (3 g, 20.8 mmol, 1.0 equiv) was dissolved in dichloromethane (30 mL) and cooled to 0 °C. TEA (14.6 g, 104.16 mmol, 5 equiv), MsCl (4.86 g, 62.5 mmol, 3.0 equiv) were added dropwise and the reaction mixture was stirred at rt for 6 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to a crude residue, which was purified by silica gel chromatography (40-45 % EtOAc/Hexane) to afford the desired product 3.1.33d (3 g, 65 % yield). $^1$H NMR (400 MHz, DMSO) δ 4.25 (d, J = 7.0 Hz, 1H), 4.14 (d, J = 6.4 Hz, 1H), 3.62 (t, J = 10.1 Hz, 3H), 3.19 (t, J = 8.7 Hz, 3H), 3.14 - 2.98 (m, 1H), 2.67 - 2.55 (m, 1H), 2.31 - 2.21 (m, 2H), 2.07 - 1.96 (m, 2H).

Step 5. Synthesis of methyl 3-((methylthio) methyl) cyclobutane-1-carboxylate [3.1.33e]
3.1.33d (3 g, 13.5 mmol, 1.0 equiv) was dissolved in N, N-dimethylformamide (25 mL). CH$_3$SnCl (1.42 g, 20.3 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.33e (2.23 g, 95 % yield). The product was directly used in the next step with no further purification. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.70 (d, J = 10.4 Hz, 3H), 3.16 - 2.99 (m, 1H), 2.65 - 2.60 (m, 1H), 2.60 - 2.55 (m, 1H), 2.52 - 2.35 (m, 3H), 2.10 (t, J = 2.5 Hz, 3H), 2.06 - 1.94 (m, 2H).

Step 6. Synthesis of methyl 3-((methylsulfonyl) methyl) cyclobutane-1-carboxylate [3.1.33f]
3.1.33e (2.23 g, 12.82 mmol, 1.0 equiv) was dissolved in dichloromethane (30
m-CPBA (70%) (6.3 g, 25.63 mmol, 2.0 equiv) was added in portions and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (50-55 % EtOAc/Hexane) to afford the desired product 3.1.33f (1.2 g, 47 % yield). 1H NMR (400 MHz, DMSO) δ 3.64 - 3.58 (m, 3H), 3.32 (s, 1H), 3.23 (d, J = 7.3 Hz, 1H), 3.19 - 3.06 (m, 1H), 2.90 (t, J = 3.3 Hz, 3H), 2.85 - 2.65 (m, 1H), 2.40 - 2.30 (m, 2H), 2.15 (ddd, J = 12.5, 9.5, 6.9 Hz, 1H), 2.02 (ddd, J = 19.2, 9.6, 2.6 Hz, 1H).

**Step 7. Synthesis of 3-((methylsulfonyl) methyl) cyclobutyl methanol [3.1.33g]**

3.1.33f (0.45 g, 2.18 mmol, 1.0 equiv) was dissolved in THF (15 mL) and methanol (2 mL). The reaction mixture was cooled to 0 °C. Sodium borohydride (0.17 g, 4.37 mmol, 2.0 equiv) was added in portions and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (5 % MeOH/dichloromethane) to afford the desired product 3.1.33g (0.42 g, 40 % yield). 1H NMR (400 MHz, DMSO) δ 4.12 - 3.93 (m, 1H), 3.64 - 3.57 (m, 2H), 3.15 (ddd, J = 26.8, 15.7, 6.6 Hz, 4H), 2.95 - 2.86 (m, 3H), 2.34 (dd, J = 15.6, 6.7 Hz, 2H), 2.19 - 2.10 (m, 1H), 2.06 - 1.98 (m, 1H).

**Step 8. Synthesis of 3-((methylsulfonyl) methyl) cyclobutane-1-carbaldehyde [3.1.33h]**

3.1.33g (0.42 g, 2.36 mmol, 1.0 equiv) was dissolved in dichloromethane (10 mL). PCC (0.92 g, 4.25 mmol, 1.8 equiv) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was filtered through celite bed, washed with dichloromethane and the filtrate was concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (70 % EtOAc/Hexane) to afford the desired product 3.1.33h (0.31 g, 75 % yield). 1H NMR (400 MHz, DMSO) δ 9.62 (dt, J = 149.4, 50.5 Hz, 1H), 3.64 - 3.58 (m, 1H), 3.25 - 3.05 (m, 2H), 2.94 - 2.87 (m, 3H), 2.85 - 2.65 (m, 1H), 2.43 - 2.26 (m, 2H), 2.20 - 1.99 (m, 2H).

**Step 9. Synthesis of 1-ethyl-3-((methylsulfonyl) methyl) cyclobutane [3.1.33j]**

3.1.33h (0.3 g, 1.7 mmol, 1.0 equiv) was dissolved in methanol (10 mL). K₂CO₃ (0.47 g, 3.4 mmol, 2.0 equiv), Ohira bestmann reagent (0.43 g, 2.21 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (50 % EtOAc/Hexane) to afford the
desired product 3.1.33j (0.13 g, 44 % yield). \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 3.62 - 3.58 (m, 2H), 3.34 - 3.17 (m, 3H), 2.94 - 2.88 (m, 3H), 2.49 - 2.41 (m, 1H), 2.23 - 2.13 (m, 2H).

**Step 10. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-3-(4-((3-((methylsulfonyl) methyl) cyclobutyl) ethynyl)-2-oxooxazolidin-5-yl) propanamide [3.1.33].** 3.1.33 was synthesized from 3.1.33i using the process described for the synthesis of 3.1.20. LCMS (m/z): 513.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.09 (s, 1H), 9.32 (s, 1H), 7.52 (dd, \(J = 8.8, 2.8\) Hz, 2H), 7.42 (t, \(J = 10.0\) Hz, 2H), 4.64 (d, \(J = 6.2\) Hz, 1H), 4.19 (d, \(J = 9.1\) Hz, 1H), 3.78 (t, \(J = 8.4\) Hz, 1H), 3.37 (s, 1H), 3.30 (d, \(J = 7.2\) Hz, 1H), 3.26 - 3.13 (m, 1H), 3.08 (s, 3H), 2.93 (d, \(J = 9.1\) Hz, 3H), 2.77 (d, \(J = 14.4\) Hz, 1H), 2.66 (d, \(J = 8.0\) Hz, 1H), 2.38 - 2.15 (m, 3H), 2.02 (d, \(J = 11.3\) Hz, 1H), 1.60 (s, 3H).

**III.1.34. Synthesis of compound 3.1.34**

**Step 1. Synthesis of ethyl (R)-3-((S)-3-(4-(5-hydroxypent-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.34a].**

1.1d (0.5 g, 1.15 mmol, 1.0 equiv), pent-4-yn-1-ol (0.13 g, 1.49 mmol, 1.3 equiv), Cul (0.022 g, 0.12 mmol, 0.1 equiv), triphenylphosphine (0.061 g, 0.23 mmol, 0.2 equiv) were dissolved in diethyl amine (5 mL) and N, N-dimethylformamide (1 mL) in sealed tube. The reaction mixture was degassed for 10 minutes. PdCl\(_2\)(pPh\(_3\))_2 (0.041 g, 0.057 mmol, 0.05 equiv) was added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (70 % EtOAc/Hexane) to afford the desired product 3.1.34a (0.46 g, 92 % yield). LCMS (m/z): 438.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.52 (d, \(J = 8.9\) Hz, 2H), 7.41 (d, \(J = 8.9\) Hz, 2H), 4.79 (dd, \(J = 14.2, 8.1\) Hz, 1H), 4.54 (dd, \(J = 6.4, 3.9\) Hz, 1H), 4.31 - 4.15 (m, 3H), 3.86 - 3.77 (m, 1H), 3.51 (dd, \(J = 11.5, 6.2\) Hz, 2H), 3.16 (s, 3H), 2.68 (dd, \(J = 14.9, 2.4\) Hz, 1H), 2.45 (t, \(J = 7.1\) Hz, 2H), 2.36 (dd, \(J = 11.6, 5.7\) Hz, 1H), 1.69 (dd, \(J = 13.5, 6.7\) Hz, 2H), 1.64 (s, 3H), 1.26 (t, \(J = 7.1\) Hz, 3H).

**Step 2. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-3-(4-(5-((methylsulfonyl) oxy) pent-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl) propanoate [3.1.34b].**

3.1.34a (0.2 g, 0.46 mmol, 1.0 equiv) was dissolved in dichloromethane (10 mL) and cooled to 0 °C. TEA (0.32 g, 2.29 mmol, 5.0 equiv), MeSO\(_2\)Cl (0.11 g, 1.37 mmol, 3.0 equiv) were added and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.34b (0.21 g, 88 % yield). LCMS (m/z): 516.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.53 (d, \(J = 8.8\) Hz, 2H), 7.43 (d, \(J = 8.7\) Hz, 2H), 4.79 (d, \(J = 6.8\) Hz, 1H), 4.30 - 4.21 (m, 3H), 3.86 - 3.78 (m, 1H), 3.21 (s, 3H), 3.08 (dd, \(J = 7.3, 4.8\) Hz, 2H), 2.69 (d, \(J = 122\)
15.0 Hz, 1H), 2.55 (d, J = 7.0 Hz, 2H), 2.46 - 2.29 (m, 4H), 1.95 (dt, J = 13.6, 6.8 Hz, 2H), 1.64 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 3. Synthesis of ethyl (R)-3-((S)-3-(4-(5-(2H-1, 2, 3-triazol-2-yl) pent-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.34c]

3.1.34b (0.21 g, 0.41 mmol, 1.0 equiv) was dissolved in N, N-dimethylformamide (8 mL) in sealed tube. 2H-1, 2, 3-triazole (0.056 g, 0.82 mmol, 2.0 equiv) were added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was quenched with water extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (40 % EtOAc/Hexane) to afford the desired product 3.1.34c (0.085 g, 42 % yield). LCMS (m/z): 489.4 [M+H].

1H NMR (400 MHz, DMSO) δ 7.95 (d, J = 5.9 Hz, 2H), 7.53 (d, J = 8.9 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H), 4.79 (d, J = 7.1 Hz, 1H), 4.56 (t, J = 6.8 Hz, 2H), 4.24 (dt, J = 17.4, 7.6 Hz, 3H), 3.86 - 3.77 (m, 1H), 3.16 (s, 3H), 2.69 (d, J = 15.0 Hz, 1H), 2.43 (t, J = 7.0 Hz, 2H), 2.40 - 2.35 (m, 1H), 2.13 (dt, J = 15.3, 7.5 Hz, 2H), 1.64 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 4. Synthesis of (R)-3-((S)-3-(4-(5-(2H-1, 2, 3-triazol-2-yl) pent-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [3.1.34]

3.1.34 was prepared by the process of example 3.1.20. LCMS (m/z): 476.4 [M+H].

1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.31 (s, 1H), 7.80 (s, 2H), 7.52 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 4.64 (d, J = 6.0 Hz, 1H), 4.56 (t, J = 6.8 Hz, 2H), 4.18 (t, J = 8.8 Hz, 1H), 3.83 - 3.75 (m, 1H), 3.08 (s, 3H), 2.77 (d, J = 12.3 Hz, 1H), 2.43 (t, J = 7.0 Hz, 2H), 2.24 - 2.18 (m, 1H), 2.17 - 2.10 (m, 2H), 1.60 (s, 3H).

III.1.35. Synthesis of compound 3.1.35

Step 1. Synthesis of allyl 4-nitrobenzoate [3.1.35a]. 4-Nitrobenzoyl chloride (15.9 g, 86.0 mmol, 1.0 equiv), prop-2-en-1-ol (5 g, 86.0 mmol, 1.0 equiv) were dissolved in dichloromethane (100 mL) and cooled to 0 °C. TEA (9.58 g, 94.0 mmol, 1.1 equiv) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.35a (9.7 g, 54.5 % yield). 1H NMR (400 MHz, DMSO) δ 8.41 - 8.31 (m, 2H), 8.28 - 8.17 (m, 2H), 6.07 (ddt, J = 17.2, 10.7, 5.5 Hz, 1H), 5.44 (dq, J = 17.2, 1.6 Hz, 1H), 5.32 (ddd, J = 10.5, 2.7, 1.3 Hz, 1H), 4.87 (dt, J = 5.4, 1.4 Hz, 2H).

Step 2. Synthesis of (2, 2-difluorocyclopropyl) methyl 4-nitrobenzoate [3.1.35b].

3.1.35a (8.7 g, 42.0 mmol, 1.0 equiv) was mixed with CsF (0.05 g) and heated to 90 °C. TFD (23.1 g, 92.0 mmol, 2.2 equiv) was added within 10 hours. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with saturated
aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude residue was purified by silica gel column chromatography (4:5 EtOAc/Hexane) to afford the desired product 3.1.35b (2.9 g, 24.2 % yield). ¹H NMR (400 MHz, DMSO) δ 8.44 - 8.33 (m, 2H), 8.28 - 8.19 (m, 2H), 4.60 - 4.46 (m, 1H), 4.37 - 4.25 (m, 1H), 2.36 - 2.19 (m, 1H), 1.84 - 1.68 (m, 1H), 1.60 (ddt, J = 12.2, 7.7, 4.4 Hz, 1H).

Step 3. Synthesis of (2, 2-difluorocyclopropyl) methanol [3.1.35c]. 3.1.35b (2.4 g, 9.3 mmol, 1.0 equiv) was added to 10 % NaOH solution (1.1 g, 28.0 mmol, 3.0 equiv) and the reaction mixture was stirred at 80 °C for 2 hours. The reaction mixture was quenched with water and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 3.1.35c (0.77 g, 77 % yield). ¹H NMR (400 MHz, DMSO) δ 4.89 (t, J = 5.6 Hz, 1H), 3.52 (ddt, J = 6.5, 5.2, 2.6 Hz, 1H), 3.41 - 3.33 (m, 2H), 1.86 (ddddd, J = 14.1, 11.6, 9.7, 7.1 Hz, 1H), 1.57 - 1.45 (m, 1H), 1.19 (ddt, J = 13.7, 7.6, 4.0 Hz, 1H).

Step 4. Synthesis of 2, 2-difluorocyclopropane-1-carbaldehyde [3.1.35d]. 3.1.35c (0.4 g, 3.7 mmol, 1.0 equiv) was dissolved in dichloromethane (5 mL) and cooled to 0 °C. PCC (1.2 g, 5.6 mmol, 1.5 equiv) was added and the reaction mixture was stirred at rt for 5 hours. The reaction mixture was diluted with diethyl ether, the solvent was decanted and concentrated without applying vacuum at 45 °C to afford the desired product 3.1.35d (1 mL solution in dichloromethane). The product was used as such in dichloromethane solution.

Step 5. Synthesis of 2-ethynyl-1, 1-difluorocyclopropane [3.1.35e]. 3.1.35d (0.2 g, 1.9 mmol, 1.0 equiv) and ohira bestmann reagent (0.55 g, 2.8 mmol, 1.5 equiv) were added in ethanol (5 mL). K₂CO₃ (0.52 g, 3.8 mmol, 2.0 equiv) was added and the reaction mixture was stirred at rt for 24 hours. The product was isolated by fractional distillation at 55 °C without applying vacuum to afford product 3.1.35e (2 mL solution in EtOH and diethyl ether). The product was used as such with solution in ethanol & diethyl ether.


3.1.35e was synthesized by the process of example 3.1.20. LCMS (m/z): 443.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 9.30 (s, 1H), 7.55 (d, J = 8.9 Hz, 2H), 7.46 (d, J = 8.9 Hz, 2H), 4.64 (d, J = 7.5 Hz, 1H), 4.19 (t, J = 8.8 Hz, 1H), 3.82 - 3.75 (m, 1H), 3.08 (s, 3H), 2.86 - 2.74 (m, 2H), 2.25 - 2.19 (m, 1H), 2.10 - 2.01 (m, 1H), 1.80 (dd, J = 12.9, 5.2 Hz, 1H), 1.60 (s, 3H).

III.1.36. Synthesis of compound 3.1.36

Step 1. Synthesis of methyl (1r, 3r)-3-ethynylcyclobutane-1-carboxylate [3.1.36a]. Methyl (1r, 3r)-3-formylcyclobutane-1-carboxylate (0.23 g, 1.62 mmol, 1.0 equiv) was
dissolved in methanol (10 ml). K$_2$CO$_3$ (0.45 g, 3.23 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 5 minutes. Ohira Bestmann reagent (0.38 g, 1.94 mmol, 1.2 equiv) was added and the reaction mixture was stirred at rt for 1 hour. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (5% diethyl ether/n-pentane) to afford the desired product 3.1.36a (0.2 g, 89.5 % yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.75 - 3.65 (m, 3H), 3.27 (dd, $J = 13.3$, 7.2 Hz, 1H), 3.19 (d, $J = 8.7$ Hz, 1H), 2.66 - 2.50 (m, 2H), 2.46 - 2.32 (m, 2H), 2.22 (dd, $J = 16.0$, 2.5 Hz, 1H).

**Step 2. Synthesis of methyl (1r, 3r)-3-((4-bromophenyl) ethynyl)cyclobutane-1-carboxylate [3.1.36b].** 3.1.36a (0.19 g, 1.41 mmol, 1.0 equiv), 1-bromo-4-iodobenzene (0.4 g, 1.41 mmol, 1.0 equiv) were mixed in diethyl amine (9 ml) and N, N-dimethylformamide (1 ml). Cul (0.026 g, 0.14 mmol, 0.1 equiv), triphenylphosphine (0.074 g, 0.28 mmol, 0.2 equiv) were added and the reaction mixture was degassed for 10 minutes. PdCl$_2$(pp$\text{h}_3$)$_2$ (0.049 g, 0.07 mmol, 0.05 equiv) was added and the reaction mixture was stirred at 120 °C for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (0-10 % EtOAc/Hexane) to afford the desired product 3.1.36b (0.18 g, 43.4 % yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.49 - 7.40 (m, 2H), 7.30 - 7.25 (m, 2H), 3.74 (s, 3H), 3.46 - 3.35 (m, 1H), 3.35 - 3.25 (m, 1H), 2.72 - 2.62 (m, 2H), 2.52 - 2.41 (m, 2H).

**Step 3. Synthesis of 2-((1r, 3r)-3-((4-bromophenyl) ethynyl)cyclobutyl)propan-2-ol [3.1.36c].** 3.1.36b (0.18 g, 0.61 mmol, 1.0 equiv) was dissolved THF (5 mL) and cooled to 20 °C. MeMgBr (3 M in ether) (0.82 g, 2.45 mmol, 4.0 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-10 % EtOAc/Hexane) to afford the desired product 3.1.36c (0.17 g, 94.4 % yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48 - 7.40 (m, 2H), 7.29 (dd, $J = 6.6$, 1.9 Hz, 2H), 3.16 - 3.06 (m, 1H), 2.70 - 2.59 (m, 1H), 2.44 - 2.30 (m, 2H), 2.21 - 2.10 (m, 2H), 1.16 (d, $J = 8.1$ Hz, 6H).

**Step 4. Synthesis of (R)-N-hydroxy-3-(((S)-3-((1r, 3S)-3-((2-hydroxypropan-2-yl)cyclobutyl) ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanamide [3.1.36].** 3.1.36 was synthesized by the process of example 2.4. LCMS (m/z): 479.3 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.52 (d, $J = 8.6$ Hz, 2H), 7.42 (d, $J = 8.5$ Hz, 2H), 4.65 (s, 1H), 4.20 (d, $J = 8.3$ Hz, 2H), 3.80 (d, $J = 8.4$ Hz, 1H).
3.06 (d, J = 14.5 Hz, 4H), 2.77 (d, J = 15.1 Hz, 1H), 2.45 (d, J = 7.9 Hz, 2H), 2.39 - 2.30 (m, 2H), 2.26 - 2.16 (m, 1H), 1.97 (s, 2H), 1.60 (s, 3H), 1.00 (s, 6H).

III.1.37. Synthesis of compound [3.1.37]

Step 1. Synthesis of ethyl (R)-3-((S)-3-(4-ethynylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.37a]. 1.1d (0.5 g, 1.15 mmol, 1.0 equiv) was dissolved in DMSO (10 ml). 1,4-Bis(diphenylphosphino) butane (0.011 g, 0.026 mmol, 0.023 equiv), DBU (0.35 g, 2.3 mmol, 2.0 equiv) were added and the reaction mixture was degassed for 10 minutes. Propionic acid (0.12 g, 1.73 mmol, 1.5 equiv), PdCl$_2$(PPh$_3$)$_2$ (0.0088 g, 0.012 mmol, 0.01 equiv) were added and the reaction mixture was stirred at 110 °C for 4 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (40-50 % EtOAc in Hexane) to afford the desired product 3.1.37a (4.3 g, 96 % yield). LCMS (m/z): 380.1 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.66 - 7.45 (m, 4H), 4.80 (d, J = 8.3 Hz, 1H), 4.24 (dt, J = 13.2, 7.9 Hz, 3H), 4.15 (s, 1H), 3.83 (t, J = 8.2 Hz, 1H), 3.17 (s, 3H), 2.69 (d, J = 14.2 Hz, 1H), 2.37 (dd, J = 14.7, 8.9 Hz, 1H), 1.65 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 2. Synthesis of ethyl (R)-3-((S)-3-(4-(5-hydroxypenta-1, 3-diyn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.37b]. Cul (0.0075 g, 0.039 mmol, 0.05 equiv) and NiCl$_2$H$_2$O (0.011 g, 0.039 mmol, 0.05 equiv) were added in THF (5 ml). TMEDA (0.018 g, 0.16 mmol, 0.2 equiv) was added and the reaction mixture was stirred at room temperature for 2 minutes. 3.1.37a (0.3 g, 0.79 mmol, 1.0 equiv), prop-2-yn-1-ol (0.044 g, 0.79 mmol, 1.0 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours under air. The reaction mixture was concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (50 % EtOAc/Hexane) to afford the desired product 3.1.37b (0.13 g, 37 % yield). LCMS (m/z): 434.3 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.71 - 7.51 (m, 4H), 5.47 (s, 1H), 4.81 (d, J = 6.8 Hz, 1H), 4.33 - 4.13 (m, 5H), 3.89 - 3.79 (m, 1H), 3.16 (s, 3H), 2.69 (d, J = 12.9 Hz, 1H), 2.37 (dd, J = 14.9, 8.9 Hz, 1H), 1.64 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 3. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-(5-hydroxypenta-1, 3-diyn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanamide [3.1.37]. 3.1.37 was synthesized from 3.1.37b by the process of example 3.1.20. LCMS (m/z): 438.1 [M+18]. $^1$H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 9.31 (s, 1H), 7.68 - 7.53 (m, 4H), 5.48 (t, J = 6.1 Hz, 1H), 4.66 (d, J = 7.6 Hz, 1H), 4.26(d, J = 6.1 Hz, 2H), 4.20(t, J = 8.8 Hz, 1H), 3.84 - 3.76 (m, 1H), 3.08 (s, 3H), 2.78 (d, J = 14.6 Hz, 1H), 2.22 (dd, J = 14.5, 8.9 Hz, 1H), 1.60 (s, 3H).

III.1.38. Synthesis of compound 3.1.38
3.1.38 was prepared from 3.1.37 by the process of example 3.1.27. LCMS (m/z): 433.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.61 (q, J = 8.9 Hz, 4H), 4.66 (s, 1H), 4.31 (s, 2H), 4.21 (s, 1H), 3.81 (dd, J = 16.2, 8.0 Hz, 1H), 3.31 (s, 3H), 3.08 (s, 3H), 2.77 (d, J = 13.4 Hz, 1H), 2.22 (dd, J = 14.4, 9.2 Hz, 1H), 1.60 (s, 3H).

111.1.39. Synthesis of compound 3.1.39

Step 1. Synthesis of hept-5-ynal [3.1.39a]. Hex-5-yn-1-ol (0.3 g, 3.06 mmol, 1.0 equiv) was dissolved in dichloromethane (10 mL). PCC (1.32 g, 6.12 mmol, 2.0 equiv) was added in portion wise and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with diethyl ether and filtered through celite bed. The filtrate was concentrated to afford the desired product 3.1.39 (0.19 g, 64.6 % yield). 1H NMR (400 MHz, DMSO) δ 9.68 (t, J = 1.3 Hz, 1H), 2.82 (q, J = 2.3 Hz, 1H), 2.56 - 2.51 (m, 2H), 2.19 (td, J = 7.1, 2.6 Hz, 2H), 1.71 (dd, J = 14.3, 7.1 Hz, 2H).

Step 2. Synthesis of hept-6-yn-2-ol [3.1.39b]. 3.1.39a (0.19 g, 1.97 mmol, 1.0 equiv) was dissolved in THF (5 mL) and cooled to -78 °C. Methyl magnesium bromide (3.0 M in THF) (0.47 g, 3.95 mmol, 2.0 equiv) was added and the reaction mixture was stirred at -20 °C for 2 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.1.39b (0.13 g, 58.6 % yield). 1H NMR (400 MHz, DMSO) δ 4.39 (d, J = 4.8 Hz, 1H), 3.58 (dd, J = 11.0, 5.8 Hz, 1H), 2.75 (t, J = 2.6 Hz, 1H), 2.17 - 2.13 (m, 2H), 1.44 (ddd, J = 20.7, 13.2, 6.6 Hz, 4H), 1.04 (d, J = 6.1 Hz, 3H).

Step 3. Synthesis of (2R)-N-hydroxy-3-((5S)-3-(4-(6-hydroxyhept-1-yn-1-yl)propanamide [3.1.39]. 3.1.39 was synthesized from 3.1.39b by the process of example 3.1.20. LCMS (m/z): 451.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.30 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.7 Hz, 2H), 4.63 (s, 1H), 4.41 (d, J = 4.7 Hz, 1H), 4.18 (s, 1H), 3.82 - 3.76 (m, 1H), 3.66 - 3.58 (m, 1H), 3.08 (s, 3H), 2.77 (d, J = 14.7 Hz, 1H), 2.41 (t, J = 6.9 Hz, 2H), 2.23 (d, J = 9.2 Hz, 1H), 1.59 (s, 3H), 1.54 (d, J = 8.1 Hz, 2H), 1.49 - 1.42 (m, 2H), 1.06 (d, J = 6.1 Hz, 3H).

111.1.40. Synthesis of compound 3.1.40

Step 1. Synthesis of hept-6-yn-2-one [3.1.40a]. 3.1.39b (0.27 g, 2.41 mmol, 1.0 equiv) was dissolved in dichloromethane (15 mL). PDC (1.81 g, 4.82 mmol, 2.0 equiv) was added in portion wise and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with diethyl ether and filtered through celite bed. The filtrate was concentrated to afford product 3.1.40a (0.22 g, 83 % yield). The crude product was used as such in next step without further purification.
Step 2. Synthesis of 2-methylhept-6-yn-2-ol [3.1.40b]. 3.1.40a (0.22 g, 2.0 mmol, 1.0 equiv) was dissolved in THF (5 mL) and cooled to -78 °C. Methyl magnesium bromide (3.0 M in THF) (0.47 g, 4.0 mmol, 2.0 equiv) was added and the mixture was stirred at -20 °C for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford 3.1.40b (0.2g, 80% yield). 1H NMR (400 MHz, DMSO) δ 4.15 (s, 1H), 2.75 (t, J = 2.6 Hz, 1H), 2.16 - 2.10 (m, 2H), 1.45 (m, 4H), 1.07 (s, 6H).

Step 3. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-hydroxy-6-methylhept-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [3.1.40]

Compound 3.1.40 was synthesized from 3.1.40b by the process of example 3.1.20. LCMS (m/z): 466.1 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.06 (s, 1H), 9.28 (s, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 4.69 - 4.60 (m, 1H), 4.22 - 4.13 (m, 2H), 3.82 - 3.76 (m, 1H), 3.08 (s, 3H), 2.78 (d, J = 14.4 Hz, 1H), 2.40 (t, J = 6.9 Hz, 2H), 2.21 (dd, J = 14.5, 8.9 Hz, 1H), 1.60 (s, 3H), 1.59 - 1.53 (m, 2H), 1.51 - 1.45 (m, 2H), 1.10 (s, 6H).

III.1.1. Synthesis of compound 3.1.41

Step 1. Synthesis of ethyl (2R)-3-((5S)-3-(4-(5-hydroxyhexa-1, 3-diyln-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.41a]. (R)-ethyl 3-((S)-3-(4-ethynylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate (0.25 g, 0.65 mmol, 1.0 equiv), CuCl (0.004 g, 0.033 mmol, 0.05 equiv) and NH2OH.HCl (0.003 g, 0.033 mmol, 0.05 equiv) were dissolved in n-butyl amine (8 mL). 4-Bromobut-3-yn-2-ol (0.15 g, 0.98 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel chromatography (15-20 % EtOAc/Hexane) to afford product 3.1.41a (0.14 g, 48 % yield). LCMS (m/z): 448.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.64 - 7.54 (m, 4H), 5.63 (d, J = 5.5 Hz, 1H), 4.81 (dd, J = 14.3, 7.9 Hz, 1H), 4.58 - 4.49 (m, 1H), 4.31 - 4.15 (m, 3H), 3.83 (dd, J = 15.2, 6.3 Hz, 1H), 3.15 (d, J = 13.5 Hz, 3H), 2.69 (dd, J = 14.8, 2.3 Hz, 1H), 2.37 (dd, J = 14.9, 9.0 Hz, 1H), 1.64 (d, J = 5.3 Hz, 3H), 1.35 (d, J = 6.6 Hz, 3H), 1.26 (dd, J = 8.5, 5.7 Hz, 4H).

Step 2. Synthesis of (2R)-N-hydroxy-3-((5S)-3-(4-(5-hydroxyhexa-1, 3-diyln-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanamide [3.1.41]

3.1.41 was synthesized from 3.1.41a using the process of example 3.1.20. LCMS (m/z): 435.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.31 (s, 1H), 7.59 (s, 4H), 5.63 (d, J = 5.7 Hz, 1H), 4.65 (s, 1H), 4.59 - 4.48 (m, 1H), 4.20 (s, 1H), 3.80 (s, 1H), 3.08 (s, 3H), 2.78 (d, J = 13.8 Hz, 1H), 2.24 (d, J = 8.8 Hz, 1H), 1.60 (s, 3H), 1.35 (d, J = 6.6 Hz, 3H).
3.1.42. Synthesis of compound 3.1.42 & 3.1.43. 3.1.36 (0.04 g, 0.084 mmol, 1.0 equiv) was dissolved in acetonitrile (2 mL) and cooled to 0 °C. Cone. H₂SO₄ (0.057 g, 0.59 mmol, 7.0 equiv) was added and the reaction mixture was stirred at rt for 3 hours. The reaction mixture was quenched with water, neutralized with solid sodium bicarbonate and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to a crude product, which was purified by preparative HPLC to afford the product: Isomer-A 3.1.42 (0.006 g, 14 % yield). LCMS (m/z): 520.5 [M+H]. ¹H NMR (400 MHz, DMSO) δ 8.42 (s, 1H), 7.61 (d, J = 9.1 Hz, 1H), 7.51 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.4 Hz, 2H), 4.66 (s, 1H), 4.16 (s, 1H), 4.04 (d, J = 8.3 Hz, 1H), 3.79 (s, 1H), 3.13 (s, 1H), 3.08 (s, 3H), 2.74 (d, J = 15.0 Hz, 1H), 2.18 (s, 1H), 1.95 (dd, J = 25.3, 13.3 Hz, 3H), 1.84 (s, 3H), 1.58 (d, J = 11.6 Hz, 4H), 1.00 (s, 3H), 0.82 (s, 3H). Isomer-B 3.1.43 (0.003 g, 7 % yield). LCMS (m/z): 520.4 [M+H]. ¹H NMR (400 MHz, MeOD) δ 8.55 (s, 1H), 7.53 (s, 2H), 7.41 (s, 2H), 4.79 - 4.75(m, 2H), 4.23(s, 1H), 3.87 (s, 1H), 3.12 (s, 4H), 2.88 (s, 1H), 2.33 (d, J = 9.5 Hz, 3H), 2.10 (s, 2H), 1.91 (s, 3H), 1.76 (s, 3H), 1.31 (s, 6H).

III.1.45. Synthesis of compound 3.1.45 & 3.1.46

Compounds 3.1.45 & 3.1.46 were synthesized from 3.1.19f by the process of example 3.1.1. The diastereomers were separated by reverse phase HPLC. 3.1.45: LCMS (m/z): 453.9 [M+18]. ¹H NMR (400 MHz, DMSO) δ 7.99 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.61 (s, 1H), 4.16 (t, J = 8.8 Hz, 1H), 3.99 - 3.90 (m, 1H), 3.78 (d, J = 8.1 Hz, 1H), 3.12 - 2.96 (m, 3H), 2.75 (d, J = 13.6 Hz, 1H), 2.69 - 2.61 (m, 1H), 2.56 (s, 2H), 2.25 - 2.14 (m, 1H), 1.92 (d, J = 9.1 Hz, 2H), 1.58 (s, 3H). 3.1.46 (0.015 g, 9.4 % yield). LCMS (m/z): 453.9 [M+18]. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.48 - 7.34 (m, 2H), 5.21 (d, J = 6.1 Hz, 1H), 4.64 (d, J = 9.7 Hz, 1H), 4.39(dd, J = 13.8, 6.8 Hz, 1H), 4.18 (t, J = 8.9 Hz, 1H), 3.85 - 3.72 (m, 1H), 3.19 - 3.11 (m, 1H), 3.11 - 2.99 (m, 3H), 2.81 - 2.74 (m, 1H), 2.34 - 2.25 (m, 2H), 2.26 - 2.12 (m, 3H), 1.66 - 1.52 (m, 3H).

