

Description

Title of Invention: TETRAHYDROPYRIDINE DERIVATIVES AND THEIR USE AS ANTIBACTERIAL AGENTS

Technical Field

- [1] This application claims the benefit of priority under 35 U.S.C. §119(e) to U.S. Provisional patent application serial No. 62/400,694 filed September 28, 2016, which is incorporated herein by reference.
- [2] The present disclosure relates to novel tetrahydropyridine derivatives that are useful for the treatment of bacterial infections, especially Gram-negative infections. The present disclosure also relates to methods of using such compounds in the treatment of bacterial infections in mammals, to use thereof for the preparation of medicaments for treating bacterial infections, and to pharmaceutical compositions containing such compounds.

Background Art

- [3] Infection by Gram-negative bacteria such as Extended Spectrum β -lactamase producing (ESBL) Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* is a major health problem, especially in the case of hospital-acquired infections. In addition, there is an increasing level of resistance to current antibiotic therapies, which severely limits treatment options.
- [4] Gram-negative bacteria are unique in that their outer membrane contains lipopolysaccharide (LPS), which is crucial for maintaining membrane integrity, and is essential for bacterial viability (Rev. Biochem 76: 295-329, 2007). The major lipid component of LPS is Lipid A and inhibition of Lipid A biosynthesis is lethal to bacteria. Lipid A synthesized on the cytoplasmic surface of the bacterial inner membrane via a pathway that consists of nine different enzymes. These enzymes are highly conserved in most Gram-negative bacteria. LpxC is the enzyme that catalyzes the first committed step in the Lipid A biosynthetic pathway, the removal of the N-acetyl group of UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine. LpxC is a Zn²⁺ dependent enzyme that has no mammalian homologue, making it a good target for the development of novel antibiotics.

Disclosure of Invention

Technical Problem

- [5] It is an object of the present disclosure to provide tetrahydropyridine derivatives capable of inhibiting UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC) and treating Gram-negative bacterial infections, stereoisomers thereof, or pharmaceutically acceptable salts thereof.

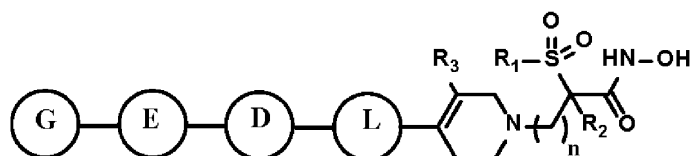
- [6] Another object of the present disclosure is to provide methods for preparing the compounds.
- [7] Still another object of the present disclosure is to provide methods for inhibiting UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC), which comprise administering a therapeutically effective amount of the compounds.
- [8] Still another object of the present disclosure is to provide methods for treating Gram-negative bacterial infections, which comprise administering a therapeutically effective amount of the compounds.
- [9] Still another object of the present disclosure is to provide the use of the compounds for the preparation of therapeutic medicaments for treating Gram-negative bacterial infections.
- [10] Still another object of the present disclosure is to provide pharmaceutical compositions for prevention or treatment of Gram-negative bacterial infections, which contain the compounds.

Solution to Problem

- [11] The present inventors have discovered novel tetrahydropyridine derivatives, which have UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC) inhibitory activity, and have found that these compounds can be used for treating Gram-negative bacterial infections, thereby completing the present invention.
- [12] **Tetrahydropyridine derivative compounds**
- [13] To achieve the above objects, the present disclosure provides a tetrahydropyridine derivative compound represented by the following formula I, a stereoisomer thereof, or a pharmaceutically acceptable salt thereof:

[14] [Formula I]

[15]



- [16] n is 1, 2 or 3;
- [17] R₁ is C1-C6 alkyl or C1-C6 haloalkyl;
- [18] R₂ is hydrogen or C1-C6 alkyl;
- [19] R₃ is hydrogen, C1-C6 alkyl, C1-C6 alkoxy, -OH or halogen;
- [20] L is C3-C7 cycloalkyl, aryl, heteroaryl or null, wherein at least one H of C3-C7 cycloalkyl, aryl or heteroaryl may be substituted with halogen, C1-C6 alkyl, C1-C6 haloalkyl, -NR_AR_B or -OH;
- [21] D is C≡C, C3-C7 cycloalkyl, aryl, heteroaryl or null, wherein at least one H of C3-C7 cycloalkyl, aryl or heteroaryl may be substituted with halogen, C1-C6 alkyl,

- C1-C6 haloalkyl, $-NR_AR_B$ or $-OH$;
- [22] E is $C\equiv C$, C3-C7 cycloalkyl, aryl, heteroaryl or null, wherein at least one H of C3-C7 cycloalkyl, aryl or heteroaryl may be substituted with halogen, C1-C6 alkyl, C1-C6 haloalkyl, $-NR_AR_B$ or $-OH$;
- [23] G is C1-C6 alkyl, C3-C7 cycloalkyl, 4-6 membered heterocycloalkyl, aryl or heteroaryl,
- [24] wherein at least one H of C1-C6 alkyl may be substituted with halogen, $-NR_AR_B$, $-OH$ or $-OR_C$,
- [25] at least one H of C3-C7 cycloalkyl or 4-6 membered heterocycloalkyl may be substituted with C1-C6 alkyl, C1-C6 alkyl- $-NR_AR_B$, C1-C6 hydroxyalkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 alkyl- $-OR_C$, $-NR_AR_B$, $-OH$, $-(C=O)-C1-C6$ alkyl or $-S(=O)_2-C1-C6$ alkyl,
- [26] at least one H of aryl or heteroaryl may be substituted with C1-C6 alkyl, C1-C6 hydroxyalkyl, C1-C6 alkyl- $-NR_AR_B$, halogen, nitro, cyano, $-NR_AR_B$, $-OH$, $-OR_C$, $-S(=O)_2-C1-C6$ alkyl, $-S(=O)_2-NR_AR_B$ or $-N-S(=O)_2-C1-C6$ alkyl;
- [27] R_A and R_B are each independently hydrogen or C1-C6 alkyl, or R_A and R_B may be linked together to form 4-6 membered ring, wherein the 4-6 membered ring may have O or S atom and at least one H of the 4-6 membered ring may be substituted with halogen, $-OH$ or C1-C6 hydroxyalkyl;
- [28] R_C is C1-C6 alkyl, C1-C6 hydroxyalkyl, $-(C=O)-NR_DR_E$ or $-S(=O)_2-C1-C6$ alkyl; and
- [29] R_D and R_E are each independently hydrogen or C1-C6 alkyl.
- [30] In one aspect,
- [31] n is 1 or 2;
- [32] R_1 is C1-C6 alkyl;
- [33] R_2 is C1-C6 alkyl;
- [34] R_3 is hydrogen;
- [35] L is aryl, heteroaryl or null, wherein at least one H of aryl or heteroaryl may be substituted with halogen, C1-C6 alkyl or C1-C6 haloalkyl;
- [36] D is $C\equiv C$ or null;
- [37] E is $C\equiv C$ or null;
- [38] G is C1-C6 alkyl, C3-C7 cycloalkyl, 4-6 membered heterocycloalkyl, aryl or heteroaryl,
- [39] wherein at least one H of C1-C6 alkyl may be substituted with halogen, $-NR_AR_B$, $-OH$ or $-OR_C$,
- [40] at least one H of 4-6 membered heterocycloalkyl may be substituted with C1-C6 alkyl, $-(C=O)-C1-C6$ alkyl or $-S(=O)_2-C1-C6$ alkyl,
- [41] at least one H of aryl or heteroaryl may be substituted with C1-C6 alkyl, C1-C6 hydroxyalkyl, C1-C6 alkyl- $-NR_AR_B$, halogen, nitro, cyano, $-NR_AR_B$, $-OH$, $-OR_C$, $-S(=O)_2-$

C1-C6 alkyl or $-S(=O)_2-NR_AR_B$;

- [42] R_A and R_B are each independently hydrogen or C1-C6 alkyl, or R_A and R_B may be linked together to form 4-6 membered ring, wherein the 4-6 membered ring may have O atom and at least one H of the 4-6 membered ring may be substituted with C1-C6 hydroxyalkyl;
- [43] R_C is C1-C6 alkyl, C1-C6 hydroxyalkyl, $-(C=O)-NR_DR_E$ or $-S(=O)_2-C1-C6$ alkyl; and
- [44] R_D and R_E are each independently hydrogen.
- [45] In another aspect,
- [46] n is 1 or 2;
- [47] R_1 is C1-C6 alkyl;
- [48] R_2 is C1-C6 alkyl;
- [49] R_3 is hydrogen;
- [50] L is phenyl, pyridinyl or null, wherein at least one H of phenyl or pyridinyl may be substituted with halogen, C1-C6 alkyl or C1-C6 haloalkyl;
- [51] D is $C\equiv C$ or null;
- [52] E is $C\equiv C$ or null;
- [53] G is C1-C6 alkyl, C3-C6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, pyridinyl, furanyl, thiophenyl or imidazolyl,
- [54] wherein at least one H of C1-C6 alkyl may be substituted with halogen, $-NR_AR_B$, -OH or $-OR_C$,
- [55] at least one H of 4-6 membered heterocycloalkyl may be substituted with C1-C6 alkyl, $-(C=O)-C1-C6$ alkyl or $-S(=O)_2-C1-C6$ alkyl,
- [56] at least one H of phenyl, pyridinyl, furanyl, thiophenyl or imidazolyl may be substituted with C1-C6 alkyl, C1-C6 hydroxyalkyl, C1-C6 alkyl- NR_AR_B , halogen, nitro, cyano, $-NR_AR_B$, -OH, $-OR_C$, $-S(=O)_2-C1-C6$ alkyl or $-S(=O)_2-NR_AR_B$;
- [57] R_A and R_B are each independently hydrogen or C1-C6 alkyl, or R_A and R_B may be linked together to form 4-6 membered ring, wherein the 4-6 membered ring may have O atom and at least one H of the 4-6 membered ring may be substituted with C1-C6 hydroxyalkyl;
- [58] R_C is C1-C6 alkyl, C1-C6 hydroxyalkyl, $-(C=O)-NR_DR_E$ or $-S(=O)_2-C1-C6$ alkyl; and
- [59] R_D and R_E are each independently hydrogen.
- [60] As used herein, including the claims, the following terms have the meaning defined below, unless specifically indicated otherwise.
- [61] The term "alkyl" refers to a branched or straight chained hydrocarbon containing from 1 to 10 carbon atoms unless otherwise specified. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl or n-decyl.

- [62] The term "alkoxy" refer to hydrogen atom of a hydroxyl group is substituted with alkyl. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, neopentyloxy or isopentyloxy.
- [63] The term "alkynyl" refers to straight chain hydrocarbon group containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited to, acetylene, propynyl, butynyl, pentynyl, hexynyl or heptynyl.
- [64] The term "aryl" refer to mono-, bi- or other multicarbocyclic aromatic ring system. Representative examples of aryl include, but are not limited to, phenyl, biphenyl, naphthyl, as well as benzo-fused carbocyclic moieties.
- [65] The term "heteroaryl" refer to mono-, bi or other multicarbocyclic aromatic ring system containing one or more heteroatoms selected from O, N, or S. Representative examples of heteroaryl include, but are not limited to, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, furyl, furanyl, thiophenyl, pyridinyl, pyrimidinyl, oxazolyl, oxadiazolyl, isoxazolyl, indolyl, quinolyl, isoquinolyl, benzimidazolyl, benzothienyl or benzofuryl.
- [66] The term "cycloalkyl" refer to a saturated cyclic hydrocarbon ring of 3 to 8 carbon atoms. Representative examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.
- [67] The term "heterocyclic" refer to a cyclic group containing one or more heteroatoms selected from O, N, or S. Representative examples of heterocyclic include, but are not limited to, azetidiny, tetrahydrofuranyl, imidazolidinyl, pyrrolidinyl, piperidinyl, piperazinyl, oxazolidinyl, thiazolidinyl, pyrazolidinyl, morpholinyl, thio-morpholinyl, oxaziny or tetrahydropyridinyl.
- [68] The term "pharmaceutically acceptable" means the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.
- [69] The term "stereoisomer" means compounds that possess one or more chiral centers and each center may exist in the R or S configuration. Stereoisomers include all diastereomeric, enantiomeric and epimeric forms as well as racemates and mixtures thereof.
- [70] In some aspect, the novel tetrahydropyridine derivatives selective from the group consisting of the following compounds:
- [71] 1)
4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [72] 2) N-

- hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(phenylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [73] 3) N-hydroxy-4-(4-(4-((4-methoxyphenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [74] 4) 4-(4-(4-(cyclopropylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [75] 5) N-hydroxy-4-(4-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [76] 6) 4-(4-(4-(hex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [77] 7) 4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [78] 8) N-hydroxy-4-(4-(4-(3-hydroxybut-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [79] 9) 4-(4-(4-(cyclopentylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [80] 10) 4-(4-(4-(cyclohexylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [81] 11) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [82] 12) 4-(4-(4-(3-cyclohexylprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [83] 13) N-hydroxy-2-methyl-4-(4-(4-(4-methylpent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide;
- [84] 14) 4-(4-(4-(5-chloropent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

- [85] 15) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [86] 16) 4-(4-(4-(3-(diethylamino)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [87] 17) N-hydroxy-4-(4-(4-(3-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [88] 18) N-hydroxy-4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [89] 19) 5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl methanesulfonate;
- [90] 20) 4-(4-(4-(5-(dimethylamino)pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [91] 21) 4-(4-(4-(5-aminopent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [92] 22) N-hydroxy-4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [93] 23) N-hydroxy-4-(4-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [94] 24) N-hydroxy-4-(4-(4-(3-(3-hydroxypropoxy)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [95] 25) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-morpholinoprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [96] 26) 3-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)prop-2-yn-1-yl carbamate;
- [97] 27) 5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydr

- opyridin-4-yl)phenyl)pent-4-yn-1-yl carbamate;
- [98] 28) N-hydroxy-4-(4-(4-(5-methoxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [99] 29) N-hydroxy-4-(4-(4-(6-hydroxyhex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [100] 30) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(6-morpholinohex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [101] 31) 4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [102] 32) 4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3,5-difluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [103] 33) 4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-2-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [104] 34) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(thiophen-2-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [105] 35) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-((4-nitrophenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [106] 36) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-3-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [107] 37) N-hydroxy-4-(4-(4-((4-hydroxyphenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [108] 38) N-hydroxy-2-methyl-4-(4-(4-((1-methyl-1H-imidazol-4-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide;
- [109] 39) N-hydroxy-2-methyl-4-(4-(4-((1-methylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide;
- [110] 40)

- 4-(4-(4-((1-acetylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [111] 41) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-((1-(methylsulfonyl)azetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [112] 42) 4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [113] 43) 4-(4-(3-fluoro-4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [114] 44) 4-(4-(4-(cyclopropylbuta-1,3-diyn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [115] 45) 4-(4-(4-(5-(dimethylamino)penta-1,3-diyn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [116] 46) N-hydroxy-4-(4-(4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [117] 47) N-hydroxy-4-(4-(4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [118] 48) N-hydroxy-4-(4-(4-(5-hydroxypenta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [119] 49) 4-(4-(4-(5-(dimethylamino)penta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [120] 50) N-hydroxy-4-(4-(4-(5-methoxypenta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [121] 51) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(phenylbuta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [122] 52) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(pyridin-4-ylethynyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

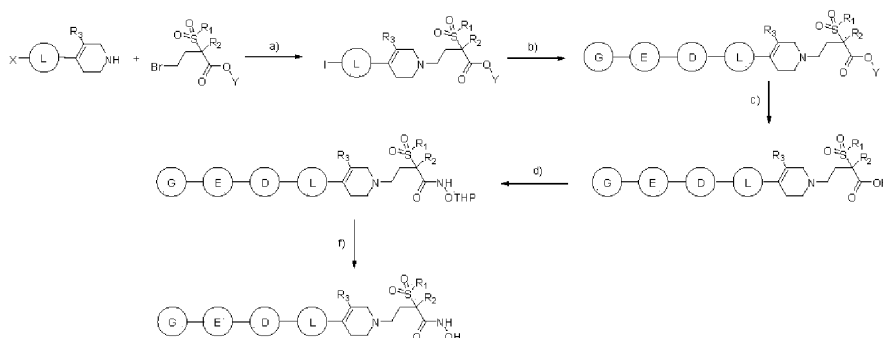
- [123] 53)
4-(4-((4-bromophenyl)ethynyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [124] 54) N-
hydroxy-4-(4-(7-hydroxyhepta-1,3-diyn-1-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [125] 55) N-
hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [126] 56)
4-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [127] 57)
4-(4-(4'-chloro-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [128] 58)
4-(4-(4'-fluoro-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [129] 59) N-
hydroxy-4-(4-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [130] 60)
4-(4-(3'-fluoro-4'-methoxy-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [131] 61) N-
hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [132] 62)
4-(4-(4-(6-fluoropyridin-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [133] 63)
4-(4-(4-(furan-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [134] 64) N-
hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [135] 65) N-
hydroxy-4-(4-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-

- 2-methyl-2-(methylsulfonyl)butanamide;
- [136] 66)
4-(4-(4'-cyano-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [137] 67) N-
hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-pentyl-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [138] 68)
4-(4-(4'-(azetidin-1-ylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [139] 69)
4'-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)-[1,1'-biphenyl]-4-yl methanesulfonate;
- [140] 70) N-
hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(thiophen-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [141] 71) N-
hydroxy-4-(4-(4-(3-methoxythiophen-2-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [142] 72) N-
hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(4-methylthiophen-2-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [143] 73)
4-(4-(4'-(ethylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- [144] 74) N-
hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-(morpholinomethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- [145] 75) N-
hydroxy-4-(6-(3-methoxyprop-1-yn-1-yl)-3',6'-dihydro-[3,4'-bipyridin]-1'(2'H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- [146] 76)
3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide;
- [147] 77)
4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-methylphenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide; and
- [148] 78)

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-(trifluoromethyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide.

- [149] In the present disclosure, the pharmaceutically acceptable salts are preferably acid addition salts formed with pharmaceutically acceptable free acids. Free acids that may be used in the present disclosure include organic acids and inorganic acids. The inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc, and the organic acids include citric acid, oxalic acid, acetic acid, lactic acid, maleic acid, coumaric acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, 4-toluenesulfonic acid, trifluoroacetic acid, glutamic acid, aspartic acid, etc.
- [150] In addition, the compounds of formula I or pharmaceutically acceptable salts thereof can show polymorphism, and can also exist as solvates (e.g., hydrates, etc.). Furthermore, the compounds of the present disclosure can also exist as individual stereoisomer or mixtures of stereoisomers.
- [151] **Methods for preparation of the tetrahydropyridine derivative compounds**
- [152] The present disclosure provides methods for the preparation of the tetrahydropyridine derivative compounds presented by formula I, stereoisomers thereof, or pharmaceutically acceptable salts thereof.
- [153] The compounds of the present disclosure can be prepared in accordance with one or more of schemes discussed below.
- [154] These methods can be used either directly or with obvious variations to trained chemists to prepare key intermediates and certain compounds of this invention
- [155] Suitable synthetic sequence are readily selected per specific structures of this invention, but within the art known to individuals practicing organic synthesis, such as method summarized in available chemistry data bases, as in CAS Scifinder and Elsevier Reaxys. Based on these general methods, the enablement for making the compounds of the present disclosure is straightforward and can be practiced within a common professional knowledge.
- [156] Some general synthetic methods to prepare the compounds of the present disclosure are illustrated below.
- [157] [General Procedure 1]

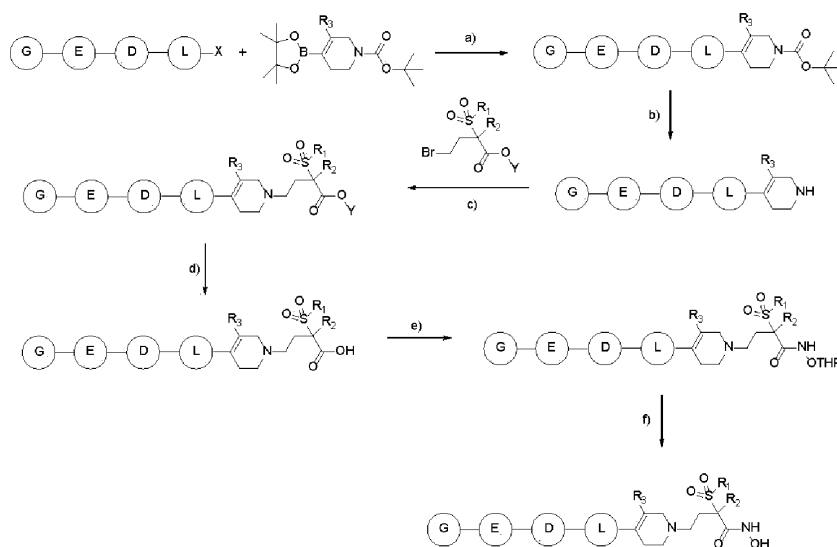
[158]



[159] a) Et₃N, DMF; b) boronic acid, Pd(PPh₃)₂Cl₂, K₂CO₃, 1,4-Dioxane, H₂O, heat or Acetylene, Pd(PPh₃)₂Cl₂, Et₃N, CuI, DMF, heat; c) LiOH, THF, MeOH, H₂O; e) HATU, HOBT, Et₃N, NH₂-OTHP, DMF; f) HCl, MeOH

[160] [General Procedure 2]

[161]



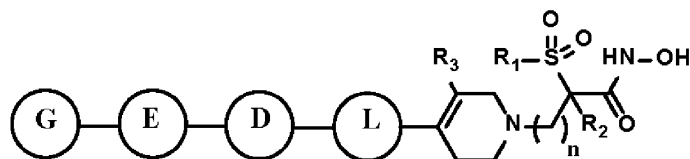
[162] a) Pd(PPh₃)₂Cl₂, K₂CO₃, 1,4-Dioxane, H₂O, heat; b) TFA, Dichloromethane; c) Et₃N, DMF; d) LiOH, THF, MeOH, H₂O; e) HATU, HOBT, Et₃N, NH₂-OTHP, DMF; f) HCl, MeOH

[163] **Use of the tetrahydropyridinederivative compounds**

[164] The present invention provides a pharmaceutical composition for preventing or treating bacterial infections, which contains a pharmaceutically acceptable carrier and, as an active ingredient, a compound represented by the following formula I, a stereoisomer thereof or a pharmaceutically acceptable salt thereof:

[165] [Formula I]

[166]



[167] wherein formula I is as defined above.

[168] The compounds of formula I according to the present disclosure, the stereoisomers thereof, or the pharmaceutically acceptable salts thereof, exhibit antibacterial activity, especially against Gram-negative organisms and are therefore suitable to treat bacterial infections in mammals, especially humans. They may therefore be used for the prevention or treatment of bacterial infection caused by Gram-negative bacteria, especially those caused by susceptible and multi-drug resistant Gram-negative bacteria. Examples of such Gram-negative bacteria include *Acinetobacter baumannii*, *Acinetobacter* spp., *Achromobacter* spp., *Aeromonas* spp., *Bacteroides* spp., *Bordetella* spp., *Borrelia* spp., *Brucella* spp., *Campylobacter* spp., *Chlamydia* spp., *Citrobacter* spp., *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Francisella tularensis*, *Fusobacterium* spp., *Haemophilus influenza* (beta-lactamase positive and negative), *Helicobacter pylori*, *Klebsiella oxytoca*, *Klebsiella pneumonia* (including those encoding extended-spectrum beta-lactamases (hereinafter "ESBLs")), *Legionella pneumophila*, *Moraxella catarrhalis* (beta-lactamase positive and negative), *Morganella morganii*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Proteus vulgaris*, *Porphyromonas* spp., *Prevotella* spp., members of the *Enterobacteriaceae* that express ESBLs KPCs, CTX-M, metallo-beta-lactamase, and AmpC-type beta-lactamases that confer resistance to currently available cephalosporins, cephamycins, carbapenems, and beta-lactam/beta-lactamase inhibitor combination, *Mannheimia haemolyticus*, *Pasteurella* spp., *Proteus mirabilis*, *Providencia* spp., *Pseudomonas aeruginosa* (including ceftazidime-, cefpirome- and cefepime-resistant *P. aeruginosa*, carbapenem-resistant *P. aeruginosa* or quinolone-resistant *P. aeruginosa*), *Pseudomonas* spp., *Salmonella* spp., *Shigella* spp., *Serratia marcescens*, *Treponema* spp., *Burkholderia cepacia*, *Vibrio* spp., *Yersinia* spp., and *Stenotrophomonas maltophilia*.

[169] In a more specific embodiment, examples of such Gram-negative bacteria include *Acinetobacter baumannii*, *Acinetobacter* spp., *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumonia*, *Serratia marcescens*, *Pseudomonas aeruginosa* and members of the *Enterobacteriaceae* and *Pseudomonas* that express ESBLs, KPSs, CTX-M, metallo-beta-lactamases, and AmpC-type beta-lactamases that confer resistance to currently available cephalosporins, cephamycins, carbapenems, and beta-lactam/beta-lactamase inhibitor combinations.

- [170] The compounds of formula I according to the present disclosure or the stereoisomers, or the pharmaceutically acceptable salts thereof, may therefore be used for the prevention or treatment of bacterial infection selected from nosocomial pneumonia, urinary tract infections, systemic infections (such as bacteraemia and sepsis), skin and soft tissue infections, surgical infections, intraabdominal infections, lung infections (including those in patients with cystic fibrosis), endocarditis, diabetic foot infection, osteomyelitis, and central nervous system infections.
- [171] The compounds of formula I according to the present disclosure or the stereoisomers display intrinsic antibacterial properties and have the ability to improve permeability of the outer membrane of Gram-negative bacteria to other antibacterial agents. Their use in combination with another antibacterial agent might offer some further advantages such as lowered side-effects of drugs due to lower doses used or shorter time of treatment, more rapid cure of infection shortening hospital stays, increasing spectrum of pathogens controlled, and decreasing incidence of development of resistance to antibiotics. The antibacterial agent for use in combination with a compound of formula I according to the present disclosure will be selected from the group consisting a penicillin antibiotic (such as ampicillin, piperacillin, penicillin G, amoxicillin, or tetracillin), a cephalosporin antibiotic (such as ceftriaxone, ceftazidime, cefepime, cefotaxime), a carbapenem antibiotic (such as imipenem, or meropenem), a monobactam antibiotic (such as aztreonam), a fluoroquinolone antibiotic (such as ciprofloxacin, moxifloxacin or levofloxacin), a macrolide antibiotics (such as erythromycin or azithromycin), an aminoglycoside antibiotic (such as amikacin, gentamycin or tobramycin), a glycopeptide antibiotic (such as vancomycin or teicoplanin), a tetracycline antibiotics (such as tetracycline), and linezolid, clindamycin, telavancin, daptomycin, novobiocin, rifampicin and polymyxin.
- [172] In order to exhibit this antibacterial activity, the compounds need to be administered in a therapeutically effective amount. A "therapeutically effective amount" is meant to describe a sufficient quantity of the compound to treat the infection, at a reasonable benefit/risk ratio applicable to any such medical treatment. It will be understood, however, that the attending physician, within the scope of sound medical judgment, will decide the total daily dosage of the compound. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorders; the activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. As a general guideline however, the total daily dose will typically range from about 0.1mg/kg/day to

about 5,000mg/kg/day in single or in divided doses. Typically, dosages for humans will range from about 10mg to about 3,000mg per day, in a single or multiple doses.

- [173] Any route typically used to treat infectious illness, including oral, parenteral, topical, rectal, transmucosal, and intestinal, can be used to administer the compounds. Parenteral administrations include injections to generate a systemic effect or injections directly into the afflicted area. Examples of parenteral administrations are subcutaneous, intravenous, intramuscular, intradermal, intrathecal, and intraocular, intranasal, intraventricular injections or infusions techniques. Topical administrations include the treatment of areas readily accessible by local application, such as, for example, eyes, ears including external and middle ear infections, vaginal, open wound, skin including the surface skin and the underneath dermal structures, or other lower intestinal tract. Transmucosal administration includes nasal aerosol or inhalation applications.
- [174] The present disclosure also provides a method of inhibiting UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC), comprising administering to a patient in need thereof a therapeutically effective amount of the compound represented by formula I, stereoisomer thereof or pharmaceutically acceptable salt thereof according to the present disclosure. In some embodiments, the present disclosure provides a method of inhibiting UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC), comprising contact a cell (e.g., in vivo or in vitro) with a therapeutically effective amount of the compound represented by formula I, stereoisomer thereof or pharmaceutically acceptable salt thereof according to the present disclosure.
- [175] The present disclosure also provides a method for treating bacterial infections, comprising administering to a patient in need thereof a therapeutically effective amount of the compound represented by formula I, stereoisomer thereof or pharmaceutically acceptable salt thereof according to the present disclosure.
- [176] The present disclosure also provides the use of the compound represented by formula I, stereoisomer thereof or pharmaceutically acceptable salt thereof according to the present disclosure in preparation of a medicament for treating bacterial infections.

Advantageous Effects of Invention

- [177] The compounds represented by formula I, stereoisomers thereof or pharmaceutically acceptable salts thereof according to the present disclosure can exhibit excellent effects on the treatment bacterial infections.

Mode for the Invention

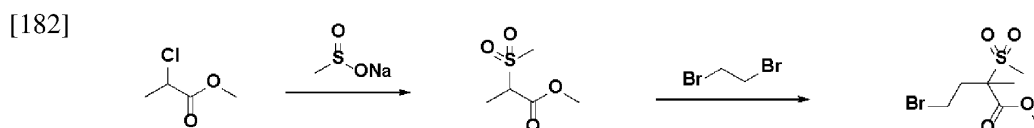
- [178] **Examples**

- [179] Embodiments of the present disclosure are described in the following examples,

which are meant to illustrate and not limit the scope of this invention. Common abbreviations well known to those with ordinary skills in the synthetic used throughout.

[180] All chemical reagents were commercially available. Flash column chromatography means silica gel chromatography unless specified otherwise, which was performed on Teledyne Combiflash-RF-200 system. ^1H NMR spectra (δ , ppm) are recorded on 400MHz or 600MHz instrument. Mass spectroscopy data for a positive ionization method are provided.

[181] **Preparation 1: Synthesis of Intermediate 1 {methyl 4-bromo - 2-methyl-2-(methylsulfonyl)butanoate }**



[183] Step 1: Synthesis of methyl 2-(methylsulfonyl)propanoate

[184] To a solution of methyl 2-chloropropionate (150g, 1eq) in MeOH (500ml) was added with sodium methanesulfinate (162g, 1.3eq) and stirred for 20hr at 77°C. The mixture was cooled down to room temperature and precipitated solid was filtered off through celite. The filtrate was concentrated in vacuo and the residue was suspended in ethyl acetate (100ml) / hexane (500ml). After then, the precipitated solid was filtered off and the filtrate was concentrated in vacuo to prepare the title compound (162g, 80%).

[185] ^1H NMR (600 MHz, CDCl_3 -d1); δ 3.90 (q, $J=7.2\text{Hz}$, 1H), 3.82 (s, 3H), 3.03 (s, 3H), 1.66 (d, $J=6.6\text{Hz}$, 3H).

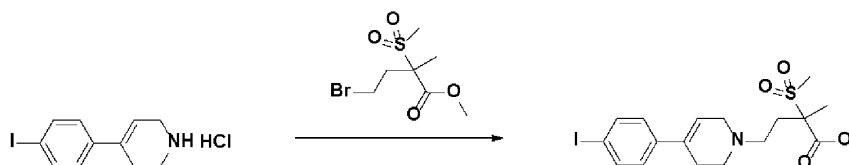
[186] Step 2: Synthesis of methyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate

[187] To a suspended solution of sodium hydride (60%, 33.7g, 2eq) in DMF (300ml) was dropwised with methyl 2-(methylsulfonyl)propanoate (70g, 1eq) in DMF (100ml) at 0°C and stirred for 30min. After then, the mixture was added with 1,2-dibromoethane (158g, 2eq) and stirred for 6hr at room temperature. The mixture was quenched with sat. aq. NH_4Cl , extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (225mg, 43%).

[188] ^1H NMR (600 MHz, CDCl_3 -d1); δ 3.81 (s, 3H), 3.49-3.45(m, 1H), 3.35-3.31 (m, 1H), 3.01 (s, 3H). 2.78-2.73 (m, 1H), 2.53-2.48 (m, 1H), 1.62 (s, 3H)

[189] **Preparation 2: Synthesis of Intermediate 2 {methyl 4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate }**

[190]

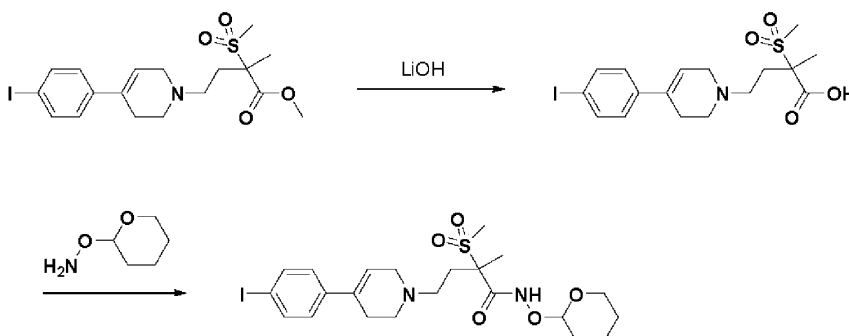


[191] To a solution of 4-(4-iodophenyl)-1,2,3,6-tetrahydropyridine hydrochloride (10g, 1eq) in a mixture of DMF (100ml) / MeOH (50ml) was added with methyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (12.74g, 1.5eq), N,N-diisopropylethylamine (16.3ml, 3eq) and stirred for 24hr at 60°C. The mixture was cooled down to room temperature, extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (11g, 74%).

[192] ¹H NMR (600 MHz, CDCl₃-d₁); δ7.68 (d, *J*=7.8 Hz, 2H), 7.10 (d, *J*=8.4 Hz, 2H), 5.98 (s, 1H), 4.20-4.14 (m, 1H), 3.88 (d, *J*=6.0 Hz, 3H), 3.72-3.66 (m, 1H), 3.62-3.48 (m, 2H), 3.46-3.36 (m, 1H), 3.30-3.14 (m, 2H), 3.13 (d, *J*=6.6 Hz, 3H), 2.94-2.84 (m, 1H), 2.80-2.65 (m, 2H), 1.76 (d, *J*=6.6 Hz, 3H).

[193] **Preparation 3: Synthesis of Intermediate 3**
{4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide}

[194]



[195] Step 1: Synthesis of 4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid

[196] To a solution of methyl 4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (2g, 1eq) in a mixture of THF (8ml) / MeOH (2ml) was added with 2N-LiOH (12.6mL, 3eq) solution and stirred for 2hr at room temperature. The solvent was removed under reduced pressure and the residue was diluted with water (10ml), adjusted the pH to 4.0. The water was concentrated in vacuo and the residue was

column chromatography to prepare the title compound (1.76g, 91%).

[197] ¹H NMR (600MHz, DMSO-d₆); δ 7.72-7.70 (m, 2H), 7.28-7.26 (m, 2H), 6.21 (s, 1H), 3.68-3.64 (m, 2H), 3.25-3.01 (m, 4H), 2.65-2.62 (m, 2H), 2.29-2.19 (m, 2H), 1.45 (s, 3H).

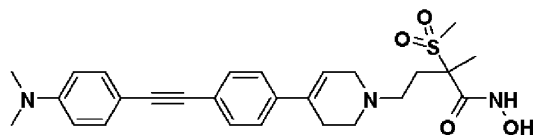
[198] Step 2: Synthesis of 4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide

[199] To a solution of 4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid (1.76g, 1eq) in DMF (10ml) was added with HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (2.02g, 1.4eq), HOBT (Hydroxybenzotriazole) (0.81g, 1.4eq), Et₃N (1.6ml, 3eq), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine hydrochloride (1.17g, 2eq) and stirred for 1hr at room temperature. The mixture was extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (0.6g, 28%).

[200] ¹H NMR (600MHz, DMSO-d₆); δ 11.58 (bs, 1H), 7.66-7.64 (m, 2H), 7.22-7.20 (m, 2H), 6.17 (s, 1H), 4.85-4.81 (m, 1H), 3.31-3.04 (m, 5H), 2.60-2.59 (m, 2H), 2.47-2.39 (m, 6H), 1.85-1.62 (m, 2H), 1.47-1.41 (s, 7H).

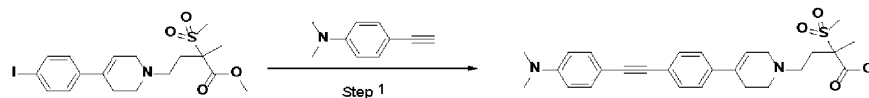
[201] **Example 1: Synthesis of 4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide**

[202]



[203] Step 1: Synthesis of methyl 4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

[204]



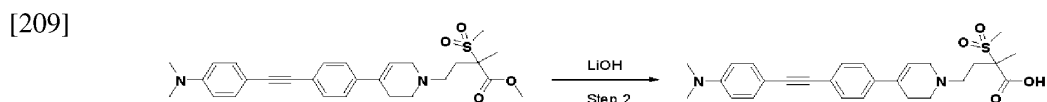
[205] To a solution of methyl 4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 2) (500mg, 1eq) in a mixture of THF (10ml)/toluene (10ml) was

added with CuI (20mg, 0.1eq), Pd(PPh₃)₂Cl₂ (74mg, 0.1eq), Et₃N (0.442ml, 3eq) and 4-ethynyl-N,N-dimethylaniline (228mg, 1.5eq) and stirred for 12hr at room temperature. The mixture was extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (225mg, 43%).

[206] ¹H NMR (600MHz, CDCl₃-d₁): δ7.43 (d, *J*=8.4Hz, 2H), 7.39 (d, *J*=9Hz, 2H), 7.32 (d, *J*=9Hz, 2H), 6.65 (d, *J*=8.4Hz, 2H), 6.08 (s, 1H), 3.87 (s, 3H), 3.24-3.22 (m, 1H), 3.07-3.05 (m, 1H), 3.04 (s, 3H), 2.98 (s, 6H), 2.82-2.76 (m, 1H), 2.67-2.56 (m, 4H), 2.62-2.58 (m, 2H), 2.03-2.00 (m, 1H), 1.63 (s, 3H).

[207] MS (ESI, *m/z*): 495.3 [M+H]⁺.

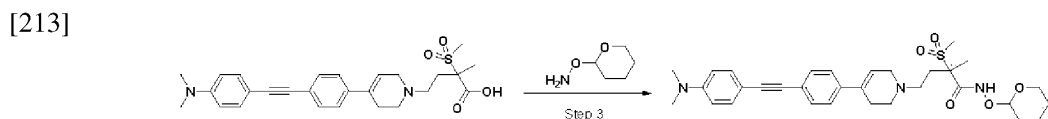
[208] Step 2: Synthesis of
4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid



[210] To a solution of methyl
4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (225mg, 1eq) in a mixture of THF (8ml)/ MeOH (2ml) was added with 2N-LiOH (0.68mL, 3eq) solution and stirred for 2hr at room temperature. The solvent was removed under reduced pressure and the residue was diluted with water (6ml), adjusted the pH to 4.0. The precipitated solid was filtered off to prepare the title compound (190mg, 87%), which was used for next step without further purification.

[211] MS (ESI, *m/z*): 481.2 [M+H]⁺.

[212] Step 3: Synthesis of
4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide



[214] (dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid (190mg, 1eq) in DMF (10ml) was added with HATU (210mg, 1.4eq), HOBT (85mg, 1.4eq), Et₃N (0.17ml, 3eq), O-((tetrahydro-2H-pyran-2-yl)hydroxylamine hydrochloride (121mg, 2eq) and stirred for 1hr at room temperature. The mixture was extracted with ethyl acetate and water. The

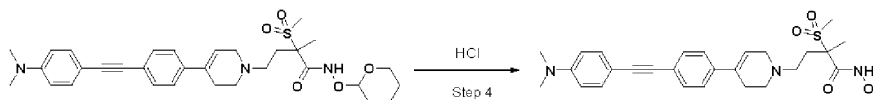
organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (200mg, 87%).

[215] MS (ESI, m/z): 580.3 $[\text{M}+\text{H}]^+$.

[216] Step 4: Synthesis of

4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[217]



[218] To a solution of

4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide (200mg, 1eq) in MeOH (6ml) was added with HCl solution in MeOH (1.25N, 0.83ml, 3eq) and stirred for 2hr at room temperature. The solvent was removed under reduced pressure and the residue was diluted with water (6ml), adjusted the pH to 7.0. The water was concentrated in vacuo and the resulting residue was purified with column chromatography to prepare the title compound (40mg, 24%).

[219] ^1H NMR (600MHz, $\text{DMSO}-d_6$): δ 11.02 (bs, 1H), 9.08 (bs, 1H), 7.42-7.39 (m, 4H), 7.32 (d, $J=8.4\text{Hz}$, 2H), 6.68 (d, $J=9\text{Hz}$, 2H), 6.21 (s, 1H), 3.12-3.08 (m, 2H), 3.04 (s, 3H), 2.92 (s, 6H), 2.67-2.56 (m, 2H), 2.47-2.39 (m, 4H), 2.36-2.28 (m, 1H), 1.85-1.80 (m, 1H), 1.44 (s, 3H).

[220] MS (ESI, m/z): 496.2 $[\text{M}+\text{H}]^+$.

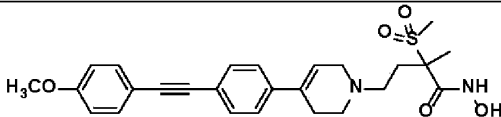
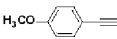
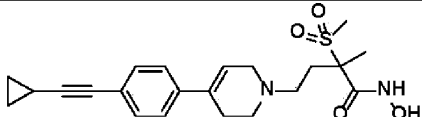
[221] **[Examples 2-14]**

[222] The terminal acetylenes listed in the following table were used to prepare compounds of Examples 2-14 in the same manner as Example 1.

[223]

Example	Structure (Name)	Terminal acetylene
2		

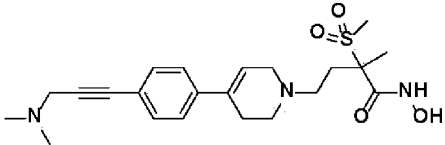
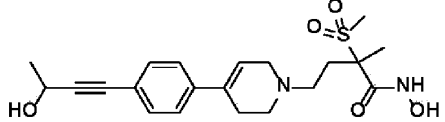
[224]

	(N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(phenylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.00 (bs, 1H), 9.09 (bs, 1H), 7.52-7.39 (m, 9H), 6.23 (s, 1H), 3.34-3.28 (m, 6H), 3.09-3.03 (m, 2H), 3.03 (s, 3H), 2.63-2.57 (m, 2H), 1.44 (s, 3H). MS (ESI, m/z): 453.2 [M+H]⁺.	
3	 (N-hydroxy-4-(4-(4-(4-methoxyphenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.10 (bs, 1H), 7.47-7.43 (m, 6H), 6.99-6.95 (m, 2H), 6.23 (s, 1H), 3.76 (s, 3H), 3.13-3.06 (m, 2H), 3.04 (s, 3H), 2.65-2.54 (m, 2H), 2.46-2.40 (m, 4H), 2.36-2.28 (m, 1H), 1.85-1.81 (m, 1H), 1.44 (s, 3H). MS (ESI, m/z): 483.2 [M+H]⁺. 	
4	 (4-(4-(4-(cyclopropylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.09 (bs, 1H), 7.36-7.35 (m, 2H), 7.28-7.27 (m, 2H), 6.17 (s, 1H), 3.10-3.04 (m, 2H), 3.03 (s, 3H), 2.63-2.54 (m, 2H), 2.46-2.39 (m, 4H), 2.31-2.26 	

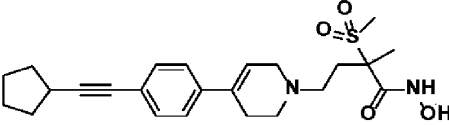
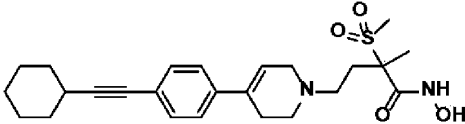
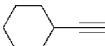
[225]

	(m, 1H), 1.83-1.77 (m, 1H), 1.53-1.47 (m, 1H), 1.44 (s, 3H), 0.86-0.82 (m, 2H), 0.70-0.65 (m, 2H). MS (ESI, m/z): 417.1 [M+H] ⁺ .	
5	(N-hydroxy-4-(4-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.03 (bs, 1H), 9.13 (bs, 1H), 7.41-7.39 (m, 2H), 7.34-7.33 (m, 2H), 6.21 (s, 1H), 4.91 (m, 1H), 3.59-3.54 (m, 2H), 3.18-3.11 (m, 2H), 3.06 (s, 3H), 2.80-2.74 (m, 4H), 2.56-2.54 (m, 2H), 2.48-2.42 (m, 2H), 2.38-2.33 (m, 1H), 1.86-1.83 (m, 1H), 1.47 (s, 3H). MS (ESI, m/z): 421.2 [M+H]⁺.	
6	(4-(4-(4-(hex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.00 (bs, 1H), 9.08 (bs, 1H), 7.39-7.35 (m, 2H), 7.29-7.28 (m, 2H), 6.17 (s, 1H), 3.34-3.31 (m, 2H), 3.10-3.01 (m, 5H), 2.60-2.35 (m, 2H), 2.48-2.06 (m, 6H), 1.48-1.29 (m, 7H), 0.97-0.88 (m, 3H). MS (ESI, m/z): 433.2 [M+H]⁺.	