III.1.47. Synthesis of compound 3.1.47 & 3.1.48

Compounds 3.1.47 & 3.1.48 were synthesized by the process of example 3.1.19.

Compound 3.1.47: LCMS (m/z): 467.7 [M+18]. ¹H NMR (400 MHz, DMSO) δ 11.29 - 10.91 (m, 1H), 9.35 (s, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.41 (d, J = 8.6 Hz, 2H), 4.65 (s, 1H), 4.18 (s, 1H), 3.84 - 3.70 (m, 2H), 3.07 (t, J = 26.2 Hz, 6H), 2.79 (dd, J = 22.9, 12.0 Hz, 2H), 2.63 (d, J = 7.2 Hz, 2H), 2.27 - 2.15 (m, 1H), 1.94 (d, J = 8.4 Hz, 2H), 1.58 (s, 3H). Compound 3.1.48: LCMS (m/z): 467.7 [M+18]. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.33 (s, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 4.64 (d, J = 7.0 Hz, 1H), 4.18 (t, J = 8.6 Hz, 1H), 4.15 - 4.09 (m, 1H), 3.83 - 3.75 (m, 1H), 3.23 (s, 1H), 3.12 (d, J = 27.1 Hz, 6H), 2.77 (d, J = 14.5 Hz, 1H), 2.35 - 2.18 (m, 5H), 1.60 (s, 3H).
111. 1.49. Synthesis of compound 3.1.49

Compound 3.1.49 was synthesized by the process of example 3.1.14. LCMS (m/z): 447.1. 
$^1$H NMR (MeOD-d$_4$): 7.82 (s, 1H), 7.61 (s, 1H), 7.57 (d, J=8.8 Hz, 2H), 7.46 (d, J=8.8 Hz, 2H), 4.23 (t, J=8.7 Hz, 1H), 3.82-3.92 (m, 5H), 3.09 (s, 3H), 2.87 (d, J=14.2 Hz, 1H), 2.33 (dd, J=1 4.5, 9.1 Hz, 1H), 1.74 (s, 3H)

111. 1.50. Synthesis of compound 3.1.50

Compound 3.1.50 was synthesized by the process of example 3.1.14. LCMS (m/z): 409.2 [M+H]. $^1$H NMR (MeOD-d$_4$): 7.48-7.54 (m, 2H), 7.34-7.41 (m, 2H), 4.69-4.79 (m, 1H), 4.17-4.25 (m, 1H), 3.82-3.87 (m, 1H), 3.06-3.11 (m, 3H), 2.82-2.89 (m, 1H), 2.36-2.41 (m, 2H), 2.28-2.35 (m, 1H), 1.69-1.77 (m, 3H), 1.57-1.66 (m, 2H), 1.01-1.11 (m, 3H)

111. 1.51. Synthesis of compound 3.1.51

Compound 3.1.51 was synthesized by the process of example 3.1.14. LCMS (m/z): 451.1 [M+H]. $^1$H NMR (MeOD-d$_4$): 7.53 (d, J=9.1 Hz, 2H), 7.39 (d, J=8.8 Hz, 2H), 4.70-4.78 (m, 1H), 4.22 (t, J=8.8 Hz, 1H), 3.75-3.95 (m, 4H), 3.60 (dd, J=8.5, 5.7 Hz, 1H), 3.09 (s, 3H), 2.87 (dd, J=14.7, 2.4 Hz, 1H), 2.52 (s, 3H), 2.33 (dd, J=14.5, 8.8 Hz, 1H), 2.14 (dd, J=1 3.1, 5.5 Hz, 2H), 1.76-1.84 (m, 1H), 1.74 (s, 3H)

111. 1.52. Synthesis of compound 3.1.52

Compound 3.1.52 was synthesized by the process of example 3.1.14. LCMS (m/z): 429.2 [M+H]. $^1$H NMR (DMSO-d$_6$): 8.55 (d, J=6.0 Hz, 2H), 7.64-7.69 (m, 2H), 7.58-7.63 (m, 2H), 7.54 (d, J=6.0 Hz, 2H), 4.72-4.80 (m, 1H), 4.26 (t, J=8.8 Hz, 1H), 3.85-3.92 (m, 1H), 3.10 (s, 3H), 2.89 (dd, J=14.5, 2.2 Hz, 1H), 2.34 (dd, J=14.5, 8.8 Hz, 1H), 1.75 (s, 3H)

111. 1.53. Synthesis of compound 3.1.53

Compound 3.1.53 was synthesized by the process of example 3.1.14. LCMS (m/z) 409.3 [M+H]

111. 1.54. Synthesis of compound 3.1.54

Compound 3.1.54 was synthesized by the process of example 3.1.14. LCMS (m/z): 512.4 [M+1]$.^1$H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.31 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.39 (d, J = 8.8 Hz, 2H), 4.64 (d, J = 6.9 Hz, 1H), 4.18 (t, J = 8.8 Hz, 1H), 3.82 - 3.74 (m, 1H), 3.62 (d, J = 4.5 Hz, 2H), 3.28 (d, J = 2.8 Hz, 6H), 3.08 (s, 3H), 2.94 - 2.86 (m, 1H), 2.77 (d, J = 12.3 Hz, 1H), 2.21 (dd, J = 14.3, 9.0 Hz, 3H), 1.82 - 1.70 (m, 2H), 1.60 (s, 3H).

III. 1.55. Synthesis of compound 3.1.55

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Compound 3.1.55 was synthesized by the process of example 3.1.14. LCMS (m/z): 458.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 8.78 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.62 (s, 4H), 7.59 (d, J = 8.2 Hz, 1H), 4.65 (d, J = 6.8 Hz, 1H), 4.20 (t, J = 8.7 Hz, 1H), 3.82 (d, J = 8.5 Hz, 1H), 3.07 (s, 3H), 2.77 (d, J = 13.4 Hz, 1H), 2.59 (s, 3H), 2.21 (dd, J = 14.5, 9.3 Hz, 1H), 1.59 (s, 3H).

111.1.56. Synthesis of compound 3.1.56

Compound 3.1.56 was synthesized by the process of example 3.1.14. LCMS (m/z) 437.1 [M+H]. 1H NMR (400 MHz, DMSO-d6) δ 11.06 (s, 1H), 9.27 (s, 1H), 7.51 (d, J = 8.9 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 4.70 - 4.56 (m, 1H), 4.17 (t, J = 8.8 Hz, 1H), 4.09 - 3.90 (m, 1H), 3.90 - 3.66 (m, 3H), 3.57 (dd, J = 8.0, 6.8 Hz, 1H), 3.31 - 3.15 (m, 1H), 3.07 (s, 3H), 2.83 - 2.71 (m, 1H), 2.31 - 2.14 (m, 3H), 2.02 - 1.85 (m, 1H), 1.59 (s, 3H).

111.1.57. Synthesis of compound 3.1.57 & 3.1.58

Step 1. Synthesis of 3-methylenecyclobutane-1-carboxylic acid [3.1.57a]. 3-methylenecyclobutane-1-carbonitrile (24 g, 258.0 mmol, 1.0 equiv) was dissolved in ethanol (180 mL) and water (180 mL). Potassium hydroxide (72.25 g, 1290.3 mmol, 5 equiv) was added and the reaction mixture was stirred at 100 °C for 4 hours. The reaction mixture was concentrated. The residue was quenched with water, acidified by 1.0 N HCl aqueous solution to the pH 2 to 4 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.1.57a (27.3 g, 94.5 % yield). LCMS (m/z): 111 [M+H]. 1H NMR (400 MHz, DMSO) δ 12.25 (s, 1H), 4.89 - 4.64 (m, 2H), 3.06 (dt, J = 16.3, 8.0 Hz, 1H), 2.83 (d, J = 8.1 Hz, 4H).

Step 2. Synthesis of methyl 3-methylenecyclobutane-1-carboxylate [3.1.57b]. 3.1.57a (24.2 g, 216 mmol, 1.0 equiv) was dissolved in acetone (100 mL). K2CO3 (59.6 g, 432.1 mmol, 2.0 equiv), Me2SO4 (32.7 g, 259.2 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 100 °C for 2 hours. The reaction mixture was filtered and filtrate was concentrated to afford a crude residue which was purified by silica gel chromatography (100 % n-pentane) to afford product 3.1.57b (24 g, 88 % yield). 1H NMR (400 MHz, DMSO) δ 4.82 - 4.77 (m, 2H), 3.62 (s, 3H), 3.22 - 3.12 (m, 1H), 2.91 - 2.83 (m, 4H).

Step 3. Synthesis of methyl 3-(hydroxymethyl) cyclobutane-1-carboxylate [3.1.57c]

3.1.57b (24 g, 190.4 mmol, 1.0 equiv) was dissolved in THF and cooled to -15 °C. BH3·Me2S (14.4 g, 190.4 mmol, 1.0 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 4 hours. Cooled the reaction mixture at -15 °C, NaOH (3M) (25 mL), H2O2 (50%) (12.9 g, 190.4 mmol, 1.0 equiv) were added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with sodium bisulphate and extracted with EtOAc. The organic layer was washed with brine,
dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (70 % EtOAc in Hexane) to afford product 3.1.57c (18.7 g, 68 % yield). 1H NMR (400 MHz, DMSO) δ 4.54 (d, J = 29.8 Hz, 1H), 3.62 - 3.55 (m, 3H), 3.41 (d, J = 6.5 Hz, 1H), 3.30 (d, J = 6.0 Hz, 1H), 3.13 - 2.95 (m, 1H), 2.37 - 2.27 (m, 1H), 2.15 (ddt, J = 8.7, 7.8, 6.2 Hz, 2H), 1.98 - 1.84 (m, 2H).

Step 4. Synthesis of methyl 3-(((4-methoxybenzyl) oxy) methyl) cyclobutane-1-carboxylate [3.1.57d]. 3.1.57c (5.8 g, 40.3 mmol, 1.0 equiv) was dissolved in DCM. DIPEA (15.62 g, 120.8 mmol, 3.0 equiv), PMB-Cl (9.42 g, 60.41 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 100 °C for 6 hours. The reaction mixture was concentrated to afford crude residue. The crude residue was purified by silica gel column chromatography (5-10 % EtOAc in Hexane) to afford product 3.1.57d (4.2 g, 40 % yield). 1H NMR (400 MHz, DMSO) δ 3.73 - 7.20 (m, 3H), 6.95 - 6.86 (m, 2H), 4.38 (m, 2H), 3.74 (s, 3H), 3.59 (dd, J = 13.7, 8.0 Hz, 3H), 3.42 (d, J = 6.7 Hz, 1H), 3.30 (d, J = 6.2 Hz, 1H), 3.08 (m, 1H), 2.45 (m, 1H), 2.27 - 2.14 (m, 2H), 2.02 - 1.84 (m, 2H).

Step 5. Synthesis of (3-((4-methoxybenzyl) oxy)cyclobutyl)methanol [3.1.57e]

3.1.57d (4.2 g, 15.9 mmol, 1.0 equiv) was dissolved in THF (50 mL) and methanol (5 mL). Sodium borohydride (1.2 g, 31.8 mmol, 2.0 equiv) was added in portions and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude residue. The crude residue was purified by silica gel column chromatography (50-60 % EtOAc/Hexane) to afford product 3.1.57e (3.1 g, 82 % yield). LCMS (m/z): 237.5 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.27 - 7.20 (m, 2H), 6.90 (m, 2H), 4.48 - 4.39 (m, 1H), 4.37 (dd, J = 9.6 Hz, 2H), 3.74 (s, 3H), 3.43 - 3.36 (m, 2H), 3.28 (dd, J = 9.1, 4.8 Hz, 2H), 2.47 - 2.20 (m, 2H), 1.99 - 1.92 (m, 1H), 1.81 - 1.65 (m, 2H), 1.42 (m, 1H).

Step 6. Synthesis of 3-(((4-methoxybenzyl) oxy) methyl) cyclobutane-1-carbaldehyde [3.1.57f]. 3.1.57e (3.1 g, 13.13 mmol, 1.0 equiv) was dissolved in dichloromethane (50 mL). Dess-Martin periodinane (11.13 g, 26.27 mmol, 2.0 equiv) was added in portions and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (20-30 % EtOAc/Hexane) to afford product 3.1.57f (1.9 g, 63 % yield). LCMS (m/z): 252.2 [M+18]. 1H NMR (400 MHz, DMSO) δ 7.24 (t, J = 8.4 Hz, 2H), 6.91 (dd, J = 8.7, 2.7 Hz, 2H), 4.38 (d, J = 13.5 Hz, 2H), 3.75 (s, 3H), 3.42 (d, J = 6.5 Hz, 1H), 3.28 (d, J = 6.3 Hz, 1H), 3.11 (m, 1H), 2.61 - 2.52 (m, 1H), 2.46 - 2.36 (m, 1H), 2.24 (m, 1H), 2.13 (m, 1H), 1.91 (m, 2H).
Step 7. Synthesis of 1-(((3-ethynylcyclobutyl)methoxy)methyl)-4-methoxybenzene [3.1.57g]. 3.1.57f (1.9 g, 8.11 mmol, 1.0 equiv) was dissolved in MeOH (30 mL). Ohira-Bestmann reagent (1.9 g, 9.74 mmol, 1.2 equiv) was added. K₂CO₃ (2.24 g, 16.23 mmol, 2.0 equiv) and the reaction mixture was stirred at rt for 5 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (5 % EtOAc in Hexane) to afford product 3.1.57g (1.6 g, 85 % yield). ¹H NMR (400 MHz, DMSO) δ 7.24 (d, J = 6.9 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 4.38 (d, J = 7.3 Hz, 2H), 3.74 (s, 3H), 3.40 (d, J = 6.8 Hz, 1H), 3.32 (d, J = 6.1 Hz, 1H), 2.99 (m, 1H), 2.83 (m, 1H), 2.46 - 2.37 (m, 1H), 2.28 (m, 1H), 2.05 (m, 2H), 1.81 - 1.74 (m, 1H).

Step 8. Synthesis of ethyl (R)-3-(((S)-3-(4-(((4-methoxybenzylkoxy)methyl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.57h]. 1.1d (0.8 g, 1.84 mmol, 1.0 equiv), 3.1.57g (0.51 g, 2.11 mmol, 1.2 equiv) were mixed with diethyl amine (10 mL) and N, N-dimethylformamide (2 mL). Cul (0.035 g, 0.18 mmol, 0.1 equiv), triphenylphosphine (0.09 g, 0.37 mmol, 0.2 equiv) were added and the reaction mixture was degassed for 15 minutes. PdCl₂[pph₃]₂ (0.065 g, 0.092 mmol, 0.05 equiv) was added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (40-45 % EtOAc in Hexane) to afford product 3.1.57h (0.74 g, 70 % yield). LCMS (m/z): 584.6 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.52 (dd, J = 9.0, 3.0 Hz, 2H), 7.46 - 7.34 (m, 2H), 7.25 (dd, J = 8.7, 2.8 Hz, 2H), 6.94 - 6.89 (m, 2H), 4.79 (m, 1H), 4.40 (d, J = 8.8 Hz, 2H), 4.24 (m, 3H), 3.84 - 3.79 (m, 1H), 3.75 (d, J = 3.0 Hz, 3H), 3.45 (d, J = 6.7 Hz, 1H), 3.37 (d, J = 6.0 Hz, 1H), 3.28 - 3.21 (m, 2H), 3.17 (s, 3H), 2.68 (m, 1H), 2.41 - 2.35 (m, 2H), 2.17 (m, 2H), 1.87 (m, 1H), 1.64 (s, 3H), 1.26 (m, 3H).

Step 9. Synthesis of ethyl (R)-3-(((S)-3-(4-(((3-hydroxymethyl)cyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.1.57i]. 3.1.57h (0.74 g, 1.26 mmol, 1.0 equiv) was dissolved in dichloromethane (50 mL). TFA (0.72 g, 6.35 mmol, 5.0 equiv) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was triturated with n-pentane, the solvent was decanted to afford product 3.1.57i (0.44 g, 75 % yield). LCMS (m/z): 464.4 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.52 (dd, J = 8.9, 2.0 Hz, 2H), 7.41 (dd, J = 8.7, 4.9 Hz, 2H), 5.37 (s, 1H), 4.79 (m, 1H), 4.30 - 4.19 (m, 3H), 3.84 - 3.79 (m, 1H), 3.73 (dd, J = 10.9, 6.5 Hz, 1H), 3.44 (d, J = 6.7 Hz,
1H), 3.25 (m, 2H), 3.15 (s, 3H), 2.67 (m, 1H), 2.40 - 2.28 (m, 2H), 2.13 (m, 2H), 1.88 (m, 1H), 1.64 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 10. Synthesis of ethyl (R)-3-((S)-3-4-((3-(methoxymethyl) cyclobutyl) ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.57i]

3.1.57i (0.44 g, 0.95 mmol, 1.0 equiv) was dissolved with acetonitrile (10 ml) in sealed tube. Ag$_2$O (0.66 g, 2.85 mmol, 3 equiv), iodomethane (0.13 g, 9.5 mmol, 10.0 equiv) were added and the reaction mixture was stirred at 100 °C for 24 hours in seal tube. The reaction mixture was filtered through celite bed and filtrate was concentrated to afford a crude product. The crude product was purified by silica gel column chromatography (30-50 % EtOAc in Hexane) to afford product 3.1.59a (39.3 g, 85% yield). LCMS (m/z): 478.6 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.52 (dd, J = 8.9, 2.0 Hz, 2H), 7.41 (dd, J = 8.7, 4.9 Hz, 2H), 5.37 (s, 1H), 4.79 (m, 1H), 4.30 - 4.19 (m, 3H), 3.84 - 3.79 (m, 1H), 3.73 (dd, J = 10.9, 6.5 Hz, 1H), 3.44 (d, J = 6.7 Hz, 1H), 2.35 (m, 5H), 3.15 (s, 3H), 2.67 (m, 1H), 2.40 - 2.28 (m, 2H), 2.13 (m, 2H), 1.88 (m, 1H), 1.64 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 11. Synthesis of (R)-N-hydroxy-3-((S)-3-4-((3-(methoxymethyl) cyclobutyl)ethynyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanamide [3.1.57 & 3.1.58]. Compound 3.1.57 & 3.1.58 were synthesized from 3.1.57i by the process of example 3.1.1. The two diastereomers were separated by reverse phase HPLC. Compound 3.1.57: LCMS (m/z): 465.5 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 11.06 (s, 1H), 9.22 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 4.66 (m, 1H), 4.17 (t, J = 8.4 Hz, 1H), 3.84 - 3.75 (m, 1H), 3.30 (d, J = 5.9 Hz, 2H), 3.24 (s, 3H), 3.18 - 3.12 (m, 1H), 3.08 (s, 3H), 2.75 (d, J = 12.6 Hz, 1H), 2.44 (m, 1H), 2.36 (m, 2H), 2.19 (m, 1H), 1.94 - 1.80 (m, 2H), 1.58 (s, 3H). Compound 3.1.58: LCMS (m/z): 465.5 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 11.12 - 10.81 (m, 1H), 9.29 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.7 Hz, 2H), 4.67 (m, 1H), 4.15 (m, 1H), 3.80 (m, 1H), 3.38 (d, J = 6.9 Hz, 2H), 3.32 - 3.21 (m, 4H), 3.08 (s, 3H), 2.76 (m, 1H), 2.55 (m, 1H), 2.25 - 2.06 (m, 5H), 1.5

III.1.59. Synthesis of compound 3.1.59 & 3.1.60

Step 1. Synthesis of methyl (1s, 3s)-3-((methylsulfonyl) o xo) cyclobutane-1-carboxylate [3.1.59]. Methyl 3-hydroxycyclobutane-1-carboxylate (25 g, 192.3 mmol, 1.0 equiv) was mixed with dichloromethane (300 mL) and cooled to 15 °C. TEA (77.7 g, 769 mmol, 4.0 equiv), Methanesulfonyl chloride (28.5 g, 0.250 mmol, 1.3 equiv) was added and the reaction mixture was stirred at rt for 6 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (0-25 % EtOAc in Hexane) to afford product 3.1.59a (39.3 g,
98.1 % yield). LCMS (m/z): 209.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 5.00 - 4.84 (m, 1H), 3.61 (s, Hz, 3H), 3.21 - 3.13 (s, Hz, 3H), 2.82 (m, 1H), 2.70 - 2.60 (m, 2H), 2.40 - 2.28 (m, 2H).

**Step 2. Synthesis of methyl (1r, 3r)-3-acetoxy-1-cyclobutane-1-carboxylate [3.1.59b]**

3.1.59a (39.2 g, 188.0 mmol, 1.0 equiv) was dissolved in N, N-dimethylformamide (392 mL). KOAc (94.3 g, 962.1 mmol, 5.1 equiv) was added and the reaction mixture was stirred at 120 °C for 21 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-10 % EtOAc in Hexane) to afford product 3.1.59b (25.3 g, 78.9 % yield).

LCMS (m/z): 190.2 [M+18]. ¹H NMR (400 MHz, CDCl₃) δ 5.27 - 5.08 (m, 1H), 3.76 - 3.67 (s, 3H), 3.21 - 3.06 (m, 1H), 2.73 - 2.61 (m, 2H), 2.42 - 2.31 (m, 2H), 2.05 (s, 3H).

**Step 3. Synthesis of methyl (1r, 3r)-3-hydroxy-1-cyclobutane-1-carboxylate [3.1.59c].**

3.1.59b (29.02 g, 168.7 mmol, 1.0 equiv) was dissolved in MeOH (290 mL). NaOMe (25 % soln” in MeOH) (7.28 g, 33.74 mmol, 0.2 equiv) was added and the reaction mixture was stirred at rt for 12 hours. The reaction mixture was concentrated, the residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford 3.1.59c (16.8 g, 87.6% yield). The product was used in the next step with no further purification. ¹H NMR (400 MHz, CDCl₃) δ 4.64 - 4.52 (m, 1H), 3.71 (s, 3H), 3.11 - 2.99 (m, 1H), 2.63 - 2.55 (m, 2H), 2.23 (m, 2H), 2.14 (s, 1H).

**Step 4. Synthesis of methyl (1r, 3r)-3-((tert-butyldiphenylsilyl) oxy) 1-cyclobutane-1-carboxylate [3.1.59d].**

3.1.59c (19.5 g, 150.0 mmol, 1.0 equiv) was mixed with dichloromethane (195 mL) and cooled to 0 °C. Imidazole (20.42 g, 300.0 mmol, 2.0 equiv), TBDPS-Cl (53.6 g, 195.0 mmol, 1.3 equiv) was added and the reaction mixture was stirred at rt for 6 hours. The reaction was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-6 % dichloromethane in Hexane) to afford product 3.1.59d (36 g, 65.4 % yield). LCMS (m/z): 369.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.65 - 7.55 (m, 4H), 7.53 - 7.38 (m, 6H), 4.49 - 4.35 (m, 1H), 3.53 (s, 3H), 3.05 - 2.91 (m, 1H), 2.32 (t, J = 6.9 Hz, 4H), 0.98 (s, 9H).

**Step 5. Synthesis of [(1r, 3r)-3-((tert-butyldiphenylsilyl) oxy) cyclobutyl] methanol [3.1.59e].**

3.1.59d (17 g, 46.1 mmol, 1.0 equiv) was dissolved in THF (170 mL). LiBH₄ (2M in THF) (45.1 g, 92.3 mmol, 2.0 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with saturated aqueous sodium sulfate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel chromatography (0-14 % EtOAc in Hexane) to afford 3.1.59e (13.7 g, 87.3 % yield). LCMS (m/z): 358.4 [M+18]. ¹H NMR (400 MHz, DMSO) δ 7.60 (dd, J = 7.5,
1.8 Hz, 4H), 7.49 - 7.40 (m, 6H), 4.50 (t, J = 5.3 Hz, 1H), 4.34 (p, J = 6.9 Hz, 1H), 3.29 - 3.23 (m, 2H), 2.22 - 2.14 (m, 1H), 2.14 - 2.04 (m, 2H), 2.03 - 1.90 (m, 2H), 0.97 (s, 9H).

**Step 6. Synthesis of (1r, 3r)-3-((tert-butyldiphenylsilyl) oxy) cyclobutane-1-carbaldehyde [3.1.59f].** 3.1.59e (13.7 g, 46.2 mmol, 1.0 equiv) was dissolved in dichloromethane (140 ml) and cooled to 10 °C. Dess-Martin periodinane (35.3 g, 83.2 mmol, 1.8 equiv) was added in portions and the reaction mixture was stirred at room temperature for 8 hours. The reaction mixture was filtered through celite bed and filtrate was concentrated under reduced pressure to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-8 % EtOAc in Hexane) to afford product 3.1.59f (9.97 g, 73.1 % yield). LCMS (m/z): 339.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 9.64 (d, J = 1.7 Hz, 1H), 7.61 - 7.58 (m, 4H), 7.49 - 7.42 (m, 6H), 4.24 (m, 1H), 3.03 (m, 1H), 2.46 - 2.36 (m, 2H), 2.29 - 2.19 (m, 2H), 0.98 (s, 9H).

**Step 7. Synthesis of tert-butyl ((1r, 3r)-3-ethynlycyclobutoxy)diphenylsilane [3.1.59g] 3.1.59f (9.9 g, 29.2 mmol, 1.0 equiv) was dissolved in MeOH (100 ml). Ohira-Bestmann reagent (5.68 g, 29.3 mmol, 1.1 equiv), K₂C₀₃ (8.08 g, 58.6 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated, the residue was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-2 % EtOAc in Hexane) to afford product 3.1.59g (6.6 g, 67.5 % yield). LCMS (m/z): 335.4 [M+H]. (as mixture of cis:trans 70:30); 1H NMR (400 MHz, DMSO) δ 7.64 - 7.55 (m, 4H), 7.49 - 7.41 (m, 6H), 4.52 - 4.44 (m, 0.3H), 4.14 - 4.03 (m, 0.7H), 2.96 (d, J = 2.0 Hz, 0.6H), 2.87 (d, J = 2.1 Hz, 0.4H), 2.49 - 1.95 (m, 5H).

**Step 8. Synthesis of ethyl (R)-3-((1s, 3R)-3-((tert-butyldiphenylsilyl) oxy)cyclobutyl) ethynyl(phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.59h].** 1.1d (1 g, 2.3 mmol, 1.0 equiv), 3.1.59g (1.54 g, 4.6 mmol, 2.0 equiv) were mixed with diethyl amine (10 ml) and N, N-dimethylformamide (2 ml). Cul (0.006 g, 0.14 mmol, 0.06 equiv), triphenylphosphine (0.06 g, 0.23 mmol, 0.1 equiv) were added and the reaction mixture was degassed for 15 minutes. PdCl₂(pph₃)₂ (0.097 g, 0.14 mmol, 0.06 equiv) was added and the reaction mixture was stirred at 125 °C for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel chromatography (0-40 % EtOAc in Hexane) to afford 3.1.59h (1.24g, 78.5% yield). LCMS (m/z): 688.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.61 (dd, J = 7.4, 1.5 Hz, 4H), 7.56 - 7.36 (m, 10H), 4.84 - 4.72 (m, 1H), 4.30 - 4.09 (m, 3H), 3.86 - 3.74 (m, 1H), 3.17 (m, 4H), 2.77 - 2.59 (m, 2H), 2.58 - 2.53 (m, 1H), 2.36 (m, 3H), 2.12 (m, 2H), 1.64 (d, J = 5.3 Hz, 3H), 1.25 (dt, J = 7.1, 3.5 Hz, 3H), 0.98 (s, 9H).
Step 9. Synthesis of ethyl (R)-3-(((S)-3-(4-(((1s, 3R)-3-hydroxycyclobutyl) ... J = 14.1 Hz, 1H), 2.69 (dt, J = 13.2, 6.3 Hz, 2H), 2.35 (m, 1H), 1.78 (s, 3H).

3.1.59h (1.23 g, 1.79 mmol, 1.0 equiv) was dissolved in THF (30 ml) and cooled to 10 °C. TBAF (2.15 g, 2.14 mmol, 1.2 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-80 % EtOAc in Hexane) to afford product 3.1.59i (0.71 g, 88.7 % yield). LCMS (m/z): 450.5 [M+H]. \( ^1 \text{H NMR (400 MHz, DMSO)} \delta \) 7.49 (d, \( J = 8.6 \) Hz, 2H), 7.38 (d, \( J = 8.8 \) Hz, 2H), 4.77 (d, \( J = 8.2 \) Hz, 1H), 4.21 (dt, \( J = 2.1 \) Hz, 8.1 Hz, 3H), 3.99 - 3.89 (m, 1H), 3.14 (m, 4H), 2.66 (d, \( J = 12.5 \) Hz, 2H), 2.56 (s, 1H), 2.38 - 2.14 (m, 3H), 1.92 (d, \( J = 7.7 \) Hz, 1H), 1.62 (s, 3H), 1.23 (t, \( J = 7.1 \) Hz, 3H).

Step 10. Synthesis of ethyl (R)-3-(((S)-3-(4-(((3-fluorocyclobutyl) ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.1.59]. 3.1.59i (0.7 g, 1.56 mmol, 1.0 equiv) was dissolved with dichloromethane (29 ml) and cooled to -78 °C. DAST (0.45 g, 2.8 mmol, 1.8 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was purified by silica gel column chromatography (0-1 % MeOH/dichloromethane) to afford product 3.1.59j (0.25 g, 39 % yield). LCMS (m/z): 452.3 [M+H]. \( ^1 \text{H NMR (400 MHz, DMSO)} \delta \) 7.59 (d, \( J = 8.9 \) Hz, 2H), 7.56 - 7.46 (m, 2H), 6.01 - 5.81 (m, 1H), 5.58 (m, 1H), 5.36 - 5.11 (m, 2H), 4.81 (m, 1H), 4.34 - 4.16 (m, 3H), 3.83 (m, 1H), 3.17 (s, 3H), 2.76 - 2.59 (m, 3H), 2.42 - 2.32 (m, 1H), 1.65 (s, 3H), 1.26 (t, \( J = 7.1 \) Hz, 3H).

Step 11. Synthesis of (R)-3-(((S)-3-(4-(((3-fluorocyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [3.1.59 & 3.1.60]. 3.1.59 & 3.1.60 were synthesized from 3.1.59j by the process of example 3.1.1. The two diastereomers were separated by reverse phase HPLC. Compound 3.1.59: LCMS (m/z): 439.4 [M+H]. \( ^1 \text{H NMR (400 MHz, MeOD)} \delta \) 7.54 (d, \( J = 7.8 \) Hz, 2H), 7.43 (dd, \( J = 23.1 \), 7.7 Hz, 2H), 5.40 - 5.31 (m, 0.5H), 5.22 (m, 0.5H), 4.76 (m, 1H), 4.24 (m, 1H), 3.85 (m, 1H), 3.11 (s, 3H), 2.89 (d, \( J = 14.2 \) Hz, 1H), 2.60 (m, 4H), 2.40 - 2.27 (m, 1H), 1.75 (s, 3H).

Compound 3.1.60: LCMS (m/z): 439.3 [M+H]. \( ^1 \text{H NMR (400 MHz, MeOD)} \delta \) 7.61 (d, \( J = 8.3 \) Hz, 2H), 7.48 (d, \( J = 8.2 \) Hz, 2H), 5.94 (m, 1H), 5.45 (t, \( J = 6.2 \) Hz, 0.5H), 5.33 (t, \( J = 6.1 \) Hz, 0.5H), 5.23 (dd, \( J = 19.4 \), 13.7 Hz, 2H), 4.77 (m, 1H), 4.25 (m, 1H), 3.87 (m, 1H), 3.11 (s, 3H), 2.89 (d, \( J = 14.1 \) Hz, 1H), 2.69 (dt, \( J = 13.2 \), 6.3 Hz, 2H), 2.35 (m, 1H), 1.78 (s, 3H).

III.2.1 Synthesis of compound 3.2.1
Reagents: Step 1: DBU, dppb, PdCl$_2$(PPh$_3$)$_2$, DMSO, 80°C. Step 2: LiOH, THF, MeOH, Water, room temperature. Step 3: NH$_2$OTHP, EDC.HCl, HOBr, TEA, THF, room temperature. Step 4: Methanolic-HCl (8% w/w), MeOH, 0°C to room temperature.