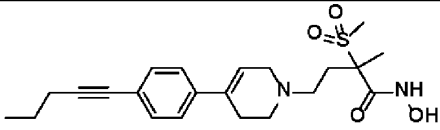
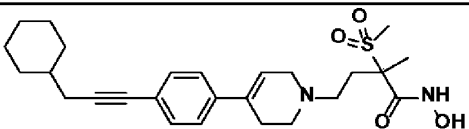
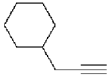
[226]

7	 (4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.03 (bs, 1H), 9.13 (bs, 1H), 7.43-7.42 (m, 2H), 7.39-7.37 (m, 2H), 6.21 (s, 1H), 3.45-3.43 (m, 2H), 3.14-3.09 (m, 2H), 3.06 (s, 3H), 2.67-2.57 (m, 2H), 2.49-2.40 (m, 4H), 2.34-2.26 (m, 2H), 2.23 (s, 6H), 1.46 (s, 3H). MS (ESI, m/z): 434.2 [M+H]⁺.	
8	 (N-hydroxy-4-(4-(4-(3-hydroxybut-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.03 (bs, 1H), 9.12 (bs, 1H), 7.43 (d, J=7.8Hz, 2H), 7.35 (d, J=9.0Hz, 2H), 6.22 (s, 1H), 5.46 (d, J=5.4Hz, 1H), 4.58 (m, 1H), 3.50 (s, 2H), 3.15-3.07 (m, 2H), 3.06 (s, 3H), 2.67-2.57 (m, 2H), 2.48-2.42 (m, 4H), 2.36-2.32 (m, 1H), 1.84-1.80 (m, 1H), 1.46 (s, 3H), 1.37 (d, J=6.0Hz, 3H). MS (ESI, m/z): 421.10 [M+H]⁺.	

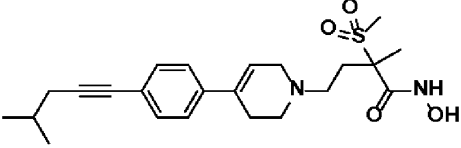
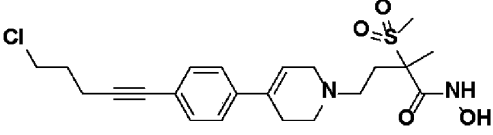
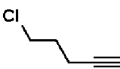
[227]

9	 (4-(4-(4-(cyclopentylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.03 (bs, 1H), 9.13 (bs, 1H), 7.39 (d, J=8Hz, 2H), 7.31 (d, J=8.8Hz, 2H), 6.19 (s, 1H), 3.85-3.83 (m, 2H), 3.07-3.04 (m, 4H), 2.81-2.79 (m, 1H), 2.61-2.58 (m, 2H), 2.47-2.44 (m, 3H), 2.00-1.95 (m, 2H), 1.84-1.81 (m, 2H), 1.76-1.74 (m, 2H), 1.62-1.52 (m, 4H), 1.46 (s, 3H). MS (ESI, m/z): 445.1 [M+H]⁺.	
10	 (4-(4-(4-(cyclohexylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.09 (bs, 1H), 7.37 (d, J=8.4Hz, 2H), 7.29 (d, J=7.8Hz, 2H), 6.17 (s, 1H), 3.10-3.01 (m, 5H), 2.66-2.54 (m, 3H), 2.46-2.39 (m, 5H), 2.31-2.28 (m, 1H), 1.81-1.78 (m, 3H), 1.67-1.64 (m, 2H), 1.48-1.41 (m, 5H), 1.33-1.28 (m, 3H). MS (ESI, m/z): 459.2 [M+H]⁺.	

[228]

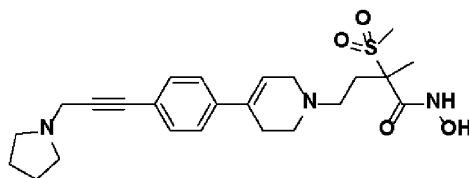
11	 (N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.09 (bs, 1H), 7.37-7.36 (m, 2H), 7.31-7.29 (m, 2H), 6.17 (s, 1H), 3.10-3.04 (m, 2H), 3.03 (s, 3H), 2.63-2.54 (m, 2H), 2.51-2.49 (m, 1H), 2.45-2.39 (m, 3H), 2.36 (t, J=6.9Hz, 2H), 2.31-2.28 (m, 1H), 1.83-1.78 (m, 1H), 1.53-1.49 (m, 2H), 1.43 (s, 3H), 0.96 (t, J=7.8 Hz, 3H). MS (ESI, m/z): 419.1 [M+H]⁺.	
12	 (4-(4-(4-(3-cyclohexylprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.11 (bs, 1H), 7.38-7.36 (m, 2H), 7.31-7.29 (m, 2H), 6.19 (s, 1H), 3.18-3.03 (m, 5H), 2.65-2.48 (m, 2H), 2.51-2.43 (m, 2H), 2.32-2.31 (m, 2H), 1.79-1.61 (m, 6H), 1.59-1.40 (m, 4H), 1.24-1.18 (m, 2H), 1.13-1.06 (m, 2H), 1.04-0.98 (m, 2H). MS (ESI, m/z): 473.2 [M+H]⁺.	

[229]

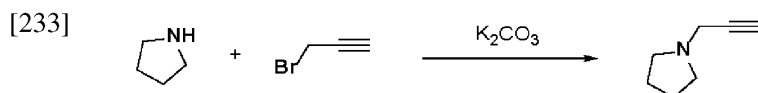
13	 (N-hydroxy-2-methyl-4-(4-(4-(4-methylpent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆) δ; 11.01 (bs, 1H), 9.10 (bs, 1H), 7.38-7.37 (m, 2H), 7.32-7.31 (m, 2H), 6.17 (s, 1H), 3.09-3.04 (m, 5H), 2.62-2.57 (m, 2H), 2.46-2.44 (m, 2H), 2.31-2.98 (m, 2H), 1.85-1.81 (m, 2H), 1.44 (s, 3H), 1.23-1.21 (m, 2H), 0.99-0.96 (m, 6H). MS (ESI, m/z): 433.2 [M+H]⁺.	
14	 (4-(4-(4-(5-chloropent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆) δ; 11.0 (bs, 1H), 9.15 (bs, 1H), 7.38-7.37 (m, 2H), 7.33-7.32 (m, 2H), 6.18 (s, 1H), 3.78 (t, J=7.2 Hz, 2H), 3.12-3.06 (m, 2H), 3.04 (s, 3H), 2.68-2.56 (m, 4H), 2.46-2.40 (m, 5H), 1.98-1.90 (m, 2H), 1.82-1.79 (m, 1H), 1.44 (s, 3H). MS (ESI, m/z): 453.2 [M+H]⁺.	

[230] **Example 15: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide**

[231]



[232] **Step 1: Synthesis of 1-(prop-2-yn-1-yl)pyrrolidine**



[234] To a solution of pyrrolidine (1.5ml, 1eq) in toluene (30ml) was added with K_2CO_3 (4.97g, 2eq) and 3-bromoprop-1-yne (2.4ml, 1.5eq). The mixture was stirred for 15hr at room temperature and filtered off, and the filtrate was concentrated in vacuo. The resulting residue was purified with column chromatography to prepare the title compound (0.32g, 16%).

[235] MS (ESI, m/z): 110.1 [M+H]⁺.

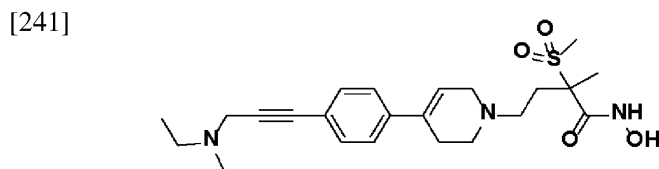
[236] Step 2: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide

[237] The title compound was prepared the procedures described for the synthesis of Example 1 using 1-(prop-2-yn-1-yl)pyrrolidine.

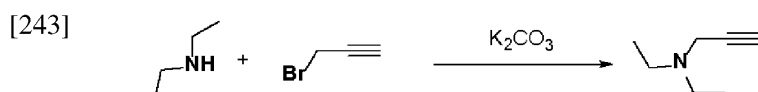
[238] ¹H NMR (600MHz, DMSO-d₆): δ 11.03 (bs, 1H), 9.14 (bs, 1H), 7.45-7.36 (m, 4H), 6.22 (s, 1H), 3.63 (s, 2H), 3.18-3.04 (m, 5H), 2.70-2.56 (m, 6H), 2.48-2.41 (m, 4H), 2.37-2.31 (m, 1H), 1.87-1.80 (m, 1H), 1.77-1.68 (m, 4H), 1.46 (s, 3H).

[239] MS (ESI, m/z): 460.2 [M+H]⁺.

[240] **Example 16: Synthesis of 4-(4-(4-(3-(diethylamino)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide**



[242] Step 1: Synthesis of N,N-diethylprop-2-yn-1-amine



[244] To a solution of diethylamine (0.46ml, 1eq) in toluene (10ml) was added with K_2CO_3 (1.23g, 2eq) and 3-bromoprop-1-yne (0.56ml, 1.5eq). The mixture was stirred for 15hr at room temperature and filtered off, and the filtrate was concentrated in vacuo. The resulting residue was purified with column chromatography to prepare the title compound (0.46g, 94%).

[245] MS (ESI, m/z): 112.1 [M+H]⁺.

[246] Step 2: Synthesis of 4-(4-(4-(3-(diethylamino)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydr

oxy-2-methyl-2-(methylsulfonyl)butanamide

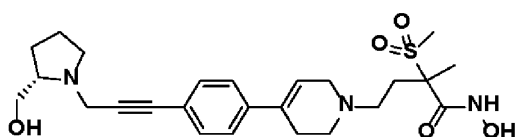
[247] The title compound was prepared the procedures described for the synthesis of Example 1 using N,N-diethylprop-2-yn-1-amine.

[248] ¹H NMR (600MHz, DMSO-d₆); δ 11.02 (bs, 1H), 9.15 (bs, 1H), 7.43-7.37 (m, 4H), 6.22 (s, 1H), 3.70-3.62 (m, 2H), 3.32-3.08 (m, 2H), 3.05 (s, 3H), 2.84-2.78 (m, 6H), 2.74-2.58 (m, 5H), 1.89-1.85 (m, 1H), 1.45 (s, 3H), 1.11-0.96 (m, 6H).

[249] MS (ESI, m/z): 462.2 [M+H]⁺.

[250] **Example 17: Synthesis of N-hydroxy-4-(4-(4-(3-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[251]



[252] Step 1: Synthesis of (R)-(1-(prop-2-yn-1-yl)pyrrolidin-2-yl)methanol

[253]



[254] To a solution of 3-bromoprop-1-yne (3g, 1eq) in toluene (30ml) was added with (R)-pyrrolidin-2-ylmethanol (3.73ml, 1.5eq) and K₂CO₃ (6.97g, 2eq). The mixture was stirred for 15hr at room temperature and extracted with ethyl acetate and water. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (2g, 57%).

[255] ¹H NMR (600MHz, CDCl₃-d₁); δ 3.65-3.51 (m, 2H), 3.45-3.41 (m, 2H), 3.04-3.01 (m, 1H), 2.87-2.84 (m, 1H), 2.71-2.67 (m, 1H), 2.20-2.19 (m, 1H), 1.93-1.72 (m, 4H).

[256] **Step 2: Synthesis of N-hydroxy-4-(4-(4-(3-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[257] The title compound was prepared the procedures described for the synthesis of Example 1 using (R)-(1-(prop-2-yn-1-yl)pyrrolidin-2-yl)methanol.

[258] ¹H NMR (600MHz, DMSO-d₆); δ 11.04 (bs, 1H), 9.21 (bs, 1H), 7.48-7.40 (m, 4H), 6.26 (s, 1H), 3.55-3.52 (m, 2H), 3.36-3.33 (m, 4H), 3.09-3.08 (m, 4H), 2.89 (s, 3H), 2.69-2.58 (m, 4H), 1.95-1.87 (m, 1H), 1.79-1.62 (m, 6H), 1.49 (s, 3H).

[259] MS (ESI, m/z): 490.2[M+H]⁺.

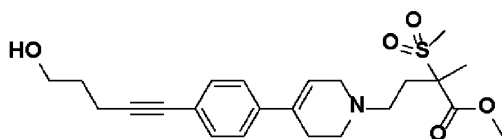
[260] **Example 18: Synthesis of N-hydroxy-4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[261] Step 1: Synthesis of methyl

4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(

methylsulfonyl)butanoate

[262]



[263]

To a solution of methyl 4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 2) (2g, 1eq) in a mixture of THF (20ml)/toluene (20ml) was added with CuI (79.8mg, 0.1eq), Pd(PPh₃)₂Cl₂ (295mg, 0.1eq), Et₃N (1.75ml, 3eq) and pent-4-yn-1-ol (705mg, 2eq). The mixture was stirred for 12hr at room temperature and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (1.5g, 83%).

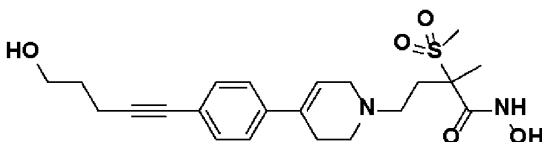
[264]

¹H NMR (600MHz, CDCl₃-d₁); δ7.33-7.32 (m, 2H), 7.28-7.27 (m, 2H), 6.05 (s, 1H), 3.82-3.79 (m, 2H), 3.75-3.72 (m, 3H), 3.69 (s, 3H), 3.05 (s, 3H), 2.70-2.62 (m, 1H), 2.53 (t, *J*=7.2 Hz, 3H), 2.38 (t, *J*=6.0 Hz, 3H), 1.78-1.64 (m, 4H), 1.64 (s, 3H).

[265]

Step 2 - 4: Synthesis of N-hydroxy-4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide

[266]



[267]

The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate.

[268]

¹H NMR (600MHz, CD₃OD-d₄); δ11.04 (bs, 1H), 9.13 (bs, 1H), 7.43-7.38 (m, 2H), 7.33-7.28 (m, 2H), 6.19 (s, 1H), 4.52 (bs, 1H), 3.54-3.50 (m, 2H), 3.17-3.15 (m, 2H), 3.06 (s, 3H), 2.64-2.54 (m, 2H), 2.48-2.38 (m, 4H), 1.90-1.84 (m, 2H), 1.69-1.57 (m, 4H), 1.46 (s, 3H).

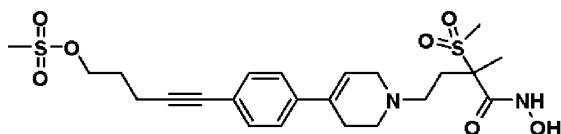
[269]

MS (ESI, *m/z*): 435.0 [M+H]⁺.

[270]

Example 19: Synthesis of 5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl methanesulfonate

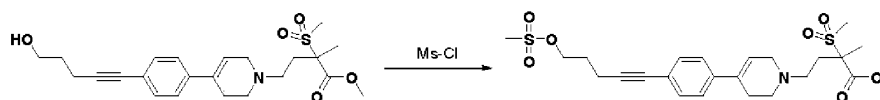
[271]



[272]

Step 1: Synthesis of methyl
2-methyl-2-(methanesulfonyl)-4-(4-(4-(5-((methanesulfonyl)oxy)pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoate

[273]



[274]

To a solution of methyl
4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methanesulfonyl)butanoate (1.5g, 1eq) in dichloromethane (17.3ml) was added with Et₃N (0.964ml, 2eq) and methanesulfonyl chloride (0.793ml, 2eq). The mixture was stirred for 2hr at room temperature and extracted with dichloromethane and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (0.9g, 51%).

[275]

¹H NMR (600MHz, CDCl₃); δ7.34-7.32 (m, 2H), 7.29-7.27 (m, 2H), 6.04 (s, 1H), 4.40 (t, J=6.0 Hz, 2H), 3.72-3.70 (m, 3H), 3.13 (s, 6H), 3.06 (s, 3H), 3.03 (s, 3H), 2.70-2.62 (m, 1H), 2.59-2.56 (m, 3H), 2.05-2.01 (m, 3H), 1.71-1.62 (m, 4H).

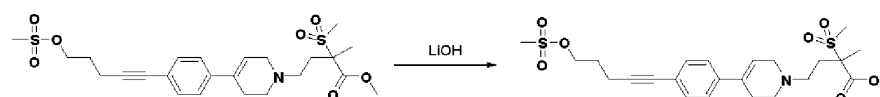
[276]

MS (ESI, m/z): 512.2 [M+H]⁺.

[277]

Step 2: Synthesis of
2-methyl-2-(methanesulfonyl)-4-(4-(4-(5-((methanesulfonyl)oxy)pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoic acid

[278]



[279]

The title compound was prepared the procedures described for the synthesis of
Example 1, step 2 from methyl
2-methyl-2-(methanesulfonyl)-4-(4-(4-(5-((methanesulfonyl)oxy)pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoate.

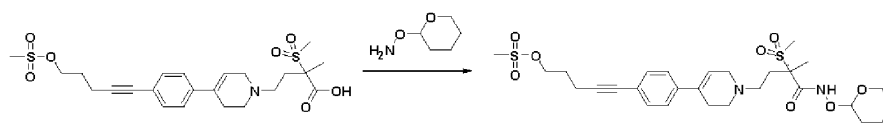
[280]

MS (ESI, m/z): 498.2 [M+H]⁺.

[281]

Step 3: Synthesis of
5-(4-(1-(3-methyl-3-(methanesulfonyl)-4-oxo-4-(((tetrahydro-2H-pyran-2-yl)oxy)amino)butyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl methanesulfonate

[282]



[283] The title compound was prepared the procedures described for the synthesis of Example 1, step 3 from

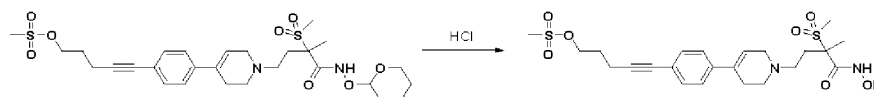
2-methyl-2-(methylsulfonyl)-4-(4-(4-(5-((methylsulfonyl)oxy)pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoic acid.

[284] MS (ESI, m/z): 597.2 [M+H]⁺.

[285] Step 4: Synthesis of

5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl methanesulfonate

[286]



[287] The title compound was prepared the procedures described for the synthesis of Example 1, step 4 from

5-(4-(1-(3-methyl-3-(methylsulfonyl)-4-oxo-4-(((tetrahydro-2H-pyran-2-yl)oxy)amino)butyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl methanesulfonate.

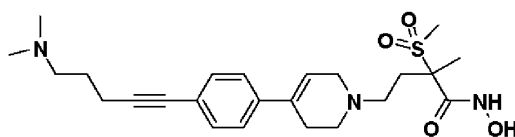
[288] ¹H NMR (600MHz, DMSO-d₆): δ 11.01 (bs, 1H), 9.10 (bs, 1H), 7.47-7.32 (m, 4H), 6.25 (s, 1H), 4.38-4.31 (m, 2H), 3.19 (s, 3H), 3.10-3.09 (m, 2H), 3.06 (s, 3H), 2.66-2.56 (m, 2H), 2.54-2.94 (m, 8H), 1.98-1.85 (m, 2H), 1.46 (s, 3H).

[289] MS (ESI, m/z): 513.1 [M+H]⁺.

[290] **Example 20: Synthesis of**

4-(4-(4-(5-(dimethylamino)pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[291]



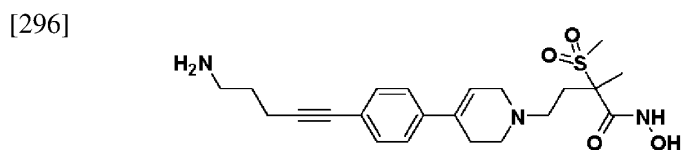
[292] To a solution of

5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl methanesulfonate (Example 19) (120mg, 1eq) in THF (3ml) was added with dimethylamine (1M in THF, 7ml, 30eq). The mixture was refluxed for 4hr and cooled room temperature, and the solvent was concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (38mg, 35%).

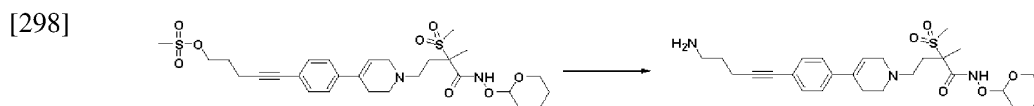
[293] ^1H NMR (600MHz, DMSO- d_6); δ 10.6 (bs, 1H), 9.2 (bs, 1H), 7.38-7.37 (m, 2H), 7.31-7.30 (m, 2H), 6.18 (s, 1H), 3.12-3.06 (m, 2H), 3.04 (s, 3H), 2.63-2.56 (m, 2H), 2.46-2.40 (m, 6H), 2.32-2.26 (m, 3H), 2.11 (s, 6H), 1.82-1.79 (m, 1H), 1.66-1.61 (m, 2H), 1.44 (s, 3H).

[294] MS (ESI, m/z): 462.2 $[\text{M}+\text{H}]^+$.

[295] **Example 21: Synthesis of 4-(4-(4-(5-aminopent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide**



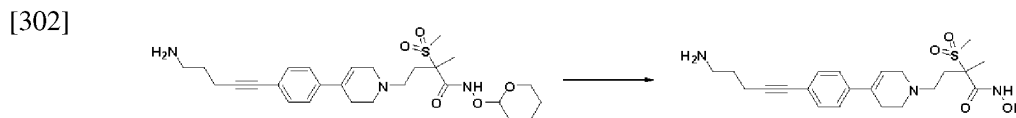
[297] Step 1: Synthesis of 4-(4-(4-(5-aminopent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide



[299] To a solution of 5-(4-(1-(3-methyl-3-(methylsulfonyl)-4-oxo-4-(((tetrahydro-2H-pyran-2-yl)oxy)amino)butyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl methanesulfonate (Example 19, step 3) (200mg, 1eq) in 1,4-dioxane (0.67ml) was added with ammonia (0.5M in 1,4-dioxane, 6.7ml, 10eq). The mixture was refluxed for 12hr and cooled room temperature, and the solvent was concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (80mg, 46%).

[300] MS (ESI, m/z): 518.3 $[\text{M}+\text{H}]^+$.