Step 1. Synthesis of ethyl (R)-2-methyl-3-((S)-3-(2-methyl-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanoate [3.2.1a]

1.1d (0.20 g, 0.45 mmol, 1.0 equiv), but-2-ynoic acid(0.031 g, 0.38 mmol, 1.0 equiv), PdCl$_2$(PPh$_3$)$_2$(0.003 g, 0.004 mmol, 0.01 equiv), 1,4-bis(diphenylphosphino)butane (0.003 g, 0.009 mmol, 0.02 equiv) and DBU(0.13 g, 0.89 mmol, 2.0 equiv) were added in DMSO (4 ml) in sealed tube. The reaction mixture was stirred at 80°C for 6 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a residue. The residue was purified by silica gel column chromatography (20-25 % EtOAc in Hexane) to afford product 3.2.1a (0.15 g, 82.5 % yield). LCMS (m/z): 408.3 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.50 - 7.19 (m, 3H), 4.83 (s, 1H), 4.26 (d, $J = 7.1$ Hz, 2H), 4.03 (d, $J = 9.7$ Hz, 1H), 3.73 (d, $J = 8.8$ Hz, 1H), 3.30 - 3.12 (m, 3H), 2.68 (d, $J = 14.6$ Hz, 1H), 2.46 - 2.32 (m, 1H), 2.20 (d, $J = 10.5$ Hz, 3H), 2.14 - 1.96 (m, 3H), 1.67 (d, $J = 10.1$ Hz, 3H), 1.25 (dd, $J = 8.1, 5.9$ Hz, 3H).

Step 2. Synthesis of (R)-2-methyl-3-((S)-3-(2-methyl-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanoic acid [3.2.1b]. 3.2.1a (0.15 g, 0.36 mmol, 1.0 equiv) was dissolved in THF (5 ml), MeOH (2 ml). LiOH (0.017 g, 0.73 mmol, 2.0 equiv) in water (1 ml) was added and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness; the residue was diluted with water, acidified by 1N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.2.1b (0.13 g, 96.2 % yield). LCMS (m/z): 380.3 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 14.13 (s, 1H), 7.32 (d, $J = 8.4$ Hz, 2H), 7.26 (d, $J = 9.8$ Hz, 1H), 4.83 (d, $J = 5.8$ Hz, 1H), 4.04 (dt, $J = 8.5, 3.9$ Hz, 1H), 3.72 (t, $J = 8.1$ Hz, 1H), 3.15 (s, 3H), 2.63 (d, $J = 11.8$ Hz, 1H), 2.34 (dd, $J = 14.5, 8.8$ Hz, 1H), 2.21 (d, $J = 10.7$ Hz, 3H), 2.05 (s, 3H), 1.61 (s, 3H).

0.13 g, 0.342 mmol, 1.0 equiv) was dissolved in THF (7 ml). Et₃N (0.17 g, 1.7 mmol, 5.0 equiv) were added and the reaction mixture was stirred at room temperature for 10 minutes. 0-((tetrahydro-2H-pyran-2-yl)hydroxylamine (0.08 g, 0.68 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated to dryness. The residue was purified by silica gel column chromatography (2-3% MeOH in dichloromethane) to afford product 3.2.1c which was carry forwarded for next step. (0.12 g, 73.2 % yield).

LCMS (m/z): 496.4 [M+18].

H NMR (400 MHz, DMSO) δ 7.70 - 7.48 (m, 1H), 7.35 - 7.26 (m, 2H), 4.95 (d, J = 9.4 Hz, 1H), 4.81 - 4.65 (m, 1H), 4.04 - 3.98 (m, 1H), 3.77 (ddd, J = 11.1, 7.8, 3.0 Hz, 2H), 3.48 - 3.38 (m, 3H), 3.16 - 3.00 (m, 3H), 2.75 (dd, J = 25.4, 14.5 Hz, 1H), 2.33 - 2.12 (m, 4H), 2.07 - 1.96 (m, 3H), 1.64 - 1.60 (m, 3H), 1.49 - 1.42 (m, 6H).

Step 8. Synthesis of (R)-N-hydroxy-2-methyl-3-((S)-3-(2-methyl-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide [3.2.1]

0.12 g, 0.24 mmol, 1.0 equiv) was dissolved in methanol (1 ml) and cooled the solution at 0°C. Methanolic-HCl solution (8% w/w, 2.0 ml) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness and the crude product was purified by preparative HPLC to afford product 3.2.1 as desired diastereomer (0.053 g, 55.9 % yield). LCMS (m/z): 395.3 [M+H].

H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.29 (s, 1H), 7.30 (dd, J = 21.6, 8.7 Hz, 3H), 4.67 (d, J = 5.8 Hz, 1H), 3.99 (t, J = 8.4 Hz, 1H), 3.69 (t, J = 8.1 Hz, 1H), 3.09 (s, 3H), 2.74 (t, J = 22.8 Hz, 1H), 2.29 - 2.20 (m, 1H), 2.19 (s, 3H), 2.04 (s, 3H), 1.60 (s, 3H).

III.3.1. Synthesis of compound 3.3.1
**Reagents:** Step 1: DBU, dppb, PdCl₂(PPh₃)₂, DMSO, 90°C. Step 2: LiOH.H₂O, THF, MeOH, Water, room temperature. Step 3: NH₂OTHP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 4: 35.5% aq. HCl, EtOH, room temperature.

**Step 1. Synthesis of ethyl 3-((S)-3-(2-fluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate** [3.3.1a]. 1.3d (0.19 g, 0.42 mmol, 1.0 equiv), but-2-ynoic acid (0.035 g, 0.42 mmol, 1.0 equiv), PdCl₂(PPh₃)₂ (0.003 g, 0.004 mmol, 0.01 equiv), 1,4-bis(diphenylphosphino)butane (0.004 g, 0.0096 mmol, 0.02 equiv) and DBU (0.13 g, 0.84 mmol, 2.0 equiv) were added in DMSO (10 mL) in sealed tube. The reaction mixture was stirred at 90°C for 4 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.3.1a (0.14 g, 70 % yield). LCMS (m/z): 401.2 [M+H].

**Step 2. Synthesis of 3-((S)-3-(2-fluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid** [3.3.1b]. 3.3.1a (0.14 g, 0.34 mmol, 1.0 equiv) was dissolved in THF (6 mL), MeOH (2 mL). LiOH.H₂O (0.043 g, 1.02 mmol, 3.0 equiv) in water (2 mL) was added and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated to dryness; the residue was diluted with water, acidified by 1N HCl aqueous solution to pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.3.1b (0.12 g, 92.3 % yield). LCMS (m/z): 401.3 [M+18]. ¹H NMR (400 MHz, DMSO) δ 12.01 (s, 1H), 7.53 (t, J = 8.3 Hz, 1H), 7.38 (dd, J = 11.8, 1.7 Hz, 1H), 7.28 (dd, J = 8.3, 1.6 Hz, 1H), 4.92 - 4.77 (m, 1H), 4.13 (t, J = 8.5 Hz, 1H), 3.81 (t, J = 8.1 Hz, 1H), 3.17 (s, 3H), 2.71 - 2.59 (m, 1H), 2.39 - 2.28 (m, 1H), 1.67 - 1.57 (s, 3H).

**Step 3. Synthesis of 3-((S)-3-(2-fluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide** [3.3.1c] 3.3.1b (0.12 g, 0.31 mmol, 1.0 equiv) was dissolved into THF (5 mL). N-methyl morpholine (0.16 g, 1.57 mmol, 5.0 equiv), HOBT (0.051 g, 0.38 mmol, 1.2 equiv), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.073 g, 0.63 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 10 minutes. EDC.HCl (0.09 g, 0.47 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was concentrated to afford a residue. The residue was purified by silica gel column chromatography (2-3 % MeOH in dichloromethane) to afford product 3.3.1c which was carry forwarded for next step. (0.12 g, 74.5 % yield). LCMS (m/z): 481.5 [M-H]. ¹H NMR (400 MHz, DMSO) δ 7.50 (s, 1H), 7.31 (dd, J = 36.4, 10.0 Hz, 2H), 4.70 (d, J = 7.7 Hz, 1H), 4.05 (d, J = 18.5 Hz, 2H), 3.89 (s, 2H), 3.07 (d, J = 9.6 Hz, 3H), 2.80 - 2.72 (m, 1H), 2.17 (m, 4H), 1.74 (s, 3H), 1.69 - 1.59 (m, 6H).

**Step 4. Synthesis of (R)-3-((S)-3-(2-fluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide** [3.3.1]
3.3.1c (0.12 g, 0.25 mmol, 1.0 equiv) was dissolved in ethanol (5 mL), 35.5% aq. HCl (0.5 mL) was added to the solution and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to dryness to afford a residue. The residue was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the crude product. The crude product was purified by preparative HPLC purification to afford 3.3.1 as desired diastereomer (0.065 g, 65.7 % yield). LCMS (m/z): 399 [M+H]. 

1H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 9.29 (s, 1H), 7.52 (t, J = 8.3 Hz, 1H), 7.38 (d, J = 11.8 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 4.67 (d, J = 5.6 Hz, 1H), 4.09 (t, J = 8.5 Hz, 1H), 3.77 (t, J = 8.2 Hz, 1H), 3.09 (s, 3H), 2.78 (d, J = 12.9 Hz, 1H), 2.21 (dd, J = 14.3, 8.7 Hz, 1H), 2.06 (s, 3H), 1.59 (s, 3H).

III.3.3. Synthesis of compound 3.3.3

3.3.3 was synthesized using the process of example 3.3.2. LCMS (m/z): 486.3 [M+18]. 1H NMR (400 MHz, DMSO) δ 11.14 (s, 1H), 9.28 (s, 1H), 7.54 (t, J = 8.3 Hz, 1H), 7.44 - 7.35 (m, 1H), 7.29 (d, J = 8.2 Hz, 1H), 4.68 (d, J = 7.9 Hz, 1H), 4.11 (dd, J = 13.4, 6.8 Hz, 2H), 3.78 (t, J = 8.3 Hz, 1H), 3.29 - 3.22 (m, 1H), 3.14 (d, J = 6.6 Hz, 3H), 3.07 (d, J = 16.6 Hz, 3H), 2.78 (d, J = 13.9 Hz, 1H), 2.36 - 2.23 (m, 5H), 1.59 (s, 3H).

III.4.1. Synthesis of compound 3.4.1

Reagents: Step 1: CBZ-Cl, NaHCO3, Acetone:Water, 0°C to room temperature. Step 2: n-BuLi (2.5M in hexane), THF, -78°C to room temperature. Step 3: Iodine, triphenylphosphine, imidazole, dichloromethane, room temperature. Step 4: NaH (60%), N,N-dimethylformamide, 0°C to room temperature. Step 5: DBU, dppb, PdCl2(PPh3)2, DMSO, 100°C. Step 6: LiOH.H2O, THF, MeOH, Water, room temperature. Step 7: NH2OTHP,
EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 8: 35.5% aq. HCl, EtOH, room temperature.

**Step 1. Synthesis of benzyl (4-bromo-3-fluorophenyl)carbamate [3.4.1a].** 4-bromo-3-fluoroaniline (2.5 g, 13.1 mmol, 1.0 equiv) was dissolved in acetone: water (2:1, 30 mL) and the solution was cooled to 0°C. NaHCO₃ (2.20 g, 26.3 mmol, 2.0 equiv), CBZ-Cl (2.68 g, 15.8 mmol, 1.2 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.4.1a (4.0 g, 94 % yield). LCMS (m/z): 322.1 [M-2]. 1H NMR (400 MHz, DMSO) δ: 10.17 (s, 1 H), 7.65 - 7.51 (m, 2H), 7.48 - 7.32 (m, 5H), 7.27 - 7.17 (m, 1H), 5.17 (s, 2H).

**Step 2. Synthesis of (R)-3-(4-bromo-3-fluorophenyl)-5-(hydroxymethyl)oxazolidin-2-one [3.4.1b].** 3.4.1a (2.5 g, 7.7 mmol, 1.0 equiv) was dissolved in THF (20 mL) and cooled to -78°C. n-BuLi (2.5M in hexane) (0.59 g, 9.3 mmol, 1.2 equiv) was gradually added and the reaction mixture was stirred at -78 °C for 1 hour. (R)-oxiran-2-ylmethyl butyrate (1.33 g, 9.3 mmol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (80-100 % EtOAc in Hexane) to afford product 3.4.1b which was carry forwarded for next step. (1.46 g, 65% yield). LCMS (m/z): 292.1 [M+H].

**Step 3. Synthesis of (R)-3-(4-bromo-3-fluorophenyl)-5-(iodomethyl)oxazolidin-2-one [3.4.1c].** Triphenylphosphine (1.64 g, 6.3 mmol, 1.3 equiv) was dissolved in dichloromethane (20 mL). imidazole (0.45 g, 6.8 mmol, 1.4 equiv) was added and the reaction mixture was stirred at room temperature for 5 minutes. Iodine (1.59 g, 6.3 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 10 minutes. A solution of 3.4.1b (1.40 g, 4.8 mmol, 1.0 equiv) in dichloromethane (10 mL) was added drop wise and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a residue. The residue was purified by silica gel column chromatography (5-20 % EtOAc in Hexane) to afford product 3.4.1c (1.3 g, 67 % yield). LCMS (m/z): 400.0 [M+H].

**Step 4. Synthesis of ethyl (R)-3-((3-4-bromo-3-fluorophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.4.1d].** Ethyl 2-(methylsulfonyl)propanoate (1.98 g, 11.0 mmol, 4.0 equiv) was dissolved in N,N-dimethylformamide (15 mL) and cooled to 0-5 °C. NaH (60%) (0.13 g, 5.5 mmol, 2.0 equiv) was added in portion wise and the reaction mixture was stirred at room temperature for 1 hour. A solution of 3.4.1c (1.10 g, 2.8 mmol, 1.0 equiv) in N,N-dimethylformamide (5 mL) was added drop wise at 0-5°C. The
reaction mixture was allowed to stir at rt for 6 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a residue. The residue was purified by silica gel chromatography (20-30% EtOAc in Hexane) to afford 3.4.1d as mixture of diastereomers. The product was further purified by preparative HPLC to afford product 3.4.1d as desired diastereomer (1.0 g, 80% yield). LCMS (m/z): 471.2 [M+18]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.79 - 7.70 (m, 1H), 7.64 (dd, \(J = 11.5, 2.5\) Hz, 1H), 7.33 (dd, \(J = 8.5, 2.3\) Hz, 1H), 4.81 (dd, \(J = 14.2, 8.3\) Hz, 1H), 4.34 - 4.14 (m, 3H), 3.91 - 3.74 (m, 1H), 3.16 (s, 3H), 2.77 - 2.61 (m, 1H), 2.38 (dd, \(J = 14.9, 8.9\) Hz, 1H), 1.64 (s, 3H). 3.4.1e

**Step 5. Synthesis of ethyl (R)-3-((S)-3-(3-fluoro-4-(prop-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.4.1]**

3.4.1d (0.26 g, 0.57 mmol, 1.0 equiv), but-2-ynoic acid (0.048 g, 0.57 mmol, 1.0 equiv), DBU (0.18 g, 1.15 mmol, 2.0 equiv) were dissolved in DMSO (10 ml) in sealed tube and the reaction mixture was degassed for 10 minutes. \(\text{PdCl}_2(\text{PPh}_3)_2\) (0.004 g, 0.0057 mmol, 0.01 equiv), 1,4-bis(diphenylphosphino)butane (0.005 g, 0.013 mmol, 0.02 equiv) were added and the reaction mixture was stirred at 100°C for 20 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a residue that was purified by silica gel chromatography (50-70% EtOAc in Hexane) to afford product 3.4.1e (0.2 g, 84% yield). LCMS (m/z): 429.4 [M+18]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.70-7.43 (m, 2H), 7.31 (dd, \(J = 8.6, 2.2\) Hz, 1H), 4.80 (dd, \(J = 14.9, 7.3\) Hz, 1H), 4.25 (tt, \(J = 11.1, 7.4\) Hz, 2H), 3.90 - 3.73 (m, 1H), 3.17 (d, \(J = 8.8\) Hz, 3H), 2.67 (dd, \(J = 14.9, 2.4\) Hz, 1H), 2.37 (dd, \(J = 14.9, 9.0\) Hz, 1H), 2.16 - 2.03 (m, 3H), 1.68 (d, \(J = 29.0\) Hz, 3H), 1.26 (dd, \(J = 8.7, 5.5\) Hz, 3H).

**Step 6. Synthesis of (R)-3-((S)-3-(3-fluoro-4-(prop-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [3.4.1f]**

3.4.1e (0.2 g, 0.49 mmol, 1.0 equiv) was dissolved in THF (8 ml), MeOH (1 ml). LiOH.H\(_2\)O (0.06 g, 1.46 mmol, 3.0 equiv) in water (1 ml) was added and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness, the residue was dissolved in water, acidified by 1.0 N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.4.1f (0.14 g, 75 % yield). The crude product was used in the next step with no further purification. LCMS (m/z): 384.4 [M+H].

**Step 7. Synthesis of (2R)-3-((S)-3-(3-fluoro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [3.4.1g]**

3.4.1f (0.14 g, 0.37 mmol, 1.0 equiv) was dissolved in THF (10 ml). N-methyl morpholine (0.18 g, 1.8 mmol, 5.0 equiv), HOBT (0.06 g, 0.4 mmol, 1.2 equiv), EDC.HCl (0.11 g, 0.5 mmol, 1.5 equiv) and 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.09 g, 0.7
mmol, 2.0 equiv) were added to the solution and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to obtain a residue. The residue was purified by silica gel column chromatography (50-70 % EtOAc in Hexane) to afford product 3.4.1g which was carry forwarded for next step. (0.1g, 87 % yield). LCMS (m/z): 500.4 [M+18].

**Step 8. Synthesis of (R)-3-((S)-3-(3-fluoro-4-(prop-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [3.4.1].**

3.4.1g (0.1 g, 0.21 mmol, 1.0 equiv) was dissolved in ethanol (5 ml), 35.5% aq. HCl (0.5 ml) was added and reaction mixture was stirred at rt for 2 hours. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by preparative HPLC to afford product 3.4.1 as desired diastereomer (0.022 g, 26 % yield). LCMS (m/z): 399.4 [M+H]. 

**III.5.1. Synthesis of compound 3.5.1**

**Reagents:** Step 1: CBZ-Cl, NaHCO₃, Acetone: Water, 5 °C to room temperature.  
Step 2: n-BuLi (2.5M in THF), THF, -70°C to room temperature.  
Step 3: Iodine, triphenylphosphine, imidazole, THF, room temperature.  
Step 4: NaH (60%), N,N-dimethyl formamide, 0 °C to room temperature.  
Step 5: DBU, dppb, PdCl₂(PPh₃)₂, DMSO, 110 °C.  
Step 6: LiOH.H₂O, THF, Water, room temperature.  
Step 7: NH₂OTH, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature.  
Step 8: 35.5% aq. HCl, EtOH, room temperature.
Step 1. Synthesis of benzyl (4-bromo-3-methylphenyl)carbamate [3.5.1a]. 4-bromo-3-methylaniline (3.0 g, 22.0 mmol, 1.0 equiv) was dissolved in acetone: water (2:1, 45 mL) and cooled it to 5 °C. NaHCO$_3$ (3.76 g, 44.0 mmol, 2.0 equiv), CBZ-Cl (5.70 g, 33.0 mmol, 1.5 equiv) were added to the reaction mixture. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue that was purified by silica gel chromatography (10-12 % EtOAc in Hexane) to afford product 3.5.1a (6.59 g, 92% yield). LCMS (m/z): 320.2 [M-H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 9.88 (s, 1H), 7.50 - 7.31 (m, 8H), 5.16 (s, 2H), 2.31 (d, $J$ = 12.3 Hz, 3H).

Step 2. Synthesis of (R)-3-(4-bromo-3-methylphenyl)-5-(hydroxymethyl)oxazolidin-2-one [3.5.1b]. 3.5.1a (2.0 g, 6.2 mmol, 1.0 equiv) was dissolved in THF (60 mL) and cooled to -70°C. n-BuLi (2.5M in THF) (1.20 g, 18.0 mmol, 3.0 equiv) was gradually added and the reaction mixture was stirred at -70 °C for 1.5 hours. (R)-oxiran-2-ylmethyl butyrate (0.88 g, 6.2 mmol, 1.0 equiv) was added and the reaction mixture was allowed to stir at rt for 7 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (40-50 % EtOAc in Hexane) to afford 3.5.1b (1.60 g, 71 % yield). LCMS (m/z): 286.2 [M-H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.56 (dd, $J$ = 12.9, 5.7 Hz, 2H), 7.43 (dd, $J$ = 8.8, 2.7 Hz, 1H), 5.23 (t, $J$ = 5.6 Hz, 1H), 4.70 (td, $J$ = 9.5, 3.6 Hz, 1H), 4.13 - 3.99 (m, 1H), 3.82 (dd, $J$ = 8.8, 6.3 Hz, 1H), 3.67 (ddd, $J$ = 12.3, 5.5, 3.4 Hz, 1H), 3.56 (ddd, $J$ = 12.3, 5.6, 4.1 Hz, 1H), 2.35 (s, 3H).

Step 3. Synthesis of (R)-3-(4-bromo-3-methylphenyl)-5-(iodomethyl)oxazolidin-2-one [3.5.1c]. Triphenylphosphine (1.66 g, 6.3 mmol, 1.3 equiv) was dissolved in THF (10 mL) imidazole (0.33 g, 6.3 mmol, 1.3 equiv) was added. Iodine (1.23 g, 6.3 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 10 minutes. A solution of 3.5.1b (1.4 g, 4.8 mmol, 1.0 equiv) in THF (10 mL) was added dropwise and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (20 % EtOAc in Hexane) to afford product 3.5.1c (1.70 g, 76 % yield). LCMS (m/z): 398.3 [M+H]. $^1$H NMR (400 MHz, DMSO) $\delta$ 7.59 (d, $J$ = 8.8 Hz, 1H), 7.53 (d, $J$ = 2.7 Hz, 1H), 7.42 (dd, $J$ = 8.8, 2.8 Hz, 1H), 4.74 (td, $J$ = 10.7, 5.1 Hz, 1H), 4.18 (t, $J$ = 9.1 Hz, 1H), 3.72 - 3.51 (m, 3H), 2.36 (s, 3H).

Step 4. Synthesis of ethyl 3-((S)-3-(4-bromo-3-methylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.5.1d]. NaH (60%) (0.099 g, 7.5 mmol, 2.0 equiv) was dissolved in DMF (40 mL) at 0-5 °C. Ethyl 2-(methylsulfonyl)propanoate (1.36 g, 7.5 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 2
hours. A solution of 3.5.1c (1.5 g, 3.7 mmol, 1.0 equiv) in N,N-dimethylformamide (10 mL) was added drop wise at 0-5 °C and the reaction mixture was stirred at room temperature for 24 hour. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (15-20 % EtOAc in Hexane) to afford product 3.5.1d (0.92 g, 48 % yield). LCMS (m/z): 467.1[M+H]. 1H NMR (400 MHz, DMSO) δ 7.59 (dd, J = 8.8, 3.5 Hz, 1H), 7.51 (s, 1H), 7.37 (dd, J = 8.7, 2.6 Hz, 1H), 4.95 - 4.73 (m, 1H), 4.23 (ddd, J = 17.7, 13.9, 7.7 Hz, 3H), 3.80 (t, J = 8.3 Hz, 1H), 3.22 - 3.11 (m, 3H), 2.66 (s, 1H), 2.32 - 2.20 (m, 1H), 1.61 (d, J = 26.7 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 5. Synthesis of ethyl 2-methyl-3-((S)-3-(3-methyl-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanoate [3.5.1e]

3.5.1d (0.40 g, 0.9 mmol, 1.0 equiv), but-2-ynoic acid (0.075 g, 0.9 mmol, 1.0 equiv) and DBU (0.27 g, 1.0 mmol, 2.0 equiv) were dissolved in DMSO (20 mL) in sealed tube and the reaction mixture was degassed for 10 minutes. PdCl₂(PPh₃)₂ (0.006 g, 0.009 mmol, 0.01 equiv) and 1,4-bis(diphenylphosphino)butane (0.007 g, 0.018 mmol, 0.02 equiv) were added and the reaction mixture was stirred at 110°C for 15 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (10 % EtOAc in Hexane) to afford product 3.5.1e (0.2 g, 55 % yield). LCMS (m/z): 408.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.38 (dd, J = 13.0, 4.8 Hz, 3H), 4.78 (d, J = 7.3 Hz, 1H), 4.30 - 4.16 (m, 3H), 3.84 - 3.75 (m, 1H), 3.14 (d, J = 14.2 Hz, 3H), 2.68 (d, J = 15.0 Hz, 1H), 2.39 - 2.34 (m, 3H), 2.25 (d, J = 14.1 Hz, 1H), 2.06 (d, J = 16.5 Hz, 3H), 1.61 (d, J = 27.0 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H).

Step 6. Synthesis of 2-methyl-3-((S)-3-(3-methyl-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanoic acid [3.5.1f]

3.5.1e (0.2 g, 0.49 mmol, 1.0 equiv) was dissolved in THF (10 mL) and water (10 mL). LiOH.H₂O (0.04 g, 0.99 mmol, 2.0 equiv) was added and the resulting mixture was stirred at rt for 4 hours. The reaction mixture was concentrated to dryness and the residue was diluted in water, acidified by 1N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was triturated with n-hexane, decanted the solvent and dried to afford product 3.5.1f which was used for next step (0.17 g, 91 % yield). LCMS (m/z): 380.4 [M+H].

Step 7. Synthesis of 2-methyl-3-((S)-3-(3-methyl-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [3.5.1g]

3.5.1f (0.17 g, 0.45 mmol, 1.0 equiv) was dissolved in THF (20 mL). N-methyl morpholine (0.22 g, 2.24 mmol, 5.0 equiv), HOBT (0.091 g, 0.67 mmol, 1.5 equiv), EDC.HCl (0.150 g, 0.81 mmol, 1.8 equiv) and 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.1g, 0.89
mmol, 2.0 equiv) were added and the reaction mixture was stirred at rt for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (10-15% EtOAc in Hexane) to afford 3.5.1g which was used for next step (0.14 g, 65% yield). LCMS (m/z): 496.5 [M+18].

**Step 8. Synthesis of (R)-N-hydroxy-2-methyl-3-((S)-3-(3-methyl-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide [3.5.1].** 3.5.1g (0.14 g, 0.290 mmol, 1.0 equiv) was dissolved in ethanol (10 mL), 35.5% aq. HCl (0.2 mL) was added and reaction mixture was stirred at rt for 4 hours. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product that was purified by preparative HPLC to afford 3.5.1 (0.025 g, 21% yield). LCMS (m/z): 412.3 [M+18].

**H NMR** (400 MHz, DMSO) δ 7.38 (d, J = 20.6 Hz, 3H), 4.65 (m, 1H), 4.25 - 4.11 (m, 1H), 3.87-3.73 (m, 1H), 3.07 (d, J = 4.6 Hz, 3H), 2.75 (d, J = 12.6 Hz, 1H), 2.36 (s, 3H), 2.19 (m, 1H), 2.08 (s, 3H), 1.56 (d, J = 9.7 Hz, 3H).

**III.6.1. Synthesis of compound 3.6.1**

**Reagents:** Step 1: CBZ-Cl, NaHCO₃, Acetone: Water, 0 °C to room temperature. Step 2: n-BuLi (2.5M in hexane), THF, -78 °C to room temperature. Step 3: Iodine, triphenylphosphine, imidazole, dichloromethane, room temperature. Step 4: NaH (60%), N,N-dimethylformamide, 0 °C to room temperature. Step 5: DBU, dpbb, PdCl₂(PPh₃)₂, DMSO, 80 °C. Step 6: LiOH, THF, MeOH, Water, room temperature. Step 7: NH₂OTHP, EDC·HCl, HOBt, TEA, THF, room temperature. Step 8: HCl (8 %w/w in MeOH), MeOH, room temperature.
Step 1. Synthesis of benzyl (4-bromo-3-chlorophenyl)carbamate [3.6.1a]. 4-bromo-3-chloroaniline (6.0 g, 29.0 mmol, 1.0 equiv) was added portionwise and the reaction mixture was stirred at room temperature for 1 hour. A solution of silica gel chromatography (2-8% EtOAc in Hexane) to afford 3.6.1a (4.4 g, 44.5 % yield). LCMS (m/z): 340.1 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 10.14 (s, 1H), 7.79 (d, \(J = 2.3\) Hz, 1H), 7.67 (d, \(J = 8.8\) Hz, 1H), 7.55 - 7.28 (m, 6H), 5.17 (s, 2H).

Step 2. Synthesis of (R)-3-(4-bromo-3-chlorophenyl)-5-(hydroxymethyl)oxazolidin-2-one [3.6.1b]. 3.6.1a (4.3 g, 12.6 mmol, 1.0 equiv) was dissolved in THF (80 mL) and cooled to -78 °C. n-BuLi (2.5M in hexane) (0.89 g, 13.8 mmol, 1.1 equiv) was gradually added and the reaction mixture was stirred at -78 °C for 45 minutes. (R)-oxiran-2-ylmethyl butyrate (2.0 g, 13.8 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 24 hours. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (20-35 % EtOAc in Hexane) to afford product 3.6.1b (2.11 g, 54.5 % yield). LCMS (m/z): 306.1 [M-H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.89 (d, \(J = 2.6\) Hz, 1H), 7.76 (dd, \(J = 7.6, 5.5\) Hz, 1H), 7.45 (ddd, \(J = 22.3, 11.7, 4.4\) Hz, 1H), 5.24 (s, 1H), 4.79 - 4.66 (m, 1H), 4.09 (tt, \(J = 7.4, 3.7\) Hz, 1H), 3.89 - 3.79 (m, 1H), 3.68 (dd, \(J = 12.3, 3.0\) Hz, 1H), 3.56 (dd, \(J = 12.4, 3.8\) Hz, 1H). 

Step 3. Synthesis of (R)-3-(4-bromo-3-chlorophenyl)-5-(iodomethyl)oxazolidin-2-one [3.6.1c]. Triphenylphosphine (2.32 g, 8.9 mmol, 1.3 equiv) and imidazole (0.60 g, 8.9 mmol, 1.3 equiv) were dissolved in dichloromethane (20 mL). Iodine (2.25 g, 8.9 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 15 minutes. A solution of 3.6.1b (2.10 g, 6.9 mmol, 1.0 equiv) in dichloromethane (8 mL) was added drop wise and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated to dryness to afford a crude residue. The residue was purified by silica gel column chromatography (10-30 % EtOAc in Hexane) to afford product 3.6.1c (2.1 g, 73.8 % yield). LCMS (m/z): 418 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.89 (d, \(J = 2.7\) Hz, 1H), 7.82 - 7.73 (m, 1H), 7.46 (ddd, \(J = 22.8, 10.5, 5.5\) Hz, 1H), 4.83 - 4.69 (m, 1H), 4.21 (td, \(J = 9.1, 3.0\) Hz, 1H), 3.68 (dd, \(J = 9.3, 5.8\) Hz, 1H), 3.65 - 3.51 (m, 2H). 

Step 4. Synthesis of (R)-ethyl 3-((S)-3-(4-bromo-3-chlorophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.6.1d]. Ethyl 2-(methylsulfonyl)propanoate (1.82 g, 10.0 mmol, 2.0 equiv) dissolved in N,N-dimethylformamide (20 mL) and cooled to 0-5 °C. NaH (60%) (0.181 g, 7.5 mmol, 1.5 equiv) was added portion wise and the reaction mixture was stirred at room temperature for 1 hour. A solution of
3.6.1c (2.10 g, 5.0 mmol, 1.0 equiv) in N,N-dimethylformamide (5 mL) was added drop wise at 0-5 °C. The reaction mixture was allowed to stir at rt for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel chromatography (15-35 % EtOAc in Hexane) to afford product 3.6.1d (1.3 g, 55.2% yield). The product 3.6.1d was further purified by preparative HPLC to afford product 3.6.1d as desired diastereomer. LCMS (m/z): 468.2 [M-H]. 1H NMR (400 MHz, DMSO) δ 7.85 (d, J=2.6 Hz, 1H), 7.79 (dd, J =8.9, 3.6 Hz, 1H), 7.53-7.41 (m, 1H), 4.80 (d, J=8.8 Hz, 1H), 4.38 (q, J =7.2 Hz, 1H), 4.31-4.16 (m, 2H), 3.88-3.78 (m, 1H), 3.13 (s,3H), 2.67 (d, J=14.9 Hz, 1H), 2.37 (dd, J=14.9, 9.0Hz, 1H), 1.64 (s,3H), 1.25-1.22 (m, 3H).

Step 5. Synthesis of ethyl (R)-3-((S)-3-(3-chloro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.6.1e]. 3.6.1d (desired diastereomer) (0.20 g, 0.43 mmol, 1.0 equiv), but-2-ynoic acid (0.037 g, 0.45 mmol, 1.05 equiv), DBU (0.13 g, 0.85 mmol, 2.0 equiv), PdCl$_2$(PPh$_3$)$_2$ (0.003 g, 0.004 mmol, 0.01 equiv), 1,4-bis(diphenylphosphino)butane (0.003 g, 0.0085 mmol, 0.02 equiv) were added in DMSO (7 mL) in a sealed tube and the reaction mixture was stirred at 80 °C for 10 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel chromatography (20-30 % EtOAc in Hexane) to afford product 3.6.1e (0.152 g, 82.1 % yield). LCMS (m/z): 428.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.74 (d, J = 2.2 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 7.45 (dd, J = 8.6, 2.2 Hz, 1H), 4.80 (d, J = 7.8 Hz, 1H), 4.33 - 4.17 (m, 3H), 3.87 - 3.78 (m, 1H), 3.16 (s, 3H), 2.67 (d, J = 12.7 Hz, 1H), 2.37 (dd, J = 14.9, 8.9 Hz, 1H), 2.10 (s, 2H), 1.64 (s, 3H), 1.28 - 1.23 (m, 3H).