[301] Step 2: Synthesis of 4-(4-(4-(5-aminopent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide



[303] The title compound was prepared the procedures described for the synthesis of Example 1, step 4 from 4-(4-(4-(5-aminopent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide.

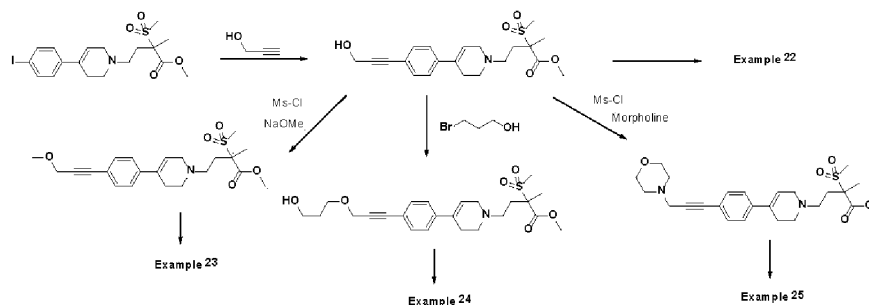
[304] ^1H NMR (600MHz, DMSO- d_6); δ 7.38-7.36 (m, 2H), 7.32-7.31 (m, 2H), 6.18 (s, 1H),

3.09-3.06 (m, 2H), 3.04 (s, 3H), 2.82 (t, $J=7.2$ Hz, 2H), 2.62-2.56 (m, 3H), 2.45-2.42 (m, 6H), 2.38-2.32 (m, 1H), 1.98-1.95 (m, 1H), 1.74-1.71 (m, 3H), 1.44 (s, 3H).

[305] MS (ESI, m/z): 434.2 $[M+H]^+$.

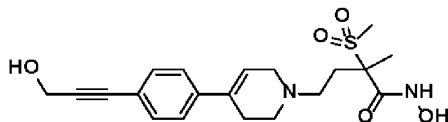
[306] **[Examples 22 - 25]**

[307]



[308] **Example 22: Synthesis of N-hydroxy-4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[309]



[310] Step 1: Synthesis of methyl

4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

[311] The title compound was prepared the procedures described for the synthesis of Example 1, step 1 using prop-2-yn-1-ol.

[312] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$) δ : 7.38-7.36 (m, 2H), 7.31-7.29 (m, 2H), 6.05 (s, 1H), 4.49 (s, 2H), 3.80-3.70 (m, 4H), 3.48-3.30 (m, 2H), 3.07-3.02 (m, 5H), 2.68-2.56 (m, 4H), 1.70-1.64 (m, 4H).

[313] MS (ESI, m/z): 406.1 $[M+H]^+$.

[314] Step 2 - 4: Synthesis of N-

hydroxy-4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide

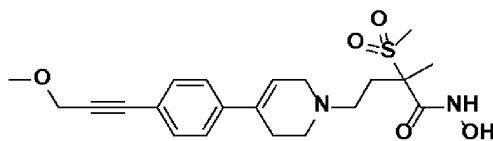
[315] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate.

[316] ^1H NMR (600MHz, DMSO-d_6): δ 11.00 (bs, 1H), 9.12 (bs, 1H), 7.40-7.35 (m, 4H), 6.16 (s, 1H), 5.31 (s, 1H), 4.37 (s, 2H), 3.40-3.34 (m, 2H), 3.07 (s, 3H), 2.95-2.92 (m, 2H), 2.86-2.85 (m, 2H), 2.64-2.56 (m, 4H), 2.14-2.10 (m, 2H), 1.59 (s, 3H).

[317] MS (ESI, m/z): 407.0 $[M+H]^+$.

- [318] **Example 23: Synthesis of N-hydroxy-4-(4-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[319]



- [320] Step 1: Synthesis of methyl 4-(4-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

- [321] To a solution of methyl 4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Example 22, Step 1) (500mg, 1eq) in dichloromethane (10ml) was added with Et₃N (0.34ml, 2eq) and methanesulfonyl chloride (0.19ml, 2eq). The mixture was and stirred for 2hr at room temperature. Sodium methoxide (25% solution in MeOH, 1.06g, 4eq) was added and stirred for 3hr at 60°C. The mixture was cooled down to room temperature, extracted with dichloromethane and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (250mg, 48%).

- [322] ¹H NMR (600MHz, CDCl₃-d1); δ7.42-7.41 (m, 2H), 7.32-7.30 (m, 2H), 6.02 (s, 1H), 4.31 (s, 2H), 3.90-3.79 (m, 3H), 3.48-3.42 (m, 4H), 3.14-3.08 (m, 5H), 2.70-2.62 (m, 3H), 1.78-1.68 (m, 3H), 1.64-1.52 (m, 4H).

- [323] MS (ESI, m/z): 420.1 [M+H]⁺.

- [324] Step 2: Sythesis of N-hydroxy-4-(4-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide

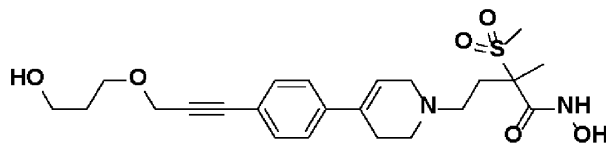
- [325] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 4-(4-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate.

- [326] ¹H NMR (600MHz, DMSO-d6); δ10.99 (bs, 1H), 9.10 (bs, 1H), 7.42-7.38 (m, 4H), 6.21 (s, 1H), 4.29 (s, 2H), 3.28-3.24 (m, 3H), 3.10-3.04 (m, 5H), 2.62-2.54 (m, 2H), 2.45-2.29 (m, 4H), 1.41 (s, 3H), 1.22-1.20 (m, 2H).

- [327] MS (ESI, m/z): 421.1 [M+H]⁺.

- [328] **Example 24: Synthesis of N-hydroxy-4-(4-(4-(3-(3-hydroxypropoxy)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[329]



[330]

Step 1: Synthesis of methyl 4-(4-(4-(3-(3-hydroxypropoxy)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

[331]

To a solution of methyl 4-(4-(4-(3-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Example 22, Step 1) (280mg, 1eq) in DMF (15ml) was added with NaH (47mg, 1.7eq, 60wt%) and 3-bromopropan-1-ol (125mg, 1.3eq). The mixture was stirred for 4hr at room temperature and extracted with ethyl acetate and water. The organic layer was dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (130g, 51%).

[332]

MS (ESI, m/z): 464.1 $[\text{M}+\text{H}]^+$.

[333]

Step 2: Synthesis of N-hydroxy-4-(4-(4-(3-(3-hydroxypropoxy)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide

[334]

The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 4-(4-(4-(3-(3-hydroxypropoxy)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate.

[335]

^1H NMR (600MHz, DMSO-d_6); δ 11.03 (bs, 1H), 9.13 (bs, 1H), 7.45-7.39 (m, 4H), 6.23 (s, 1H), 3.59-3.57 (m, 2H), 3.44-3.41 (m, 2H), 3.18-3.09 (m, 2H), 3.06 (s, 3H), 2.65-2.57 (m, 2H), 2.47-2.38 (m, 4H), 1.70-1.62 (m, 2H), 1.44 (s, 3H), 1.42-1.35 (m, 2H).

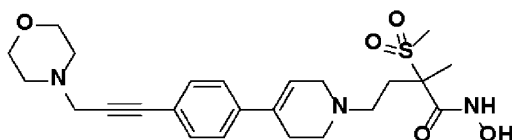
[336]

MS (ESI, m/z): 465.1 $[\text{M}+\text{H}]^+$.

[337]

Example 25: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-morpholinoprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide

[338]



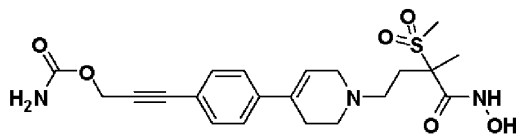
[339]

Step 1: Synthesis of methyl 2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-morpholinoprop-1-yn-1-yl)phenyl)-3,6-dihydr

opyridin-1(2H)-yl)butanoate

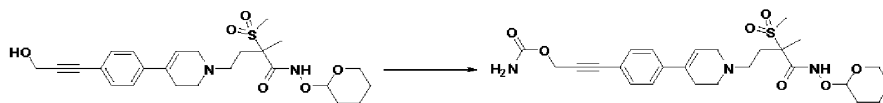
- [340] To a solution of methyl 4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Example 22, Step 1) (500mg, 1eq) in dichloromethane (10ml) was added with Et₃N (0.34ml, 2eq) and methanesulfonyl chloride (0.19ml, 2eq), and the mixture was stirred for 2hr at room temperature. Morpholine (0.22ml, 2eq) was added and stirred for 3hr at 60°C. The mixture was cooled room temperature and extracted with dichloromethane and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (450mg, 77%).
- [341] ¹H NMR (600MHz, CDCl₃-d1); δ7.38-7.36 (m, 2H), 7.31-7.29 (m, 2H), 6.06 (s, 1H), 4.49 (s, 2H), 3.78-3.74 (m, 6H), 3.70-3.64 (m, 2H), 3.54-3.44 (m, 2H), 3.22-3.18 (m, 2H), 3.05 (s, 3H), 2.78 (s, 3H), 2.72-2.62 (m, 6H), 2.58-2.48 (m, 2H), 1.72-1.62 (m, 4H).
- [342] MS (ESI, m/z): 475.2 [M+H]⁺.
- [343] Step 2: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-morpholinoprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide
- [344] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-morpholinoprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoate.
- [345] ¹H NMR (600MHz, DMSO-d6); δ11.00 (bs, 1H), 9.10 (bs, 1H), 7.41-7.39 (m, 2H), 7.37-7.35 (m, 2H), 6.19 (s, 1H), 3.62-3.56 (m, 4H), 3.48 (s, 2H), 3.14-3.07 (m, 2H), 3.06 (s, 3H), 2.64-2.52 (m, 4H), 2.46-2.38 (m, 5H), 2.32-2.26 (m, 1H), 2.00-1.96 (m, 1H), 1.82-1.76 (m, 1H), 1.44 (s, 3H).
- [346] MS (ESI, m/z): 476.2 [M+H]⁺.
- [347] **Example 26: Synthesis of 3-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)prop-2-yn-1-yl carbamate**

[348]



- [349] Step 1: Synthesis of 3-(4-(1-(3-methyl-3-(methylsulfonyl)-4-oxo-4-(((tetrahydro-2H-pyran-2-yl)oxy)amino)butyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)prop-2-yn-1-yl carbamate

[350]



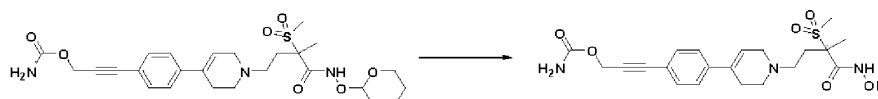
[351]

To a solution of 4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide (200mg, 1eq) in THF (10ml) was added with CDI (500mg, 8eq) and Et₃N (0.16ml, 3eq), and the mixture was stirred for 4hr at room temperature. NH₄OH (0.15ml, 10eq) was added and stirred for 2hr at 0°C. The mixture was extracted with ethyl acetate and water. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (50mg, 23%).

[352]

Step 2: Synthesis of 3-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)prop-2-yn-1-yl carbamate

[353]



[354]

The title compound was prepared the procedures described for the synthesis of Example 1, step 4 using 3-(4-(1-(3-methyl-3-(methylsulfonyl)-4-oxo-4-(((tetrahydro-2H-pyran-2-yl)oxy)amino)butyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)prop-2-yn-1-yl carbamate.

[355]

¹H NMR (600MHz, DMSO-d₆): δ 11.01 (bs, 1H), 9.09 (bs, 1H), 7.44-7.37 (m, 4H), 6.22 (s, 1H), 4.80 (s, 2H), 3.10-3.88 (m, 2H), 3.04 (s, 3H), 2.65-2.53 (m, 2H), 2.47-2.43 (m, 2H), 1.97-1.80 (m, 2H), 1.44 (s, 3H).

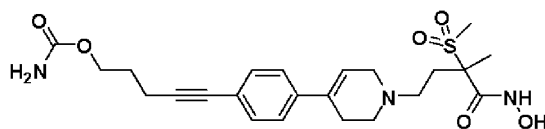
[356]

MS (ESI, m/z): 450.1 [M+H]⁺.

[357]

Example 27: Synthesis of 5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl carbamate

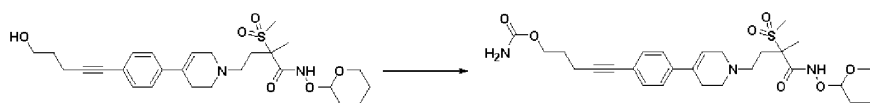
[358]



[359]

Step 1: Synthesis of 5-(4-(1-(3-methyl-3-(methylsulfonyl)-4-oxo-4-(((tetrahydro-2H-pyran-2-yl)oxy)amino)butyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl carbamate

[360]



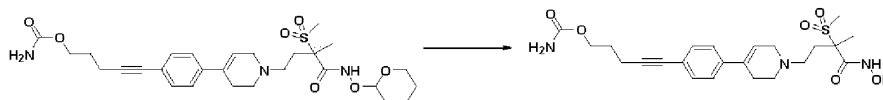
[361] The title compound was prepared the procedures described for the synthesis of Example 26, step 1 using

4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide.

[362] Step 2: Synthesis of

5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl carbamate

[363]



[364] The title compound was prepared the procedures described for the synthesis of Example 1, step 4 using of

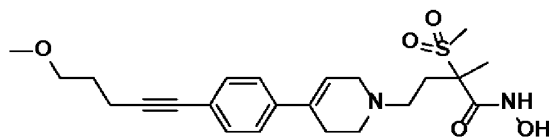
5-(4-(1-(3-methyl-3-(methylsulfonyl)-4-oxo-4-(((tetrahydro-2H-pyran-2-yl)oxy)amino)butyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl carbamate

[365] ^1H NMR (600MHz, DMSO- d_6): δ 11.01 (bs, 1H), 9.11 (bs, 1H), 7.38-7.37 (m, 2H), 7.32-7.31 (m, 2H), 6.18 (s, 1H), 3.98-3.97 (m, 2H), 3.09-3.04 (m, 5H), 2.62-2.57 (m, 2H), 2.48-2.46 (m, 2H), 2.30-2.28 (m, 2H), 1.81-1.78 (m, 4H), 1.44 (s, 3H), 1.23-1.21 (m, 2H).

[366] MS (ESI, m/z): 478.2 $[\text{M}+\text{H}]^+$.

[367] **Example 28: Synthesis of** N-hydroxy-4-(4-(4-(5-methoxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide

[368]



[369] The title compound was prepared the procedures described for the synthesis of Example 23 from methyl

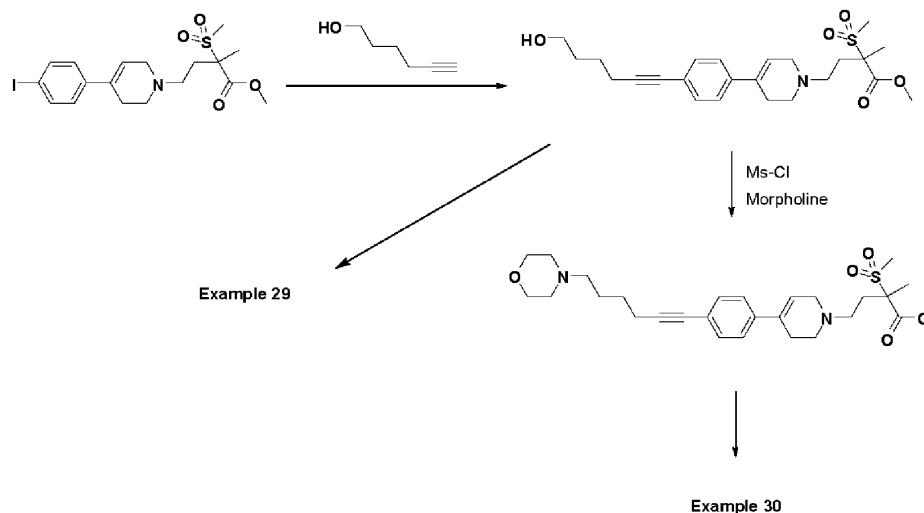
4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Example 18, Step 1).

[370] ^1H NMR (600MHz, DMSO- d_6): δ 11.02 (bs, 1H), 9.12 (bs, 1H), 7.41-7.38 (m, 2H), 7.34-7.32 (m, 2H), 6.19 (s, 1H), 3.75-3.41 (m, 2H), 3.25 (s, 2H), 3.17-3.10 (m, 2H), 3.06 (s, 3H), 2.67-2.54 (m, 2H), 2.45-2.28 (m, 6H), 1.78-1.72 (m, 2H), 1.46 (s, 3H).

[371] MS (ESI, m/z): 449.2 [M+H]⁺.

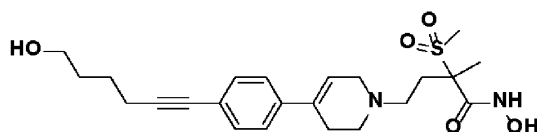
[372] [Examples 29 - 30]

[373]



[374] **Example 29: Synthesis of N-hydroxy-4-(4-(4-(6-hydroxyhex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[375]



[376] Step 1: Synthesis of methyl 4-(4-(4-(6-hydroxyhex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

[377] The title compound was prepared the procedures described for the synthesis of Example 1, step 1 using hex-5-yn-1-ol.

[378] ¹H NMR (600MHz, CDCl₃-d₁); δ7.33-7.31 (m, 2H), 7.28-7.26 (m, 2H), 6.05 (s, 1H), 3.72-3.62 (m, 5H), 3.18-3.10 (m, 2H), 3.04 (s, 3H), 2.72-2.58 (m, 3H), 2.52-2.40 (m, 5H), 1.78-1.65 (m, 6H), 1.63 (s, 3H).

[379] Step 2 - 4: Synthesis of N-hydroxy-4-(4-(4-(6-hydroxyhex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide

[380] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 4-(4-(4-(6-hydroxyhex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate.

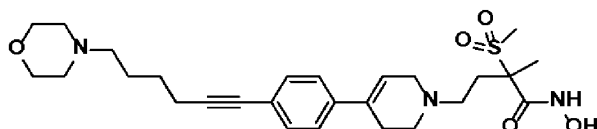
[381] ¹H NMR (600MHz, DMSO-d₆); δ11.04 (bs, 1H), 9.10 (bs, 1H), 7.37-7.36 (m, 2H),

7.30-7.28 (m, 2H), 6.17 (s, 1H), 4.43-4.28 (m, 2H), 3.40-3.5 (m, 4H), 3.09-3.05 (m, 2H), 3.04 (s, 3H), 2.6-2.58 (m, 2H), 2.43-2.39 (m, 4H), 1.47 (s, 3H), 1.41-1.38 (m, 4H).

[382] MS (ESI, m/z): 449.1 [M+H]⁺.

[383] **Example 30: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(6-morpholinohex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide**

[384]



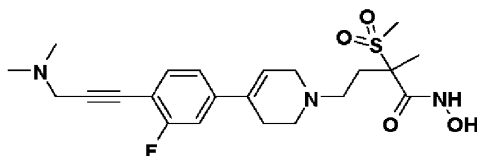
[385] The title compound was prepared the procedures described for the synthesis of Example 25 using methyl 4-(4-(4-(6-hydroxyhex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Example 29, Step 1).

[386] ¹H NMR (600MHz, DMSO-d₆); δ 11.06 (bs, 1H), 9.15 (bs, 1H), 7.43-7.41 (m, 2H), 7.35-7.33 (m, 2H), 6.22 (s, 1H), 3.62-3.56 (m, 4H), 3.18-3.10 (m, 2H), 3.08 (s, 3H), 2.72-2.58 (m, 3H), 2.48-2.40 (m, 5H), 2.40-2.28 (m, 6H), 2.05-1.98 (m, 1H), 1.82-1.70 (m, 1H), 1.62-1.56 (m, 4H), 1.48 (s, 3H).

[387] MS (ESI, m/z): 518.3 [M+H]⁺.

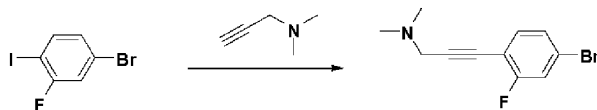
[388] **Example 31: Synthesis of 4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide**

[389]



[390] Step 1: Synthesis of 3-(4-bromo-2-fluorophenyl)-N,N-dimethylprop-2-yn-1-amine

[391]



[392] To a solution of 4-bromo-2-fluoro-1-iodobenzene (3g, 1eq) in a mixture of THF (10ml)/ toluene(10ml) was added with CuI (0.19g, 0.1eq), Pd(PPh₃)₂Cl₂ (0.7g, 0.1eq), Et₃N (4.2ml, 3eq) and N,N-dimethylprop-2-yn-1-amine (1.61ml, 1.5eq). The mixture was stirred for 12hr at room temperature and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare

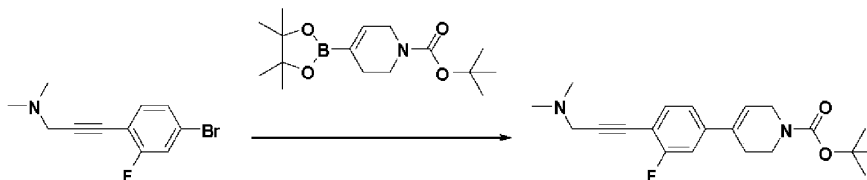
the title compound (1.87g, 73%).

[393] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$); δ 7.29-7.22 (m, 3H), 3.49 (s, 2H), 2.36 (s, 6H).

[394] Step 2: Synthesis of tert-butyl

4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate

[395]



[396] To a solution of 3-(4-bromo-2-fluorophenyl)-N,N-dimethylprop-2-yn-1-amine (1.87g, 1eq) in a mixture of 1,4-dioxane (16ml)/water (4ml) was added with $\text{Pd}(\text{PPh}_3)_2$ Cl_2 (0.51g, 0.1eq), K_2CO_3 (3.03g, 3eq), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (2.71g, 1.2eq). The mixture was stirred for 2hr at 110°C and cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (2g, 76%).

[397] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$); δ 7.36 (t, $J=7.2\text{Hz}$, 1H), 7.25-7.07 (m, 2H), 6.07 (s, 1H), 4.11-4.07 (m, 2H), 3.64-3.59 (m, 2H), 3.47 (s, 2H), 2.49-2.45 (m, 2H), 2.36 (s, 6H), 1.58 (s, 9H).

[398] MS (ESI, m/z): 359.2 $[\text{M}+\text{H}]^+$.