Step 6. Synthesis of (R)-3-((S)-3-(3-chloro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [3.6.1f]. 3.6.1e (0.145 g, 0.3 mmol, 1.0 equiv) was dissolved in THF (6 mL) and MeOH (1 mL). LiOH (0.016 g, 0.7 mmol, 2.0 equiv) in water (1 mL) was added and the reaction mixture was stirred at rt for 4 hours. The reaction mixture was diluted with water, acidified by 1.0 N HCl aqueous to pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 3.6.1f (0.115 g, 84.9 % yield), which was used in the next step with no further purification. LCMS (m/z): 400 [M-H]. 1H NMR (400 MHz, DMSO) δ 14.46 - 14.05 (m, 1H), 7.73 (d, J = 2.2 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.45 (dd, J = 8.6, 2.1 Hz, 1H), 4.81 (d, J = 7.8 Hz, 1H), 4.23 (t, J = 8.8 Hz, 1H), 3.87-3.78 (m, 1H), 3.14 (s,3H), 2.68-2.59 (m,1H), 2.31 (dd, J = 14.6, 8.6Hz, 1H), 2.00 (s, 3H), 1.61 (d, J = 18.0 Hz, 3H).

Step 7. Synthesis of (2R)-3-((S)-3-(3-chloro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [3.6.1g]. 3.6.1f (0.11 g, 0.28 mmol, 1.0 equiv) was dissolved in THF (10 mL). Et$_3$N (0.138
g, 1.37 mmol, 5.0 equiv), EDC.HCl (0.093 g, 0.49 mmol, 1.8 equiv) and HOBT (0.055 g, 0.41 mmol, 1.5 equiv) were added and the reaction mixture was stirred at room temperature for 10 minutes. 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.063 g, 0.54 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated to dryness. The residue was purified by flash chromatography (1-5 % MeOH in dichloromethane) to afford product **3.6.1** g which was used for next step (0.1 g, 72.8 % yield). LCMS (m/z): 518.5 [M+18]. 

1H NMR (400 MHz, DMSO) δ 7.71 (dd, J = 8.2, 2.2 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.49 - 7.42 (m, 1H), 4.70 (s, 1H), 4.12 (d, J = 5.3 Hz, 1H), 3.80 - 3.72 (m, 3H), 3.43 (dd, J = 7.1, 5.3 Hz, 2H), 3.05 (m, 3H), 2.80 - 2.72 (m, 1H), 2.25 (m, 1H), 1.62 (d, J = 8.2 Hz, 3H), 1.48 - 1.40 (m, 9H).

**Step 8. Synthesis of (R)-3-((S)-3-(3-chloro-4-(prop-1-yn-1-yl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [3.6.1]**. 3.6.1 g (0.095 g, 0.2 mmol, 1.0 equiv) dissolved in methanol (1 ml), HCl (8 w/w % in MeOH) (2 ml) was added and the reaction mixture was stirred at rt for 4 hours. The reaction mixture was concentrated to dryness. The crude product was purified by preparative HPLC to afford **3.6.1** as desired diastereomer (0.032 g, 40.5 % yield). LCMS (m/z): 415.3 [M+H].

1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.33 (s, 1H), 7.74 (d, J = 2.2 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.44 (dd, J = 8.6, 2.2 Hz, 1H), 4.64 (d, J = 7.3 Hz, 1H), 4.20 (t, J = 8.8 Hz, 1H), 3.88 - 3.74 (m, 1H), 3.08 (s, 3H), 2.76 (d, J = 11.8 Hz, 1H), 2.22 (dd, J = 14.6, 8.9 Hz, 1H), 2.09 (d, J = 7.1 Hz, 3H), 1.59 (s, 3H).

**III.7. Synthesis of compound 3.7**

**Step 1. Synthesis of ethyl (R)-3-((S)-3-(4-bromo-2, 3-difluorophenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [3.7a]**. (R)-ethyl 2-methyl-2-(methylsulfonyl)-3-((S)-2-oxooxazolidin-5-yl)propanoate (0.17 g, 0.62 mmol, 1.0 equiv), 1, 4-dibromo-2, 3-difluorobenzene (0.17 g, 0.62 mmol, 1.0 equiv) were dissolved in 1, 4-dioxane (10 ml). Cul (0.14 g, 0.75 mmol, 1.2 equiv), (1R, 2R)-(−)-1, 2-diamino cyclohexane (0.099 g, 0.87 mmol, 1.4 equiv), Cs₂CO₃ (0.3 g, 0.94 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 100 °C for 5 hours. The reaction mixture was filtered and filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (30-40 % EtOAc/Hexane) to afford the desired product **3.7a** (0.12 g, 41.9 % yield). LCMS (m/z): 470.2 [M+H].

1H NMR (400 MHz, DMSO) δ 7.64 (dd, J = 11.5, 4.7 Hz, 1H), 7.42 (dd, J = 11.8, 4.7 Hz, 1H), 4.87 (dd, J = 11.2, 5.3 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 4.16 (t, J = 8.5 Hz, 1H), 3.86 (t, J = 8.3 Hz, 1H), 3.17 (t, J = 2.6 Hz, 3H), 2.73 - 2.67 (m, 1H), 2.38 (dd, J = 14.8, 8.7 Hz, 1H), 1.65 (s, 3H), 1.27 - 1.23 (m, 3H).
Step 2. Synthesis of ethyl (R)-3-((S)-3-(2,3-difluoro-4-(prop-1-yn-1-yl)-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [3.7b]. 3.7a (0.16 g, 0.33 mmol, 1.0 equiv), but-2-ynoic acid (0.041 g, 0.49 mmol, 1.5 equiv), 1, 4-bis(diphenylphosphino)butane (0.003 g, 0.007 mmol, 0.02 equiv), DBU (0.1 g, 0.65 mmol, 2.0 equiv) were dissolved in DMSO (11 ml) and the reaction mixture was degassed. PdCl₂(PPh₃)₂ (0.0025 g, 0.0036 mmol, 0.01 equiv) was added and the reaction mixture was stirred at 100 °C for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel chromatography (30-40 % EtOAc/Hexane) to afford the desired product 3.7b (0.13 g, 92.2% yield). LCMS (m/z): 430.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.37 (t, J = 5.2 Hz, 2H), 4.86 (d, J = 8.4 Hz, 1H), 4.25 (dd, J = 14.2, 7.1 Hz, 2H), 4.17 (t, J = 8.3 Hz, 1H), 3.87 (t, J = 8.0 Hz, 1H), 3.17 (s, 3H), 3.70 (d, J = 1.49 Hz, 1H), 2.42-2.35 (m, 1H), 2.08 (s, 3H), 1.64 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H).


3.7 was prepared from 3.7b using the process of example 1.2. LCMS (m/z): 417.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.31 (s, 1H), 7.36 (dd, J = 12.6, 7.2 Hz, 2H), 4.70 (d, J = 7.2 Hz, 1H), 4.14 (t, J = 8.1 Hz, 1H), 3.84 (t, J = 8.1 Hz, 1H), 3.09 (s, 3H), 2.78 (d, J = 14.0 Hz, 1H), 2.22 (dd, J = 14.5, 8.9 Hz, 1H), 2.13 (s, 3H), 1.59 (s, 3H).

111.8. Synthesis of compound 3.8

Compound 3.8 was synthesized by the process of example 3.4.1. LCMS (m/z): 417.4 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 9.32 (s, 1H), 7.55 - 7.21 (m, 2H), 4.66 (dd, J = 15.1, 6.9 Hz, 1H), 4.19 (t, J = 8.8 Hz, 1H), 3.85 - 3.67 (m, 1H), 3.17 - 2.98 (m, 3H), 2.72 (t, J = 15.8 Hz, 1H), 2.30 - 2.18 (m, 1H), 1.69 - 1.47 (m, 3H).

111.9. Synthesis of compound 3.9

Compound 3.8 was synthesized by the process of example 3.4.1. LCMS (m/z): 429.9 [M+18]. ¹H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.32 (s, 1H), 7.60 - 7.43 (m, 2H), 7.31 (dd, J = 8.6, 2.0 Hz, 1H), 4.73 - 4.58 (m, 1H), 4.19 (t, J = 8.8 Hz, 1H), 3.79 (dd, J = 13.6, 5.9 Hz, 1H), 3.18 - 2.94 (m, 3H), 2.76 (d, J = 12.3 Hz, 1H), 2.45 (t, J = 7.5 Hz, 2H), 2.23 (dd, J = 14.4, 9.0 Hz, 1H), 1.69 - 1.50 (m, 3H), 1.23 - 1.10 (m, 3H).

111.1.0. Synthesis of compound 3.10

Compound 3.10 was synthesized by the process of example 3.1.48. LCMS (m/z): 469.4 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.26 - 10.97 (m, 1H), 9.31 (s, 1H), 7.60 - 7.43 (m, 2H), 7.32 (d, J = 8.6 Hz, 1H), 4.65 (d, J = 8.0 Hz, 1H), 4.20 (t, J = 8.8 Hz, 1H), 3.76 (dd,
J = 16.7, 9.8 Hz, 2H), 3.15 (d, J = 6.4 Hz, 3H), 3.08 (s, 3H), 2.85 (dd, J = 16.6, 8.8 Hz, 1H),
2.76 (d, J = 17.1 Hz, 1H), 2.69 - 2.59 (m, 2H), 2.23 (dd, J = 14.4, 9.0 Hz, 1H), 2.00 - 1.90
(m, 2H), 1.59 (s, 3H).

111.11. Synthesis of compound 3.11

Step 1. Synthesis of ethyl 3-((S)-3-(4-(cyclopropylethynyl)-2-fluorophenyl)-2-oxo
oxazolidin-5-y1)-2-methyl-2-(methylsulfonyl)propanoate [3.11a]. 1.3d (0.27 g, 0.59
mmol, 1.0 equiv), PdCl₂(pph₃)₂ (0.021 g, 0.03 mmol, 0.05 equiv), CuI (0.006 g, 0.03 mmol,
0.05 equiv), triphenyl phosphine (0.031 g, 0.11 mmol, 0.2 equiv) were added in diethyl amine
(5 mL) and N,N-dimethylformamide (2 mL) and the reaction mixture was degassed for 15
minutes. Ethynylcyclopropane (0.08 g, 1.19 mmol, 2.0 equiv) was added and the reaction
mixture was stirred at 120 °C for 4 hours. The reaction mixture was quenched with water
and extracted with EtOAc. The organic layer was washed with brine, dried over sodium
sulfate and concentrated to afford a residue that was purified by silica gel chromatography
(25-30 % EtOAc in Hexane) to afford product 3.11a (0.18 g, 68.9 % yield). LCMS (m/z):
438.6 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.51 (t, J = 8.4 Hz, 1H), 7.35 (d, J = 11.6 Hz,
1H), 7.25 (d, J = 8.3 Hz, 1H), 4.83 (d, J = 6.0 Hz, 1H), 4.28 - 4.12 (m, 3H), 3.80 (t, J = 8.2
Hz, 1H), 3.16 (d, J = 10.6 Hz, 3H), 2.67 (s, 1H), 2.36 (dd, J = 14.8, 8.8 Hz, 1H), 1.67 - 1.51
(m, 4H), 1.25 (dd, J = 7.0, 4.9 Hz, 3H), 0.91 (dt, J = 6.4, 4.1 Hz, 2H), 0.81 - 0.71 (m, 2H).

Step 2. Synthesis of (R)-3-((S)-3-(4-(cyclopropylethynyl)-2-fluorophenyl)-2-oxo-
oxazolidin-5-y1)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [3.11].
Compound 3.11 was synthesized by the process of example 1.1. LCMS (m/z): 441.9 [M+18].
¹H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 9.16 (s, 1H), 7.51 (t, J = 8.3 Hz, 1H), 7.35 (dd, J
= 11.8, 1.7 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 4.68 (d, J = 5.2 Hz, 1H), 4.08 (t, J = 8.4 Hz,
1H), 3.77 (t, J = 8.3 Hz, 1H), 3.09 (s, 3H), 2.76 (d, J = 11.7 Hz, 1H), 2.19 (dd, J = 14.3, 8.5
Hz, 1H), 1.67 - 1.44 (m, 4H), 0.91 (dt, J = 6.3, 4.0 Hz, 2H), 0.76 (td, J = 6.5, 3.9 Hz, 2H).


Compound 3.12 was synthesized by the process of example 3.11. LCMS (m/z): 423.3
[M-1]. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.61 - 7.41 (m, 2H), 7.29
(dd, J = 8.7, 2.1 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H), 4.19 (t, J = 8.9 Hz, 1H), 3.83 - 3.71 (m,
1H), 3.08 (s, 3H), 2.76 (d, J = 11.7 Hz, 1H), 2.22 (dd, J = 14.4, 9.0 Hz, 1H), 1.70 - 1.45 (m,
4H), 0.95 - 0.83 (m, 2H), 0.80 - 0.65 (m, 2H).

IV.1. Synthesis of compound 4.1

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**Reagents:** Step 1: 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane), KOAc, PdCl₂(dppf)₂, 1,4-dioxane, 95°C. Step 2: H₂O₂ (30% in H₂O), 1,4-Dioxane, room temperature. Step 3: 1-bromobut-2-yne, NaH (60%), N,N-dimethylformamide, 5°C to room temperature. Step 4: LiOH.H₂O, THF, MeOH, Water, room temperature. Step 5: NH₂OTHP, EDC.HCl, HOBT, TEA, DCM, room temperature. Step 6: 35.5% aq. HCl, EtOH, room temperature.

**Step 1. Synthesis of ethyl 2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)oxazolidin-5-yl)propanoate [4.1a].** 1.1d (1.0 g, 2.3 mmol, 1.0 equiv)(mixture of isomers), potassium acetate (1.0 g, 10.37 mmol, 4.5 equiv), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (0.6 g, 2.3 mmol, 1.0 equiv), PdCl₂(dppf)₂ (0.34 g, 0.46 mmol, 0.2 equiv) were dissolved in 1,4-dioxane (15 mL) in a sealed tube. The mixture was stirred at 95°C for 24 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (30-40% EtOAc in Hexane) to afford 4.1a (0.55 g, 49.6% yield). LCMS (m/z): 482.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.68 (t, J=10.0 Hz, 2H), 7.61-7.52 (m, 2H), 4.95-4.72 (m, 1H), 4.25 (dt, J=12.4, 7.8 Hz, 3H), 3.84 (t, J=8.2 Hz, 1H), 3.23-3.11 (m, 13H), 2.70(d, J=16.0 Hz, 1H), 2.41-2.30(m, 1H), 1.61(d, J=26.6 Hz, 3H), 1.36-1.19 (m, 13H).

**Step 2. Synthesis of ethyl 3-((S)-3-(4-hydroxyphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [4.1b].** H₂O₂ (30% in H₂O, 1.0 mL) was added to a mixture
of 4.1a (0.55 g, 1.14 mmol, 1.0 equiv) in 1,4-dioxane (10 mL) and the resulting mixture was stirred at rt for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with water, brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (2-3 % MeOH in dichloromethane) to afford product 4.1b which was used as such for next step (0.19 g, 44.8 % yield). LCMS (m/z): 372.3 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 9.38 (s, 1H), 7.35 - 7.28 (m, 2H), 6.81 - 6.74 (m, 2H), 4.90 - 4.66 (m, 1H), 4.26 (d, $J = 7.1$ Hz, 2H), 4.12 (t, $J = 8.7$ Hz, 1H), 3.74 (t, $J = 8.2$ Hz, 1H), 3.15 (d, $J = 12.0$ Hz, 3H), 2.67 (d, $J = 12.8$ Hz, 1H), 2.39 - 2.25 (m, 1H), 1.69 - 1.51 (m, 3H), 1.25 (d, $J = 6.6$ Hz, 3H).

**Step 3. Synthesis of ethyl 3-((S)-3-(4-(but-2-yn-1-yl)oxy)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [4.1c].** 4.1b (0.19 g, 0.51 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide (4 mL) and cooled the reaction mixture to 5 °C. NaH (0.025 g, 0.62 mmol, 1.2 equiv) was added portion wise and the reaction mixture was stirred at room temperature for 1 hour. A solution of 1-bromobut-2-yn (0.10 g, 0.77 mmol, 1.5 equiv) in N,N-dimethylformamide (3 mL) was added drop wise at 5 °C. The reaction mixture was allowed to stir at room temperature for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (30-40 % EtOAc in Hexane) to afford product 4.1c (0.19 g, 62.1 % yield). LCMS (m/z): 424.4 [M+H]. $^1$H NMR (400 MHz, CD$_3$CN) δ 7.46 (qd, $J = 5.7, 2.9$ Hz, 2H), 7.00 (dt, $J = 10.4, 2.5$ Hz, 2H), 4.76 (tt, $J = 14.3, 4.2$ Hz, 1H), 4.69 (q, $J = 2.3$ Hz, 2H), 4.34 - 4.24 (m, 2H), 4.22 - 4.11 (m, 1H), 3.81 - 3.69 (m, 1H), 3.10 - 3.07 (m, 3H), 2.75 - 2.65 (m, 1H), 2.42 (ddd, $J = 11.5, 8.8, 5.9$ Hz, 1H), 2.19 (s, 3H), 1.74 (d, $J = 5.7$ Hz, 3H), 1.35 - 1.31 (m, 3H).

**Step 4. Synthesis of 3-((S)-3-(4-(but-2-yn-1-yl)oxy)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [4.1 d].** 4.1c (0.13 g, 0.31 mmol, 1.0 equiv) was dissolved in THF (1 mL), MeOH (2 mL) and LiOH-H$_2$O (0.015 g, 0.37 mmol, 1.2 equiv) in water (1 mL). The resulting mixture was stirred at rt for 2 hours. The reaction mixture was concentrated to dryness and the residue was acidified by addition of 1N HCl aqueous solution until the pH 4 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was triturated with n-pentane, the solvent was decanted to obtain product 4.1d (0.10 g, 82.6 % yield). The crude material was used in the next step with no further purification. LCMS (m/z): 396.3 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 14.26 - 14.06 (m, 1H), 7.45 (dd, $J = 9.2, 2.7$ Hz, 2H), 7.05 - 6.97 (m, 2H), 4.74 (t, $J = 9.4$ Hz, 3H), 4.18 (t, $J = 8.8$ Hz, 1H), 3.77 (dd, $J = 14.9, 6.2$ Hz, 1H), 3.14 (d, $J = 6.9$ Hz, 3H), 2.70 - 2.62 (m, 1H), 2.32 - 2.26 (m, 1H), 1.83 (t, $J = 2.2$ Hz, 3H), 1.59 (d, $J = 12.4$ Hz, 3H).
Step 5. Synthesis of 3-((S)-3-(4-(but-2-yn-1-yloxy)phenyl)-2-oxooxazolidin-5-yl)-2-
methyl-2-(methylsulfonyl)-(tetrahydro-2H-pyran-2-yl)oxy)propanamide [4.1 e]. 4.1 d
(0.100 g, 0.25 mmol, 1.0 equiv) was dissolved in dichloromethane (5 ml). TEA (0.128 g, 1.27 mmol, 5.0 equiv), EDC.HCl (0.073 g, 0.38 mmol, 1.5 equiv), HOBT (0.061 g, 0.46 mmol, 1.8 equiv) and 0-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.060 g, 0.51 mmol, 2.0 equiv) were added to the solution. The reaction mixture was stirred at rt for 24 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel chromatography (2-3 % MeOH in dichloromethane) to afford product 4.1 e which was used as such for next step (0.09 g, 71.9 % yield). LCMS (m/z): 512.5 [M+18]. 1H NMR (400 MHz, DMSO) δ 7.44 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 9.0 Hz, 2H), 4.73 (s, 2H), 4.65 (s, 1H), 4.14 (t, J = 8.5 Hz, 1H), 3.76 (s, 2H), 3.44 (s, 2H), 3.09 (dd, J = 19.9, 10.4 Hz, 3H), 2.78 (d, J = 15.3 Hz, 1H), 2.24 (s, 1H), 1.82 (d, J = 5.0 Hz, 3H), 1.62 (s, 3H), 1.49 (d, J = 38.1 Hz, 6H).

Step 6. Synthesis of (R)-3-((S)-3-(4-(but-2-yn-1-yloxy)phenyl)-2-oxooxazolidin-5-yl)-N-
hydroxy-2-methyl-2-(methylsulfonyl)propanamide [4.1]

4.1e (0.085 g, 0.17 mmol, 1.0 equiv) was dissolved in ethanol (5 ml). 35.5 % aqueous HCl (0.5 ml) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated under reduced pressure. The residue was poured to saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by preparative HPLC to afford 4.1 as the desired diastereomer (0.016 g, 22.7 % yield). LCMS (m/z): 411.3 [M+H]. 1H NMR (400 MHz, CD3CN) δ 9.67 (s, 1H), 7.60 - 7.42 (m, 2H), 7.32 (s, 1H), 7.07 - 6.97 (m, 2H), 4.79 - 4.60 (m, 3H), 4.14 (t, J = 8.8 Hz, 1H), 3.75 (t, J = 8.1 Hz, 1H), 3.03 (d, J = 1.5 Hz, 3H), 2.75 (d, J = 14.2 Hz, 1H), 2.33 (dd, J = 13.7, 8.4 Hz, 2H), 1.92 - 1.79 (m, 3H), 1.70 (s, 3H).

IV.2 Synthesis of compound 4.2

**Reagents:** Step 1: K2CO3, N,N-dimethylformamide, 100°C. Step 2: LiOH.H2O, THF, MeOH,
Water, room temperature. Step 3: NH$_2$OTHP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 4: 35.5% aq. HCl, EtOH, room temperature.

**Step 1. Synthesis of ethyl 2-methyl-2-((methylsulfonyl)-3-((S)-2-oxo-3-(4-(2,2,2-trifluoroethoxy)phenyl)oxazolidin-5-yl)propanoate [4.2a].** 4.1b (0.2 g, 0.54 mmol, 1.0 equiv), K$_2$CO$_3$ (0.29 g, 2.16 mmol, 4.0 equiv) were added in N,N-dimethylformamide (4 mL) in sealed tube. The reaction mixture was stirred at room temperature for 15 minutes. A solution of 1,1,1-trifluoro-2-iodoethane (0.23 g, 1.07 mmol, 2.0 equiv) in N,N-dimethylformamide (1 mL) was drop wise added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the crude product. The crude product was purified by column chromatography (30-35 % EtOAc in Hexane) to afford product 4.2a (0.172 g, 55.7 % yield). LCMS (m/z): 454.4 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.66 - 7.46 (m, 2H), 7.30 - 7.07 (m, 2H), 5.10 - 4.65 (m, 3H), 4.33 - 4.13 (m, 3H), 3.95 (d, J = 5.5 Hz, 1H), 3.81 (dd, J = 17.9, 10.2 Hz, 1H), 3.15 (d, J = 13.2 Hz, 3H), 2.67 (d, J = 3.4 Hz, 1H), 2.41 - 2.30 (m, 1H), 1.67 - 1.54 (m, 3H), 1.30 - 1.20 (m, 3H).

**Step 2. Synthesis of 2-methyl-2-((methylsulfonyl)-3-((S)-2-oxo-3-(4-(2,2,2-trifluoroethoxy) phenyl)oxazolidin-5-yl)propanoic acid [4.2b].** 4.2a (0.17 g, 0.3 mmol, 1.0 equiv) was dissolved in THF (4 mL), MeOH (2 mL). LiOH.H$_2$O (0.031 g, 0.7 mmol, 2.0 equiv) in water (2 mL) was added and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with water, acidified by 1.0 N HCl aqueous solution to the pH 1 to 2 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the crude product. The crude product was triturated with n-pentane, decanted the solvent and dried to afford product 4.2b (0.14 g, 87.5 % yield). The product was used in the next step with no further purification. LCMS (m/z): 426.3 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.58 - 7.47 (m, 2H), 7.25 - 7.08 (m, 2H), 5.03 - 4.55 (m, 3H), 4.19 (t, J = 8.2 Hz, 1H), 3.81 (d, J = 7.7 Hz, 1H), 3.15 (s, 3H), 2.64 (d, J = 14.9 Hz, 1H), 2.32 (d, J = 8.4 Hz, 1H), 1.61 (s, 3H).

**Step 3. Synthesis of 2-methyl-2-((methylsulfonyl)-3-((S)-2-oxo-3-(4-(2,2,2-trifluoroethoxy) phenyl)oxazolidin-5-yl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [4.2c].** 4.2b (0.14 g, 0.32 mmol, 1.0 equiv) was dissolved in THF (5 mL). N-methyl morpholine (0.167 g, 1.64 mmol, 5.0 equiv), EDC.HCl (0.059 g, 0.49 mmol, 1.5 equiv), HOBT (0.053 g, 0.40 mmol, 1.2 equiv), 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.077 g, 0.65 mmol, 2.0 equiv) were added to the solution and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the crude product. The crude product was purified by column chromatography (30-35 % EtOAc in Hexane) to afford product 4.2c (0.14 g, 87.5 % yield). LCMS (m/z): 554.3 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 7.25 - 7.08 (m, 2H), 7.08 - 6.93 (m, 2H), 5.70 - 5.56 (m, 2H), 5.10 - 4.65 (m, 3H), 4.31 - 4.13 (m, 3H), 3.95 (d, J = 5.5 Hz, 1H), 3.81 (dd, J = 17.9, 10.2 Hz, 1H), 3.15 (d, J = 13.2 Hz, 3H), 2.67 (d, J = 3.4 Hz, 1H), 2.41 - 2.30 (m, 1H), 1.67 - 1.54 (m, 3H), 1.30 - 1.20 (m, 3H).
chromatography (1-2 % MeOH in dichloromethane) to afford product 4.2c which was carry forwarded for next step. (0.1g, 58 % yield). LCMS (m/z): 542.4 [M+18].

**Step 4. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(2,2,2-trifluoroethoxy)phenyl)oxazolidin-5-yl)propanamide [4.2].** 4.2c (0.1 g, 0.19 mmol, 1.0 equiv) was dissolved in ethanol (5 ml). 35.5% aq. HCl (1 ml) was added and the reaction mixture was stirred at rt for 2 hours. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude product. The crude product was purified by preparative HPLC to afford 4.2 as desired diastereomer (0.02 g, 23.8 % yield). LCMS (m/z): 443.3 [M+18]. ^1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 9.26 (s, 1H), 7.48 (d, J = 9.1 Hz, 2H), 7.38 (d, J = 5.7 Hz, 2H), 4.75 (q, J = 9.1 Hz, 2H), 4.63 (d, J = 6.5 Hz, 1H), 4.14 (t, J = 8.8 Hz, 1H), 3.83 - 3.73 (m, 1H), 3.08 (s, 3H), 2.75 (d, J = 11.8 Hz, 1H), 2.18 (dd, J = 14.3, 8.7 Hz, 1H), 1.58 (s, 3H).

**V.1.1. Synthesis of compound 5.1.1**

**Reagents:** Step 1: Pd(OAc)$_2$, P(Cy)$_3$, K$_2$PO$_4$, Toluene, Water, 100°C. Step 2: LiOH, THF, MeOH, Water, room temperature. Step 3: NH$_2$OTHP, EDC.HCl, HOBT, N-Methyl morpholine, THF, room temperature. Step 4: Methanolic-HCl (8%w/w), MeOH, 0°C to room temperature.

**Step 1. Synthesis of ethyl 3-((S)-3-(4-cyclopropylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [5.1.1a].** 1.1d (0.35 g, 0.8 mmol, 1.0 equiv), cyclopropyl boronic acid (0.21 g, 2.4 mmol, 3.0 equiv) and K$_2$P$_4$ (0.51 g, 2.4 mmol, 3.0 equiv) were added in toluene: water (10:1, 5.5 ml) and degassed for 15 min. Pd(OAc)$_2$ (0.009 g, 0.04 mmol, 0.05 equiv) and P(Cy)$_3$ (0.002 g, 0.08 mmol, 0.1 equiv) were added to the reaction mixture and the reaction mixture was stirred at 100 °C under microwave irradiation for 1 hour. The reaction mixture was filtered through Celite bed and concentrated. The residue was purified by silica gel column chromatography (10-35 % EtOAc in Hexane) to afford product 5.1.1a (0.25 g, 78.4 % yield). LCMS (m/z): 396.3 [M+H]. ^1H NMR (400
MHz, DMSO) δ 7.40 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H), 4.76 (d, J = 8.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 4.17 (t, J = 8.8 Hz, 1H), 3.82 - 3.76 (m, 1H), 2.72 - 2.65 (m, 1H), 2.34 (dd, J = 14.8, 9.0 Hz, 1H), 1.89 (td, J = 8.3, 4.3 Hz, 1H), 1.64 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 0.96 - 0.89 (m, 2H), 0.67 - 0.61 (m, 2H).

Step 2. Synthesis of 3-((S)-3-(4-cyclopropylphenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [5.1.1b]. 5.1.1a (0.25 g, 0.63 mmol, 1.0 equiv) was dissolved in THF (10 ml_), MeOH (2 ml_). LiOH (0.04 g, 0.94 mmol, 1.5 equiv) in water (1 ml_) was added. The resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was concentrated to dryness and the residue was diluted with water, acidified by 1.0 N HCl aqueous solution to the pH 4 to 5 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 5.1.1b (0.18 g, 77.5 % yield). LCMS (m/z): 368.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 1.07 (s, 1H), 9.30 (td, J = 6.3, 4.1 Hz, 2H), 0.69 - 0.59 (m, 2H).


5.1.1b (0.14 g, 0.36 mmol, 1.0 equiv) was dissolved in THF (7 ml_). N-methyl morpholine (0.19 g, 1.8 mmol, 5.0 equiv), EDC.HCl (0.07 g, 0.55 mmol, 1.5 equiv), HOBT (0.06 g, 0.44 mmol, 1.2 equiv) and 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.09 g, 0.73 mmol, 2.0 equiv) were added to the solution. The reaction mixture was stirred at room temperature for 10 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (30-50 % EtOAc in Hexane) to afford product 5.1.1c which was used as such for next step (0.09 g, 52.5 % yield). LCMS (m/z): 484.5 [M+18]. 1H NMR (400 MHz, DMSO) δ 11.55 - 11.43 (m, 1H), 7.48 - 7.35 (m, 2H), 7.10 (d, J = 8.5 Hz, 2H), 4.97 (d, J = 9.4 Hz, 1H), 4.63 (s, 1H), 4.24 - 4.01 (m, 2H), 3.82 - 3.70 (m, 1H), 3.51 (s, 1H), 3.07 (t, J = 7.9 Hz, 3H), 2.78 (d, J = 11.9 Hz, 1H), 2.26 - 2.16 (m, 1H), 1.89 (dd, J = 9.2, 4.1 Hz, 1H), 1.64 - 1.49 (m, 6H), 1.25 (d, J = 11.3 Hz, 3H), 1.00 - 0.87 (m, 2H), 0.79 - 0.56 (m, 2H).

Step 4. Synthesis of (R)-3-((S)-3-(4-cyclopropylphenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [5.1.1]. 5.1.1g (0.12 g, 0.24 mmol, 1.0 equiv) was dissolved in methanol (1 ml_) and cooled the solution at 0 °C. Methanolic-HCl solution (8% w/w, 2.1 ml_) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness and the crude product was purified by preparative HPLC to afford 5.1.1 as desired diastereomer (0.04 g, 42.4 % yield). LCMS (m/z): 383.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 9.30
V.3 Synthesis of compound 5.3

Reagents: Step 1: Iodomethane, NaH (60%), THF, 0°C to room temperature. Step 2: NH₄OH, Cul, acetyl acetone, Cs₂CO₃, N,N-dimethylformamide, 100 °C. Step 3: CBZ-Cl, NaHCO₃, Acetone: Water, 0°C to room temperature. Step 4: n-BuLi (23% in Hexane), THF, -78 °C to room temperature. Step 5: Iodine, triphenylphosphine, imidazole, dichloromethane, room temperature. Step 6: NaH (60%), N,N-dimethylformamide, 0°C to room temperature. Step 7: LiOH·H₂O, THF, MeOH, Water, room temperature. Step 8: NH₂OTHp, EDC·HCl, HOBT, N-methyl morpholine, THF, rt. Step 9: 35.5% aq. HCl, EtOH, room temperature.

Step 1. Synthesis of 1-bromo-4-(methoxymethyl)benzene [5.3a]. NaH (60%) (0.51 g, 2.14 mmol, 2.0 equiv) was dissolved in THF (50 mL) and cooled to 0 °C. (4-bromophenyl) methanol (2 g, 10.7 mmol, 1.0 equiv) in THF (5 mL) was added drop wise and the reaction mixture was stirred at room temperature for 1 hour. A solution Iodomethane (1.82 g, 12.8 mmol, 1.2 equiv) in THF (5 mL) was added at 0 °C and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 5.3a (1.9 g, 88.4 % yield). ¹H NMR (400 MHz, DMSO) δ 7.60 - 7.50 (m, 2H), 7.28 (d, J = 8.4 Hz, 2H), 4.44 - 4.32 (m, 2H), 3.29 (s, 3H).