[399] Step 3: Synthesis of

3-(2-fluoro-4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)-N,N-dimethylprop-2-yn-1-amine hydrochloride

[400]



[401] To a solution of tert-butyl

4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (2g, 1eq) in MeOH (16ml) was added with acetyl chloride (3.97ml, 10eq). The mixture was stirred for 3hr at 60°C and cooled down to room temperature, and the solvent was concentrated in vacuo to prepare the title compound (1.6g, 97%).

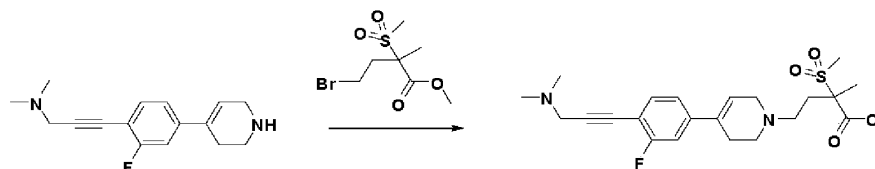
[402] ^1H NMR (600MHz, DMSO-d_6); δ 11.52 (bs, 1H), 9.56 (bs, 2H), 7.61 (t, $J=8.4\text{Hz}$, 1H), 7.48, (dd, $J=11.4\text{Hz}$, 1.8Hz, 1H), 7.38 (dd, $J=8.4\text{Hz}$, 1.8Hz, 1H), 6.39 (bs, 1H), 4.36 (s, 2H), 3.72-3.70 (m, 2H), 3.27-3.23 (m, 2H), 2.78 (s, 6H), 2.68-2.64 (m, 2H).

[403] MS (ESI, m/z): 259.2 [M+H]⁺.

[404] Step 4: Synthesis of methyl

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

[405]



[406] To a solution of

3-(2-fluoro-4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)-N,N-dimethylprop-2-yn-1-amine hydrochloride (600mg, 1eq) in DMF (10ml) was added with

N,N-diisopropylethylamine (1.42ml, 4eq) and methyl

4-bromo-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 1) (778mg, 1.4eq). The mixture was stirred for 12hr at 60°C, cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (280mg, 28%).

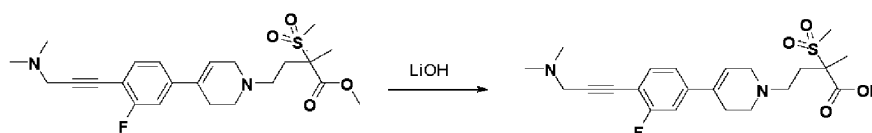
[407] ¹H NMR (600MHz, CDCl₃-d₁); δ 7.35 (t, J=8.4Hz, 1H), 7.10-7.05 (m, 2H), 6.11 (bs, 1H), 3.66 (s, 3H), 3.54 (s, 2H), 3.23-3.18 (m, 1H), 3.04 (s, 3H), 3.03-3.00 (m, 1H), 2.79-2.75 (1H), 2.67-2.60 (m, 2H), 2.58-2.54 (m, 2H), 2.46-2.42 (m, 2H), 2.36 (s, 6H), 2.00-1.97 (m, 1H), 1.62 (s, 3H).

[408] MS (ESI, m/z): 451.2 [M+H]⁺.

[409] Step 5: Synthesis of

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid

[410]

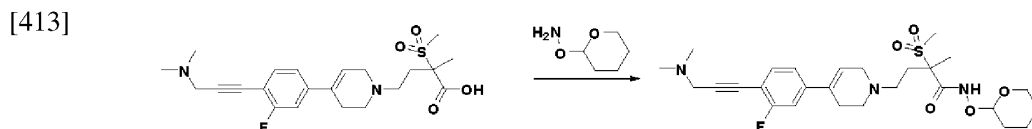


[411] To a solution of methyl

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (230mg, 1eq) in a mixture of THF

(8ml)/MeOH (2ml) was added with 2N-LiOH (0.77ml, 3eq) solution, and the mixture was stirred for 2hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (10ml) and adjusted the pH to 4.0. The precipitated solid was filtered off to prepare the title compound (200mg, 90%), which was used for next step without further purification.

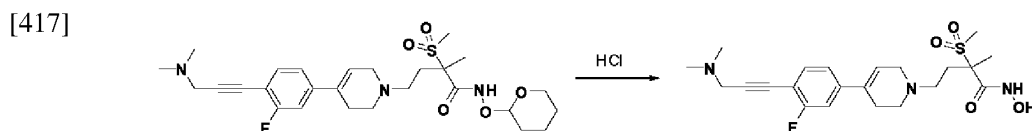
- [412] Step 6: Synthesis of
4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide



- [414] To a solution of
4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid (200mg, 1eq) in DMF (10ml) was added with HATU (244mg, 1.4eq), HOBT (98mg, 1.4eq), Et₃N (0.19ml, 3eq) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine hydrochloride (141mg, 2eq). The mixture was stirred for 1hr at room temperature and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (166mg, 68%).

[415] MS (ESI, m/z): 536.2 [M+H]⁺.

- [416] Step 7:
4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide



- [418] To a solution of
4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide (160mg, 1eq) in MeOH (6ml) was added with HCl solution in MeOH (1.25N, 0.72ml, 3eq), and the mixture was stirred for 2hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (6ml) and adjusted the pH to 7.0. The water was concentrated and the resulting residue was purified with column chromatography to prepare the title compound (89mg, 57%).

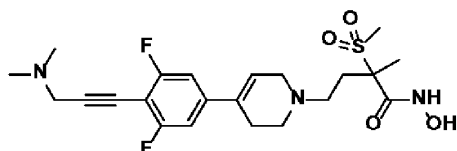
[419] ¹H NMR (600MHz, DMSO-d₆); δ 10.98 (bs, 1H), 9.11 (bs, 1H), 7.44-7.41 (m, 1H), 7.33-7.71 (m, 1H), 7.26-7.25 (m, 1H), 6.30 (s, 1H), 3.48 (s, 2H), 3.13-3.06 (m, 2H), 3.04 (s, 3H), 2.64-2.61 (m, 1H), 2.59-2.55 (m, 1H), 2.47-2.38 (m, 4H), 2.33-2.29 (m, 1H), 2.22 (s, 6H), 1.84-1.79 (m, 1H), 1.44 (s, 3H).

[420] MS (ESI, m/z): 452.2 [M+H]⁺.

- [421] **Example 32:** Synthesis of

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3,5-difluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[422]



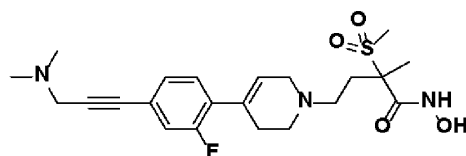
[423] The title compound was prepared the procedures described for the synthesis of Example 31 using 5-bromo-1,3-difluoro-2-iodobenzene as a starting material.

[424] MS (ESI, m/z): 470.2 [M+H]⁺.

[425] **Example 33:** Synthesis of

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-2-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[426]

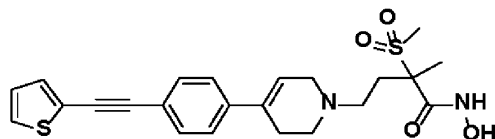


[427] The title compound was prepared the procedures described for the synthesis of Example 31 using 1-bromo-2-fluoro-4-iodobenzene as a starting material.

[428] MS (ESI, m/z): 452.2 [M+H]⁺.

[429] **Example 34: Synthesis of** N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(thiophen-2-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide

[430]



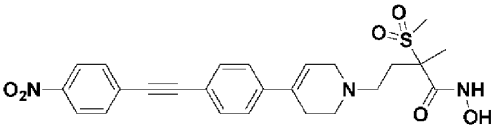
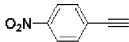
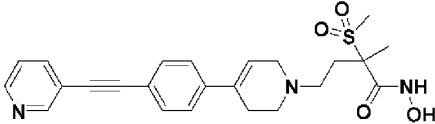
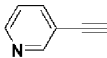
[431] Step 1: Synthesis of 2-methyl-2-(methylsulfonyl)-N-(((tetrahydro-2H-pyran-2-yl)oxy)-4-(4-(4-(thiophen-2-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide

[432] To a solution of 4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(((tetrahydro-2H-pyran-2-yl)oxy)butanamide (Intermediate 3) (220mg, 1eq) in THF (4ml)/toluene(4ml) was added with CuI (7.5mg, 0.1eq), Pd(PPh₃)₂Cl₂ (27.4mg, 0.1eq), Et₃N (0.165ml, 3eq) and 2-ethynylthiophene (64mg, 1.5eq). The mixture was stirred for 12hr at room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound

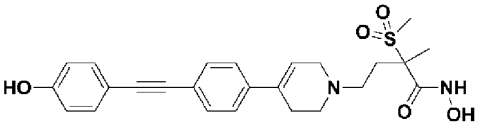
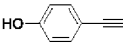
(60mg, 28%)

- [433] ¹H NMR (600MHz, CDCl₃-d₁); δ 7.67-7.64 (m, 1H), 7.45-7.43 (m, 2H), 7.35-7.34 (m, 2H), 7.28-7.26 (m, 1H), 7.01-6.99 (m, 1H), 6.12 (s, 1H), 4.92-4.90 (m, 1H), 3.43-3.29 (m, 4H), 3.11 (s, 3H), 2.90-2.83 (m, 4H), 2.72-2.65 (m, 4H), 1.80-1.57 (m, 7H), 1.52-1.45 (s, 2 H).).
- [434] MS (ESI, m/z): 543.2 [M+H]⁺.
- [435] Step 2: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(thiophen-2-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide
- [436] To a solution of 2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)-4-(4-(4-(thiophen-2-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide (60mg, 1eq) in MeOH (2ml) was added with HCl solution in MeOH (1.25N, 0.27ml, 3eq), and the mixture was stirred for 2hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (4ml) and adjusted the pH to 7.0. The water was concentrated and the resulting residue was purified with column chromatography to prepare the title compound (7.7mg, 15%).
- [437] ¹H NMR (600MHz, DMSO-d₆); δ 11.00 (bs, 1H), 9.08 (bs, 1H), 7.65-7.64 (m, 1H), 7.48-7.45 (m, 4H), 7.40-7.39 (m, 1H), 7.11-7.10 (m, 1H), 6.25 (s, 1H), 3.11-3.06 (m, 2H), 3.04 (s, 3H), 2.63-2.58 (m, 2H), 2.46-2.31 (m, 2H), 2.00-1.80 (m, 2H), 1.45 (s, 3H), 1.23-1.20 (m, 2 H).
- [438] MS (ESI, m/z): 454.2 [M+H]⁺.
- [439] **[Examples 35-37]**
- [440] The terminal acetylenes listed in the following table were used to prepare compounds of Examples 35-37 in the same manner as Example 34.

[441]

Example	Structure (Name)	Terminal acetylene
35	 (N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(4-nitrophenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide)	
	¹ H NMR (600MHz, DMSO-d ₆): δ 11.01 (bs, 1H), 9.06 (bs, 1H), 8.25-8.23 (m, 2H), 7.80-7.78 (m, 2H), 7.57-7.55 (m, 2H), 7.51-7.49 (m, 2H), 6.28 (s, 1H), 3.11-3.98 (m, 2H), 3.04 (s, 3H), 2.63-2.58 (m, 4H), 2.44-2.32 (m, 4H), 1.45 (s, 3H). MS (ESI, m/z): 498.2 [M+H] ⁺ .	
36	 (N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-3-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide)	
	¹ H NMR (600MHz, DMSO-d ₆) δ; 11.01 (bs, 1H), 9.10 (bs, 1H), 8.75-8.74 (m, 1H), 8.57-8.56 (m, 1H), 7.97-7.95 (m, 1H), 7.59-7.39 (m, 5H), 6.27 (s, 1H), 3.15-3.11 (m, 2H), 3.05 (s, 3H), 2.65-2.59 (m, 2H), 2.42-2.31 (m, 2H), 1.85-1.83 (m, 2H), 1.45 (s, 3H), 1.21-1.17 (m, 2H). MS (ESI, m/z): 454.2 [M+H] ⁺ .	

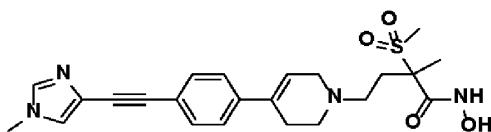
[442]

37	 (N-hydroxy-4-(4-(4-(4-hydroxyphenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆): δ 11.02 (bs, 1H), 10.16 (s, 1H), 9.07 (bs, 1H), 7.44-7.41 (m, 4H), 7.34-7.32 (m, 2H), 6.78-6.76 (m, 2H), 6.21 (s, 1H), 3.15-3.06 (m, 2H), 3.03 (s, 3H), 2.68-2.54 (m, 3H), 2.44-2.30 (m, 4H), 1.86-1.80 (m, 1H), 1.45 (s, 3H). MS (ESI, m/z): 469.2 [M+H]⁺.	
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[443]

Example 38: Synthesis of N-hydroxy-2-methyl-4-(4-(4-((1-methyl-1H-imidazol-4-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide

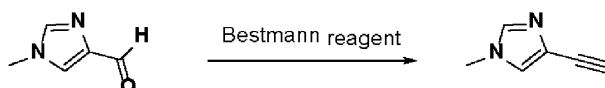
[444]



[445]

Step 1: Synthesis of 4-ethynyl-1-methyl-1H-imidazole

[446]



[447]

A solution of 1-methyl-1H-imidazole-4-carbaldehyde (2g, 1eq) in MeOH (180ml) was cooled at 0°C. K₂CO₃ (5.02g, 2eq) and dimethyl (1-diazo-2-oxopropyl)phosphonate (7.7 g, 2.2eq) was added. The mixture was stirred for 4hr at 0°C, and extracted with dichloromethane and water. The organic layer was washed with sat. aq. NH₄Cl, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (1.2g, 62%).

[448]

¹H NMR (600MHz, CDCl₃-d₁): δ 7.60 (s, 1H), 7.32 (m, 1H), 3.37 (s, 3H), 3.48 (s, 1H).

[449]

MS (ESI, m/z): 107.1 [M+H]⁺.

[450]

Step 2: Synthesis of N-

hydroxy-2-methyl-4-(4-(4-((1-methyl-1H-imidazol-4-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide

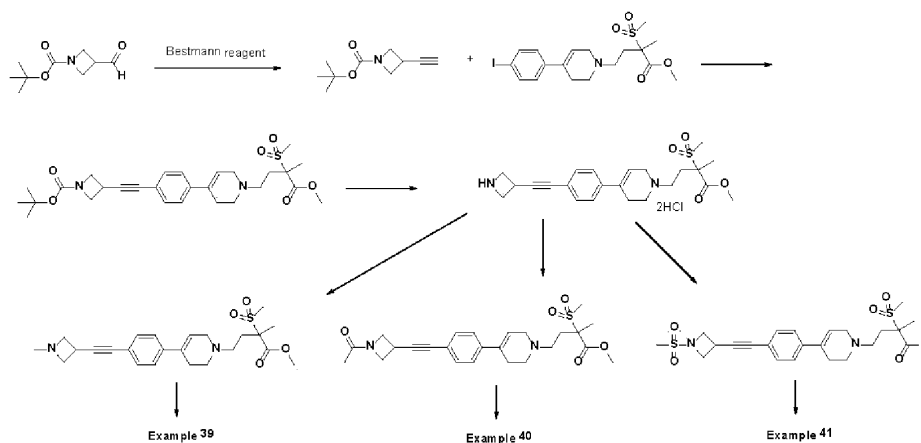
[451] The title compound was prepared the procedures described for the synthesis of Example 1 (Synthesis of Hydroxamate) using 4-ethynyl-1-methyl-1H-imidazole.

[452] ^1H NMR (600MHz, DMSO- d_6); δ 11.02 (bs, 1H), 9.14 (bs, 1H), 7.76 (s, 1H), 7.52-7.48 (m, 4H), 7.29 (s, 1H), 6.26 (s, 1H), 3.69 (s, 3H), 3.16-3.04 (m, 5H), 2.66-2.56 (m, 3H), 2.46-2.38 (m, 4H), 1.86-1.76 (m, 1H), 1.44 (s, 3H).

[453] MS (ESI, m/z): 457.2 $[\text{M}+\text{H}]^+$.

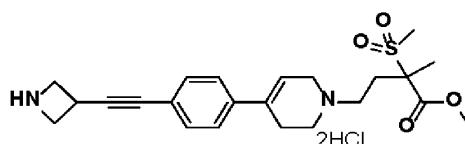
[454] **[Examples 39-41]**

[455]



[456] **Preparation 4: Synthesis of Intermediate 4 {methyl 4-(4-(4-(azetidin-3-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate dihydrochloride}**

[457]



[458] Step 1: Synthesis of tert-butyl 3-ethynylazetidine-1-carboxylate

[459] A solution of tert-butyl 3-formylazetidine-1-carboxylate (7g, 1eq) in MeOH (378ml) was cooled at 0°C. K_2CO_3 (10.5g, 2eq), dimethyl (1-diazo-2-oxopropyl)phosphonate (15.8g, 2.2eq) was added. The mixture was stirred for 4hr at 0°C, and extracted with dichloromethane and water. The organic layer was washed with sat. aq. NH_4Cl , dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (5.95g, 87%).

[460] ^1H NMR (600MHz, CDCl_3 - d_1); δ 4.10-4.07 (m, 2H), 3.90-3.87 (m, 2H), 3.27-3.24 (m, 1H), 2.26-2.25 (m, 1H), 1.39 (s, 9H).

[461] Step 2: Synthesis of tert-butyl

3-((4-(1-(4-methoxy-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)ethynyl)azetidine-1-carboxylate

[462] To a solution of methyl

4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 2) (7g, 1eq) in a mixture of THF (30ml)/toluene (30ml) was added with CuI (0.28g, 0.1eq), Pd(PPh₃)₂Cl₂ (1.03g, 0.1eq), Et₃N (6.18ml, 3eq) and tert-butyl 3-ethynylazetidine-1-carboxylate (3.99g, 1.5eq). The mixture was stirred for 12hr at room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (5g, 64%).

[463] ¹H NMR (600MHz, CDCl₃-d1); δ7.35-7.25 (m, 4H), 6.07 (s, 1H), 4.30 (s, 2H), 4.21-4.17 (m, 2H), 4.02-4.00 (m, 2H), 3.67 (s, 3H), 3.54-3.50 (m, 2H), 3.04 (s, 3H), 2.77-2.49 (m, 8H), 1.63 (s, 3H), 1.44 (s, 9H).

[464] MS (ESI, m/z): 531.3 [M+H]⁺.

[465] Step 3: Synthesis of methyl

4-(4-(4-(azetidin-3-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate dihydrochloride

[466] To a solution of tert-butyl

3-((4-(1-(4-methoxy-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)ethynyl)azetidine-1-carboxylate (5g, 1eq) in dichloromethane (100ml) was added with HCl solution (4N in cyclopentyl methyl ether, 24ml, 10eq). The mixture was stirred for 3hr at room temperature. After then, the solvent was concentrated in vacuo to prepare the title compound (4.2g, 89%).

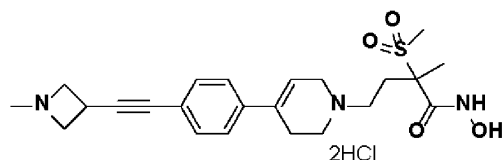
[467] ¹H NMR (600MHz, CD₃OD-d4); δ7.50-7.45 (m, 4H), 6.21 (s, 1H), 4.36-4.34 (m, 2H), 4.19-4.15 (m, 2H), 4.10-4.06 (m, 2H), 3.88-3.87 (m, 5H), 3.62-3.59 (m, 1H), 3.41-3.39 (m, 2H), 3.17 (s, 3H), 2.98-2.84 (m, 2H), 2.71-2.49 (m, 2H), 1.70 (s, 3H).

[468] MS (ESI, m/z): 431.2 [M+H]⁺.

[469] **Example 39: Synthesis of N-**

hydroxy-2-methyl-4-(4-(4-((1-methylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide dihydrochloride

[470]



[471] Step 1: Synthesis of methyl

2-methyl-4-(4-(4-((1-methylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanoate

[472] To a solution of methyl

4-(4-(4-(azetidin-3-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate dihydrochloride (Intermediate 4) (1.5g, 1eq) in dichloromethane (30ml) was added with formaldehyde (37wt%, 0.89ml, 4eq) and sodium triacetoxyborohydride (2.53g, 4eq). The mixture was stirred for 5hr at room temperature, and extracted with ethyl acetate and water. The organic layer was washed with sat. aq. NaHCO₃, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (0.9g, 68%).

[473] ¹H NMR (600MHz, CDCl₃-d₁); δ7.34-7.32 (m, 2H), 7.29-7.28 (m, 2H), 6.07 (s, 1H), 3.76-3.74 (m, 2H), 3.66 (s, 3H), 3.46-3.45 (m, 1H), 3.22-3.19 (m, 3H), 3.02-2.99 (m, 4H), 2.78-2.76 (m, 1H), 2.65-2.53 (m, 4H), 2.47-2.46 (m, 2H), 2.38 (s, 3H), 1.97-1.96 (m, 1H), 1.62 (s, 3H).

[474] MS (ESI, m/z): 445.2 [M+H]⁺.

[475] Step 2 - 4: N-

hydroxy-2-methyl-4-(4-(4-((1-methylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide

[476] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 2-methyl-4-(4-(4-((1-methylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanoate.

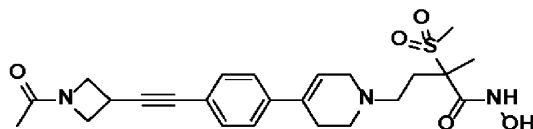
[477] ¹H NMR (600MHz, DMSO-d₆); δ11.22-11.04 (m, 3H), 9.35 (bs, 1H), 7.52-7.50 (m, 2H), 7.47-7.44 (m, 2H), 6.28 (s, 1H), 4.38-4.00 (m, 4H), 3.83-3.77 (m, 2H), 3.36-3.34 (m, 2H), 3.11 (s, 3H), 3.08-2.82 (m, 5H), 2.73-2.69 (m, 2H), 2.23-2.21 (m, 1H), 1.51 (s, 3H).

[478] MS (ESI, m/z): 446.2 [M+H]⁺.

[479] **Example 40: Synthesis of**

4-(4-(4-((1-acetylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[480]



[481] Step 1: Synthesis of methyl

4-(4-(4-((1-acetylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

[482] To a solution of methyl

4-(4-(4-(azetidin-3-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate dihydrochloride (Intermediate 4) (800mg, 1eq) in dichloromethane (15ml) was added with Et₃N (0.89ml, 4eq) and acetyl chloride (0.17ml, 1.5eq). The mixture was stirred for 2hr at 0°C, and extracted with dichloromethane and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (560mg, 75%).