Step 2. Synthesis of 4-(methoxymethyl) aniline [5.3b]. 5.3a (1.9 g, 9.45 mmol, 1.0 equiv), Cul (0.180 g, 0.94 mmol, 0.1 equiv), acetyl acetone (0.95 g, 9.45 mmol, 1.0 equiv) and Cs₂CO₃ (6.15 g, 18.9 mmol, 2.0 equiv) were suspended in N,N-dimethylformamide (28
ml) in sealed tube and ammonium hydroxide (2.18 ml, 5.67 mmol, 6.0 equiv) was added and the reaction mixture was stirred at 100 °C for 5 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (0.7 % MeOH in dichloromethane) to afford product 5.3b (1.1 g, 85 % yield). LCMS (m/z): 138.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 6.96 (d, J = 8.1 Hz, 2H), 6.52 (d, J = 8.1 Hz, 2H), 5.06 (s, 2H), 4.18 (s, 2H). 3.19 (s, 3H).

Step 3. Synthesis of benzyl (4-(methoxymethyl)phenyl)carbamate [5.3c]

5.3b (1.1 g, 8.02 mmol, 1.0 equiv) was dissolved in acetone: water (2:1, 9 ml) and cooled to 0 °C. NaHCO₃ (1.42 g, 16.86 mmol, 2.1 equiv) and CBZ-Cl (1.78 g, 10.44 mmol, 1.3 equiv) were added and the reaction mixture was stirred at room temperature for 7 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (2-5 % EtOAc in Hexane) to afford product 5.3c (1.56 g, 72 % yield). 1H NMR (400 MHz, DMSO) δ 9.80 - 7.38 (m, 6H), 7.23 (t, J = 6.5 Hz, 2H), 5.15 (s, 2H), 4.32 (s, 2H), 3.25 (s, 3H).

Step 4. Synthesis of (R)-5-(hydroxymethyl)-3-(4-(methoxymethyl)phenyl)oxazolidin-2-one [5.3d]. 5.3c (1.56 g, 5.76 mmol, 1.0 equiv) was dissolved in THF (55 ml) and cooled to -78 °C. n-BuLi (23% in Hexane) (2.36 ml, 8.63 mmol, 1.5 equiv) was gradually added and the reaction mixture was stirred at -70 °C for 1 hour. (R)-oxirane-2-ylmethyl butyrate (0.99 g, 6.90 mmol, 1.2 equiv) in THF (5 ml) was added drop wise and the reaction mixture was allowed to stir at room temperature for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel chromatography (70 % EtOAc in Hexane) to afford product 5.3d (0.91 g, 67 % yield). LCMS (m/z): 238.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.54 (dd, J = 14.9, 8.6 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 5.33 - 5.15 (m, 1H), 4.80 - 4.64 (m, 1H), 4.35 (d, J = 19.6 Hz, 2H), 4.06 (dt, J = 16.3, 8.1 Hz, 1H), 3.83 (dd, J = 8.8, 6.3 Hz, 1H), 3.68 (ddd, J = 12.3, 5.5, 3.4 Hz, 1H), 3.61 - 3.48 (m, 1H), 3.28 (d, J = 7.5 Hz, 3H).

Step 5. Synthesis of (R)-5-(iodomethyl)-3-(4-(methoxymethyl)phenyl)oxazolidin-2-one [5.3e]. Triphenylphosphinie (1.16 g, 4.44 mmol, 1.3 equiv) was dissolved in dichloromethane (30 ml), imidazole (0.30 g, 4.44 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 5 minutes. Iodine (1.27 g, 4.44 mmol, 1.3 equiv) was added and the reaction mixture was stirred at room temperature for 10 minutes. 5.3d (0.81 g, 3.41 mmol, 1.0 equiv) in dichloromethane (10 ml) was added drop wise and the reaction mixture was stirred at rt for 24 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and
concentrated to afford a residue. The residue was purified by silica gel chromatography (25 % EtOAc in Hexane) to afford product 5.3e (0.83 g, 70 % yield). LCMS (m/z): 348.2 [M+H]. 

\(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.53 (t, J = 12.7 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 4.73 (dd, J = 8.5, 5.1 Hz, 1H), 4.38 (s, 2H), 4.20 (t, J = 9.0 Hz, 1H), 3.73 - 3.51 (m, 3H), 3.29 (s, 3H).

**Step 6. Synthesis of ethyl 3-((S)-3-(4-(methoxymethyl)phenyl)-2-oxoazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [5.3f].** Ethyl 2-(methylsulfonyl)propanoate (1.62 g, 8.99 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide (15 mL) and cooled to 0 °C. NaH (60%) (0.108 g, 4.49 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for 2 hours. 5.3d (0.780 g, 2.24 mmol, 1.0 equiv) in N,N-dimethylformamide (6 mL) was added drop wise at 0 °C. The reaction mixture was stirred at room temperature for 24 hour. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was purified by silica gel column chromatography (28-30 % EtOAc in Hexane) to afford product 5.3f (0.55 g, 61.3 % yield). LCMS (m/z): 400.4 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.64 - 7.49 (m, 2H), 7.35 (t, J = 5.8 Hz, 2H), 5.00 - 4.72 (m, 1H), 4.38 (s, 2H), 4.32 - 4.17 (m, 3H), 3.81 (dd, J = 17.1, 8.3 Hz, 1H), 3.34 (s, 3H), 3.21 - 3.10 (m, 3H), 2.75 - 2.66 (m, 1H), 2.41 - 2.24 (m, 1H), 1.70 - 1.55 (m, 3H), 1.26 (dd, J = 10.0, 4.2 Hz, 3H).

**Step 7. Synthesis of 3-((S)-3-(4-(methoxymethyl)phenyl)-2-oxoazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [5.3g].** 5.3f (0.55 g, 1.37 mmol, 1.0 equiv) was dissolved in THF (10 mL), methanol (2.5 mL) and water (2.5 mL). LiOH.H₂O (0.17g, 4.13 mmol, 3.0 equiv) was added and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was concentrated to dryness; the residue was diluted in water, acidified by 1N HCl aqueous solution to the pH 2 to 3 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was triturated with n-pentane, decanted the solvent and dried to afford product 5.3g (0.36 g, 70.5 % yield). LCMS (m/z): 372.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.52 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 4.80 (d, J = 8.1 Hz, 1H), 4.38 (s, 2H), 4.22 (t, J = 8.7 Hz, 1H), 3.87 - 3.78 (m, 1H), 3.27 (s, 3H), 3.15 (s, 3H), 2.65 (d, J = 12.3 Hz, 1H), 2.32 (dd, J = 14.7, 8.8 Hz, 1H), 1.61 (s, 3H).

**Step 8. Synthesis of 3-((S)-3-(4-(methoxymethyl)phenyl)-2-oxoazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [5.3h].** 5.3g (0.3 g, 0.8 mmol, 1.0 equiv) was dissolved in THF (20 mL). N-methyl morpholine (0.40 g, 4.0 mmol, 5.0 equiv), HOBT (0.131 g, 0.97 mmol, 1.2 equiv), 0-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.19 g, 1.61 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 5 minutes. EDC.HCl (0.23 g, 1.21 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction
mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (2 % MeOH in dichloromethane) to afford product 5.3h which is a mixture of mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated to afford a crude product.

Step 9. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-(methoxymethyl)phenyl)-2-oxoazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [5.3]. 5.3h (0.274 g, 0.58 mmol, 1.0 equiv) was dissolved in ethanol (10 mL). 35.5% aq. HCl (0.27 mL) was added and reaction mixture was stirred at rt for 1 hour. The reaction mixture was diluted with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was purified by preparative HPLC to afford product 5.3 (0.055 g, 24.4 % yield). LCMS (m/z): 404.3 [M+18]. H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 4.67 (d, J = 7.9 Hz, 1H), 4.38 (s, 2H), 4.18 (t, J = 8.5 Hz, 1H), 3.55 - 3.48 (m, 1H), 3.46 - 3.40 (m, 1H), 3.27 (s, 3H), 3.08 (t, J = 8.2 Hz, 3H), 2.84 - 2.72 (m, 1H), 2.23 (dd, J = 13.3, 7.7 Hz, 1H), 1.63 (s, 3H), 1.56 - 1.43 (m, 6H).

V.4. Synthesis of compound 5.4


Step 1. Synthesis of potassium 2-cyanoacetate. Ethyl 2-cyanoacetate (1.0 g, 8.9 mmol, 1.0 equiv) was dissolved in EtOH: Water (1:1, 10 mL). Potassium t-butoxide (1.19 g, 10.6 mmol, 1.2 equiv) was added portion wise and the reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated to afford a crude product.
The crude product was triturated in diethyl ether, solvent was decanted and dried to afford product which was used as such for next step. (0.78 g, 71.6 % yield).

**Step 1. Synthesis of ethyl 3-((S)-3-(4-(cyanomethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl -2-(methylsulfonyl)propanoate [5.4a].** 1.1d (0.7 g, 1.61 mmol, 1.0 equiv), potassium 2-cyanoacetate (0.24 g, 1.93 mmol, 1.2 equiv) were added in mesitylene (6 ml_) and the reaction mixture was degassed for 10 minutes. Pd(ii)(Allyl)Cl (0.029 g, 0.08 mmol, 0.5 equiv), S-phos (0.066 g, 0.16 mmol, 0.1 equiv) were added and the reaction mixture was stirred at 140°C for 6 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue that was purified by silica gel chromatography (40-50 % EtOAc in Hexane) to afford product 5.4a (0.24 g, 37.7 % yield). LCMS (m/z): 395.4 [M+H].

1H NMR (400 MHz, DMSO) δ 7.61 - 7.54 (m, 2H), 7.38 (d, J = 8.7 Hz, 2H), 4.79 (d, J = 8.5 Hz, 1H), 4.33 - 4.16 (m, 3H), 4.03 (d, J = 9.4 Hz, 2H), 3.87 - 3.76 (m, 1H), 3.17 (s, 3H), 2.70 (d, J = 15.0 Hz, 1H), 2.36 (dd, J = 14.8, 8.9 Hz, 1H), 1.65 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

**Step 2. Synthesis of 3-((S)-3-(4-(cyanomethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [5.4b].** 5.4a (0.24 g, 0.60 mmol, 1.0 equiv) was dissolved in THF (2 ml_), MeOH (1 ml_). LiOH.H2O (0.076 g, 1.82 mmol, 3.0 equiv) in water (1 ml_) was added and the reaction mixture was stirred at rt for 3 hours. The reaction mixture was concentrated to dryness, the residue was diluted with water, acidified by 1N HCl aqueous solution to pH 4 to 5 and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 5.4b (0.2 g, 89.7 % yield). 1H NMR (400 MHz, DMSO) δ 14.10 (s, 1H), 7.56 (d, J = 8.7 Hz, 2H), 7.37 (d, J = 8.6 Hz, 2H), 4.80 (d, J = 8.8 Hz, 1H), 4.22 (t, J = 8.5 Hz, 1H), 4.02 (s, 2H), 3.85 - 3.79 (m, 1H), 3.15 (s, 3H), 2.65 (d, J = 15.3 Hz, 1H), 2.37 - 2.30 (m, 1H), 1.62 (s, 3H).

**Step 3. Synthesis of 3-((S)-3-(4-(cyanomethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)-N-(tetrahydro-2H-pyran-2-yloxy)propanamide [5.4c].** 5.4b (0.15 g, 0.41 mmol, 1.0 equiv) was dissolved in THF (6 ml_) . N-methyl morpholine (0.20 g, 2.0 mmol, 5.0 equiv), EDC.HCl (0.11 g, 0.61 mmol, 1.5 equiv), HOBT (0.066 g, 0.49 mmol, 1.2 equiv), 0-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.096 g, 0.82 mmol, 2.0 equiv) were added and the reaction mixture was stirred at rt for 12 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (0-30 % EtOAc in Hexane) to afford product 5.4c which was used for next step. (0.18 g, 70.7 % yield). LCMS (m/z): 464.3 [M-H]. 1H NMR (400 MHz, DMSO) δ 7.55 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 8.7 Hz, 2H), 4.67 (s, 1H), 4.57 (d, J = 4.8 Hz, 1H), 4.19 (d, J = 8.9 Hz, 1H), 4.02 (s, 2H), 3.77 (dd, J = 11.2, 7.9 Hz, 2H), 3.43 (d, J = 11.7 Hz, 2H), 3.08 (t, J = 8.1 Hz, 3H), 2.79 (d, J = 15.4 Hz, 1H), 2.24 (m, 1H), 1.63 (s, 3H), 1.50 (m, 6H).
Step 4. Synthesis of 3-((S)-3-(4-(cyanomethyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [5.4]. 5.4c (0.18 g, 0.38 mmol, 1.0 equiv) was dissolved in ethanol (5 mL), 35.5% aq. HCl (0.27 mL) was added and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude product 5.4. The crude product was purified by preparative HPLC purification to afford 5.4 as desired diastereomer (0.05 g, 33.9% yield). LCMS (m/z): 382.4 [M+H].

\[ ^1H \text{NMR (400 MHz, DMSO) } \delta 11.09 (s, 1H), 9.32 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 4.64 (d, J = 7.7 Hz, 1H), 4.18 (t, J = 8.8 Hz, 1H), 4.02 (s, 2H), 3.85 - 3.74 (m, 1H), 3.09 (s, 3H), 2.78 (d, J = 13.8 Hz, 1H), 2.22 (dd, J = 14.1, 9.0 Hz, 1H), 1.61 (s, 3H). \]

V.5. Synthesis of compound 5.5

Reagents: Step 1: Cone. H$_2$SO$_4$, MeOH, room temperature. Step 2: LiBH$_4$ (2M in THF), THF, 0°C to room temperature. Step 3: NaH (60%), iodomethane, N,N-dimethylformamide, 0°C to room temperature. Step 4: Liq. NH$_3$, Cul, acetyl acetone, Cs$_2$CO$_3$, N,N-dimethylformamide, 100°C. Step 5: CBZ-Cl, NaHCO$_3$, Acetone: Water, 0°C to room temperature. Step 6: n-BuLi (2.5M in hexane), THF, -78°C to room temperature. Step 7: Iodine, triphenylphosphine, imidazole, THF, room temperature. Step 8: NaH (60%), N,N-dimethylformamide, 0°C to room temperature. Step 9: LiOH.H$_2$O, THF, Water, room temperature. Step 10: NH$_2$OTHP, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 11: 35.5% aq. HCl, EtOH, room temperature.
Step 1. Synthesis of methyl 2-(4-bromophenyl)acetate [5.5a]. 2-(4-Bromophenyl) acetic acid (10.0 g, 46.5 mmol, 1.0 equiv) was dissolved in methanol (30 mL). Concentrated H₂SO₄ (7 mL) was added drop wise at room temperature and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 5.5a (10 g, 94 % yield). ¹H NMR (400 MHz, DMSO) δ 7.52 (d, J = 8.4 Hz, 2H), 7.26 (t, J = 14.0 Hz, 2H), 3.69 (s, 2H), 3.62 (s, 3H).

Step 2. Synthesis of 2-(4-bromophenyl)ethanol-1-ol [5.5b]. 5.5a (6 g, 26.2 mmol, 1.0 equiv) was dissolved in THF (100 mL) and cooled to 0 °C. LiBH₄ (2M in THF) (1.41 g, 52.4 mmol, 2.0 equiv) was added drop wise at 0 °C and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 5.5b (4.5 g, 85.5 % yield). LCMS (m/z): 204.8 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.56 - 7.35 (m, 2H), 7.27 - 7.07 (m, 2H), 4.67 (t, J = 5.2 Hz, 1H), 3.58 (td, J = 6.8, 5.4 Hz, 2H), 2.69 (t, J = 6.9 Hz, 2H).

Step 3. Synthesis of 1-bromo-4-(2-methoxyethyl)benzene [5.5c]. 5.5b (4.5 g, 22.4 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide (50 mL) and cooled to 0 °C. NaH (60%) (2.23 g, 55.9 mmol, 2.5 equiv) was added in portion wise and the reaction mixture was stirred at rt for 1 hour. Cooled the reaction mixture to 0°C, iodomethane (4.76 g, 33.4 mmol, 1.5 equiv) was added dropwise and the reaction mixture was stirred at rt for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (5 % EtOAc in Hexane) to afford product 5.5c (4 g, 83 % yield). ¹H NMR (400 MHz, DMSO) δ 7.50 - 7.44 (m, 2H), 7.25 - 7.16 (m, 2H), 3.51 (t, J = 6.7 Hz, 2H), 3.23 (d, J = 4.4 Hz, 3H), 2.82 - 2.75 (m, 2H).

Step 4. Synthesis of 4-(2-methoxyethyl)aniline [5.5d]. 5.5c (4.0 g, 18.6 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide (60 mL) and Cul (0.35 g, 18.6 mmol, 0.1 equiv), acetyl acetone (1.86 g, 18.6 mmol, 1.0 equiv), Cs₂CO₃ (12.09 g, 37.2 mmol, 2.0 equiv), ammonium hydroxide (3.9 g, 111.6 mmol, 6.0 equiv) were added in sealed tube and the reaction was stirred at 100 °C for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude product. The crude product was purified by silica gel column chromatography (25 % EtOAc in Hexane) to afford product 5.5d (2 g, 71.4 % yield). LCMS (m/z): 152.1 [M+H]. ¹H NMR (400 MHz, DMSO) δ 6.86 (d, J = 8.1 Hz, 2H), 6.47 (d, J = 8.0 Hz, 2H), 4.83 (s, 2H), 3.42 (q, J = 7.2 Hz, 2H), 3.22 (s, 3H), 2.61 (t, J = 7.1 Hz, 2H).

Step 5. Synthesis of benzyl (4-(2-methoxyethyl)phenyl)carbamate [5.5e]. 5.5d (2.0 g, 13.2 mmol, 1.0 equiv) was dissolved in acetone:water (2:1, 45 mL), NaHCO₃ (2.2 g, 26.5
mmol, 2.0 equiv) was added and cooled the reaction mixture to 0-5 °C. CBZ-CI (3.38 g, 19.8 mmol, 1.5 equiv) was added and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (10 % EtOAc in Hexane) to afford product 5.5e (2 g, 53 % yield). LCMS (m/z): 286 [M+H]. 1H NMR (400 MHz, DMSO) δ 9.70 (s, 1H), 7.48 - 7.30 (m, 7H), 7.14 (t, J = 7.8 Hz, 2H), 5.22 - 5.07 (m, 2H), 3.52 - 3.44 (m, 2H), 3.23 (d, J = 3.3 Hz, 3H), 2.73 (t, J = 6.9 Hz, 2H).

**Step 6. Synthesis of (R)-5-(hydroxymethyl)-3-(4-(2-methoxyethyl)phenyl)oxazolidin-2-one [5.5f].** 5.5e (1.2 g, 4.21 mmol, 1.0 equiv) was dissolved in THF (35 mL) and cooled to -78 °C. n-BuLi (2.5M in hexane) (0.40 g, 6.31 mmol, 1.5 equiv) was gradually added and the reaction mixture was stirred at -78 °C for 2.5 hours. (R)-oxiran-2-ylmethy butyrate (0.60 g, 4.21 mmol, 1.0 equiv) was added drop-wise and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (50 % EtOAc in Hexane) to afford product 5.5f (0.8 g, 79.2 % yield). LCMS (m/z): 252.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.48 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 5.22 (t, J = 5.7 Hz, 1H), 4.75 - 4.63 (m, 1H), 4.06 (t, J = 9.0 Hz, 1H), 3.80 (dt, J = 13.7, 6.8 Hz, 1H), 3.73 - 3.63 (m, 1H), 3.62 - 3.55 (m, 1H), 3.52 (dd, J = 13.4, 6.5 Hz, 2H), 3.23 (s, 3H), 2.78 (t, J = 6.8 Hz, 2H).

**Step 7. Synthesis of (R)-5-(iodomethyl)-3-(4-(2-methoxyethyl)phenyl)oxazolidin-2-one [5.5g].** Triphenylphosphine (1.08 g, 4.14 mmol, 1.3 equiv) was dissolved in THF (25 mL), imidazole (0.28 g, 4.14 mmol, 1.3 equiv) and iodine (1.05 g, 4.14 mmol, 1.3 equiv) were added and the reaction mixture was stirred at room temperature for 10 minutes. 5.5f (0.8 g, 3.18 mmol, 1.0 equiv) in THF (5 mL) was added drop wise and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (10 % EtOAc in Hexane) to afford product 5.5g (0.6 g, 52.2 % yield). LCMS (m/z): 362.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.47 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 4.72 (td, J = 10.6, 5.0 Hz, 1H), 4.18 (t, J = 9.1 Hz, 1H), 3.68 - 3.54 (m, 3H), 3.51 (t, J = 6.8 Hz, 2H), 3.23 (s, 3H), 2.78 (t, J = 6.8 Hz, 2H).

**Step 8. Synthesis of ethyl 3-((S)-3-(4-(2-methoxyethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [5.5h].** Ethyl 2-(methylsulfonyl) propanoate (1.2 g, 6.64 mmol, 4.0 equiv) was dissolved in N,N-dimethylformamide (15 mL) and cooled to 0-5 °C. NaH (60%) (0.13 g, 3.32 mmol, 2.0 equiv) was added in portion wise and the reaction
mixture was stirred at room temperature for 2 hours. A solution of 5.5g (0.6 g, 1.66 mmol, 1.0 equiv) in DMF (5 mL) was added drop-wise at 0-5°C. The reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (40 % EtOAc in Hexane) to afford product 5.5h (0.3 g, 38.2 % yield). LCMS (m/z): 414.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.56 - 7.40 (m, 2H), 7.30 - 7.17 (m, 2H), 4.85 - 4.54 (m, 1H), 4.34 - 4.09 (m, 3H), 3.88 (ddd, J = 26.2, 16.2, 8.3 Hz, 1H), 3.76 - 3.46 (m, 3H), 3.21 (d, J = 17.2 Hz, 2H), 3.19 - 3.07 (m, 3H), 2.83 - 2.72 (m, 1H), 2.34 (dd, J = 14.8, 8.8 Hz, 1H), 1.71 - 1.51 (m, 3H), 1.26 - 1.20 (m, 3H).

Step 9. Synthesis of 3-((S)-3-(4-(2-methoxyethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoic acid [5.5i]. 5.5h (0.3 g, 0.73 mmol, 1.0 equiv) was dissolved in THF (12 mL) and water (4 mL). LiOH.H2O (0.091g, 2.18 mmol, 3.0 equiv) was added and the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with water, acidified by 1.0 N HCl aqueous solution to the pH 3 to 4 and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 5.5i (0.2 g, 71.7 % yield). LCMS (m/z): 386.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 14.02 (s, 1H), 7.55 - 7.38 (m, 2H), 7.30 - 7.21 (m, 2H), 4.78 (ddd, J = 16.5, 8.6, 2.8 Hz, 1H), 4.24 - 4.15 (m, 1H), 3.79 (dt, J = 12.0, 6.0 Hz, 1H), 3.56 - 3.48 (m, 2H), 3.23 (s, 3H), 3.16 - 3.11 (m, 3H), 2.78 (t, J = 6.8 Hz, 2H), 2.65 (dd, J = 14.7, 2.6 Hz, 1H), 2.34 - 2.27 (m, 1H), 1.63 - 1.52 (m, 3H).


5.5i (0.18 g, 0.47 mmol, 1.0 equiv) was dissolved in THF (10 mL). N-methyl morpholine (024 g, 2.33 mmol, 5.0 equiv) was added to afford a clear solution. EDC.HCl (0.12 g, 0.84 mmol, 1.8 equiv), HOBT (0.094 g, 0.70 mmol, 1.5 equiv), O-(tetrahydro-2H-pyran-2-yl) hydroxylamine (0.109 g, 0.93 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (2 % MeOH in dichloromethane) to afford product 5.5j which was carry forwarded for next step. (0.18 g, 72 % yield). LCMS (m/z): 483.5 [M-H]. 1H NMR (400 MHz, DMSO) δ 7.44 (dd, J = 8.1 , 5.8 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 4.66 (d, J = 8.2 Hz, 1H), 4.57 (d, J = 4.9 Hz, 2H), 4.20 - 4.13 (m, 1H), 3.77 (m, 2H), 3.51 (t, J = 6.8 Hz, 3H), 3.46 - 3.38 (m, 3H), 3.23 (s, 3H), 3.17 (d, J = 5.2 Hz, 2H), 3.07 (t, J = 8.0 Hz, 3H), 2.78 (t, J = 6.8 Hz, 3H), 2.22 (dd, J = 13.8, 10.0 Hz, 1H), 1.68 - 1.59 (m, 9H).
Step 11. Synthesis of (R)-N-hydroxy-3-((S)-3-(4-(2-methoxyethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [5.5]. 5.5 (0.17 g, 0.35 mmol, 1.0 equiv) was dissolved in ethanol (10 mL). 35.5% aq. HCl (0.3 mL) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and neutralized by saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by preparative HPLC purification to afford 5.5 (0.063 g, 42.6 % yield). LCMS (m/z): 401.5 [M+H]+. 1H NMR (400 MHz, DMSO) δ 9.43 (s, 2H), 7.43 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.6 Hz, 2H), 4.63 (dd, J = 13.8, 7.9 Hz, 1H), 4.15 (t, J = 8.8 Hz, 1H), 3.83 - 3.72 (m, 1H), 3.51 (t, J = 6.8 Hz, 2H), 3.23 (d, J = 3.9 Hz, 3H), 3.08 (s, 3H), 2.81 - 2.72 (m, 3H), 2.19 (dd, J = 14.3, 8.8 Hz, 1H), 1.59 (s, 3H).

V.6. Synthesis of compound 5.6

Step 1. Synthesis of (3-methoxypropyl)triphosphorphonium bromide [5.6a]. 1-Bromo-3-methoxypropane (3.5 g, 22.87 mmol, 1.0 equiv) was dissolved in toluene (7 mL). Triphenylphosphine (6.3 g, 24.01 mmol, 1.05 equiv) was added and the reaction mixture was stirred at 150 °C for 24 hours. The reaction mixture was diluted with n-hexane and the precipitated solid was filtered to afford the desired product 5.6a (9.2 g, 96.9 % yield). 1H NMR (400 MHz, DMSO) δ 7.94 - 7.88 (m, 3H), 7.85 - 7.76 (m, 11H), 3.58 (ddd, J = 14.3, 12.6, 7.1 Hz, 2H), 3.44 (t, J = 5.9 Hz, 2H), 3.20 (d, J = 12.7 Hz, 3H), 1.83 - 1.70 (m, 2H).

Step 2. Synthesis of (E)-1-bromo-4-(4-methoxybut-1-en-1-yl) benzene [5.6b]. 5.6a (8.7 g, 20.9 mmol, 1.0 equiv) was dissolved in THF (80 mL) and cooled to -20 °C. LiHMDS (1M in THF) (21 mL, 20.9 mmol, 1.0 equiv) was added and the reaction mixture was stirred at -20 for 1 hour. 4-Bromobenzaldehyde (3.1 g, 16.75 mmol, 0.8 equiv) in THF (10 mL) was added and the reaction mixture was stirred at rt for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-3 % EtOAc/Hexane) to afford the desired product 5.6b (1 g, 25 % yield). 1H NMR (400 MHz, CDCl3) δ 7.46 - 7.39 (m, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.42 (d, J = 15.9 Hz, 1H), 6.25 (dt, J = 15.9, 6.9 Hz, 1H), 3.59 - 3.47 (m, 2H), 3.46 - 3.32 (m, 3H), 2.50 (qd, J = 6.7, 1.3 Hz, 2H).

Step 3. Synthesis of 1-bromo-2-(2-methoxyethyl)cyclopropylbenzene [5.6c]. 5.6b (0.65 g, 2.69 mmol, 1.0 equiv) was dissolved in toluene (13 mL) and cooled to 0 °C. Et2Zn (1 M in Hexane) (13.48 g, 13.48 mmol, 5.0 equiv), Diiodomethane (7.2 g, 26.9 mmol, 10.0 equiv) was added dropwise and the reaction mixture was stirred at room temperature for 5 minutes. The reaction mixture was stirred at 50 °C for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc.
The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-3 % EtOAc in Hexane) to afford the desired product 5.6c (0.55 g, 79.9 % yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.40 - 7.31 (m, 2H), 7.03 - 6.71 (m, 2H), 3.51 (dt, \(J = 11.3, 6.6\) Hz, 2H), 3.38 (d, \(J = 9.3\) Hz, 3H), 1.77 - 1.50 (m, 3H), 1.15 - 1.04 (m, 1H), 0.93 - 0.81 (m, 2H).

**Step 4. Synthesis of (2R)-N-hydroxy-3-((5S)-3-(4-(2-(3-ethoxycyclobutyl)ethynyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanamide [5.6].** 5.6c (0.27 g, 0.51 mmol, 1.0 equiv) was dissolved in dichloromethane (5 ml). HCl (in IPA) (0.25 ml) was added and the reaction mixture was stirred at room temperature for 30 minutes. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was triturated with n-pentane, the solvent was decanted to afford the desired product 5.6 (0.185 g, 81.9 % yield).

**V.7. Synthesis of compound 5.7**

5.7 was synthesized by the process of example 2.4 from 1-bromo-4-propylbenzene.

**V.8. Synthesis of compound 5.8**

**Step 1. Synthesis of ethyl (R)-3-((S)-3-(4-(2-(3-ethoxycyclobutyl)ethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [5.8a].** (R)-ethyl 3-((S)-3-(4-(3-ethoxycyclobutyl)ethyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate (0.35 g, 0.73 mmol, 1.0 equiv) was dissolved in methanol (15 ml). Pd-catalyst (10% on carbon) (0.05 g) was added and H\(_2\) (gas) was purged at rt for 12 hours. The reaction mixture was filtered through celite bed and the filtrate was concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (50 % EtOAc in Hexane) to afford the desired product 5.8a (0.42 g, 92.7 % yield). LCMS (m/z): 482.5 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.47 - 7.39 (m, 2H), 7.20 (d, \(J = 8.4\) Hz, 2H), 4.77 (dd, \(J = 14.0, 8.1\) Hz, 1H), 4.26 (q, \(J = 7.0\) Hz, 2H), 4.18 (t, \(J = 8.8\) Hz, 1H), 3.84 - 3.76
(m, 1H), 3.77 - 3.57 (m, 1H), 3.29 (q, J = 7.0 Hz, 2H), 3.17 (s, 3H), 2.69 (dd, J = 14.7, 2.4 Hz, 1H), 2.46 (d, J = 7.5 Hz, 2H), 2.31 (ddd, J = 15.8, 12.1, 7.8 Hz, 3H), 1.97 - 1.90 (m, 1H), 1.73 - 1.56 (m, 6H), 1.45 - 0.8 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H), 1.08 (td, J = 7.0, 5.1 Hz, 3H).

**Step 2. Synthesis of (R)-3-((S)-3-(4-((E)-but-2-en-2-yl)ethyl)phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [5.8 & 5.10]**

5.8 & 5.10 were synthesized from 5.8a using the process of example 1.2. **Isomer i:** LCMS (m/z): 469.5 [M+H]. ¹H NMR (400 MHz, DMSO) δ 9.47 - 9.10 (m, 1H), 7.42 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.5 Hz, 2H), 4.63 (d, J = 7.8 Hz, 1H), 4.15 (t, J = 8.6 Hz, 1H), 3.81 - 3.67 (m, 2H), 3.29 (q, J = 7.0 Hz, 2H), 3.08 (s, 3H), 2.77 (d, J = 14.4 Hz, 1H), 2.47 (s, 2H), 2.29 (d, J = 6.2 Hz, 2H), 2.18 (dd, J = 14.5, 8.7 Hz, 1H), 1.72 - 1.62 (m, 3H), 1.59 (s, 3H), 1.41 (d, J = 8.2 Hz, 2H), 1.07 (t, J = 7.0 Hz, 3H). **Isomer ii:** (0.033 g, 9.7 % yield). LCMS (m/z): 469.5 [M+H]. ¹H NMR (400 MHz, DMSO) δ 9.33 (s, 1H), 7.42 (d, J = 7.1 Hz, 2H), 7.21 (d, J = 7.1 Hz, 2H), 4.62 (m, 1H), 4.15 (m, 1H), 4.01 (s, 1H), 3.76 (m, 1H), 3.29 (d, J = 6.5 Hz, 2H), 3.09 (s, 3H), 2.91 (m, 2H), 2.77 (d, J = 14.3 Hz, 1H), 2.20 (m, 1H), 2.08 (m, 1H), 1.92 (m, 4H), 1.66 (m, 2H), 1.60 (s, 3H), 1.08 (m, 3H).

**V.9. Synthesis of compound 5.9**

**Step 1. Synthesis of (E)-1-bromo-4-(but-2-en-2-yl) benzene [5.9a].** Ethyl phosphonium bromide (3.73 g, 10.0 mmol, 2.0 equiv) was suspended in THF (20 mL) and cooled to -5 °C. n-BuLi (2.5 M in hexane) (4 mL, 10.0 mmol, 2.0 equiv) was gradually added and the reaction mixture was stirred at -5 °C for 30 minutes. 1-(4-bromophenyl) ethan-1-one (1 g, 5.1 mmol, 1.0 equiv) in THF (8 mL) was added drop wise and the reaction mixture was stirred at rt for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (100 % n-Hexane) to afford the desired product 5.9a as mixture of E:Z (-66:33 by NMR) (0.82 g, 76.9 % yield). ¹H NMR (400 MHz, CDCl₃) δ 7.50 - 7.41 (m, 2H), 7.28 - 7.22 (m, 1.5H), 7.12 - 7.07 (m, 0.5H), 5.93 - 5.83 (m, 0.7H), 5.64 - 5.56 (m, 0.3H), 2.02 (dd, J = 2.4, 1.2 Hz, 3H), 1.81 (dd, J = 6.9, 1.0 Hz, 2H), 1.62 - 1.59 (m, 1H).

**Step 2. Synthesis of (R)-3-((S)-3-(4-(E)-but-2-en-2-yl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [5.9].** 5.9 was synthesized from 5.9a using the process of example 2.4. LCMS (m/z): 414.3 [M+18]. ¹H NMR (400 MHz, DMSO) δ II 1.08 (s, 1H), 9.31 (s, 1H), 7.48 (d, J = 9.0 Hz, 2H), 7.42 (d, J = 8.9 Hz, 2H), 5.94 - 5.83 (m, 1H), 4.63 (d, J = 8.2 Hz, 1H), 4.18 (t, J = 8.8 Hz, 1H), 3.83 - 3.75 (m, 1H), 3.09 (s, 3H), 2.78 (d, J = 12.7 Hz, 1H), 2.20 (dd, J = 14.4, 8.9 Hz, 1H), 1.97 (s, 3H), 1.77 (d, J = 6.8 Hz, 3H), 1.60 (s, 3H).
V.11. Synthesis of compound 5.11

5.11 was synthesized from (E)-1-bromo-4-(prop-1-en-1-yl)benzene using the process of example 2.4. LCMS (m/z): 383.2 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.08 (s, 1H), 9.30 (s, 1H), 7.50 (dd, \(J = 24.2, 8.6\) Hz, 2H), 7.37 (dd, \(J = 21.3, 8.7\) Hz, 2H), 6.39 (d, \(J = 16.3\) Hz, 1H), 6.25 (dd, \(J = 15.8, 6.5\) Hz, 1H), 4.63 (d, \(J = 6.2\) Hz, 1H), 4.17 (t, \(J = 8.8\) Hz, 1H), 3.83 - 3.73 (m, 1H), 3.09 (s, 3H), 2.77 (d, \(J = 14.4\) Hz, 1H), 2.20 (dd, \(J = 14.2, 8.7\) Hz, 1H), 1.85 (t, \(J = 7.8\) Hz, 3H), 1.59 (s, 3H).

V.13. Synthesis of compound 5.13

3.1.2 (0.1 g, 0.2 mmol, 1.0 equiv) was dissolved in methanol (10 ml). Pd/C (0.02 g) was added to the solution and the reaction mixture was stirred at room temperature for 2 hours under \(H_2\) (1atm) pressure. The reaction mixture was filtered through celite bed under nitrogen atmosphere and the filtrate was concentrated to afford a crude product. The crude product was purified by preparative HPLC purification to afford the desired product 5.13 (0.047 g, 34% yield). LCMS (m/z): 411.4 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.08 (s, 1H), 9.28 (s, 1H), 7.43 (d, \(J = 8.5\) Hz, 2H), 7.22 (d, \(J = 8.4\) Hz, 2H), 4.62 (d, \(J = 7.7\) Hz, 1H), 4.15 (t, \(J = 8.7\) Hz, 1H), 3.80 - 3.73 (m, 1H), 3.09 (s, 3H), 2.77 (d, \(J = 12.4\) Hz, 1H), 2.67 - 2.59 (m, 2H), 2.19 (dd, \(J = 14.1, 8.8\) Hz, 1H), 1.60 (s, 3H), 1.45 (dd, \(J = 14.7, 7.3\) Hz, 2H), 0.67 (s, 1H), 0.39 (d, \(J = 7.7\) Hz, 2H), 0.04 (d, \(J = 4.4\) Hz, 2H).

V.14. Synthesis of compound 5.14

Step 1. Synthesis of ethyl (R)-3-((S)-3-(4-(3-hydroxyprop-1-yn-1-yl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [5.14a]. 1.1d (2 g, 4.6 mmol, 1.0 equiv) was suspended into diethyl amine (30 ml) and N, N-dimethylformamide (6 ml). Cul (0.087 g, 0.46 mmol, 0.1 equiv), triphenylphosphine (0.24 g, 0.92 mmol, 0.2 equiv) were added and the reaction mixture was degassed for 15 minutes. Prop-2-yn-1-ol (0.39 g, 6.91 mmol, 1.5 equiv), PdCl_2(pph_3)_2 (0.16 g, 0.23 mmol, 0.05 equiv) were added and the reaction mixture was stirred at 100 °C for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (62-65% EtOAc/Hexane) to afford the desired product 5.14a (1.2 g, 64.9% yield). LCMS (m/z): 410.2 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.55 (d, \(J = 8.8\) Hz, 2H), 7.46 (d, \(J = 8.8\) Hz, 2H), 5.34 (t, \(J = 6.0\) Hz, 1H), 4.79 (d, \(J = 7.5\) Hz, 1H), 4.25 (dd, \(J = 17.5, 13.6\) Hz, 2H), 3.88 - 3.78 (m, 1H), 3.17 (s, 3H), 2.68 (d, \(J = 12.9\) Hz, 1H), 2.40 - 2.34 (m, 1H), 1.64 (s, 3H), 1.26 (t, \(J = 7.1\) Hz, 3H).

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Step 2. Synthesis of ethyl (R)-3-((S)-3-(4-(3-hydroxypropyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [5.14b]. 5.14a (1.2 g, 2.98 mmol, 1.0 equiv) was dissolved in methanol (40 mL). Pd/C (50% moisture) (0.48 g) was added and the reaction mixture was stirred at room temperature for 3 hours under H₂ atmosphere. The reaction mixture was filtered through celite bed under N₂ atmosphere, washed with methanol and the filtrate was concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (75-80 % EtOAc/Hexane) to afford the desired product 5.14b (0.84 g, 68.2 % yield). LCMS (m/z): 414.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.43 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H), 4.77 (d, J = 6.2 Hz, 1H), 4.47 (t, J = 5.1 Hz, 1H), 4.26 (dd, J = 14.0, 6.9 Hz, 2H), 4.18 (t, J = 8.8 Hz, 1H), 3.84 - 3.77 (m, 1H), 3.40 (dd, J = 11.7, 6.3 Hz, 2H), 3.17 (d, J = 5.1 Hz, 3H), 2.69 (d, J = 14.9 Hz, 1H), 2.62 - 2.54 (m, 2H), 2.38 - 2.32 (m, 1H), 1.75 - 1.59 (m, 5H), 1.26 (t, J = 7.1 Hz, 3H).

Step 3. Synthesis of ethyl (R)-3-((S)-3-(4-(3-fluoropropyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [5.14c]. 5.14b (0.32 g, 0.77 mmol, 1.0 equiv) was suspended in dichloromethane (30 mL) and cooled to -78 °C. DAST (0.25 g, 1.55 mmol, 2.0 equiv) was added drop wise and the reaction mixture was stirred at -78 °C for 10 minutes. The reaction mixture was stirred at rt for 2 hours. The reaction mixture was quenched with water, basified with solid sodium bicarbonate and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (35-40 % EtOAc/Hexane) to afford the desired product 5.14c (0.23 g, 71.7 % yield). LCMS (m/z): 416.2 [M+H]. ¹H NMR (400 MHz, DMSO) δ 7.46 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 4.83 - 4.73 (m, 1H), 4.50 (t, J = 6.0 Hz, 1H), 4.38 (t, J = 6.0 Hz, 1H), 4.31 - 4.24 (m, 2H), 4.19 (t, J = 8.8 Hz, 1H), 3.86 - 3.76 (m, 1H), 3.17 (s, 3H), 2.69 (dd, J = 16.4, 6.1 Hz, 3H), 2.35 (dd, J = 14.8, 8.9 Hz, 1H), 2.03 - 1.87 (m, 2H), 1.65 (s, 3H), 1.29 - 1.22 (m, 3H).

Step 4. Synthesis of (R)-3-((S)-3-(4-(3-fluoropropyl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [5.14] 5.14 was synthesized from 5.14c using the process of example 1.2. LCMS (m/z): 403.1 [M+H]. ¹H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.45 (d, J = 8.6 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 4.62 (d, J = 6.1 Hz, 1H), 4.50 (t, J = 6.0 Hz, 1H), 4.38 (t, J = 6.0 Hz, 1H), 4.16 (t, J = 8.7 Hz, 1H), 3.81 - 3.72 (m, 1H), 3.09 (s, 3H), 2.78 (d, J = 14.4 Hz, 1H), 2.69 - 2.62 (m, 2H), 2.20 (dd, J = 14.4, 8.9 Hz, 1H), 2.00 - 1.89 (m, 2H), 1.60 (s, 3H).

V.15. Synthesis of compound 5.15
Step 1. Synthesis of 1-bromo-4-(2, 2-difluoropropyl) benzene [5.15a]. 1-(4-Bromophenyl) propan-2-one (1 g, 4.6 mmol, 1.0 equiv) was dissolved in dichloromethane (17 mL) and cooled to -70 °C. DAST (3.78 g, 23.46 mmol, 5.0 equiv) was added drop wise
and the reaction mixture was stirred at rt for 24 hours. The reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue, which was purified by silica gel column chromatography (0-5 % EtOAc/Hexane) to afford the desired product 5.15a (0.8 g, 72.5 % yield). 1H NMR (400 MHz, DMSO) δ 7.59 - 7.52 (m, 2H), 7.26 (d, J = 8.2 Hz, 2H), 3.22 (t, J = 16.4 Hz, 2H), 1.56 (t, J = 18.8 Hz, 3H).

**Step 2. Synthesis of (R)-3-((S)-3-(4-(2, 2-difluoropropyl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [5.15]**. 5.15 was synthesized from 5.15a using the process of example 2.4. LCMS (m/z): 421.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.30 (s, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.63 (d, J = 6.0 Hz, 1H), 4.18 (t, J = 8.7 Hz, 1H), 3.83 - 3.75 (m, 1H), 3.20 (t, J = 16.3 Hz, 2H), 3.09 (s, 3H), 2.78 (d, J = 14.4 Hz, 1H), 2.20 (dd, J = 14.4, 8.9 Hz, 1H), 1.72 - 1.44 (m, 6H).

V.16. Synthesis of compound 5.16

**Step 1. Synthesis of (4-bromophenyl) (2, 2, 2-trifluoroethyl) sulfane [5.16a]**

4-Bromobenzenethiol (0.5 g, 2.64 mmol, 1.0 equiv) was dissolved in N. N-dimethylformamide (5 mL). Cs₂CO₃ (1.2 g, 3.96 mmol, 1.5 equiv), 2-Bromo-1, 1, 1-trifluoroethane (0.28 mL, 3.17 mmol, 1.2 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 5.16a (0.065 g, 90 % yield). The product was used in the next step with no further purification. LCMS (m/z): 289.9 [M+H]. 1H NMR (400 MHz, CDCl₃) δ 7.52 - 7.44 (m, 1H), 7.41 - 7.35 (m, 1H), 3.44 (q, J = 9.6 Hz, 1H).

**Step 2. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-((2, 2, 2-trifluoroethyl) thio) phenyl) oxazolidin-5-yl) propanamide [5.16]**

5.16 was synthesized from 5.16a using the process of example 2.4. LCMS (m/z): 457.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.31 (s, 1H), 7.55 (d, J = 3.6 Hz, 4H), 4.63 (s, 1H), 4.18 (t, J = 8.5 Hz, 1H), 3.95 (dd, J = 20.3, 10.3 Hz, 2H), 3.80 (d, J = 7.7 Hz, 1H), 3.08 (s, 3H), 2.78 (d, J = 14.3 Hz, 1H), 2.25 - 2.18 (m, 1H), 1.60 (s, 3H).

V.17. Synthesis of compound 5.17

**Step 1. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(3-oxopropyl) phenyl) oxazolidin-5-yl) propanoate [5.17a]**. (R)-ethyl 3-((S)-3-(4-(3-hydroxypropyl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate (0.32 g, 0.77 mmol, 1.0 equiv) was added in dichloromethane (60 mL) and cooled to 0 °C. Dess-Martin periodinane (0.49 g, 1.16 mmol, 1.5 equiv) was added in portions and the reaction mixture was stirred at rt for 4 hours. The reaction mixture was added to mixture of saturated
aqueous sodium bicarbonate solution, sodium thiosulphate solution and extracted with
EtOAc. The organic layer was washed with saturated aqueous sodium bicarbonate solution, brine, dried over sodium sulfate and concentrated to afford the desired product 5.17a (0.29 g, 8.16 % yield). LCMS (m/z): 412.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 9.71 (s, 1H), 7.44 (d, \(J = 8.7\) Hz, 2H), 7.25 (d, \(J = 8.7\) Hz, 2H), 4.78 (m, 1H), 4.26 (m, 2H), 4.18 (m, 1H), 3.80 (m, 1H), 3.17 (s, 3H), 2.84 (d, \(J = 6.4\) Hz, 2H), 2.77 (d, \(J = 7.0\) Hz, 2H), 2.68 (m, 1H), 2.33 (s, 1H), 1.65 (s, 3H), 1.29 - 1.24 (m, 3H).

**Step 2. Synthesis of ethyl (R)-3-((S)-3-(4-(3, 3-difluoropropyl) phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [5.17b].** 5.17a (0.28 g, 0.69 mmol, 1.0 equiv) was dissolved in dichloromethane (40 mL) and cooled to -78 °C. DAST (0.56 g, 3.47 mmol, 5.0 equiv) was added drop wise and the reaction mixture was stirred at -78 °C for 10 minutes. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched with water, basified with solid sodium bicarbonate and extracted with EtOAc. The organic layer was washed with brine, dissolved over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (40-45 % EtOAc/Hexane) to afford the product 5.17b (0.22 g, 73 % yield). LCMS (m/z): 434.2 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 7.46 (d, \(J = 8.6\) Hz, 2H), 7.26 (dd, \(J = 19.3, 8.2\) Hz, 2H), 6.08 (tt, \(J = 56.7, 4.4\) Hz, 1H), 4.77 (dd, \(J = 14.3, 7.7\) Hz, 1H), 4.26 (q, \(J = 7.1\) Hz, 2H), 4.19 (t, \(J = 8.8\) Hz, 1H), 3.85 - 3.74 (m, 1H), 3.17 (s, 3H), 2.74 - 2.64 (m, 3H), 2.39 - 2.32 (m, 1H), 2.19 - 2.05 (m, 2H), 1.65 (s, 3H), 1.26 (t, \(J = 7.1\) Hz, 3H).

**Step 3. Synthesis of (R)-3-((S)-3-(4-(3, 3-difluoropropyl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [5.17].** 5.17 was synthesized from 5.17b using the process of example 1.2. LCMS (m/z): 421.3 [M+H]. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.09 (s, 1H), 9.31 (s, 1H), 7.46 (d, \(J = 8.6\) Hz, 2H), 7.28 (d, \(J = 8.6\) Hz, 2H), 6.08 (tt, \(J = 56.7, 4.3\) Hz, 1H), 4.63 (d, \(J = 8.5\) Hz, 1H), 4.16 (t, \(J = 8.7\) Hz, 1H), 3.82 - 3.74 (m, 1H), 3.09 (s, 3H), 2.78 (d, \(J = 14.4\) Hz, 1H), 2.73 - 2.67 (m, 2H), 2.24 - 2.18 (m, 1H), 2.16 - 1.97 (m, 2H), 1.60 (s, 3H).

**V.18. Synthesis of compound 5.18**

**Step 1. Synthesis of (4-bromophenyl) (ethyl) sulfane [5.18a].** 4-Bromobenzenethiol (0.3 g, 1.59 mmol, 1.0 equiv) was dissolved in N,N-dimethylformamide (6 mL). Cs$_2$CO$_3$ (1.55 g, 4.76 mmol, 3.0 equiv), lodoethane (0.15 mL, 1.9 mmol, 1.2 equiv) were added and the reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-5 % EtOAc/Hexane) to afford the desired
product 5.18a (0.32 g, 93 % yield). 1H NMR (400 MHz, DMSO) δ 7.50 (d, J = 8.6 Hz, 2H),
7.26 (d, J = 8.6 Hz, 2H), 2.99 (q, J = 7.3 Hz, 2H), 1.23 (t, J = 7.3 Hz, 3H).

Step 2. Synthesis of (R)-3-((S)-3-(4(ethylthio) phenyl)-2-oxooxazolidin-5-yl)-N-
hydroxy-2-methyl-2-(methylsulfonyl) propanamide [5.18]

5.18 was synthesized from 5.18a using the process of example 2.4. LCMS (m/z):
402.7 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.23 - 10.69 (m, 1H), 9.34 (s, 1H), 7.50 (d, J =
8.9 Hz, 2H), 7.42 - 7.35 (m, 2H), 4.63 (dd, J = 13.3, 7.8 Hz, 1H), 4.16 (t, J = 8.8 Hz, 1H),
3.81 - 3.74 (m, 1H), 3.08 (s, 3H), 2.94 (q, J = 7.3 Hz, 2H), 2.76 (dd, J = 14.4, 2.7 Hz, 1H),
2.19 (dd, J = 14.4, 8.8 Hz, 1H), 1.59 (s, 3H), 1.20 (t, J = 7.3 Hz, 3H).

V.19. Synthesis of compound 5.19

Step 1. Synthesis of 3-(4-bromophenyl)-2, 2-dichlorocyclobutan-1-one [5.19a]
1-Bromo-4-vinylbenzene (1 g, 5.46 mmol, 1.0 equiv) and Zn-Cu couple (1.07 g, 16.4 mmol,
3.0 equiv) was added to diethyl ether (10 mL). Trichloroacetyl chloride (1.99 g, 10.9 mmol,
2.0 equiv), POCl₃ (0.92 g, 6.0 mmol, 1.1 equiv) in diethyl ether (5 mL) were added and the
reaction mixture was stirred at 40 °C for 2 hours and at room temperature for 24 hours. The
reaction mixture was filtered through celite bed and washed with diethyl ether. Filtrate was
washed with saturated aqueous ammonium chloride solution. The organic layer was
washed with brine, dried over sodium sulfate and concentrated to afford a crude residue.
The crude residue was purified by silica gel column chromatography (0-10 %
EtOAc/Hexane) to afford the desired product 5.19a (1 g, 62.2 % yield). 1H NMR (400 MHz,
DMSO) δ 7.66 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 4.51 (t, J = 10.5 Hz, 1H), 4.06
(dd, J = 18.2, 10.7 Hz, 1H), 3.69 (dd, J = 18.2, 10.4 Hz, 1H).

Step 2. Synthesis of 3-(4-bromophenyl) cyclobutan-1-one [5.19b]. 5.19a (1 g, 3.40
mmol, 1.0 equiv) was dissolved in acetic acid (10 mL). Zn-dust (1.1 g, 17.0 mmol, 5.0 equiv)
was added and the reaction mixture was stirred at rt for 2 hours. The reaction mixture was
stirred at reflux temperature for 4 hours. The reaction mixture was diluted with water,
neutralized with solid sodium bicarbonate and extracted with EtOAc. The organic layer was
washed with brine, dried over sodium sulfate and concentrated to afford a crude residue that
was purified by silica gel chromatography (0-5 % EtOAc/Hexane) to afford the desired
product 5.19b (0.66 g, 86.2 % yield). 1H NMR (400 MHz, DMSO) δ 7.54 (d, J = 8.4 Hz, 2H),
7.36 (d, J = 8.5 Hz, 2H), 3.70 - 3.60 (m, 1H), 3.51 - 3.38 (m, 2H), 3.28 - 3.12 (m, 2H).

Step 3. Synthesis of 1-bromo-4-(3, 3-difluorocyclobutyl) benzene [5.19c]
5.19b (0.66 g, 2.93 mmol, 1.0 equiv) was dissolved in dichloromethane (15 mL) and cooled
to -70 °C. DAST (1.18 g, 7.33 mmol, 2.5 equiv) was added drop wise and the reaction
mixture was stirred at room temperature for 2 hours. The reaction mixture was quenched
with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with
dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (0-2 % EtOAc/Hexane) to afford the desired product 5.19c (0.6 g, 82.8 % yield). 1H NMR (400 MHz, DMSO) δ 7.53 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 3.47 - 3.36 (m, 1H), 3.08 - 2.91 (m, 2H), 2.67 (ddd, J = 18.4, 14.4, 10.5, 6.2 Hz, 2H).

5.19 was synthesized from 5.19c using the process of example 2.4. LCMS (m/z): 432.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.30 (s, 1H), 7.50 (d, J = 8.6 Hz, 2H), 7.34 (d, J = 8.6 Hz, 2H), 4.63 (d, J = 5.8 Hz, 1H), 4.17 (t, J = 8.7 Hz, 1H), 3.82 - 3.74 (m, 1H), 3.44 - 3.36 (m, 1H), 3.09 (s, 3H), 2.99 (tdd, J = 14.2, 8.9, 5.5 Hz, 2H), 2.78 (d, J = 12.3 Hz, 1H), 2.72 - 2.60 (m, 2H), 2.20 (dd, J = 14.5, 8.8 Hz, 1H), 1.60 (s, 3H)

V.20. Synthesis of compound 5.20

Step 1. Synthesis of 1-bromo-4-(1, 1-difluoropropyl) benzene [5.20a]. 1-(4-Bromophenyl) propan-1-one (0.5 g, 2.3 mmol, 1.0 equiv) was dissolved in dichloromethane (10 mL) and cooled to -70 °C. DAST (1.89 g, 11.7 mmol, 5.0 equiv) was added dropwise and the reaction mixture was stirred at rt for 24 hours. The reaction mixture was stirred at 50 °C for 48 hours. The reaction mixture was quenched with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (100 % hexane) to afford the desired product 5.20a (0.3 g, 54.5 % yield). 1H NMR (400 MHz, CDCl3) δ 7.59 (t, J = 9.5 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 2.12 (ddd, J = 16.5, 12.5, 4.5 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H).

Step 2. Synthesis of (R)-3-((S)-3-(4-(1, 1-difluoropropyl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [5.20]
5.20 was synthesized from 5.20a using the process of example 2.4. LCMS (m/z): 421.1 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.32 (s, 1H), 7.64 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 2H), 4.66 (d, J = 7.0 Hz, 1H), 4.22 (t, J = 8.7 Hz, 1H), 3.87 - 3.79 (m, 1H), 3.09 (s, 3H), 2.79 (d, J = 12.4 Hz, 1H), 2.29 - 2.13 (m, 3H), 1.61 (s, 3H), 0.90 (t, J = 7.4 Hz, 3H).

V.21. Synthesis of compound 5.21

Step 1. Synthesis of 3-(4-bromophenyl) propanal [5.21a]. 3-(4-Bromophenyl) propan-1-ol (4 g, 18.5 mmol, 1.0 equiv) was dissolved into dichloromethane (60 mL) and cooled to 0 °C. PCC (5.21 g, 24.1 mmol, 1.5 equiv) was added in portions and the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was filtered through celite bed
and the filtrate was concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (10-20 % diethyl ether/n-pentane) to afford the desired product 5.21a (3.05 g, 76.9 % yield). 1H NMR (400 MHz, CDCl3) δ 9.83 (s, 1H), 7.43 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 2.94 (t, J = 7.3 Hz, 2H), 2.79 (t, J = 7.4 Hz, 2H).

Step 2. Synthesis of 1-bromo-4-(but-3-yn-1-yl) benzene [5.21b]. 5.21a (3 g, 14.0 mmol, 1.0 equiv) was dissolved in methanol (30 mL). K2CO3 (0.52 g, 1.6 mmol, 1.5 equiv), Cul (0.24 g, 1.3 mmol, 1.2 equiv), and 1-(2-oxo-1H-1,2,4-triazol-5-yl)benzene were added to the reaction mixture and stirred for 8 hours. The reaction mixture was concentrated, diluted with water and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude residue. The crude residue was purified by silica gel column chromatography (5-10 % diethyl ether/n-pentane) to afford the desired product 5.21b (1.7 g, 57.7 % yield). 1H NMR (400 MHz, CDCl3) δ 7.44 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 2.82 (t, J = 7.4 Hz, 2H), 2.49 (td, J = 7.3, 2.5 Hz, 2H), 2.00 (t, J = 2.6 Hz, 1H).

Step 3. Synthesis of 1-bromo-4-(pent-3-yn-1-yl) benzene [5.21c]. 5.21b (0.5 g, 2.39 mmol, 1.0 equiv) was dissolved into THF (10 mL) and cooled to -78 °C. NaHMDS (1M in THF) (1.75 g, 9.56 mmol, 4.0 equiv) was added drop wise and the reaction mixture was stirred at 0 °C for 2 hours. The reaction mixture was cooled to -78 °C, iodomethane (1.01 g, 7.17 mmol, 3.0 equiv) was added and the reaction mixture was stirred for 24 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with diethyl ether. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the crude product 5.21c (0.75 g). The product was crude having SM and product. 1H NMR (400 MHz, CDCl3) δ 7.43 (dd, J = 8.2, 5.4 Hz, 2H), 7.12 (t, J = 7.7 Hz, 2H), 2.78 (dt, J = 22.4, 7.4 Hz, 2H), 2.53 - 2.36 (m, 2H), 1.87 (s, 3H).

Step 4. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(pent-3-yn-1-yl) phenyl) oxazolidin-5-yl) propanamide [5.21]

5.21 was synthesized from 5.21c using the process of example 2.4. LCMS (m/z): 409.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.31 (s, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.6 Hz, 2H), 4.67 - 4.56 (m, 1H), 4.16 (t, J = 8.8 Hz, 1H), 3.84 - 3.73 (m, 1H), 3.09 (s, 3H), 2.78 (dd, J = 14.5, 2.5 Hz, 1H), 2.70 (t, J = 7.4 Hz, 2H), 2.38 (td, J = 7.3, 2.5 Hz, 2H), 2.22 - 2.14 (m, 1H), 1.71 (t, J = 2.5 Hz, 3H), 1.60 (s, 3H).

V.22. Synthesis of compound 5.22

Step 1. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-((E)-prop-1-en-1-yl) phenyl) oxazolidin-5-yl) propanoate [5.22a]. (E)-1-bromo-4-((prop-1-en-1-yl)benzene (0.29 g, 1.28 mmol, 1.2 equiv) and (R)-ethyl 2-methyl-2-(methylsulfonyl)-3-((S)-2-oxooxazolidin-5-yl)propanoate (0.3 g, 1.07 mmol, 1.0 equiv) were added in 1, 4-dioxane (12 mL) in sealed tube. Cs2CO3 (0.52 g, 1.6 mmol, 1.5 equiv), Cul (0.24 g, 1.3 mmol, 1.2
equiv), (1R, 2R)-(-)-2-diamino cyclohexane (0.17 g, 1.5 mmol, 1.4 equiv) were added and the reaction mixture was stirred at 125 °C for 4 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (25-30 % EtOAc/Hexane) to afford product as E/Z isomer mixture. The E/Z isomers were further separated by preparative HPLC purification to afford product 5.22a. LCMS (m/z): 396.1 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.57 - 7.49 (m, 2H), 7.35 (d, J = 8.7 Hz, 2H), 6.40 (dd, J = 11.6, 1.8 Hz, 1H), 5.81 - 5.71 (m, 1H), 4.79 (dd, J = 15.0, 7.2 Hz, 1H), 4.25 (dt, J = 16.8, 7.9 Hz, 3H), 3.83 (dd, J = 9.0, 7.6 Hz, 1H), 3.17 (s, 3H), 2.70 (dd, J = 15.0, 2.6 Hz, 1H), 2.36 (dd, J = 14.8, 8.9 Hz, 1H), 1.87 (dd, J = 7.2, 1.8 Hz, 3H), 1.65 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).

Step 2. Synthesis of ethyl (R)-2-methyl-3-((S)-3-(4-((1R, 2R)-2-methylcyclopropyl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanoate [5.22b]. 5.22a (0.1 g, 0.25 mmol, 1.0 equiv) was added to toluene (1.26 ml) and cooled to 0 °C. Et2Zn (1 M in Hexane) (0.16 g, 1.26 mmol, 5.0 equiv). Diiodomethane (0.68 g, 2.52 mmol, 10.0 equiv) was added drop wise and the reaction mixture was stirred at room temperature for 5 minutes. The reaction mixture was stirred at 50 °C for 30 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated (Repeated the process three times) to afford product 5.22b (0.1 g, 96.6 % yield). LCMS (m/z): 410.3 [M+H]. 1H NMR (400 MHz, CDCl3) δ 7.40 (dt, J = 24.0, 9.1 Hz, 4H), 4.90 - 4.80 (m, 1H), 4.37 (ddt, J = 7.1, 5.4, 1.7 Hz, 2H), 4.27 - 4.15 (m, 2H), 3.76 (dd, J = 17.3, 9.7 Hz, 1H), 3.21 (t, J = 7.1 Hz, 1H), 3.10 (d, J = 1.9 Hz, 3H), 2.70 (dd, J = 10.5, 7.3 Hz, 1H), 2.55 - 2.47 (m, 1H), 1.94 - 1.80 (m, 5H), 1.38 (td, J = 7.1, 1.5 Hz, 3H), 0.94 - 0.89 (m, 3H).

Step. Synthesis of (2R)-N-hydroxy-2-methyl-3-((5S)-3-(4-(2-methylcyclopropyl)phenyl)-2-oxooxazolidin-5-yl)-2-(methylsulfonyl)propanamide [5.22]

5.22 was synthesized using the process of example 2.4. LCMS (m/z): 397.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.30 (s, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.06 (d, J = 8.7 Hz, 2H), 4.61 (d, J = 5.6 Hz, 1H), 4.14 (t, J = 8.7 Hz, 1H), 3.79 - 3.71 (m, 1H), 3.08 (s, 3H), 2.77 (d, J = 14.6 Hz, 1H), 2.25 - 2.16 (m, 1H), 1.60 (s, 3H), 1.14 (d, J = 5.9 Hz, 3H), 1.00 (s, 1H), 0.86 - 0.80 (m, 1H), 0.75 - 0.69 (m, 1H).

V.23. Synthesis of compound 5.23

Step 1. Synthesis of 4-hydroxycyclopent-2-en-1-one [5.23a]. Furan-2-ylmethanol (20 g, 203.8 mmol, 1.0 equiv) was suspended in water (400 mL). K2HP04 (1.86 g, 8.15 mmol, 0.04 equiv), H2P04 (0.46 mL) was added drop wise to adjust pH 4.5 to 4.8 and the reaction mixture was stirred at 99 °C for 24 hours. The reaction mixture was washed with
dichloromethane. The aqueous layer was concentrated to afford a crude residue. The crude residue was dissolved in dichloromethane, dried over sodium sulfate and concentrated to afford the desired product 5.23a (4.7 g, 23.5 % yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.60 (dd, $J = 5.7, 2.3$ Hz, 1H), 6.27 (dd, $J = 5.7, 1.2$ Hz, 1H), 5.09 (d, $J = 5.8$ Hz, 1H), 2.82 (dd, $J = 18.5, 6.1$ Hz, 1H), 2.31 (dd, $J = 18.5, 2.2$ Hz, 1H), 2.09 (d, $J = 17.8$ Hz, 1H).

**Step 2. Synthesis of 4-((tert-butyldimethylsilyl) oxy) cyclopent-2-en-1-one [5.23b]**

5.23a (4.7 g, 47.9 mmol, 1.0 equiv), DMAP (0.58 g, 4.79 mmol, 0.1 equiv), TEA (17 mL, 122.6 mmol, 2.56 equiv) were suspended in dichloromethane (90 mL) and cooled to 0 °C. TBDMS-Cl (8.66 g, 57.5 mmol, 1.2 equiv) in dichloromethane (30 mL) was added and the reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (5 % EtOAc/n-pentane) to afford the desired product 5.23b (7 g, 68.9 % yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.48 (dd, $J = 5.7, 2.3$ Hz, 1H), 6.21 (dd, $J = 5.7, 1.2$ Hz, 1H), 5.09 - 4.94 (m, 1H), 2.73 (dd, $J = 18.2, 6.0$ Hz, 1H), 2.27 (dd, $J = 18.2, 2.2$ Hz, 1H), 0.95 (d, $J = 13.8$ Hz, 9H), 0.18 - 0.10 (m, 6H).

**Step 3. Synthesis of 4-((tert-butyldimethylsilyl) oxy) cyclopent-1-en-1-yl trifluoromethanesulfonate [5.23c]**

L-selectride (1M in THF) (9.4 g, 9.43 mmol, 1.0 equiv) was suspended in THF (80 mL) and cooled to -78 °C. 5.23b (2 g, 9.43 mmol, 1.0 equiv), TEA (0.39 g, 2.83 mmol, 0.3 equiv) in THF (40 mL) was added drop wise within 30 minutes and the reaction mixture was stirred at -78 °C for 30 minutes. N-phenyl bis trifluoromethanesulfonimide (2.93 g, 8.21 mmol, 0.87 equiv) was added in two portions and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was concentrated, the residue was added to saturated aqueous sodium bicarbonate solution and extracted with hexane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (2-5 % EtOAc/Hexane) to afford the desired product 5.23c (1.8 g, 55.2 % yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.61 - 5.55 (m, 1H), 4.58 (ddd, $J = 11.0, 7.3, 3.8$ Hz, 1H), 2.84 (dd, $J = 16.3, 6.1$ Hz, 1H), 2.77 - 2.67 (m, 1H), 2.54 (ddd, $J = 16.3, 4.0, 2.1$ Hz, 1H), 2.39 - 2.33 (m, 1H), 0.90 (s, 9H), 0.09 (s, 6H).