[483] ¹H NMR (600MHz, CDCl₃-d₁); δ7.35-7.32 (m, 4H), 6.06 (s, 1H), 4.41-4.29 (m, 2H), 4.20-4.07 (m, 2H), 3.87-3.61 (m, 7H), 3.14-3.07 (m, 5H), 2.77-2.59 (m, 4H), 2.04-2.03 (m, 1H), 1.88 (s, 3H), 1.67 (s, 3H).

[484] MS (ESI, m/z): 473.2 [M+H]⁺.

[485] Step 2 - 4: Synthesis of

4-(4-(4-((1-acetylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

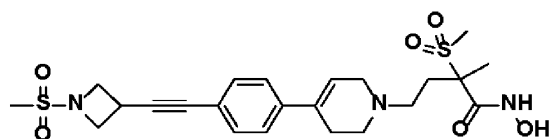
[486] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 4-(4-(4-((1-acetylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate.

[487] ¹H NMR (600MHz, DMSO-d₆); δ11.0 (bs, 1H), 9.11 (bs, 1H), 7.42-7.40 (m, 2H), 7.38-7.36 (m, 2H), 6.20 (s, 1H), 4.41-4.38 (m, 2H), 4.13-4.10 (m, 2H), 3.78-3.67 (m, 2H), 3.15-3.14 (m, 2H), 3.04 (s, 3H), 2.62-2.56 (m, 2H), 2.49-2.43 (m, 4H), 2.32-2.30 (m, 1H), 1.74 (s, 3H), 1.44 (s, 3H).

[488] MS (ESI, m/z): 474.1 [M+H]⁺.

[489] **Example 41: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-((1-(methylsulfonyl)azetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide**

[490]



[491] Step 1: Synthesis of methyl 2-methyl-2-(methylsulfonyl)-4-(4-(4-((1-(methylsulfonyl)azetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoate

[492] To a solution of methyl 4-(4-(4-(azetidin-3-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate dihydrochloride (Intermediate 4) (600mg, 1eq) in DMF (15ml) was added with N,N-diisopropylethylamine (0.83ml, 4eq) and methanesulfonyl

chloride (0.14ml, 1.5eq). The mixture was stirred for 2hr at 0°C, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (220mg, 36%).

[493] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$); δ 7.37-7.36 (m, 2H), 7.31-7.30 (m, 2H), 6.03 (s, 1H), 4.19-4.02 (m, 6H), 3.63-3.60 (m, 2H), 3.13-3.02 (m, 5H), 2.94-2.87 (m, 2H), 2.75-2.69 (m, 1H), 2.26-2.20 (m, 2H), 2.03 (s, 3H), 1.23 (s, 3H).

[494] MS (ESI, m/z): 509.2 $[\text{M}+\text{H}]^+$.

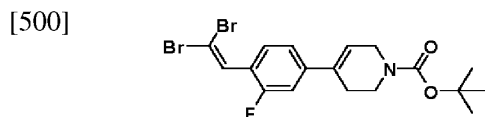
[495] Step 2 - 4: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-((1-(methylsulfonyl)azetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide

[496] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 2-methyl-2-(methylsulfonyl)-4-(4-(4-((1-(methylsulfonyl)azetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoate.

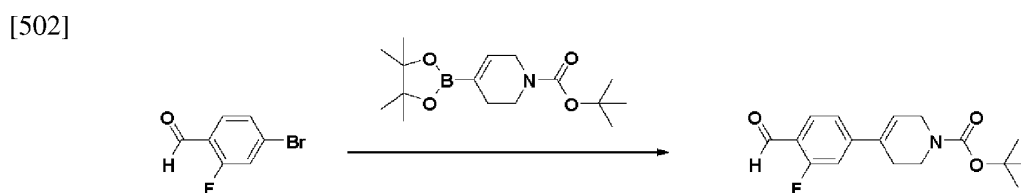
[497] ^1H NMR (600MHz, $\text{CD}_3\text{OD-d}_4$); δ 7.41-7.36 (m, 4H), 6.17 (s, 1H), 4.19-4.16 (m, 2H), 3.98-3.95 (m, 2H), 3.13 (s, 3H), 2.97 (s, 3H), 2.88-2.84 (m, 2H), 2.61-2.54 (m, 4H), 2.23-2.21 (m, 1H), 1.59 (s, 3H).

[498] MS (ESI, m/z): 510.2 $[\text{M}+\text{H}]^+$.

[499] **Preparation 5: Synthesis of Intermediate 5** {tert-butyl 4-(4-(2,2-dibromovinyl)-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate}



[501] Step 1: Synthesis of tert-butyl 4-(3-fluoro-4-formylphenyl)-3,6-dihydropyridine-1(2H)-carboxylate



[503] To a solution of 4-bromo-2-fluorobenzaldehyde (6g, 1eq) in a mixture of 1,4-dioxane (100ml)/ water (20ml) was added with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2.07g, 0.1eq), K_2CO_3 (12.25g, 3eq) and tert-butyl

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (10.97g, 1.2eq). The mixture was stirred for 4hr at 110°C, cooled down to room temperature and extracted with ethyl acetate and water. The organic layer was washed with

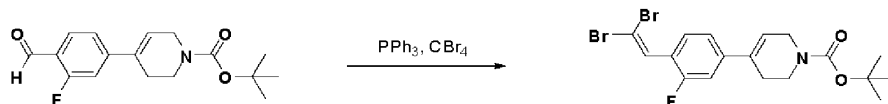
brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (7.8g, 86%).

[504] ^1H NMR (600MHz, CDCl_3 -d1); δ 10.32 (s, 1H), 7.84-7.82 (m, 1H), 7.29-7.26 (m, 1H), 7.16-7.14 (m, 1H), 6.24 (bs, 1H), 4.14-4.10 (m, 2H), 3.66-3.64 (m, 2H), 2.54-2.50 (m, 2H), 1.49 (s, 9H).

[505] Step 2: Synthesis of tert-butyl

4-(4-(2,2-dibromovinyl)-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate

[506]



[507] To a solution of tert-butyl

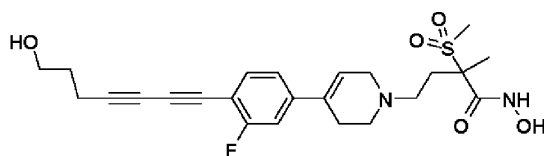
4-(3-fluoro-4-formylphenyl)-3,6-dihydropyridine-1(2H)-carboxylate (3g, 1eq) in dichloromethane (50ml) was added with carbon tetrabromide (4.89g, 1.5eq) and triphenylphosphine (7.73g, 3eq). The mixture was stirred for 1hr at 0°C , and extracted with dichloromethane and water. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (4.13g, 91%).

[508] ^1H NMR (600MHz, CDCl_3 -d1); δ 7.78-7.76 (m, 1H), 7.54 (s, 1H), 7.18-7.16 (m, 1H), 7.08-7.06 (m, 1H), 6.11 (bs, 1H), 4.11-4.09 (m, 2H), 3.65-3.60 (m, 2H), 2.51-2.47 (m, 2H), 1.49 (s, 9H).

[509] **Example 42: Synthesis of**

4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[510]



[511] Step 1: Synthesis of tert-butyl

4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate

[512]



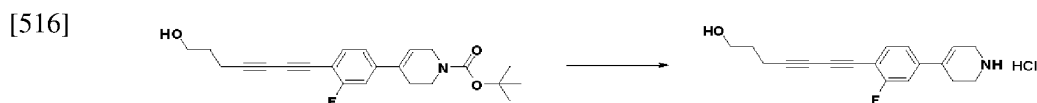
[513] To a solution of tert-butyl

4-(4-(2,2-dibromovinyl)-3-fluorophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (Intermediate 5) (2.29g, 1eq) in DMF was added with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.35g, 0.1eq), triphenylphosphine (0.13g, 0.1eq), Et_3N (2.1ml, 3eq) and pent-4-yn-1-ol (0.93ml, 2eq).

The mixture was stirred for 2hr at 80°C, cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (790mg, 42%).

[514] ¹H NMR (600MHz, CDCl₃-d1); δ7.41-7.38 (m, 1H), 7.11-7.09 (m, 1H), 7.07-7.06 (m, 1H), 6.10 (bs, 1H), 4.10-4.06 (m, 2H), 3.78 (t, *J*=6Hz, 2H), 3.64-3.60 (m, 2H), 2.52 (t, *J*=6.6Hz, 2H), 2.49-2.45 (m, 2H), 1.86-1.81 (m, 2H), 1.48 (s, 9H).

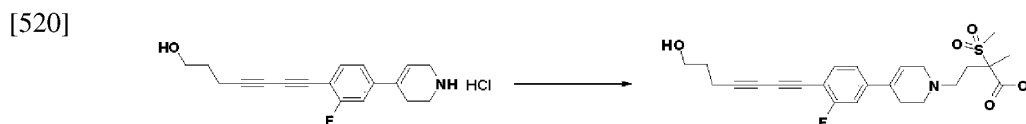
[515] Step 2: Synthesis of
7-(2-fluoro-4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)hepta-4,6-diyn-1-ol hydrochloride



[517] To a solution of tert-butyl
4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate (790mg, 1eq) in MeOH was added with conc-HCl (1.7ml, 10eq). The mixture was stirred for 1hr at 110°C, cooled down to room temperature, and concentrated in vacuo. The residue was diluted in MeOH (2ml) and poured into diethyl ether (50ml). The precipitated solid was filtered off to prepare the title compound (576mg, 87%).

[518] ¹H NMR (600MHz, DMSO-d₆); δ9.34 (bs, 2H), 7.63-7.60 (m, 1H), 7.49-7.47 (m, 1H), 7.37-7.36 (m, 1H), 6.41 (s, 1H), 3.78-3.74 (m, 2H), 3.47 (t, *J*=5.4Hz, 2H), 3.30-3.26 (m, 2H), 2.69-2.65 (m, 2H), 2.50-2.47 (m, 2H), 1.68-1.63 (m, 2H).

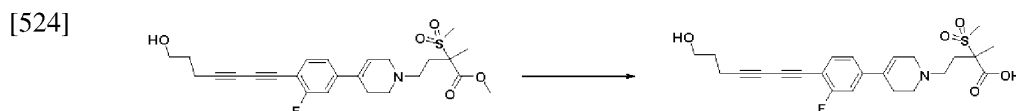
[519] Step 3: Synthesis of methyl
4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate



[521] To a solution of
7-(2-fluoro-4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)hepta-4,6-diyn-1-ol hydrochloride (570mg, 1eq) in DMF (12ml) was added with N,N-diisopropylethylamine (0.93ml, 3eq) and methyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 1) (584mg, 1.2eq). The mixture was stirred for 12hr at 60°C, cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (230mg, 27%).

[522] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$); δ 7.39-7.37 (m, 1H), 7.11-7.09 (m, 1H), 7.07-7.05 (m, 1H), 6.13 (s, 1H), 3.78 (t, $J=6\text{Hz}$, 2H), 3.67 (s, 3H), 3.24-3.21 (m, 1H), 3.05 (s, 3H), 3.04-3.01 (1H), 2.79-2.76 (m, 1H), 2.67-2.53 (m, 4H), 2.51 (t, $J=6.6\text{Hz}$, 2H), 2.45-2.42 (m, 2H), 2.00-1.98 (m, 1H), 1.85-1.81 (m, 2H), 1.63 (s, 3H).

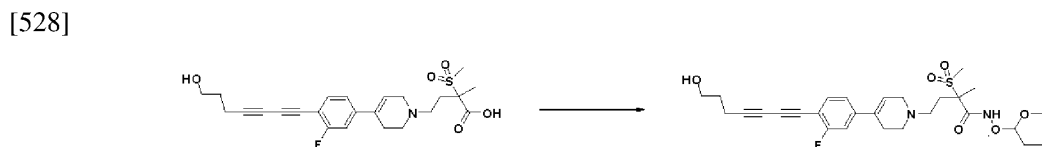
[523] Step 4: Synthesis of
4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid



[525] To a solution of methyl
4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (230mg, 1eq) in a mixture of THF (8ml)/MeOH (2ml) was added with 2N-LiOH (0.73mL, 3eq) solution. The mixture was stirred for 2hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (10ml) and adjusted the pH to 4.0. The precipitated solid was filtered off to prepare the title compound (119mg, 53%), which was used for next step without further purification.

[526] MS (ESI, m/z): 462.1 $[\text{M}+\text{H}]^+$.

[527] Step 5: Synthesis of
4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide



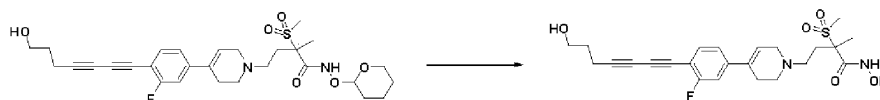
[529] To a solution of of
4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoic acid (119mg, 1eq) in DMF (10ml) was added with HATU (137mg, 1.4eq), HOBT (55mg, 1.4eq), Et_3N (0.11ml, 3eq) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine hydrochloride (60mg, 2eq). The mixture was stirred for 1hr at room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (127mg, 88%).

[530] MS (ESI, m/z): 561.2 $[\text{M}+\text{H}]^+$.

[531] Step 6: Synthesis of
4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-

N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[532]



[533]

To a solution of 4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-(((tetrahydro-2H-pyran-2-yl)oxy)butanamide (127mg, 1eq) in MeOH (6ml) was added with HCl solution in MeOH (1.25N, 0.54ml, 3eq). The mixture was stirred for 2hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (6ml) and adjusted the pH to 7.0. The water was concentrated in vacuo and the resulting residue was purified with column chromatography to prepare the title compound (40mg, 37%).

[534]

^1H NMR (600MHz, DMSO- d_6); δ 10.99 (bs, 1H), 9.12 (bs, 1H), 7.56-7.54 (m, 1H), 7.39-7.36 (m, 1H), 7.31-7.28 (m, 1H), 6.37 (s, 1H), 4.60-4.58 (m, 1H), 3.48-3.45 (m, 2H), 3.35-3.33 (m, 2H), 3.13-3.08 (m, 2H), 3.06 (s, 3H), 2.64-2.58 (m, 2H), 2.51-2.43 (m, 4H), 2.37-2.29 (m, 1H), 1.85-1.78 (m, 1H), 1.66-1.62 (m, 2H), 1.46 (s, 3H).

[535]

MS (ESI, m/z): 477.2 $[\text{M}+\text{H}]^+$.

[536]

[Examples 43-45]

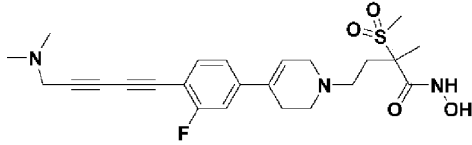
[537]

The terminal acetylenes listed in the following table were used to prepare compounds of Examples 43-45 in the same manner as Example 42.

[538]

Example	Structure (Name)	Terminal acetylene
43	(4-(4-(3-fluoro-4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 10.99 (bs, 1H), 9.11 (bs, 1H), 7.56-7.53 (m, 1H), 7.39-7.37 (m, 1H), 7.31-7.29 (m, 1H), 6.36 (s, 1H), 3.57-3.55 (m, 2H), 3.17-3.10 (m, 2H), 3.06 (s, 3H), 2.65-2.29 (m, 10H), 1.45 (s, 3H). MS (ESI, m/z): 463.2 [M+H]⁺.	
44	(4-(4-(4-(cyclopropylbuta-1,3-diyn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 10.99 (bs, 1H), 9.12 (bs, 1H), 7.54-7.52 (m, 1H), 7.38-7.36 (m, 1H), 7.30-7.28 (m, 1H), 6.36 (s, 1H), 3.15-3.07 (m, 2H), 3.06 (s, 3H), 2.66-2.56 (m, 2H), 2.48-2.31 (m, 6H), 1.61-1.59 (m, 1H), 1.46 (s, 3H), 0.95-0.91 (m, 2H), 0.82-0.79 (m, 2H). MS (ESI, m/z): 463.2 [M+H]⁺.	

[539]

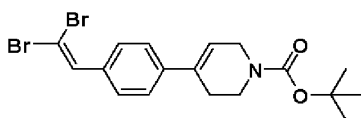
45	 (4-(4-(4-(5-(dimethylamino)penta-1,3-diyn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 10.97 (bs, 1H), 9.11 (bs, 1H), 7.58-7.56 (m, 1H), 7.39-7.37 (m, 1H), 7.31-7.29 (m, 1H), 6.36 (s, 1H), 3.48 (s, 2H), 3.16-3.08 (2H), 3.04 (s, 3H), 2.66-2.56 (m, 3H), 2.48-2.38 (m, 3H), 2.36-2.28 (m, 1H), 2.19 (s, 6H), 1.86-1.76 (m, 1H), 1.44 (s, 3H). MS (ESI, m/z): 476.2 [M+H]⁺.	
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[540]

Preparation 6: Synthesis of Intermediate 6 {tert-butyl

4-(4-(2,2-dibromovinyl)phenyl)-3,6-dihydropyridine-1(2H)-carboxylate}

[541]



[542]

The title compound was prepared the procedures described for the Preparation 5 using 4-bromobenzaldehyde.

[543]

¹H NMR (600MHz, CDCl₃-d₁); δ 7.52 (d, J=9Hz, 2H), 7.46 (s, 1H), 7.37 (d, J=8.4Hz, 2H), 6.09 (bs, 1H), 4.09-4.06 (m, 2H), 3.66- 3.61 (m, 2H), 2.55-2.49 (m, 2H), 1.49 (s, 9H).

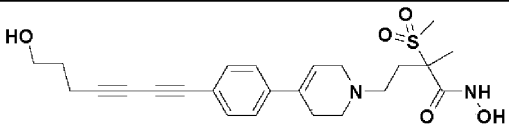
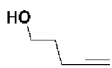
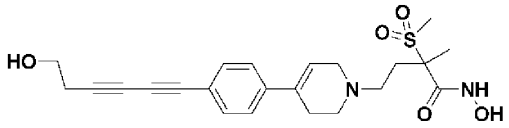
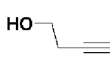
[544]

[Examples 46-51]

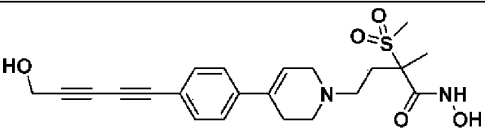
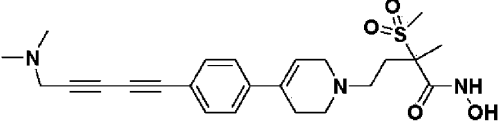
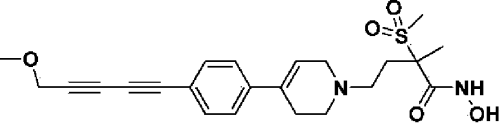
[545]

The Intermediate 6 as a starting material and the terminal acetylenes listed in the following table were used to prepare compounds of Example 46-51 in the same manner as Example 42.

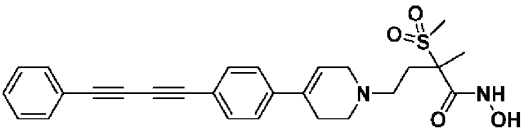
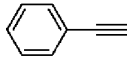
[546]

Example	Structure (Name)	Terminal acetylene
46	 (N-hydroxy-4-(4-(4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.10 (bs, 1H), 7.49-7.43 (m, 4H), 6.26 (s, 1H), 4.60-4.57 (m, 2H), 3.49-3.44 (m, 2H), 3.16-3.06 (m, 5H), 2.66-2.56 (m, 2H), 2.47-2.30 (m, 6H), 1.67-1.61 (m, 2H), 1.46 (s, 3H). MS (ESI, m/z): 431.0 [M+H]⁺.	
47	 (N-hydroxy-4-(4-(4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.00 (bs, 1H), 9.11 (bs, 1H), 7.48-7.46 (m, 2H), 7.44-7.43 (m, 2H), 6.24 (s, 1H), 4.96 (t, J=6.0 Hz, 1H), 3.54-3.51 (m, 2H), 3.14-3.06 (m, 2H), 3.04 (s, 3H), 2.66-2.56 (m, 2H), 2.52 (t, J=6.0 Hz, 2H), 2.48-2.38 (m, 4H), 2.34-2.26 (m, 1H), 1.84-1.76 (m, 1H), 1.44 (s, 3H).	

[547]

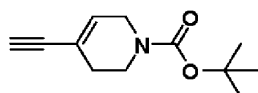
	MS (ESI, m/z): 445.2 [M+H] ⁺ .	
48	 (N-hydroxy-4-(4-(4-(5-hydroxypenta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 10.99 (bs, 1H), 9.10 (bs, 1H), 7.49-7.48 (m, 2H), 7.45-7.43 (m, 2H), 6.25 (s, 1H), 5.45 (t, J=6.0 Hz, 1H), 4.23 (d, J=6.0 Hz, 2H), 3.14-3.08 (m, 2H), 3.03 (s, 3H), 2.66-2.56 (m, 2H), 2.48-2.38 (m, 4H), 2.42-2.38 (m, 1H), 1.86-1.76 (m, 1H), 1.44 (s, 3H). MS (ESI, m/z): 431.0 [M+H]⁺.	
49	 (4-(4-(4-(5-(dimethylamino)penta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.13 (bs, 1H), 7.53-7.46 (m, 4H), 6.28 (s, 1H), 3.49-3.48 (m, 2H), 3.10-3.09 (m, 2H), 3.06 (s, 3H), 2.61-2.60 (m, 2H), 2.47-2.34 (m, 6H), 2.22 (s, 6H), 1.46 (s, 3H). MS (ESI, m/z): 458.2 [M+H]⁺.	
50		

[548]

	(N-hydroxy-4-(4-(4-(5-methoxypenta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆) δ; 11.02 (bs, 1H), 9.08 (bs, 1H), 7.54-7.47 (m, 4H), 6.29 (s, 1H), 4.31 (s, 2H), 3.33 (s, 3H), 3.18-3.10 (m, 2H), 3.06 (s, 3H), 2.65-2.57 (m, 2H), 2.48-2.42 (m, 4H), 2.36-2.30 (m, 1H), 1.88-1.80 (m, 1H), 1.45 (s, 3H). MS (ESI, m/z): 445.2 [M+H]⁺.	
51	 (N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(phenylbuta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide) ¹H NMR (600MHz, DMSO-d₆) δ; 10.99 (bs, 1H), 9.10 (bs, 1H), 7.59-7.57 (m, 2H), 7.55-7.53 (m, 2H), 7.48-7.46 (m, 2H), 7.43-7.41 (m, 2H), 6.27 (s, 1H), 3.18-3.08 (m, 2H), 3.04 (s, 3H), 2.66-2.56 (m, 3H), 2.48-2.38 (m, 3H), 2.36-2.28 (m, 1H), 1.86-1.76 (m, 1H), 1.44 (s, 3H). MS (ESI, m/z): 477.2 [M+H]⁺. 	