**Step 4. Synthesis of ([3-(4-bromophenyl) cyclopent-3-en-1-yl) oxy] (tert-butyl) dimethylsilane [5.23d]**

5.23c (1.7 g, 4.91 mmol, 1.0 equiv), (4-bromophenyl)boronic acid (1.48 g, 7.37 mmol, 1.5 equiv), K$_2$P(4 (3.13 g, 14.74 mmol, 3.0 equiv) were suspended in 1, 4-dioxane (40 mL) in sealed tube and the reaction mixture was degassed for 10 minutes. PdCl$_2$(dppe) (0.18 g, 0.25 mmol, 0.05 equiv) was added and the reaction mixture was stirred at reflux for 5 hours. The reaction mixture was quenched with water and extracted with
EtOAc. The organic layer was washed with saturated aqueous sodium bicarbonate solution, brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (5-10 % EtOAc/Hexane) to afford the desired product 5.23d (0.8 g, 46.2 % yield). ¹H NMR (400 MHz, DMSO) δ 7.52 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 6.26 (s, 1H), 4.68 - 4.60 (m, 1H), 3.00 - 2.89 (m, 1H), 2.79 (d, J = 11.6 Hz, 1H), 2.35 (d, J = 16.5 Hz, 2H), 0.87 (s, 9H), 0.07 (s, 6H).

Step 5. Synthesis of 3-(4-bromophenyl) cyclopent-3-en-1-ol [5.23e]. 5.23d (0.5 g, 1.41 mmol, 1.0 equiv) was suspended in THF (30 ml). TEA (0.03 ml, 0.22 mmol, 0.15 equiv) was added drop wise. TBAF (1 M in THF) (1.41 g, 1.41 mmol, 1.0 equiv) was added and the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (30 % EtOAc/Hexane) to afford the desired product 5.23e (0.27 g, 80.1 % yield).

Step 6. Synthesis of 1-bromo-4-(4-fluorocyclopent-1-en-1-yl) benzene [5.23f]. 5.23e (0.27 g, 1.13 mmol, 1.0 equiv) was suspended in dichloromethane (30 ml) and cooled to -78 °C. DAST (0.36 g, 2.26 mmol, 2.0 equiv) was added drop wise and the reaction mixture was stirred at -78 °C for 10 minutes. The reaction mixture was stirred at rt for 4 hours. The reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (8-10 % EtOAc/Hexane) to afford the desired product 5.23f (0.23 g, 84.9 % yield). ¹H NMR (400 MHz, CDCl₃) δ 7.56 - 7.45 (m, 4H), 6.20 (d, J = 19.8 Hz, 1H), 5.46 (d, J = 54.0 Hz, 1H), 5.03 (d, J = 54.9 Hz, 1H), 3.15 - 2.80 (m, 4H).

Step 7. Synthesis of (2R)-3-(3S)-3-(4-(4-fluorocyclopent-1-en-1-yl) phenyl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [5.23]. 5.23 was synthesized from 5.23f using the process of example 2.4. LCMS (m/z): 444.3 [M+18].

³H NMR (400 MHz, DMSO) δ 11.06 (s, 1H), 9.30 (s, 1H), 7.53 (s, 4H), 6.23 (s, 1H), 5.46 (d, J = 54.4 Hz, 1H), 4.64 (d, J = 8.0 Hz, 1H), 4.19 (d, J = 8.7 Hz, 1H), 3.86 - 3.75 (m, 1H), 3.09 (s, 3H), 2.82 (ddd, J = 50.6, 32.6, 17.5 Hz, 5H), 2.25 - 2.20 (m, 1H), 1.60 (s, 3H).

V.24. Synthesis of compound 5.24

Step 1. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(4-(Z)-prop-1-en-1-yl) phenyl) oxazolidin-5-yl) propanoate [5.24a]. 1.1d (0.3 g, 0.69 mmol, 1.0 equiv), (Z)-prop-1-en-1-ylboronic acid (0.078 g, 0.89 mmol, 1.3 equiv) were suspended in 1, 4-dioxane (18 ml) in sealed tube. Cs₂CO₃ (0.67 g, 2.07 mmol, 3.0 equiv) was added and the reaction mixture was degassed for 10 minutes. PdCl₂(dppe) (0.036 g, 0.048 mmol, 0.07
equiv) was added and the reaction mixture was stirred at 120 °C for 24 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel column chromatography (35-38 % EtOAc/Hexane) to afford the desired product 5.24a (0.23 g, 85 % yield). LCMS (m/z): 396.5 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.50 (dd, J = 23.6, 8.8 Hz, 2H), 7.37 (dd, J = 21.1, 8.8 Hz, 2H), 6.40 (d, J = 9.9 Hz, 1H), 5.76 (td, J = 14.4, 7.2 Hz, 1H), 4.83 - 4.75 (m, 1H), 4.25 (dt, J = 16.4, 7.9 Hz, 3H), 3.86 - 3.79 (m, 1H), 3.17 (s, 3H), 2.70 (d, J = 14.8 Hz, 1H), 2.40 - 2.34 (m, 1H), 1.86 (dt, J = 9.5, 4.7 Hz, 3H), 1.65 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H).

Step 2. Synthesis of ethyl (R)-3-((S)-3-(4-((Z)-1-fluoroprop-1-en-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [5.24b]. 5.24a (0.23 g, 0.58 mmol, 1.0 equiv) was suspended in dichloromethane (20 mL) and cooled to 0 °C. NEt3, 3HF (0.14 g, 0.88 mmol, 1.5 equiv), NBS (0.12 g, 0.65 mmol, 1.1 equiv) were added and the reaction mixture was stirred at 0 °C for 10 minutes. The reaction mixture was stirred at rt for 24 hours. The reaction was quenched with water (slightly basic, adjusted with NH₄OH) and extracted with dichloromethane. The organic layer was washed with 1.0 N HCl and 1.0 N sodium bicarbonate solution, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (30-35 % EtOAc/Hexane) to afford 5.24b (0.23 g, 80 % yield). LCMS (m/z): 495 [M+H].

Step 3. Synthesis of ethyl (R)-3-((S)-3-(4-((Z)-1-fluoroprop-1-en-1-yl)phenyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [5.24c]

5.24b (0.2 g, 0.4 mmol, 1.0 equiv) was suspended in DBU (0.06 mL, 0.4 mmol, 1.0 equiv). The reaction mixture was stirred at 85 °C for 45 minutes. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford the desired product 5.24c (0.16 g, 95.8 % yield). LCMS (m/z): 414.2 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.76 - 7.61 (m, 2H), 7.54 (t, J = 11.0 Hz, 2H), 5.50 (dq, J = 22.6, 7.5 Hz, 1H), 4.86 - 4.75 (m, 1H), 4.24 (dq, J = 15.2, 7.1 Hz, 3H), 3.90 - 3.82 (m, 1H), 3.17 (s, 3H), 2.70 (d, J = 15.2 Hz, 1H), 2.38 (dd, J = 14.8, 8.9 Hz, 1H), 1.76 (dd, J = 7.5, 2.3 Hz, 2H), 1.65 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H).


5.24 was synthesized from 5.24c using the process of example 1.2. LCMS (m/z): 401.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.06 - 10.45 (m, 1H), 9.82 - 9.21 (m, 1H), 7.63 (d, J = 8.6 Hz, 2H), 7.52 (d, J = 8.8 Hz, 2H), 5.49 (dq, J = 22.6, 7.5 Hz, 1H), 4.67 (dd, J = 13.7, 7.9 Hz, 1H), 4.22 (t, J = 8.8 Hz, 1H), 3.88 - 3.78 (m, 1H), 3.09 (s, 3H), 2.78 (dd, J = 14.4, 2.6 Hz, 1H), 2.22 (dd, J = 14.4, 8.8 Hz, 1H), 1.76 (dd, J = 7.5, 2.3 Hz, 3H), 1.60 (s, 3H).
V.25. Synthesis of compound 5.25

Compound 5.25 was synthesized by the process of example of 2.1. LCMS (m/z): 532.6 [M+H].$^1$H NMR (400 MHz, DMSO) $\delta$ 7.44 (m, 8H), 4.58 (m, 1H), 4.30 - 4.06 (m, 1H), 3.94 - 3.67 (m, 1H), 3.59 (m, 2H), 3.49 (m, 2H), 3.39 (m, 4H), 3.10 (m, 2H), 2.77 (m, 2H), 2.56 (m, 1H), 2.03 - 1.92 (m, 1H), 1.60 (s, 3H).

V.26. Synthesis of compound 5.26

Compound 5.26 was synthesized by the example of 2.1. LCMS (m/z): 547.5 [M-H].$^1$H NMR (400 MHz, DMSO) $\delta$ 8.24 (s, 1H), 7.66 (d, $J = 8.7$ Hz, 2H), 7.59 (d, $J = 5.7$ Hz, 4H), 7.03 (d, $J = 8.8$ Hz, 2H), 4.67 (s, 1H), 4.24 - 4.19 (m, 1H), 4.13 (s, 2H), 3.83 (s, 1H), 3.59 (s, 4H), 3.10 (s, 3H), 2.82 - 2.76 (m, 1H), 2.70 (d, $J = 5.5$ Hz, 2H), 2.26 - 2.21 (m, 1H), 1.61 (s, 3H).

V.27. Synthesis of compound 5.27

Compound 5.27 was synthesized by the example of 2.1. LCMS (m/z): 463.5 [M+H].$^1$H NMR (400 MHz, DMSO) $\delta$ 11.10 (s, 1H), 9.31 (s, 1H), 7.69 (d, $J = 8.6$ Hz, 2H), 7.59 (dd, $J = 13.1$, 8.4 Hz, 4H), 7.30 (d, $J = 7.9$ Hz, 2H), 4.67 (s, 2H), 4.22 (t, $J = 8.8$ Hz, 1H), 3.83 (t, $J = 8.1$ Hz, 1H), 3.70 - 3.56 (m, 2H), 3.10 (s, 3H), 2.77 (dd, $J = 18.3$, 11.1 Hz, 3H), 2.22 (dd, $J = 14.3$, 8.6 Hz, 1H), 1.61 (s, 3H).

V.28. Synthesis of compound 5.28

Compound 5.28 was synthesized by the process of example of 2.4. LCMS (m/z): 425.5 [M+H].$^1$H NMR (400 MHz, DMSO) $\delta$ 11.08 (s, 1H), 9.31 (s, 1H), 7.50 (q, $J = 8.8$ Hz, 4H), 6.25 (s, 1H), 4.64 (d, $J = 7.7$ Hz, 1H), 4.20 (dd, $J = 18.2$, 5.4 Hz, 3H), 3.81 (dt, $J = 14.0$, 6.9 Hz, 3H), 3.09 (s, 3H), 2.79 (d, $J = 14.6$ Hz, 1H), 2.44 (s, 2H), 2.21 (dd, $J = 14.4$, 8.9 Hz, 1H), 1.61 (s, 3H).

V.29. Synthesis of compound 5.29

Compound 5.29 was synthesized by the process of example 2.4. LCMS (m/z): 426.6 [M+H].$^1$H NMR (400 MHz, DMSO) $\delta$ 11.07 (s, 1H), 9.29 (s, 1H), 7.50 - 7.39 (m, 2H), 7.28 (d, $J = 8.6$ Hz, 2H), 4.62 (d, $J = 5.8$ Hz, 1H), 4.16 (t, $J = 8.8$ Hz, 1H), 3.94 (d, $J = 10.8$ Hz, 2H), 3.81 - 3.71 (m, 1H), 3.47 - 3.39 (m, 2H), 3.06 (d, $J = 19.9$ Hz, 3H), 2.75 (t, $J = 15.4$ Hz, 2H), 2.19 (dd, $J = 14.4$, 8.8 Hz, 1H), 1.78 - 1.62 (m, 4H), 1.60 (s, 3H).

VI.1. Synthesis of compound 6.1
Reagents: Step 1: CBZ-CI, 2M NaOH, acetone:water, 0 °C to room temperature. Step 2: n-BuLi (2.5M in hexane), THF, -70°C to room temperature. Step 3: Iodine, triphenylphosphine, imidazole, dichloromethane, room temperature. Step 4: NaH (60%), N, N-dimethylformamide, 0 °C to room temperature. Step 5: CAN, CH₂CN:Water, room temperature. Step 6: Cul, Cs₂CO₃, trans-cyclohexane-1,2-diamine, 1,4-dioxane, 125 °C. Step 7: DBU, dppb, PdCl₂(PPh₃)₂, DMSO, 100°C. Step 8: LiOH·H₂O, THF, MeOH, Water, room temperature. Step 9: NH₂OTH, EDC.HCl, HOBT, N-methyl morpholine, THF, room temperature. Step 10: 35.5% aq. HCl, EtOH, room temperature.

Step 1. Synthesis of benzyl (4-methoxybenzyl)carbamate [6.1a]. (4-methoxyphenyl) methanamine (2 g, 14.6 mmol, 1.0 equiv) was dissolved in THF (20 ml). NaOH (2M solution) (1.16 g, 29.2 mmol, 2.0 equiv) was added and the reaction mixture was cooled to 0-5 °C. CBZ-CI (2.74 g, 16.0 mmol, 1.1 equiv) was added and the reaction mixture was stirred at rt for 3 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford product 6.1a (3.7 g, 92.5 % yield). ¹H NMR (400 MHz, DMSO) δ 7.76 (t, J = 5.8 Hz, 1H), 7.41 - 7.30 (m, 5H), 7.18 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.04 (s, 2H), 4.13 (d, J = 6.2 Hz, 2H), 3.73 (s, 3H).

Step 2. Synthesis of (R)-5-(hydroxymethyl)-3-(4-methoxybenzyl)oxazolidin-2-one [6.1b]
6.1a (3.7 g, 13.6 mmol, 1.0 equiv) was dissolved in THF (40 mL) and cooled to -70°C. n-BuLi (2.5M in hexane) (0.96 g, 15.0 mmol, 1.1 equiv) was gradually added and the reaction mixture was stirred at -70 °C for 1 hour. (R)-oxiran-2-ylmethyl butyrate (2.16 g, 15.0 mmol, 1.1 equiv) was added drop wise and the reaction mixture was stirred at -70 °C for 1 hour. The reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (50-60 % EtOAc in Hexane) to afford product 6.1b (2.54 g, 79.4 % yield).

LCMS (m/z): 238.3 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.21 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.6 Hz, 2H), 4.50 (d, J = 8.9 Hz, 1H), 4.35 - 4.17 (m, 2H), 3.74 (d, J = 5.1 Hz, 3H), 3.60 - 3.49 (m, 1H), 3.47 - 3.37 (m, 2H), 3.18 (dd, J = 8.5, 6.6 Hz, 1H).

Step 3. Synthesis of (R)-5-(iodomethyl)-3-(4-methoxybenzyl)oxazolidin-2-one [6.1c]

Triphenylphosphine (3.65 g, 13.9 mmol, 1.3 equiv) was dissolved in dichloromethane (30 mL). imidazole (1.02 g, 15.0 mmol, 1.4 equiv) and iodine (3.53 g, 13.9 mmol, 1.3 equiv) were added and the reaction mixture was stirred at room temperature for 15 minutes. 6.1b (2.54 g, 10.7 mmol, 1.0 equiv) was added and the reaction mixture was stirred at room temperature for 7 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (40-70 % EtOAc in Hexane) to afford product 6.1c (2.6 g, 70.2 % yield).

LCMS (m/z): 348.1 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.32 - 7.13 (m, 2H), 6.91 (t, J = 10.1 Hz, 2H), 4.52 (dt, J = 11.1, 5.0 Hz, 1H), 4.38 - 4.17 (m, 2H), 3.81 - 3.66 (m, 3H), 3.64 - 3.37 (m, 3H), 3.02 (dd, J = 9.1, 6.2 Hz, 1H).

Step 4. Synthesis of ethyl (R)-3-((S)-3-(4-methoxybenzyl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [6.1d]. Ethyl 2-(methylsulfonyl)propanoate (5.45 g, 30.1 mmol, 4.0 equiv) was dissolved in N,N-dimethylformamide (20 mL) and cooled to 0-5 °C. NaH (60%) (0.45 g, 11.2 mmol, 1.5 equiv) was added in portion wise and the reaction mixture was stirred at room temperature for 1 hour. A solution of 6.1c (2.61 g, 7.5 mmol, 1.0 equiv) in N,N-dimethylformamide (10 mL) was added drop wise at 0-5 °C, stirred at the same temperature for 30 minutes and the reaction mixture was allowed to stir at room temperature for 2 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The residue was purified by silica gel column chromatography (20-30 % EtOAc in Hexane) to afford product 6.1d as mixture of diastereomers (1.9 g, 63.3 % yield). 6.1d was further purified by the preparative HPLC to afford 6.1d as desired diastereomer.

LCMS (m/z): 400.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 7.21 (d, J = 8.6 Hz, 2H), 6.93 (d, J 

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= 8.6 Hz, 2H), 4.59 (tt, J = 8.4, 4.2 Hz, 1H), 4.28 (t, J = 8.3 Hz, 2H), 4.20 (q, J = 7.1 Hz, 2H),
3.75 (s, 3H), 3.53 (dd, J = 14.8, 2.9 Hz, 1H), 2.42 -
2.33 (m, 1H), 2.07 (s, 3H), 1.61 (d, J = 19.9 Hz, 3H), 1.26 (dd, J = 9.1 , 5.1 Hz, 3H).

Step 5. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxooxazolidin-5-yl)
propanoate [6.1e]. 6.1d (0.8 g, 2.0 mmol, 1.0 equiv) was dissolved in acetonitrile: water
(9:1 , 30 mL). eerie ammonium nitrate (4.39 g, 8.0 mmol, 4.0 equiv) was added and the
reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was
quenched with water and extracted with EtOAc. The organic layer was washed with brine,
dried over sodium sulfate and concentrated to afford a crude residue. The residue was
purified by silica gel column chromatography (70-90 % EtOAc in Hexane) to afford product
6.1e (0.41 g, 84 % yield). LCMS (m/z): 280.2 [M+H].

Step 6. Synthesis of ethyl (R)-3-((S)-3-(5-bromopyridin-2-yl)-2-oxooxazolidin-5-yl)-2-
methyl-2-(methylsulfonyl)propanoate [6.1f]. 6.1e (0.3 g, 1.1 mmol, 1.0 equiv), 2,5-
dibromopyridine (0.28 g, 1.2 mmol, 1.1 equiv) were dissolved in 1,4-dioxane (5 mL). Cul
(0.24 g, 1.3 mmol, 1.2 equiv), trans-cyclohexane-1,2-diamine (0.17 g, 1.5 mmol, 1.4 equiv),
Cs₂CO₃ (0.52 g, 1.6 mmol, 1.5 equiv) were added and the reaction mixture was stirred at
125 °C for 4 hours. The reaction mixture was quenched with water and extracted with
EtOAc. The organic layer was washed with brine, dried over sodium sulfate and
concentrated to afford a residue. The residue was purified by silica gel column chromatography
(30-50 % EtOAc in Hexane) to afford product 6.1f (0.31 g, 66.4 % yield).
LCMS (m/z): 437.3 [M+H]. ¹H NMR (400 MHz, DMSO) δ 8.52 (dd, J = 3.5, 2.7 Hz, 3H), 8.11 -
8.04 (m, 6H), 4.88 - 4.75 (m, 4H), 4.33 - 4.24 (m, 10H), 3.87 (dd, J = 10.3, 7.5 Hz, 4H),
3.17 (s, 9H), 2.78 - 2.66 (m, 4H), 2.42 - 2.32 (m, 5H), 1.64 (s, 10H), 1.28 - 1.25 (m, 9H).

Step 7. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-(prop-1-yn-
1-yl)pyridin-2-yl)oxazolidin-5-yl)propanoate [6.1g]. 6.1f (0.15 g, 0.3 mmol, 1.0 equiv),
but-2-ynoic acid (0.032 g, 0.4 mmol, 1.1 equiv), 1,4-bis(diphenylphosphino)butane (0.003 g,
0.007 mmol, 0.02 equiv) and DBU(0.10 g, 0.7 mmol, 2.0 equiv) were dissolved in DMSO (2
mL). The reaction mixture was degassed for 10 minutes, PdCl₂(PPh₃)₂ (0.002 g, 0.003
mmol, 0.01 equiv) was added and the reaction mixture was stirred at 100 °C for 3 hours.
The reaction mixture was quenched with water and extracted with EtOAc. The organic layer
was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The
residue was purified by silica gel chromatography (30-50 % EtOAc in Hexane) to afford 6.1g
(0.1 g, 80.9 % yield). ¹H NMR (400 MHz, DMSO) δ 8.41 (t, J = 3.1 Hz, 1H), 8.04 (d, J = 8.8
Hz, 1H), 7.86 (dt, J = 8.8, 2.8 Hz, 1H), 4.90 - 4.74 (m, 1H), 4.39 - 4.31 (m, 1H), 4.30 - 4.21
(m, 2H), 3.95 - 3.84 (m, 1H), 3.21 - 3.10 (m, 3H), 2.71 (dd, J = 14.8, 2.9 Hz, 1H), 2.42 -
2.33 (m, 1H), 2.07 (s, 3H), 1.61 (d, J = 19.9 Hz, 3H), 1.26 (dd, J = 9.1 , 5.1 Hz, 3H).
Step 8. Synthesis of (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-(prop-1-yn-1-yl)pyridin-2-yl)oxazolidin-5-yl)propanoic acid [6.1 h]. 6.1 g (0.11 g, 0.3 mmol, 1.0 equiv) was dissolved in THF (2 mL), MeOH (1 mL). LiOH.H2O (0.012 g, 0.3 mmol, 1.0 equiv) in water (1 mL) was added and the reaction mixture was stirred at room temperature for 364 minutes. The reaction mixture was acidified by 1N HCl aqueous solution to pH 4 to 5 and concentrated under reduced pressure to afford product 6.1 h as HCl salt which was used as such for next step (0.14 g, 100 % yield as crude product). LCMS (m/z): 367.4 [M+H].

Step 9. Synthesis of (2R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-(prop-1-yn-1-yl)pyridin-2-yl)oxazolidin-5-yl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide [6.1 i]. 6.1 h (0.14 g, 0.4 mmol, 1.0 equiv) was dissolved in THF (5 mL). N-methyl morpholine (0.19 g, 2.0 mmol, 5.0 equiv), EDC.HCl (0.11 g, 0.6 mmol, 1.5 equiv), HOBT (0.093 g, 0.7 mmol, 1.8 equiv), 0-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.089 g, 0.8 mmol, 2.0 equiv) were added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was concentrated to afford a residue. The residue was purified by silica gel column chromatography (1-2 % MeOH in dichloromethane) to afford product 6.1 i (0.09 g, 70 % yield). Which was used as such for next step LCMS (m/z): 466.5 [M+H].

Step 10. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-(prop-1-yn-1-yl)pyridin-2-yl)oxazolidin-5-yl)propanamide [6.1 j]. 6.1 i (0.09 g, 0.2 mmol, 1.0 equiv) was dissolved in ethanol (5 mL). 35.5% aq. HCl (0.2 mL) was added and the reaction mixture was stirred at rt for 1 hour. The reaction mixture was quenched with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude product. The crude product was purified by preparative HPLC purification to afford 6.1 as desired diastereomer (0.022 g, 30.1 % yield). LCMS (m/z): 382.3 [M+H].

1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.33 (s, 1H), 8.40 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.85 (d, J = 8.3 Hz, 1H), 4.68 (d, J = 6.4 Hz, 1H), 4.29 (t, J = 9.1 Hz, 1H), 3.93 - 3.74 (m, 1H), 3.08 (s, 3H), 2.79 (d, J = 13.5 Hz, 1H), 2.27 - 2.15 (m, 1H), 2.07 (s, 3H), 1.59 (s, 3H).

VI.2. Synthesis of compound 6.2

Step 1. Synthesis of 5-bromo-2-(cyclopropylethynyl) pyridine [6.2a]. 2.5-
Dibromopyridine (0.4 g, 1.7 mmol, 1.0 equiv), PdCl2(PPh3)2 (0.07 g, 0.1 mmol, 0.05 equiv), Cul (0.032 g, 0.2 mmol, 0.1 equiv), triphenyl phosphine (0.088 g, 0.3 mmol, 0.2 equiv) were added in diethyl amine (5 mL), N,N-dimethylformamide (1 mL) and the reaction mixture was degassed for 10 minutes. Ethynylcyclopropane (0.13 g, 2.0 mmol, 1.2 equiv) was added and the reaction mixture was stirred at 100 °C for 24 hours in sealed tube. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica
gel column chromatography (1-2 % EtOAc in Hexane) to afford product 6.2a (0.15 g, 32.1 % yield). LCMS (m/z): 222.1 [M+H]. 1H NMR (400 MHz, DMSO) δ 8.63 (d, J = 1.8 Hz, 1H), 8.01 (dd, J = 8.4, 2.4 Hz, 1H), 7.39 (t, J = 10.3 Hz, 1H), 1.59 (ddd, J = 13.2, 8.3, 5.0 Hz, 1H), 0.94 (dt, J = 6.3, 4.0 Hz, 2H), 0.80 (dt, J = 6.9, 4.0 Hz, 2H).

**Step 2. Synthesis of (R)-3-((S)-3-(5-cyclopropylethynyl)pyridin-3-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [6.2]**

Compound 6.2 was synthesized from 6.2a by the process of example 2.4. LCMS (m/z): 408.4 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.31 (s, 1H), 8.64 (d, J = 2.4 Hz, 1H), 7.95 (dd, J = 8.7, 2.7 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 4.68 (d, J = 8.3 Hz, 1H), 4.23 (t, J = 8.7 Hz, 1H), 3.86 - 3.76 (m, 1H), 3.08 (s, 3H), 2.77 (d, J = 12.2 Hz, 1H), 2.24 (dd, J = 14.5, 9.1 Hz, 1H), 1.66 - 1.52 (m, 4H), 0.92 (dt, J = 6.3, 4.0 Hz, 2H), 0.77 (td, J = 6.6, 4.0 Hz, 2H).

**VI.3. Synthesis of compound 6.3**

Compound 6.3 was synthesized by the process of example 6.4. LCMS (m/z): 436.6 [M+H]. 1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.83 (dd, J = 8.8, 2.2 Hz, 1H), 4.67 (d, J = 5.9 Hz, 1H), 4.34 - 4.26 (m, 1H), 3.86 (dd, J = 10.3, 7.5 Hz, 1H), 3.11 (d, J = 24.1 Hz, 3H), 2.87 (dd, J = 15.0, 7.5 Hz, 1H), 2.85 - 2.75 (m, 1H), 2.22 (dd, J = 14.5, 8.7 Hz, 1H), 2.10 - 1.85 (m, 2H), 1.72 (s, 2H), 1.59 (s, 6H).

**VI.4. Synthesis of compound 6.4**

**Step 1. Synthesis of ethynylcyclobutane [6.4a].** Cyclobutanecarbaldehyde (1 g, 11.8 mmol, 1.0 equiv) was dissolved in EtOH (15 mL) and cooled to 0 °C. Ohira-Bestmann reagent (2.23 g, 11.8 mmol, 1.0 equiv), K₂CO₃ (3.27 g, 23.9 mmol, 2.0 equiv) was added and the reaction mixture was stirred at rt for 24 hours. The crude reaction mass was subjected to fractional distillation at 70-75 °C at atmospheric pressure to afford the desired product 6.4a with EtOH (2 mL). The solution of product was directly used in next step as such. 1H NMR (400 MHz, CDCl₃) δ 2.98 - 2.85 (m, 1H), 2.23 - 2.13 (m, 2H), 2.11 (t, J = 3.6 Hz, 1H), 2.09 - 1.98 (m, 2H), 1.91 - 1.75 (m, 2H). NMR shows Ethanol peaks as product was distilled out along with ethanol.

**Step 2. Synthesis of ethyl 3-((S)-3-(5-cyclobutylethynyl) pyridin-2-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl) propanoate [6.4b].** (R)-ethyl 3-((S)-3-(5-bromopyridin-2-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate (0.2 g, 0.4 mmol, 1.0 equiv), PdCl₂(dppm)₂ (0.016 g, 0.02 mmol, 0.05 equiv), Cul (0.008 g, 0.04 mmol, 0.1 equiv) and triphenylphosphine (0.023 g, 0.08 mmol, 0.2 equiv) were added in diethyl amine (5 mL) and N, N-dimethylformamide (1 mL). The reaction mixture was degassed for 10 minutes. Ethynylcyclobutane (2 mL with ethanol) was added and the reaction mixture was stirred at
130 °C for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a crude residue. The crude residue was purified by silica gel chromatography (1 % EtOAc in dichloromethane) to afford 6.4b (0.16 g, 53.3% yield).

LCMS (m/z): 435.8 [M+H]. ^1H NMR (400 MHz, DMSO) δ 8.08 - 8.03 (m, 1H), 7.98 (d, J = 15.3 Hz, 1H), 7.90 - 7.82 (m, 1H), 4.82 (ddd, J = 16.6, 8.6, 3.1 Hz, 1H), 4.37 - 4.20 (m, 3H), 3.88 (dd, J = 10.4, 7.5 Hz, 1H), 3.30 - 3.21 (m, 1H), 3.17 (d, J = 3.4 Hz, 3H), 2.70 (d, J = 2.8 Hz, 1H), 2.40 - 2.26 (m, 3H), 2.20 - 2.09 (m, 2H), 1.98 - 1.83 (m, 2H), 1.65 (d, J = 9.4 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H).

**Step 3. Synthesis of (R)-3-((S)-3-(5-(cyclobutylethynyl) pyridin-2-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl) propanamide [6.4]**

6.4 was synthesized from 6.4b using the process of example 6.1. LCMS (m/z): 422.3 [M+H]. ^1H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.33 (s, 1H), 8.40 (s, 1H), 8.06 (s, 1H), 7.86 (s, 1H), 4.68 (m, 1H), 4.30 (m, 1H), 3.87 (m, 1H), 3.56 (m, 1H), 3.09 (s, 3H), 2.80 (d, J = 12.1 Hz, 1H), 2.30 (m, 2H), 2.15 (m, 3H), 1.92 (m, 3H), 1.59 (s, 3H).

**VI.5. Synthesis of compound 6.5**

6.5 was synthesized by the process of 6.1. LCMS (m/z): 396.2 [M+H]. ^1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 8.40 (d, J = 1.8 Hz, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.85 (dd, J = 8.8, 2.3 Hz, 1H), 4.67 (d, J = 7.8 Hz, 1H), 4.31 (d, J = 10.2 Hz, 1H), 3.90 - 3.84 (m, 1H), 3.08 (s, 3H), 2.80 (d, J = 14.9 Hz, 1H), 2.48 - 2.42 (m, 2H), 2.22 (dd, J = 14.5, 8.8 Hz, 1H), 1.17 (t, J = 7.5 Hz, 3H).

**VI.6. Synthesis of compound 6.6**

6.6 was synthesized by the process of 6.4. LCMS (m/z): 410.3 [M+H]. ^1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 8.38 (d, J = 1.6 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.84 (dd, J = 8.8, 2.3 Hz, 1H), 4.67 (d, J = 5.6 Hz, 1H), 4.30 (dd, J = 10.2, 8.6 Hz, 1H), 3.86 (dd, J = 10.3, 7.4 Hz, 1H), 3.08 (s, 3H), 2.88 - 2.77 (m, 2H), 2.22 (dd, J = 14.5, 8.8 Hz, 1H), 1.59 (s, 3H), 1.22 (d, J = 6.9 Hz, 6H).

**VI.7. Synthesis of compound 6.7**

6.7 was synthesized by the process of 6.4. LCMS (m/z): 414.2 [M+H]. ^1H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 8.20 (s, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 4.65 (d, J = 6.1 Hz, 1H), 4.29 (t, J = 9.5 Hz, 1H), 3.92 - 3.79 (m, 1H), 3.09 (s, 3H), 2.81 (d, J = 14.3 Hz, 1H), 2.59 - 2.53 (m, 2H), 2.20 (dd, J = 14.3, 8.8 Hz, 1H), 1.67 - 1.50 (m, 5H), 1.32 - 1.22 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H).
VI.8. Synthesis of compound 6.8

Compound 6.8 was synthesized from 6.1f by the process of example 6.1. LCMS (m/z): 424.2 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 9.31 (s, 1H), 8.51 (s, 1H), 8.06 (s, 2H), 4.67 (d, $J = 6.5$ Hz, 1H), 4.27 (t, $J = 9.1$ Hz, 1H), 3.94 - 3.76 (m, 1H), 3.08 (s, 3H), 2.80 (d, $J = 13.6$ Hz, 1H), 2.21 (dd, $J = 14.0$, 8.9 Hz, 1H), 1.59 (s, 3H).