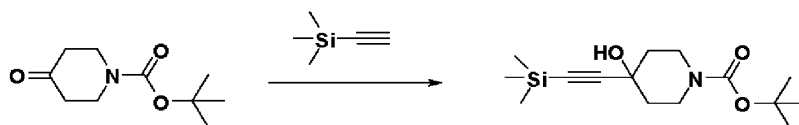
[549] **Preparation 7: Synthesis of Intermediate 7 {tert-butyl 4-ethynyl - 3,6-dihydropyridine-1(2H)-carboxylate}**

[550]



[551] Step 1: Synthesis of tert-butyl 4-hydroxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate

[552]



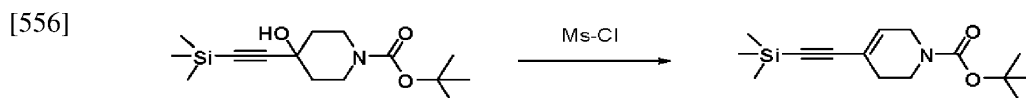
[553] To a solution of tert-butyl 4-oxopiperidine-1-carboxylate (20g, 1eq) in THF (335ml) was added with n-BuLi (2.5M, 64ml, 1.6eq) at -78°C. The mixture was stirred for 1hr. A solution of ethynyltrimethylsilane (14.8g, 1.5eq) in THF (335ml) was slowly added at -78°C and stirred for 12hr at room temperature. The mixture was quenched with

water and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (9g, 30%).

[554] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$); δ 3.82-3.76 (m, 2H), 3.22-3.18 (m, 2H), 2.08 (bs, 1H), 1.88-1.80 (m, 2H), 1.68-1.62 (m, 2H), 1.44 (s, 9H), 0.16 (s, 9H).

[555] Step 2: Synthesis of tert-butyl

4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2H)-carboxylate

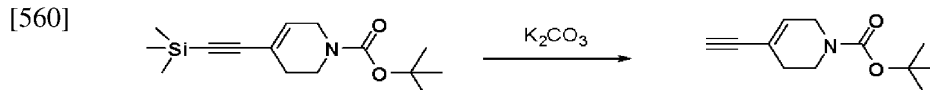


[557] To a solution of tert-butyl

4-hydroxy-4-((trimethylsilyl)ethynyl)piperidine-1-carboxylate (5.8g, 1eq) in dichloromethane (195ml) was added with Et_3N (5.44ml, 2eq) and methanesulfonyl chloride (3.04ml, 2eq) at -10°C . The mixture was stirred for 12hr at room temperature and then extracted with dichloromethane and water. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (3.3g, 61%).

[558] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$); δ 6.04 (s, 1H), 3.96-3.90 (m, 2H), 3.50-3.42 (m, 2H), 2.28-2.18 (m, 2H), 1.45 (s, 9H), 0.17 (s, 9H).

[559] Step 3: Synthesis of tert-butyl 4-ethynyl-3,6-dihydropyridine-1(2H)-carboxylate



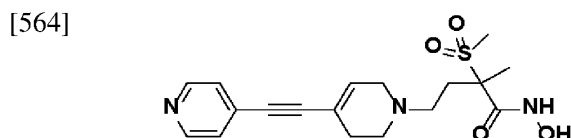
[561] To a solution of tert-butyl

4-((trimethylsilyl)ethynyl)-3,6-dihydropyridine-1(2H)-carboxylate (3.3g, 1eq) in MeOH (100ml) was added with K_2CO_3 (2.45g, 1.5eq). The mixture was stirred for 4hr at room temperature, and extracted with ethyl acetate and water. The organic layer was dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (2.38g, 97%).

[562] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$); δ 6.08 (s, 1H), 3.96-3.90 (m, 2H), 3.50-3.42 (m, 2H), 2.88 (s, 1H), 2.28-2.18 (m, 2H), 1.45 (s, 9H).

[563] **Example 52: Synthesis of N-**

hydroxy-2-methyl-2-(methanesulfonyl)-4-(4-(pyridin-4-ylethynyl)-3,6-dihydropyridin-1(2H)-yl)butanamide



- [565] Step 1: Synthesis of tert-butyl 4-(pyridin-4-ylethynyl)-3,6-dihydropyridine-1(2H)-carboxylate
- [566] To a solution of tert-butyl 4-ethynyl-3,6-dihydropyridine-1(2H)-carboxylate (Intermediate 7) (900mg, 1eq) in THF (10ml) was added with CuI (83mg, 0.1eq), Pd(PPh₃)₂Cl₂ (152mg, 0.05eq), Et₃N (2.4ml, 4eq) and 4-iodopyridine (890mg, 1eq). The mixture was stirred for 2days at room temperature, and extracted with ethyl acetate and water. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (500mg, 41%).
- [567] ¹H NMR (600MHz, CDCl₃-d1); δ 8.90-8.56 (m, 2H), 7.58-7.34 (m, 2H), 6.20 (s, 1H), 4.08-4.00 (m, 2H), 3.56-3.50 (m, 2H), 2.48-2.40 (m, 2H), 1.47 (s, 9H).
- [568] Step 2: Synthesis of 4-((1,2,3,6-tetrahydropyridin-4-yl)ethynyl)pyridine hydrochloride
- [569] To a solution of tert-butyl 4-(pyridin-4-ylethynyl)-3,6-dihydropyridine-1(2H)-carboxylate (500mg, 1eq) in MeOH (10ml) was added with acetyl chloride (1.25ml, 10eq). The mixture was stirred for 4hr at 60°C, cooled down to room temperature and concentrated in vacuo to prepare the title compound (380mg, 98%).
- [570] ¹H NMR (600MHz, CD₃OD-d4); δ 8.84-8.82 (m, 2H), 8.08-8.07 (m, 2H), 6.52 (m, 1H), 3.90-3.88 (m, 2H), 3.43-3.41 (m, 2H), 2.68-2.66 (m, 2H).
- [571] Step 3: Synthesis of methyl 2-methyl-2-(methylsulfonyl)-4-(4-(pyridin-4-ylethynyl)-3,6-dihydropyridin-1(2H)-yl)butanoate
- [572] To a solution of 4-((1,2,3,6-tetrahydropyridin-4-yl)ethynyl)pyridine hydrochloride (380mg, 1eq) in DMF (10ml) was added with N,N-diisopropylethylamine (1.2ml, 4eq) and methyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 1) (940mg, 2eq). The mixture was stirred for 12hr at 60°C, cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (85mg, 13%).
- [573] ¹H NMR (600MHz, CDCl₃-d1); δ 8.54-8.53 (m, 2H), 7.26-7.25 (m, 2H), 6.16 (s, 1H), 3.74 (s, 3H), 3.18-3.14 (m, 1H), 3.03 (s, 3H), 2.98-2.94 (m, 1H), 2.72-2.46 (m, 4H), 2.32-2.28 (m, 2H), 1.88-1.82 (m, 1H), 1.61 (s, 3H), 1.29-1.24 (m, 1H).
- [574] MS (ESI, m/z): 377.1 [M+H]⁺.
- [575] Step 4 - 6: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(pyridin-4-ylethynyl)-3,6-dihydropyridin-1(2H)-yl)butanamide
- [576] The title compound was prepared the procedures described for the synthesis of

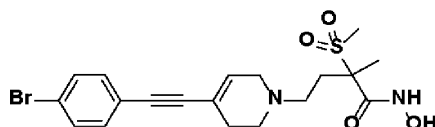
Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 2-methyl-2-(methylsulfonyl)-4-(4-(pyridin-4-ylethynyl)-3,6-dihydropyridin-1(2H)-yl)butanoate.

[577] ^1H NMR (600MHz, DMSO- d_6); δ 10.93 (bs, 1H), 9.10 (bs, 1H), 8.55-8.53 (m, 2H), 7.37-7.36 (m, 2H), 6.23 (s, 1H), 3.10-3.04 (m, 2H), 3.03 (s, 3H), 2.60-2.54 (m, 2H), 2.48-2.42 (m, 2H), 2.36-2.18 (m, 3H), 1.82-1.76 (m, 1H), 1.43 (s, 3H).

[578] MS (ESI, m/z): 378.1 [M+H] $^+$.

[579] **Example 53: Synthesis of 4-(4-((4-bromophenyl)ethynyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide**

[580]



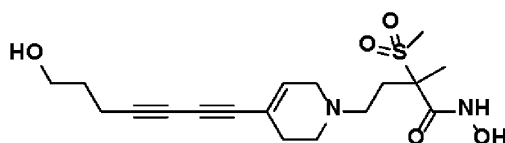
[581] The title compound was prepared the procedures described for the synthesis of Example 52 using 1-bromo-4-iodobenzene.

[582] ^1H NMR (600MHz, DMSO- d_6); δ 10.94 (bs, 1H), 9.10 (bs, 1H), 7.55-7.54 (m, 2H), 7.35-7.34 (m, 2H), 6.14 (s, 1H), 3.06-2.98 (m, 5H), 2.58-2.43 (m, 4H), 2.32-2.16 (m, 3H), 1.80-1.72 (m, 1H), 1.48 (s, 3H).

[583] MS (ESI, m/z): 454.9 [M+H] $^+$.

[584] **Example 54: Synthesis of N-hydroxy-4-(4-(7-hydroxyhepta-1,3-diyn-1-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[585]

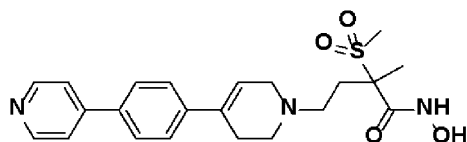


[586] Step 1: Synthesis of tert-butyl 4-(7-hydroxyhepta-1,3-diyn-1-yl)-3,6-dihydropyridine-1(2H)-carboxylate

[587] To a solution of tert-butyl 4-ethynyl-3,6-dihydropyridine-1(2H)-carboxylate (5g, 1eq) in a mixture of MeOH (60ml) / pyridine (60ml) was added with Copper (II) acetate (8.76g, 2eq) and pent-4-yn-1-ol (8.12g, 4eq). The mixture was stirred for 24hr at room temperature, and extracted with ethyl acetate and water. The organic layer was dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (1.8g, 26%).

[588] ^1H NMR (600MHz, CDCl_3 - d_1); δ 6.12 (s, 1H), 3.96-3.94 (m, 2H), 3.76-3.73 (m, 2H), 3.48-3.44 (m, 2H), 2.47-2.44 (m, 2H), 2.22-2.20 (m, 2H), 1.82-1.76 (m, 2H), 1.45 (s, 9H).

- [589] Step 2: Synthesis of 7-(1,2,3,6-tetrahydropyridin-4-yl)hepta-4,6-diyn-1-ol hydrochloride
- [590] To a solution of tert-butyl 4-(7-hydroxyhepta-1,3-diyn-1-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.8g, 1eq) in MeOH (30ml) was added with acetyl chloride (4.42ml, 10eq). The mixture was stirred for 4hr at 60°C, cooled down to room temperature and diluted in diethyl ether. The precipitated solid was filtered off to prepare the title compound (1g, 71%).
- [591] ¹H NMR (600MHz, CDCl₃-d₁); δ 6.17 (m, 1H), 3.76-3.74 (m, 2H), 3.62-3.59 (m, 2H), 3.33-3.29 (m, 2H), 2.48-2.46 (m, 2H), 2.44-2.42 (m, 2H), 1.75-1.70 (m, 2H).
- [592] Step 3: Synthesis of methyl 4-(4-(7-hydroxyhepta-1,3-diyn-1-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate
- [593] To a solution of 7-(1,2,3,6-tetrahydropyridin-4-yl)hepta-4,6-diyn-1-ol hydrochloride (900mg, 1eq) in DMF (20ml) was added with N,N-diisopropylethylamine (2.79ml, 4eq) and methyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 1) (2.18g, 2eq). The mixture was stirred for 12hr at 60°C, cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (300mg, 19.8%).
- [594] MS (ESI, m/z): 382.2 [M+H]⁺.
- [595] Step 4 - 6: Synthesis of N-hydroxy-4-(4-(7-hydroxyhepta-1,3-diyn-1-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide
- [596] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 4-(4-(7-hydroxyhepta-1,3-diyn-1-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate.
- [597] ¹H NMR (600MHz, DMSO-d₆); δ 10.90 (bs, 1H), 9.09 (bs, 1H), 6.19 (s, 1H), 4.53 (t, J=5.4Hz, 1H), 3.43-3.40 (m, 2H), 3.02 (s, 3H), 2.93-2.99 (m, 2H), 2.52-2.50 (m, 1H), 2.44-2.36 (m, 5H), 2.27-2.24 (m, 1H), 2.16-2.07 (m, 2H), 1.77-1.73 (m, 1H), 1.61-1.56 (m, 2H), 1.41 (s, 3H).
- [598] MS (ESI, m/z): 383.1 [M+H]⁺.
- [599] **Example 55: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide**
- [600]



- [601] Step 1: Synthesis of methyl
2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoate
- [602] To a solution of methyl
4-(4-(4-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 2) (1.27g, 1eq) in a mixture of 1,4-dioxane (12ml)/water (3ml) was added with Pd(PPh₃)₂Cl₂ (0.21g, 0.1eq), K₂CO₃ (1.27g, 3eq) and pyridin-4-ylboronic acid (0.75g, 2eq). The mixture was stirred for 2hr at 110°C, cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (536mg, 41%).
- [603] ¹H NMR (600MHz, CDCl₃-d₁): δ8.65 (d, *J*=6Hz, 2H), 7.61 (d, *J*=8.4Hz, 2H), 7.51-7.49 (m, 4H), 6.16 (s, 1H), 3.70 (s, 3H), 3.28-3.25 (m, 1H), 3.09-3.07 (m, 1H), 3.06 (s, 3H), 2.84-2.82 (m, 1H), 2.70-2.55 (m, 6H), 2.04-2.02 (m, 1H), 2.65 (s, 3H).
- [604] MS (ESI, *m/z*): 429.1 [M+H]⁺.
- [605] Step 2: Synthesis of
2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoic acid
- [606] To a solution methyl
2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoate (536mg, 1eq) in a mixture of THF (8ml)/MeOH (2ml) was added with 2N-LiOH (1.88mL, 3eq) solution. The mixture was stirred for 2hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (10ml) and adjusted the pH to 4.0. The precipitated solid was filtered off to prepare the title compound (476mg, 92%), which was used for next step without further purification.
- [607] MS (ESI, *m/z*): 415.2 [M+H]⁺.
- [608] Step 3: Synthesis of
2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide
- [609] To a solution of of
2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanoic acid (476mg, 1eq) in DMF (10ml) was added with HATU (611mg, 1.4eq), HOBT (246mg, 1.4eq), Et₃N (0.48ml, 3eq) and O-((tetrahydro-2H-pyran-2-yl)hydroxylamine hydrochloride (353mg, 2eq). The mixture was stirred for 1hr at room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare

the title compound (400mg, 68%).

[610] MS (ESI, m/z): 514.3 [M+H]⁺.

[611] Step 4: Synthesis of N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide

[612] To a solution of

2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide (400mg, 1eq) in MeOH (10ml) was added with HCl solution in MeOH (1.25N, 1.87ml, 3eq). The mixture was stirred for 2hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (6ml) and adjusted the pH to 7.0. The water was concentrated in vacuo and the resulting residue was purified with column chromatography to prepare the title compound (91mg, 27%).

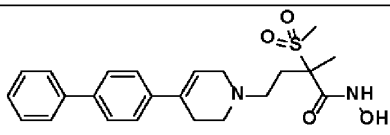
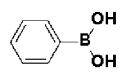
[613] ¹H NMR (600MHz, DMSO-d₆); δ 11.02 (bs, 1H), 9.11 (bs, 1H), 8.59 (d, J=6Hz, 2H), 7.76 (d, J=8.4Hz, 2H), 7.69 (dd, J=4.8Hz, 1.8Hz, 2H), 7.55 (d, J=7.8Hz, 2H), 6.26 (s, 1H), 3.14-3.09 (m, 2H), 3.05 (s, 3H), 2.67-2.58 (m, 2H), 2.52-2.44 (m, 4H), 2.36-2.30 (m, 1H), 1.84-1.80 (m, 1H), 1.45 (s, 3H).

[614] MS (ESI, m/z): 430.1 [M+H]⁺.

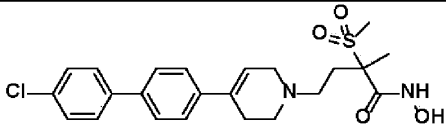
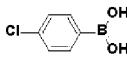
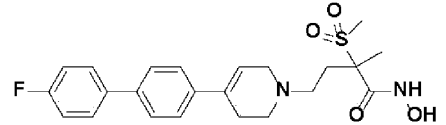
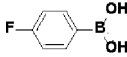
[615] [Examples 56-73]

[616] The Intermediate 2 as a starting material and boronic acid derivatives listed in the following table were used to prepare compounds of Examples 56-73 in the same manner as Example 55.

[617]

Example	Structure (Name)	Boronic acid
56	 (4-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.02 (bs, 1H), 9.10 (bs, 1H), 7.68-7.60 (m, 4H), 7.50-7.48 (m, 2H), 7.45-7.41 (m, 2H), 7.33-7.31 (m, 1H), 6.19 (s, 1H), 3.34-3.28 (m, 6H), 3.15-3.07 (m, 2H), 3.04 (s, 3H), 2.64-2.58 (m, 2H), 1.45 (s, 3H).	

[618]

	MS (ESI, m/z): 429.2 [M+H] ⁺ .	
57	 (4-(4-(4'-chloro-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.02 (bs, 1H), 9.10 (bs, 2H), 7.69-7.66 (m, 2H), 7.62-7.59 (m, 2H), 7.50-7.46 (m, 4H), 6.20 (s, 1H), 3.11-3.08 (m, 2H), 3.04 (s, 3H), 2.65-2.58 (m, 3H), 2.53-2.42 (m, 3H), 2.32-2.28 (m, 1H), 1.85-1.81 (m, 1H), 1.44 (s, 3H). MS (ESI, m/z): 463.1 [M+H]⁺.	
58	 (4-(4-(4'-fluoro-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.10 (bs, 1H), 7.70-7.67 (m, 2H), 7.59-7.58 (m, 2H), 7.49-7.48 (m, 2H), 7.27-7.23 (m, 2H), 6.19 (s, 1H), 3.13-3.05 (m, 2H), 3.04 (s, 3H), 2.66-2.58 (m, 2H), 2.53-2.42 (m, 4H), 2.35-2.28 (m, 2H), 1.45 (s, 3H). MS (ESI, m/z): 447.0 [M+H]⁺.	

[619]

59	(N-hydroxy-4-(4-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆): δ 11.04 (bs, 1H), 10.8 (bs, 1H), 7.60-7.48 (m, 6H), 6.84-6.82 (m, 2H), 6.21 (s, 1H), 4.10-4.00 (m, 2H), 3.99-3.63 (m, 2H), 3.10 (s, 3H), 2.66-2.64 (m, 4H), 2.29-2.21 (m, 2H), 1.53 (s, 3H). MS (ESI, m/z): 445.1 [M+H]⁺.	
60	(4-(4-(3'-fluoro-4'-methoxy-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆): δ 11.03 (bs, 1H), 9.10 (bs, 1H), 7.60-7.44 (m, 6H), 7.22-7.19 (m, 1H), 6.18 (s, 1H), 3.84 (s, 3H), 3.10-3.08 (m, 2H), 3.04 (s, 3H), 2.66-2.57 (m, 2H), 2.50-2.42 (m, 4H), 2.34-2.30 (m, 1H), 1.84-1.80 (m, 1H), 1.45 (s, 3H). MS (ESI, m/z): 477.2 [M+H]⁺.	
61	(N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide)	

[620]

	¹ H NMR (600MHz, DMSO-d ₆); δ 11.00 (bs, 1H), 9.12 (bs, 1H), 8.87 (s, 1H), 8.53-8.52 (m, 1H), 8.05-8.04 (m, 1H), 7.68-7.67 (m, 2H), 7.45-7.44 (m, 2H), 7.45-7.44 (m, 1H), 6.22 (s, 1H), 3.10-3.08 (m, 4H), 3.05 (s, 3H), 2.72-2.69 (m, 2H), 2.58-2.35 (m, 4H), 1.45 (s, 3H). MS (ESI, m/z): 430.1 [M+H] ⁺ .	
62	(4-(4-(4-(6-fluoropyridin-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹ H NMR (600MHz, DMSO-d ₆); δ 11.00 (bs, 1H), 9.11 (bs, 1H), 8.54-8.53 (m, 1H), 8.29 (m, 1H), 7.68-7.66 (m, 2H), 7.54-7.50 (m, 2H), 7.27-7.24 (m, 1H), 6.23 (s, 1H), 3.27-3.26 (m, 4H), 3.16-3.09 (m, 2H), 3.05 (s, 3H), 2.67-2.57 (m, 2H), 2.35-2.30 (m, 2H), 1.45 (s, 3H). MS (ESI, m/z): 448.0 [M+H] ⁺ .	
63	(4-(4-(4-(furan-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹ H NMR (600MHz, DMSO-d ₆); δ 11.02 (bs, 1H), 9.08 (bs, 1H), 8.15 (s, 1H), 7.71-7.70 (m, 1H), 7.53-7.51 (m, 2H), 7.42-7.40 (m, 2H), 6.93 (s, 1H), 6.16 (s, 1H), 3.15-3.06 (m, 2H), 3.04 (s, 3H), 2.68-2.54 (m, 3H), 2.44-2.30 (m, 4H), 1.86-1.80 (m, 1H), 1.45 (s, 3H).	