VI.9. Synthesis of compound 6.9

Step 1. Synthesis of ethyl (R)-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-phenylpyridin-2-yl)oxazolidin-5-yl)propanoate [6.9a]

6.1f (0.21 g, 0.5 mmol, 1.0 equiv), phenylboronic acid (0.071 g, 0.6 mmol, 1.2 equiv), Cs$_2$CO$_3$ (0.47 g, 1.4 mmol, 3.0 equiv) were added in 1, 4-dioxane (5 mL) and degassed for 10 minutes. PdCl$_2$(dpdp) (0.035 g, 0.05 mmol, 0.1 equiv) was added and the reaction mixture was stirred at 90 °C for 3 hours. The reaction mixture was quenched with water and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (20-30% EtOAc in Hexane) to afford product 6.9a (0.17 g, 66 % yield). LCMS (m/z): 433.6 [M+H].

Step 2. Synthesis of (R)-N-hydroxy-2-methyl-2-(methylsulfonyl)-3-((S)-2-oxo-3-(5-phenyl pyridin-2-yl)oxazolidin-5-yl)propanamide [6.9]. Compound 6.9 was synthesized from 6.9a by the example of 6.1. LCMS (m/z): 420.4 [M+H]. $^1$H NMR (400 MHz, DMSO) δ 11.08 (s, 1H), 9.36 (s, 1H), 8.78 - 8.62 (m, 1H), 8.26 - 8.05 (m, 2H), 7.71 (t, $J = 13.7$ Hz, 2H), 7.50 (t, $J = 7.6$ Hz, 2H), 7.41 (t, $J = 7.3$ Hz, 1H), 4.71 (d, $J = 5.1$ Hz, 1H), 4.43 - 4.29 (m, 1H), 3.93 (dd, $J = 10.3$, 7.5 Hz, 1H), 3.20 - 2.97 (m, 3H), 2.88 - 2.77 (m, 1H), 2.24 (dd, $J = 14.5$, 8.7 Hz, 1H), 1.72 - 1.46 (m, 3H).

VI.10. Synthesis of compound 6.10

Step 1. Synthesis of ethyl 3-((S)-3-(5-cyclopropylethynyl)pyridin-2-yl)-2-oxooxazolidin-5-yl)-2-methyl-2-(methylsulfonyl)propanoate [6.10a]. 6.1f (0.25 g, 0.6 mmol, 1.0 equiv), 3-cyclopropylpropionic acid (0.076 g, 0.7 mmol, 1.0 equiv), 1,4-bis(diphenylphosphino)butane (0.005 g, 0.013 mmol, 0.02 equiv) and DBU (0.18 g, 1.1 mmol, 2.0 equiv) were added in DMSO (5 mL). The reaction mixture was degassed for 10 minutes, PdCl$_2$(PPh$_3$)$_2$ (0.004 g, 0.006 mmol, 0.01 equiv) was added and the reaction mixture was stirred at 125 °C for 5 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford a residue. The residue was purified by silica gel column chromatography (20-30 % ethyl acetate in Hexane) to afford product 6.10a which was carry forwarded in next step (0.18 g, 72.6 % yield). LCMS (m/z): 421.4 [M+H].
Step 2. Synthesis of (R)-3-((S)-3-(5-(cyclopropylethynyl)pyridin-2-yl)-2-oxooxazolidin-5-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide [6.10]. 6.10a (0.14 g, 0.3 mmol, 1.0 equiv) was dissolved in ethanol (5 ml). 35.5% aq. HCl (0.2 ml) was added and the reaction mixture was stirred at rt for 1 hour. The reaction was quenched with water, neutralized by saturated aqueous sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed with brine, dried over sodium sulfate and concentrated to afford crude product. The crude product was purified by preparative HPLC purification to afford 6.10 as desired diastereomer (0.040 g, 34.5% yield). LCMS (m/z): 408.3 [M+H].

\[
\begin{align*}
\text{H NMR (400 MHz, DMSO)} & \delta 11.06 (s, 1H), 9.30 (s, 1H), 8.38 (d, J = 1.5 Hz, 1H), 8.11 - 7.97 (m, 1H), 7.82 (dd, J = 8.8, 2.3 Hz, 1H), 4.67 (d, J = 8.3 Hz, 1H), 4.29 (t, J = 9.4 Hz, 1H), 3.86 (dd, J = 10.3, 7.5 Hz, 1H), 3.13 - 3.01 (m, 3H), 2.79 (d, J = 14.7 Hz, 1H), 2.21 (dd, J = 14.5, 8.7 Hz, 1H), 1.62 - 1.46 (m, 4H), 0.90 (dt, J = 6.4, 4.0 Hz, 2H), 0.79 - 0.70 (m, 2H).
\end{align*}
\]

VI.11. Synthesis of compound 6.11

Compound 6.11 was synthesized by the process of example 6.9. LCMS (m/z): 452.4 [M-1]. \( ^1 \text{H NMR (400 MHz, DMSO)} \) \( \delta 11.06 (s, 1H), 9.33 (s, 1H), 8.73 (d, J = 1.5 Hz, 1H), 8.18 (dt, J = 15.2, 5.5 Hz, 2H), 7.77 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 4.70 (d, J = 5.6 Hz, 1H), 4.36 (t, J = 9.4 Hz, 1H), 3.92 (dd, J = 10.3, 7.4 Hz, 1H), 3.16 - 3.00 (m, 3H), 2.83 (d, J = 12.0 Hz, 1H), 2.24 (dd, J = 14.5, 8.8 Hz, 1H), 1.61 (s, 3H).

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Pharmaceutical Activity

Example P. aeruginosa LpxC Inhibition Assay

The P. aeruginosa LpxC protein is produced according to the general method of Hyland et al (Journal of Bacteriology 1997 179, 2029-2037: Cloning, expression and purification of UDP-3-O-acyl-GlcNAc deacetylase from Pseudomonas aeruginosa: a metalloamidase of the lipid A biosynthesis pathway). The LC-MS/MS method for quantitation of LpxC product was developed using an Agilent 1200 Capillary HPLC system coupled to an Applied Biosystems MDS Sciex 4000QTRAP mass spectrometer. Both instruments are controlled using the Applied Biosystems MDS Sciex Analyst software. LpxC reaction product (UDP-3-0-(R-3-hydroxyacyl)-glucosamine) was produced by hydrolysis of LpxC substrate catalyzed by P.a. LpxC and purified using reversed phase chromatography on a Phenomenex Luna C18(2) 4.6 x 50 mm column. A LpxC product calibration curve was generated to evaluate the sensitivity and dynamic range of the LC-MS/MS method. Briefly, compounds are pre-incubated with 1 nM P. aeruginosa LpxC for 30 min at room temperature. Reactions are initiated by the addition of 2 µM UDP-3-O-(R-3-hydroxydecanoyl)-GlcNAc. Reactions are conducted in a 384-well plate with a total volume of 50 µL in each well containing 50 mM Sodium phosphate pH 7.5, 0.005% Triton X-100 for 20 min at room temperature. After quenching with 1.8% HOAc (5 µL of a 20% HOAc added to each well), reaction mixtures are analyzed using the LC-MS/MS method and peak areas are transformed into product concentration using a LpxC product calibration curve. Total activity (0% inhibition control) is obtained from reactions with no inhibitors and 100% inhibition control is the background using quenched samples before reaction starts. For IC_{50} determinations, peak areas are converted to percent inhibition in Microsoft Excel. Percent
inhibition values are plotted vs. log compound concentration using XLfit. Data is fit to the four-parameter logistic equation using the non-linear regression algorithm in XLfit to return the IC₅₀ and hill slope values.

Bacterial Screens and Cultures

Bacterial isolates were cultivated from -70°C frozen stocks by two consecutive overnight passages at 35°C in ambient air on 5% blood agar (Remel, Lenexa, Kans.). Quality control and P. aeruginosa ATCC 27853) is from the American Type Culture Collection (ATCC; Rockville, Md.) and PA01 was received from Dr. K. Poole.

Susceptibility Testing

Minimal Inhibitory Concentrations (MICs) were determined by the broth microdilution method in accordance with Clinical and Laboratories Institute (CLSI) guidelines. In brief, fresh bacterial overnight cultures were resuspended in sterile saline, adjusted to a 0.5 McFarland turbidity standard and then diluted 20010-fold in cation adjusted Mueller-Hinton Broth (MHB; Remel BBL) to yield a final inoculum of approximately 5x10⁵ colony-forming units (CFU)/mL. Two-fold serial dilutions of compounds were prepared in 100% dimethyl sulfoxide (DMSO) at 100-fold the highest final assay concentration; the resulting dilution series of compounds were diluted 1:10 with sterile water. Ten µL of the drug dilution series in 10% DMSO was transferred to microtiter wells and 90 µL of bacterial suspension was inoculated into the wells. All inoculated microdilution trays were incubated in ambient air at 37 35°C for 20 hours. Following incubation, assay plates were read in a microtiter plate reader at 600 nm and visually inspected to confirm the MIC endpoint well with the OD value. The lowest concentration of the compound that prevented visible growth was recorded as the MIC. Performance of the assay was monitored by testing ciprofloxacin against laboratory quality control strains in accordance with guidelines of the CLSI. Compounds of Examples 1-6, 8-19, 21, 23-26 and 28-53 exhibit an MIC of 64 µg/mL against at least one P. aeruginosa strain selected from PA01 and ATCC27853.

The LpxC inhibitory activity for compounds of the Examples is shown in Table A.

Table A: Biological data

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Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.
We Claim:

1. A compound of the formula (I):

![Chemical Structure](image)

or a pharmaceutically acceptable salt thereof, wherein:

- \( X \) is N or C, wherein when \( X \) is N, \( R^4 \) is absent;
- \( Y \) is N or C, wherein when \( Y \) is N, \( R^5 \) is absent;

\( R^1, R^2, R^4 \) and \( R^5 \) are independently selected from the group consisting of hydrogen, halogen, -CH\(_3\), and -C\(_n\)-haloalkyl;

\( R^3 \) is \( L-R \);

\( L \) is a divalent bond, or \(-CH_2-\);

\( R \) is selected from group consisting of halogen,
- \( \text{CrC}_4 \text{alkyl} \) optionally substituted with one or more groups selected from halogen, \( \text{C}_1-\text{C}_4 \text{alkoxy} \), \( \text{-CN} \), and \( \text{-OH} \);
- \( \text{-CN} \),
- \( \text{-CrC}_4 \text{alkoxy} \) optionally substituted with one or more groups selected from halogen, \( \text{C}_1-\text{C}_4 \text{alkoxy} \), \( \text{-CN} \), and \( \text{-OH} \);
- \( \text{-S-CrC}_4 \text{alkyl} \) wherein the alkyl is optionally substituted with one or more groups selected from halogen, \( \text{C}_1-\text{C}_4 \text{alkoxy} \), \( \text{-CN} \), and \( \text{-OH} \);
- \( \text{-C}_2\text{-C}_6 \text{alkenyl} \) optionally substituted with one or more groups selected from halogen, \( \text{-CN} \), \( \text{-OH} \) and \( \text{C}_1-\text{C}_4 \text{alkoxy} \);
- \( \text{-C}_2\text{-C}_6 \text{alkynyl} \) optionally substituted with one or more groups selected from halogen,
C₁₋C₄ alkoxy, -CN and -OH;
- C₃₋C₇ cycloalkyl optionally substituted with one or more groups selected from halogen, CrC₄ alkyl, -Ci-C₄ alkyl CrC₄ alkoxy, CrC₄ alkoxy, CrC₄ haloalkyl, nitrile, -S(0)₂C₁₋C₄ alkyl and -OH;
- C₆₋Ci₄ aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl and C₁₋C₄ alkyl;
- CrC₄ alkyl-C₆-Ci₄ aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, Ci-C₄ alkoxy, Ci-C₄ haloalkoxy, CrC₄ haloalkyl and Ci-C₄ alkyl;
- CrC₄ alkyl-C₃₋C₇ cycloalkyl, wherein the cycloalkyl is optionally substituted with one or more groups selected from halogen, Ci-C₄ alkoxy, Ci-C₄ haloalkoxy, CrC₄ haloalkyl and Ci-C₄ alkyl;
- C₅₋C₆ cycloalkenyl optionally substituted with one or more groups selected from halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, Ci-C₄ haloalkyl and C₁₋C₄ alkyl;
- 4 to 7 membered heterocycl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocycl is optionally substituted with one or more groups selected from halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, Ci-C₄ alkyl, nitrile, -S(0)₂CrC₄alkyl and -OH, and said heterocycl may contain one unsaturated bond;
- CrC₄ alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocycl is optionally substituted with one or more groups selected from halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, Ci-C₄ alkyl, nitrile, -S(0)₂C₁₋C₄ alkyl and -OH;
- C₅₋C₆ cycloalkenyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocycl is optionally substituted with one or more groups selected from halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, Ci-C₄ alkyl, nitrile, -S(0)₂C₁₋C₄ alkyl and -OH;
- 5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, Ci-C₄ alkyl, nitrile, -S(0)₂C₁₋C₄ alkyl and -OH;
- C₁₋C₄ alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, Ci-C₄ alkyl, nitrile, -S(0)₂C₁₋C₄ alkyl and -OH; and
- C₃₋C₆ cycloalkenyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁₋C₄ alkoxy, CrC₄ haloalkoxy, CrC₄ haloalkyl, Ci-C₄ alkyl, nitrile, -S(0)₂C₁₋C₄ alkyl and -OH; or
R is selected from group consisting of 
-CrCealkyl optionally substituted with one or more groups selected from halogen, C1-C4alkoxy, -CN, -OH and a 5-6 membered heterocyclyl containing one or two heteroatoms selected from N, O and S as ring members and optionally substituted with up to two halo, oxo or C1-C3 alkyl;
- C2-C8alkenyl optionally substituted with one or more groups selected from halogen, -CN, -OH and C1-C4alkoxy;
- C2-C4alkynyl optionally substituted with one or more groups selected from halogen, C1-C4alkoxy, -CN and -OH;
- C3-C7cycloalkyl optionally substituted with one or more groups selected from halogen, C1-C4alkyl, -Cl-C4alkylCrC 4alkoxy, C1-C2alkoxy, CrC 4haloalkyl, nitrile, -S(0)R', -S02CR', -NHC (0)R', and a 5-6 membered heterocyclyl containing one or two heteroatoms selected from N, O and S as ring members and optionally substituted with up to two halo, oxo or R', and wherein R' is C1-C3 alkyl;
- C6-C10aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C1-C4alkoxy, CrC 4haloalkoxy, CrC 4haloalkyl and C1-C4 alkyl;
- CrC 4alkyl-C6-C10aryl, wherein the aryl is optionally substituted with one or more groups selected from halogen, C1-C4alkoxy, C1-C4haloalkoxy, CrC 4haloalkyl and C1-C4 alkyl;
- 4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C1-C4alkoxy, CrC 4haloalkoxy, CrC 4haloalkyl, C1-C4 alkyl, nitrile, -S(0)2C1-C4alkyl and -OH;
- CrC 4alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C1-C4alkoxy, C1-C4haloalkoxy, CrC 4haloalkyl, C1-C4 alkyl, nitrile, -S(0)2C1-C4alkyl and -OH;
- C3-C5cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more groups selected from halogen, C1-C4alkoxy, C1-C4haloalkoxy, CrC 4haloalkyl, C1-C4 alkyl, nitrile, -S(0)2C1-C4alkyl and -OH;
- 5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, CrC₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, c₁-c₄ alkyl, nitrile, -S(0)₂CrC₄alkyl and -OH;
-CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, C₁-C₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl and -OH; and
-C₅cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl and -OH; or

R² and R³ taken together form a 4 to 7 membered heteroaryl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more groups selected from halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, C₁-C₄alkyl and C₁-C₄alkyl.

2. The compound of claim 1, wherein X is N and Y is C, and R⁴ is absent.
3. The compound of claim 1, wherein X is C and Y is N, and R⁵ is absent.
4. The compound of claim 1, wherein X is C and Y is C.

5. The compound of any of the preceding claims, wherein L is

6. The compound of any of claims 1-4, wherein L is a bond.

7. The compound of any of claims 1-4, wherein L is

8. The compound of any of the preceding claims, wherein R is -C₃-C₇cycloalkyl optionally substituted with one to three groups selected from halogen, C₁-C₄alkyl, -C₅-C₇alkylCrC₄alkoxy, CrC₄alkoxy, CrC₄haloalkoxy, nitrile, -S(0)₂CrC₄alkyl and -OH.

9. The compound of any of claims 1-7, wherein R is phenyl optionally substituted with one to three groups selected from halogen, C₁-C₄alkoxy, C₁-C₄haloalkoxy, CrC₄haloalkyl and C₁-C₄alkyl.

10. The compound of any of the preceding claims, wherein Z is H.

11. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
X is N or C, wherein when X is N, R^4 is absent;

Y is N or C, wherein when Y is N, R^5 is absent;

R^1, R^2, R^4 or R^5 are independently selected from the group consisting of hydrogen, halogen, -CH_3, and -Cihaloalkyl;

R^3 is L-R;

L is a divalent bond, or -CH_2-;

R is selected from group consisting of

-CrC_4alkyl optionally substituted with halogen, CrC_4alkoxy, -CN or -OH,
-CN,
-CrC_4alkoxy optionally substituted with halogen or CrC_4alkoxy,
-C_2-C_6alkenyl optionally substituted with halogen, -CN, -OH or C_1-C_4alkoxy,
-C_2-C_4alkynyl optionally substituted with halogen, C_1-C_4alkoxy, -CN or -OH,
-C_3-C_7cycloalkyl optionally substituted with halogen, CrC_4alkyl, -C_1-C_4alkylCr
C_2alkoxy, C_1-C_4alkoxy, C_1-C_4haloalkyl, nitrile, -S(0)=C_1-C_4alkyl or -OH,
-C_6-CrC_iaryl, wherein the aryl is optionally substituted with one or more halogen, C_1-C_4alkoxy, CrC_4haloalkoxy, CrC_4haloalkyl or C_1-C_4alkyl,
-CrC_4aryl-C_6-CrC_iaryl, wherein the aryl is optionally substituted with one or more halogen, C_1-C_4alkoxy, CrC_4haloalkoxy, CrC_4haloalkyl or C_1-C_4alkyl,

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_1-C_4haloalkyl, C_1-C_4alkyl, nitrile, -S(0)=C_1-C_4alkyl or -OH,
-CrC_4alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C_1-C_4alkoxy, CrC_4haloalkoxy, CrC_4haloalkyl, C_1-C_4alkyl, nitrile, -S(0)=C_1-C_4alkyl or -OH,
-CrC_4alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C_1-C_4alkoxy, CrC_4haloalkoxy, CrC_4haloalkyl, C_1-C_4alkyl, nitrile, -S(0)=C_1-C_4alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and
O, wherein said heteroaryl is optionally substituted with one or more halogen, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_1-C_4haloalkyl, C_1-C_4alkyl, nitrile, -S(0)\_2CrC\_4alkyl or -OH, -CrC\_4alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C_1-C_4alkoxy, CrC\_4haloalkoxy, CrC\_4haloalkyl, C_1-C_4alkyl, nitrile, -S(0)\_2CrC\_4alkyl or -OH, and -C_5-C_5cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C_1-C_4alkoxy, C_1-C_4haloalkoxy, d-C\_4haloalkyl, d-dalkyl, nitrile, -S(0)\_2d-dalkyl or -OH; or

L is

R is selected from group consisting of
-CrC\_4alkyl optionally substituted with halogen, C\_2-C\_4alkoxy, -CN or -OH,
-C\_2-C\_6alkenyl optionally substituted with halogen, -CN, -OH or d-dalkoxy,
-C\_2-C\_alkynyl optionally substituted with halogen, d-dalkoxy, -CN or -OH,
-C\_7cycloalkyl optionally substituted with halogen, CrC\_4alkyl, d-dalkyld-C\_4alkoxy, d-dalkoxy, C\_1-C\_4haloalkoxy, nitrile, -S(0)\_2C\_1-C\_4alkyl or -OH,
-C\_6-C\_aryl, wherein the aryl is optionally substituted with one or more halogen, d-dalkoxy,
-CrC\_4alkyl-C\_6-C\_aryl, wherein the aryl is optionally substituted with one or more halogen, d-dalkoxy,
CrC\_4haloalkoxy, CrC\_4haloalkyl or C\_1-C\_4alkyl,

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, d-dalkoxy, CrC\_4haloalkoxy, C\_1-C\_4haloalkyl, C\_1-C\_4alkyl, nitrile, -S(0)\_2C\_1-C\_4alkyl or -OH,

-CrC\_4alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, d-dalkoxy, CrC\_4haloalkoxy, CrC\_4haloalkyl, d-dalkyl, nitrile, -S(0)\_2C\_1-C\_4alkyl or -OH,

-C\_5-C\_5cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C\_1-C\_4alkoxy, d-dhaloalkoxy, CrC\_4haloalkyl, C\_1-C\_4alkyl, nitrile, -S(0)\_2C\_1-C\_4alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C\_1-C\_4alkoxy, C\_1-C\_4haloalkoxy, d-C\_4haloalkyl, d-dalkyl, nitrile, -S(0)\_2C\_1-C\_4alkyl or -OH,
-CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄heteroaryl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH, and
-C₅-C₅cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, C₁-C₄heteroaryl, C₁-C₄alkyl, nitrile, -S(0)₂C₁-C₄alkyl or -OH; or

R² and R³ taken together form a 4 to 7 membered heteroaryl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocycl is optionally substituted with one or more halogen, Cl-C₄alkoxy, C₁-C₄heteroaryl, Cl-C₄heteroalkoxy, or C₁-C₄alkyl.

12. The compound or a pharmaceutically acceptable salt thereof according to claim 1 or claim 11, which is represented by formula II:

![Formula II](image)

wherein X, Y, R¹, R², R³, R⁴ and R⁵ are as defined in claim 1 or claim 11.

13. The compound or a pharmaceutically acceptable salt thereof according to claim 12, which is represented by formula III:

![Formula III](image)

wherein

X is N or C, wherein when X is N, R⁴ is absent;
Y is N or C, wherein when Y is N, R₅ is absent;

R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen, halogen, -CH₃, and C haloalkyl:

R is selected from group consisting of

-C₁₋₄alkyl optionally substituted with halogen, CrC₂alkoxy, -CN or -OH,
-C₂₋₆alkeny1 optionally substituted with halogen, -CN, -OH or CrC₄alkoxy,
-C₂-C₄alkynyl optionally substituted with halogen, Ci-C₄alkoxy, -CN or -OH,
-C₃₋₇cycloalkyl optionally substituted with halogen, CrC₄alkyl, -CrC₄alkylCrC₄alkoxy, C₁₋₄alkoxy, C₁₋₄ haloalkyl, nitrile, -S(0)₂Cr₁₋₄alkyl or -OH,

-Ce-Ciaryl, wherein the aryl is optionally substituted with one or more halogen, CrC₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or C₁₋₄alkyl,

-CrC₄alkyl-CiCl₁aryl, wherein the aryl is optionally substituted with one or more halogen, C₁₋₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or Ci-C₄alkyl,

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁₋₄alkoxy, C₁₋₄haloalkoxy, C₁₋₄haloalkyl, C₁₋₄alkyl, nitrile, -S(0)₂Cr₁₋₄alkyl or -OH,

-CrC₄alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C₁₋₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁₋₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH,

-C₃₋₅cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, Ci-C₄alkoxy, Ci-C₄haloalkoxy, Ci-C₄haloalkyl, Ci-C₄alkyl, nitrile, -S(0)₂Ci-C₄alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁₋₄alkoxy, C₁₋₄haloalkoxy, C₁₋₄haloalkyl, C₁₋₄alkyl, nitrile, -S(0)₂C₁₋₄alkyl or -OH,

-CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁₋₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁₋₄alkyl, nitrile, -S(0)₂C₁₋₄alkyl or -OH,

-C₅₋₇cycloalkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁₋₄alkoxy, C₁₋₄haloalkoxy, C₁₋₄haloalkyl, C₁₋₄alkyl, nitrile, -S(0)₂C₁₋₄alkyl or -OH.

14. The compound or a pharmaceutically acceptable salt thereof according to any preceding claim, wherein
X is C,

Y is N or C, wherein when Y is N, R$^5$ is absent;

R$^1$, R$^2$, R$^4$ or R$^5$ are independently selected from the group consisting of hydrogen and halogen;

R is selected from group consisting of

-CrC$_4$alkyl optionally substituted with halogen, CrC$_4$alkoxy, -CN or -OH,
-C$_2$-C$_6$alkene optionally substituted with halogen, CrC$_4$alkoxy, -CN or -OH,
-C$_3$-C$_7$cycloalkyl optionally substituted with halogen, CrC$_4$alkyl, -Ci-C$_4$alkylCrC$_4$alkoxy, C$_1$-C$_4$alkoxy, C$_1$-C$_4$haloalkyl, nitrile, -S(0)$_2$C$_1$-C$_4$alkyl or -OH,
-C$_6$-Ci$_3$aryl, wherein the aryl is optionally substituted with one or more halogen, C$_1$-C$_4$alkoxy, CrC$_4$haloalkoxy, CrC$_4$haloalkyl or C$_1$-C$_4$alkyl,
-CrC$_4$alkyl-C$_5$Cl$_3$aryl, wherein the aryl is optionally substituted with one or more halogen, C$_1$-C$_4$alkoxy, CrC$_4$haloalkoxy, CrC$_4$haloalkyl or CrC$_4$alkyl,

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C$_1$-C$_4$alkoxy, C$_1$-C$_4$haloalkoxy, C$_1$-C$_4$haloalkyl, C$_1$-C$_4$alkyl, nitrile, -S(0)$_2$C$_1$-C$_4$alkyl or -OH,
-CrC$_4$alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, C$_1$-C$_4$alkoxy, CrC$_4$haloalkoxy, CrC$_4$haloalkyl, C$_1$-C$_4$alkyl, nitrile, -S(0)$_2$CrC$_4$alkyl or -OH,
-C$_3$-C$_5$cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC$_4$alkoxy, C$_1$-C$_4$haloalkoxy, CrC$_4$haloalkyl, CrC$_4$alkyl, nitrile, -S(0)$_2$CrC$_4$alkyl or -OH,

5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, CrC$_4$alkoxy, CrC$_4$haloalkoxy, CrC$_4$haloalkyl or CrC$_4$alkyl, and

-CrC$_4$alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, CrC$_4$alkoxy, CrC$_4$haloalkoxy, CrC$_4$haloalkyl or CrC$_4$alkyl.

15. The compound or a pharmaceutically acceptable salt thereof according to any proceeding claim, wherein the compound is formula III

X is C,
Y is C,

R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen and halogen;

R is selected from group consisting of
- C₁-C₄alkyl optionally substituted with halogen, C₁-C₄alkoxy, -CN or -OH,
- C₃-C₇cycloalkyl optionally substituted with halogen, C₁-C₄alkyl, -CrC₄alkylCr
C₄alkoxy, C₁-C₄alkoxy, C₁-C₄haloalkyl, nitrile, -S(0)₂CrC₄alkyl or -OH,
- Ce-Cioaryl, wherein the aryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or C₁-C₄alkyl,
- CrC₄alkyl-C6-Cioaryl, wherein the aryl is optionally substituted with one or more halogen, CrC₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or CrC₄alkyl,
- 4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC₄alkoxy, C₁-C₄haloalkoxy, C₁-C₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH,
- CrC₄alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH,
- C₃-C₅cycloalkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatoms selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl, C₁-C₄alkyl, nitrile, -S(0)₂CrC₄alkyl or -OH,
- 5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, CrC₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or CrC₄alkyl, and
- CrC₄alkyl-5 to 10 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heteroaryl is optionally substituted with one or more halogen, C₁-C₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or C₁-C₄alkyl.

16. The compound or a pharmaceutically acceptable salt thereof according to any preceding claim, wherein the compound is formula III, wherein

X is C,
Y is C,
R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen and halogen;

R is selected from group consisting of

4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC₄alkoxy, CrC₄haloalkoxy, CrC₄haloalkyl or CrC₄alkyl,

-CrC₄alkyl-4 to 7 membered heterocyclyl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, CrC₄alkoxy, C₁-C₂haloalkoxy, CrC₂haloalkyl or C₁-C₂alkyl,

-C₃-C₇cycloalkyl optionally substituted with halogen, C₁-C₂alkyl, -CrC₄alkylCr

C₄alkoxy, C₁-C₂alkoxy, CrC₄haloalkyl or -OH, and

-CrC₄alkyl optionally substituted with halogen, C₁-C₂alkoxy, -CN or -OH .

17. The compound or a pharmaceutically acceptable salt thereof according to any preceding claim, wherein the compound is formula III,

wherein

X is C,

Y is C,

R¹, R², R⁴ or R⁵ are independently selected from the group consisting of hydrogen and halogen;

R is selected from group consisting of
18. The compound of claim 12, represented by formula III, wherein:
   - $X$ is C;
   - $Y$ is C;
   - $R^1$, $R^2$, $R^4$, or $R^5$ are independently selected from the group consisting of hydrogen, halogen, $-\text{CH}_3$, and C-haloalkyl;
   - $R^3$ is $L-R$;
   - $L$ is a divalent bond, or $-\text{CH}_2$;
   - $R$ is halogen, $-\text{CrC}_4$alkyl optionally substituted with halogen, $\text{CrC}_4$alkoxy, $-\text{CN}$ or $-\text{OH}$, $-\text{CN}$, $-\text{CrC}_4$alkoxy optionally substituted with halogen or $\text{CrC}_4$alkoxy, or
   - $R^2$ and $R^3$ taken together form a 4 to 7 membered heteroaryl containing 1 to 3 heteroatom selected from N, S, and O, wherein said heterocyclyl is optionally substituted with one or more halogen, $\text{C}_1\text{-C}_4$alkoxy, $\text{C}_1\text{-C}_4$haloalkoxy, $\text{Cl-C}_4$haloalkyl or $\text{C}_1\text{-C}_4$alkyl.

19. The compound according to claim 12, wherein
   - $L$ is a direct bond;
   - $R$ is selected from group consisting of $\text{Br}$, $\text{F}$, and
20. A pharmaceutical composition, comprising the compound according to any of claims 1-19 and a pharmaceutically acceptable carrier.

21. A pharmaceutical combination composition, comprising:
   a compound according to any of claims 1-19,
   an antibacterial effective amount of a second therapeutic agent, and
   a pharmaceutically acceptable carrier.

22. The pharmaceutical combination composition according to claim 21, wherein the second therapeutic agent is selected from the group consisting of Ampicillin, Piperacillin, Penicillin G, Ticarcillin, Imipenem, Meropenem, Azithromycin, erythromycin, Aztreonam, Cefepime, Cefotaxime, Ceftriaxone, Cefatazidime, Ciprofloxacin, Levofoxacin, Clindamycin, Doxycycline, Gentamycin, Amikacin, Tobramycin, Tetracycline, Tegacyclin, Rifampicin, Vancomycin and Polymyxin.

23. A method of inhibiting a deacetylase enzyme in a Gram-negative bacterium, comprising contacting the Gram-negative bacteria with a compound according to any one of claims 1-19.

24. A method for treating a subject with a Gram-negative bacterial infection, comprising:
   administering to the subject in need thereof an antibacterial effective amount of the compound according to any one of claims 1-19 and a pharmaceutically acceptable carrier.

25. The method of claim 24, wherein the Gram-negative bacterial infection is an infection comprising at least one bacterium selected from the group consisting of Pseudomonas, Stenotrophomonas maltophilia, Burkholderia, Alcaligenes xylosoxidans, Acinetobacter, Enterobacteriaceae, Haemophilus, Moraxella, Bacteroids, Fransicella, Shigella, Proteus, Vibrio, Salmonella, Bordetella, Helicobactor, Legionella, Citrobactor, Serratia, Campylobactor, Yersinia and Neisseria.

26. The method of claim 25, wherein the bacterium is a Enterobacteriaceae which is selected from the group consisting of Serratia, Proteus, Klebsiella, Enterobacter, Citrobacter, Salmonella, Providencia, Morganella, Cedecea, Yersinia, and Edwardsiella species and Escherichia coli.
27. A compound according to any one of claims 1-19 or a pharmaceutically acceptable salt thereof, for use as a medicament.

28. The compound according to claim 27, for use in treatment of a Gram-negative bacterial infection.

29. The compound according to claims 28 or a pharmaceutically acceptable salt thereof for use in treatment of a Gram-negative bacterial infection, wherein the Gram-negative bacterial infection is caused by a bacterium selected from Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Burkholderia cepacia, Alcaligenes xylosoxidans, Acinetobacter, Enterobacteriaceae, Haemophilus, and Neisseria species.

30. Use of the compound according to any one of claims 1-19, for the preparation of a medicament for the treatment of a Gram-negative bacterial infection in a subject, wherein the bacterial infection is selected from Pseudomonas aeruginosa, Stenotrophomonas maltophilia, Burkholderia cepacia, Alcaligenes xylosoxidans, Acinetobacter, Enterobacteriaceae, Haemophilus, and Neisseria species.

31. The use of claim 30, wherein the bacterial infection is an Enterobacteriaceae selected from the group consisting of Serratia, Proteus, Klebsiella, Enterobacter, Citrobacter, Salmonella, Providencia, Morganella, Cedecea, and Edwardsiella species and Escherichia coli.
## A. CLASSIFICATION OF SUBJECT MATTER

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## B. FIELDS SEARCHED

- Minimum documentation searched (classification system followed by classification symbols)
  - C07D A61K A61P

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

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

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Date of the actual completion of the international search: 12 December 2014

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