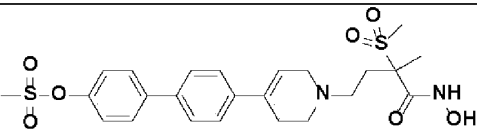
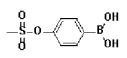
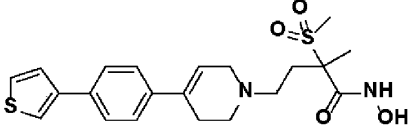
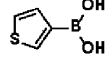
[621]

	MS (ESI, m/z): 419.2 [M+H] ⁺ .	
64	(N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (bs, 1H), 9.10 (bs, 1H), 7.98-7.93 (m, 4H), 7.72-7.70 (m, 2H), 7.55-7.54 (m, 2H), 6.24 (s, 1H), 3.25 (s, 3H), 3.07-3.06 (m, 4H), 3.04 (s, 3H), 2.66-2.59 (m, 4H), 2.35-2.31 (m, 2H), 1.45 (s, 3H). MS (ESI, m/z): 506.9 [M+H]⁺.	
65	(N-hydroxy-4-(4-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.03 (bs, 1H), 9.12 (bs, 1H), 7.61-7.60 (m, 4H), 7.49-7.48 (m, 2H), 7.37-7.36 (m, 2H), 6.19 (s, 1H), 5.20-5.18 (m, 1H), 4.51-4.50 (m, 2H), 3.16-3.06 (m, 2H), 3.05 (s, 3H), 2.74-2.52 (m, 3H), 2.48-2.38 (m, 4H), 1.86-1.80 (m, 1H), 1.46 (s, 3H). MS (ESI, m/z): 459.2 [M+H]⁺.	
66	(4-(4-(4'-cyano-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide)	

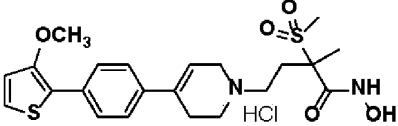
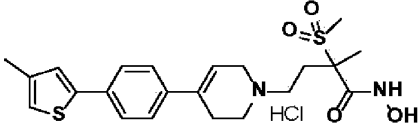
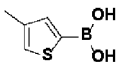
[622]

	(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.02 (bs, 1H), 9.12 (bs, 1H), 7.92-7.86 (m, 4H), 7.71 (d, J=14.4Hz, 2H), 7.54 (d, J=8.4Hz, 2H), 6.25 (s, 1H), 3.16-3.06 (m, 2H), 3.05 (s, 3H), 2.66-2.57 (m, 2H), 2.54-2.46 (m, 4H), 2.36-2.33 (m, 1H), 1.87-1.83 (m, 1H), 1.45 (s, 3H). MS (ESI, m/z): 454.1 [M+H]⁺.	
67	(N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-pentyl-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.03 (bs, 1H), 9.12 (bs, 1H), 7.58 (d, J=9.0Hz, 2H), 7.54 (d, J=8.4Hz, 2H), 7.46 (d, J=9.0Hz, 2H), 7.23 (d, J=7.2Hz, 2H), 6.18 (s, 1H), 3.10-3.07 (m, 2H), 3.04 (s, 3H), 2.65-2.53 (m, 4H), 2.46-2.42 (m, 2H), 2.35-2.28 (m, 1H), 1.87-1.80 (m, 1H), 1.58-1.53 (m, 3H), 1.44 (s, 3H), 1.31-1.18 (m, 5H), 0.85-0.81 (m, 3H). MS (ESI, m/z): 499.2 [M+H]⁺.	
68	(4-(4-(4'-(azetidin-1-ylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.03 (bs, 1H), 9.12 (bs, 1H), 7.98-7.97 (m, 2H), 7.84-7.83 (m, 2H), 7.75-7.74 (m, 2H), 7.57-7.56 (m, 2H), 6.26 (s,	

[623]

	1H), 3.68-3.66 (m, 4H), 3.31-3.30 (m, 2H), 3.13-3.11 (m, 2H), 3.05 (s, 3H), 2.65-2.59 (m, 2H), 2.36-2.32 (m, 2H), 2.01-1.96 (m, 2H), 1.84-1.82 (m, 2H), 1.45 (s, 3H). MS (ESI, m/z): 548.2 [M+H]⁺.	
69	 (4'-(1-(4-(hydroxyamino)-3-methyl-3-(methanesulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)-[1,1'-biphenyl]-4-yl methanesulfonate) ¹H NMR (600MHz, DMSO-d₆); δ 11.02 (bs, 1H), 9.11 (bs, 1H), 7.97-7.92 (m, 4H), 7.22-7.21 (m, 2H), 7.56-7.54 (m, 2H), 6.25 (s, 1H), 3.28 (s, 3H), 3.13-3.09 (m, 4H), 3.05 (s, 3H), 2.66-2.59 (m, 2H), 2.45-2.31 (m, 2H), 1.85-1.82 (m, 2H), 1.45 (s, 3H). MS (ESI, m/z): 506.9 [M+H]⁺.	
70	 (N-hydroxy-2-methyl-2-(methanesulfonyl)-4-(4-(thiophen-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide) ¹H NMR (600MHz, DMSO-d₆); δ 11.05 (bs, 1H), 9.13 (bs, 1H), 7.87 (s, 1H), 7.68-7.67 (m, 2H), 7.63-7.62 (m, 1H), 7.56-7.55 (m, 1H), 7.46-7.45 (m, 2H), 6.20 (s, 1H), 3.15-3.08 (m, 2H), 3.01 (s, 3H), 2.64-2.60 (m, 2H), 2.49-2.32 (m, 5H), 1.85-1.83 (m, 1H), 1.47 (s, 3H). MS (ESI, m/z): 435.2 [M+H]⁺.	

[624]

71	 (N-hydroxy-4-(4-(4-(3-methoxythiophen-2-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide hydrochloride) ¹H NMR (600MHz, DMSO-d₆): δ 11.06 (bs, 1H), 11.11-11.00 (m, 1H), 9.13 (bs, 1H), 7.68-7.67 (m, 2H), 7.51-7.49 (m, 3H), 7.15-7.14 (m, 1H), 6.22 (s, 1H), 4.03-3.97 (m, 2H), 3.90 (s, 3H), 3.77-3.74 (m, 2H), 3.35-3.31 (m, 2H), 3.12 (s, 3H), 3.02-2.85 (m, 2H), 2.74-2.69 (m, 2H), 1.53-1.52 (m, 3H). MS (ESI, m/z): 465.1 [M+H]⁺.	
72	 (N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-methylthiophen-2-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide hydrochloride) ¹H NMR (600MHz, DMSO-d₆): δ 11.06 (bs, 1H), 10.45-10.40 (m, 1H), 9.15 (bs, 1H), 7.63-7.62 (m, 2H), 7.53-7.52 (m, 2H), 7.38 (s, 1H), 7.13 (s, 1H), 6.26 (s, 1H), 4.23-3.70 (m, 2H), 3.42-3.31 (m, 5H), 3.11 (s, 3H), 3.01-2.69 (m, 3H), 2.23 (s, 3H), 1.53-1.52 (m, 3H). MS (ESI, m/z): 449.1 [M+H]⁺.	

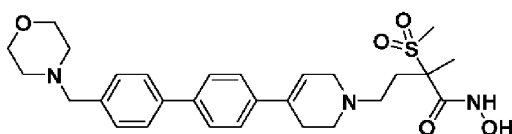
[625]

73	 (4-(4-(4'-(ethylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide hydrochloride) ¹ H NMR (600MHz, DMSO-d ₆): δ 11.06 (m, 1H), 10.06 (bs, 1H), 9.31 (s, 1H), 7.99-7.95 (m, 4H), 7.82 (d, J=7.8Hz, 2H), 7.66 (d, J=7.8Hz, 2H), 6.34 (s, 1H), 4.18-4.06 (m, 1H), 3.92-3.70 (m, 2H), 3.11 (s, 3H), 3.08-3.02 (m, 1H), 2.86-2.82 (m, 2H), 2.72-2.54 (m, 2H), 2.22-2.14 (m, 2H), 2.02-1.98 (m, 2H), 1.52 (s, 3H), 1.12 (t, J=7.2Hz, 3H). MS (ESI, m/z): 521.1 [M+H] ⁺ .	
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[626]

Example 74: Synthesis of N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-(morpholinomethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide

[627]



[628]

Step 1: Synthesis of methyl 4-(4-(4'-formyl-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

[629]

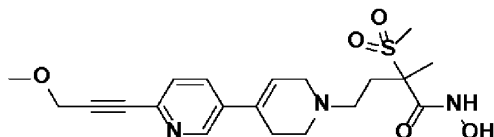
To a solution of methyl 4-(4-(4'-iodophenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 2) (1.5g, 1eq) in a mixture of 1,4-dioxane (12ml)/ water (3ml) was added with Pd(PPh₃)₂Cl₂ (0.37g, 0.1eq), K₂CO₃ (1.34g, 3eq) and (4-formylphenyl)boronic acid (0.97g, 2eq). The mixture was stirred for 2hr at 110°C, cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (1g, 68%).

[630]

¹H NMR (600MHz, CDCl₃-d₁): δ 10.04 (s, 1H), 7.94-7.92 (m, 2H), 7.74-7.71 (m, 2H), 7.63-7.60 (m, 2H), 7.49-7.45 (m, 2H), 6.08 (s, 1H), 3.87 (s, 3H), 3.79-76 (m, 2H), 3.66-3.56 (m, 2H), 3.42-3.26 (m, 2H), 3.13 (s, 3H), 2.92-2.72 (m, 4H), 1.74 (s, 3H).

- [631] MS (ESI, m/z): 456.2 [M+H]⁺.
- [632] Step 2: Synthesis of methyl
2-methyl-2-(methylsulfonyl)-4-(4-(4'-(morpholinomethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanoate
- [633] To a solution of methyl
4-(4-(4'-formyl-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanoate (500mg, 1eq) in THF (11ml) was added with morpholine (0.19ml, 2eq) and sodium triacetoxyborohydride (930mg, 4eq). The mixture was stirred for 2hr at room temperature, quenched with sat. aq. NaHCO₃, and extracted with dichloromethane and water. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (450mg, 78%).
- [634] ¹H NMR (600MHz, CDCl₃-d1); δ 7.55-7.53 (m, 4H), 7.44-7.43 (m, 2H), 7.40-7.38 (m, 2H), 6.11-6.10 (m, 1H), 3.74-3.72 (m, 4H), 3.69 (s, 3H), 3.55 (s, 2H), 3.28-3.24 (m, 1H), 3.10-3.02 (m, 1H), 3.05 (s, 3H), 2.86-2.78 (m, 1H), 2.68-2.58 (m, 4H), 2.56-2.46 (m, 6H), 2.06-1.98 (m, 1H), 1.64 (s, 3H).
- [635] Step 3 - 5: Synthesis of N-
hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-(morpholinomethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide
- [636] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 from methyl
2-methyl-2-(methylsulfonyl)-4-(4-(4'-(morpholinomethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanoate.
- [637] ¹H NMR (600MHz, DMSO-d₆); δ 11.01 (s, 1H), 9.12 (s, 1H), 7.61-7.60 (m, 4H), 7.50-7.48 (m, 2H), 7.37-7.35 (m, 2H), 6.20 (s, 1H), 3.56-3.55 (m, 4H), 3.10-3.08 (m, 2H), 3.05 (s, 3H), 2.66-2.59 (m, 2H), 2.51-2.43 (m, 4H), 2.37-2.30 (m, 5H), 1.84-1.80 (m, 1H), 1.45 (s, 3H).
- [638] MS (ESI, m/z): 528.25 [M+H]⁺.
- [639] **Example 75: Synthesis of N-
hydroxy-4-(6-(3-methoxyprop-1-yn-1-yl)-3',6'-dihydro-[3,4'-bipyridin]-1'(2'H)-yl)-2-methyl-2-(methylsulfonyl)butanamide**

[640]



- [641] Step 1: Synthesis of 5-bromo-2-(3-methoxyprop-1-yn-1-yl)pyridine
- [642] To a solution of 2,5-dibromopyridine (5g, 1eq) in toluene (60ml) was added with CuI

(80mg, 0.02eq), Pd(PPh₃)₂Cl₂ (150mg, 0.01eq), Et₃N (5.96ml, 2eq) and 3-methoxyprop-1-yne (1.6g, 1.05eq). The mixture was stirred for 24hr at room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (4.3g, 90%).

[643] ¹H NMR (600MHz, CDCl₃-d₁) δ: 8.62 (s, 1H), 7.78 (m, 1H), 7.73 (d, 1H), 4.32 (s, 2H), 3.45 (s, 3H). MS (ESI, m/z) : 228.0 [M+H]⁺.

[644] Step 2: Synthesis of tert-butyl

6-(3-methoxyprop-1-yn-1-yl)-3',6'-dihydro-[3,4'-bipyridine]-1'-(2'H)-carboxylate

[645] To a solution of 5-bromo-2-(3-methoxyprop-1-yn-1-yl)pyridine (4.3g, 1eq) in a mixture of 1,4-dioxane (80ml) / water (20ml) was added with Pd(PPh₃)₂Cl₂ (1.3g, 0.1eq), K₂CO₃ (5.3g, 2eq) and tert-butyl

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (7.7g, 1.3eq). The mixture was stirred for 2hr at 110°C, cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (2g, 32%).

[646] ¹H NMR (600MHz, CDCl₃-d₁) δ: 7.64 (dd, 1H), 7.52 (m, 1H), 7.47 (m, 1H), 4.36 (s, 2H), 4.02 (m, 2H), 3.46-3.45 (m, 2H), 2.82 (m, 1H), 1.26 (s, 9H).

[647] MS (ESI, m/z): 329.1 [M+H]⁺.

[648] Step 3: Synthesis of

6-(3-methoxyprop-1-yn-1-yl)-1',2',3',6'-tetrahydro-3,4'-bipyridine 2,2,2-trifluoroacetate

[649] To a solution of tert-butyl

6-(3-methoxyprop-1-yn-1-yl)-3',6'-dihydro-[3,4'-bipyridine]-1'-(2'H)-carboxylate (2g, 1eq) in dichloromethane (90ml) was added with trifluoroacetic acid (50ml, excess) at 0 °C. The mixture was stirred for 2hr at room temperature and concentrated in vacuo to prepare the title compound (2g, 96%).

[650] MS (ESI, m/z): 229.1 [M+H]⁺.

[651] Step 4: Synthesis of methyl

4-(6-(3-methoxyprop-1-yn-1-yl)-3',6'-dihydro-[3,4'-bipyridin]-1'-(2'H)-yl)-2-methyl-2-(methylsulfonyl)butanoate

[652] To a solution of 6-(3-methoxyprop-1-yn-1-yl)-1',2',3',6'-tetrahydro-3,4'-bipyridine 2,2,2-trifluoroacetate (1g, 1eq) in DMF (15ml) was added with Et₃N (1.23ml, 3eq) and methyl 4-bromo-2-methyl-2-(methylsulfonyl)butanoate (Intermediate 1) (957mg, 1.2eq). The mixture was stirred for 12hr at 60°C, cooled room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (1.1g, 89%).

[653] ^1H NMR (600MHz, $\text{CDCl}_3\text{-d}_1$); δ 7.62 (m, 1H), 7.95 (m, 1 H), 7.66 (m, 1 H), 6.15 (s, 1H), 4.33(s, 2H), 3.67,(s, 3H), 3.45(s, 3H), 3.25(m, 1H), 3.07(m, 1H), 3.03(s, 3H), 2.81(m, 1H) 2.63-2.57(m, 3H), 2.57(m, 2H), 1.62(s, 3H).

[654] MS (ESI, m/z): 421.2 $[\text{M}+\text{H}]^+$.

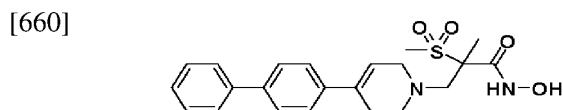
[655] Step 5 - 7: Synthesis of N-hydroxy-4-(6-(3-methoxyprop-1-yn-1-yl)-3',6'-dihydro-[3,4'-bipyridin]-1'(2'H)-yl)-2-methyl-2-(methylsulfonyl)butanamide

[656] The title compound was prepared the procedures described for the synthesis of Example 1, step 2 - 4 (Synthesis of Hydroxamate) from methyl 4-(6-(3-methoxyprop-1-yn-1-yl)-3',6'-dihydro-[3,4'-bipyridin]-1'(2'H)-yl)-2-methyl-2-(methylsulfonyl)butanoate.

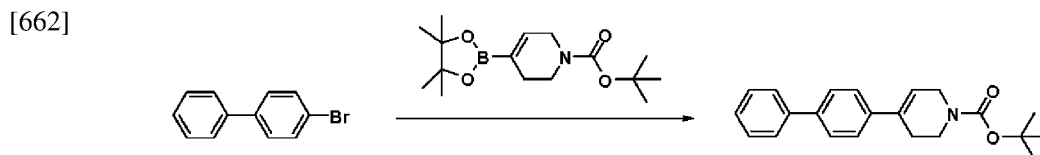
[657] ^1H NMR (600MHz, DMSO-d_6); δ 11.01 (bs, 1H), 8.72 (bs, 1 H), 7.93 (dd, 1 H), 7.57 (d, 1H), 6.41(s, 2H), 4.35,(s, 2H), 4.13(m, 1H), 4.01(m, 1H), 3.84(m, 1H), 3.76(m, 1H), 3.27(m, 1H), 3.19(m, 1H), 3.14(s, 3H), 2.98(m, 1H,) 2.87(m, 1H) 2.68(m, 1H), 2.25(m, 1H), 1.50(s, 3H).

[658] MS (ESI, m/z): 415.1 $[\text{M}+\text{H}]^+$.

[659] **Example 76: Synthesis of 3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide**



[661] Step 1: Synthesis of tert-butyl 4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate

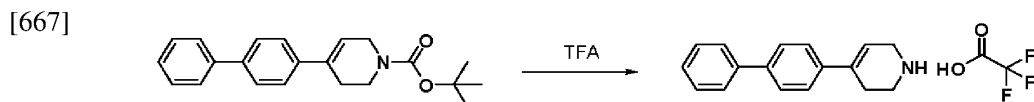


[663] To a solution of 4-bromo-1,1'-biphenyl (2g, 1eq) in a mixture of 1,4-dioxane (24ml) / water (6ml) was added with $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (0.6g, 0.1eq), K_2CO_3 (2.37g, 2eq) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (3.45g, 1.3eq). The mixture was stirred for 2hr at 110°C , cooled down to room temperature, and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (1.65g, 57%).

[664] ^1H NMR (600MHz, DMSO-d_6); δ 7.40-7.37 (m, 4H), 7.26-7.16 (m, 4H), 7.08-7.05 (m, 1H), 6.15 (s, 1H), 4.11 (s, 2H), 3.62 (s, 2H), 2.50 (s, 2H), 1.49(s, 9H).

[665] MS (ESI, m/z): 336.3 [M+H]⁺.

[666] Step 2: Synthesis of 4-([1,1'-biphenyl]-4-yl)-1,2,3,6-tetrahydropyridine 2,2,2-trifluoroacetate

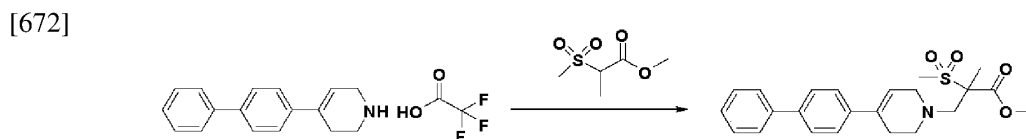


[668] To a solution of tert-butyl 4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridine-1(2H)-carboxylate (1.1g, 1eq) in dichloromethane (10ml) was added with trifluoroacetic acid (2ml, 8eq). The mixture was stirred for 1hr at room temperature and concentrated in vacuo. The residue was diluted with dichloromethane and poured into excess diethyl ether. The precipitated solid was filtered off to prepare the title compound (1.08g, 94%).

[669] ¹H NMR (600MHz, DMSO-d₆): δ8.68 (brs, 2H), 7.52-7.48 (m, 4H), 7.43-7.39 (m, 4H), 7.08-7.05 (m, 1H), 6.15 (s, 1H), 3.76 (s, 2H), 3.25 (s, 2H), 2.65 (s, 2H).

[670] MS (ESI, m/z): 236.1 [M+H]⁺.

[671] Step 3: Synthesis of methyl 3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)propanoate



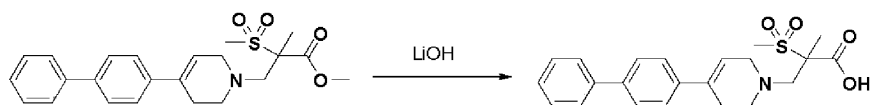
[673] To a solution of 4-([1,1'-biphenyl]-4-yl)-1,2,3,6-tetrahydropyridine 2,2,2-trifluoroacetate (1g, 1eq) in a mixture of MeOH (30ml) / THF (10ml) was added with Et₃N (2ml, 5eq), formaldehyde (37% in water, 0.5ml, 2.2eq) and methyl 2-(methylsulfonyl)propanoate (0.95g, 2eq). The mixture was stirred for 24hr at room temperature and concentrated in vacuo. The residue was extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (0.25g, 21%).

[674] ¹H NMR (600MHz, CDCl₃-d₁): δ7.70-7.65 (m, 4H), 7.61-7.58 (m, 2H), 7.48-7.42 (m, 2H), 7.40-7.35 (m, 1H), 6.03 (s, 1H), 3.85 (s, 3H), 3.31 (d, 1H, J=14.4 Hz), 3.26 (s, 2H), 3.18 (s, 3H), 3.05 (d, 1H, J=13.8 Hz), 2.81 (t, 2H, J=6.0Hz), 2.58-2.46 (m, 2H), 1.69(s, 3H).

[675] MS (ESI, m/z): 413.2 [M+H]⁺.

[676] Step 4: Synthesis of 3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)propanoic acid

[677]



[678]

To a solution of methyl 3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)propanoate (200mg, 1eq) in THF (10ml) was added with 1N-LiOH in MeOH (5ml, 8.3eq). The mixture was stirred for 3hr at room temperature. The solvent was removed under reduced pressure. The residue was acidified with 2N-HCl and extracted ethyl acetate. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo to prepare the title compound (200mg, 83%).

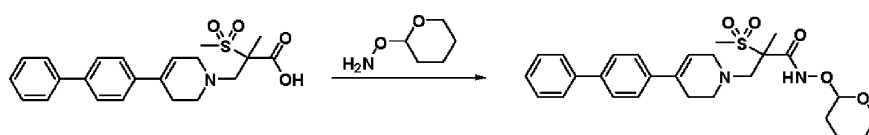
[679]

MS (ESI, m/z): 400.10 $[\text{M}+\text{H}]^+$.

[680]

Step 5: Synthesis of 3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide

[681]



[682]

To a solution of methyl 3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)propanoate (50mg, 1eq) in DMF (2ml) was added with HATU (67mg, 1.4eq), HOBT (24mg, 1.4eq), Et_3N (0.053ml, 3eq) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine hydrochloride (29mg, 2eq). The mixture was stirred for 1hr at room temperature and extracted with ethyl acetate and water. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (50mg, 80%).

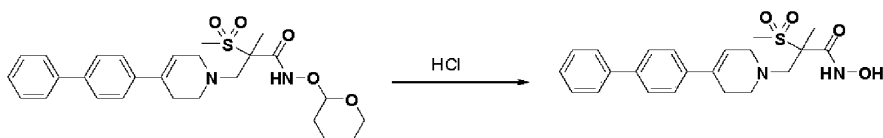
[683]

MS (ESI, m/z): 499.2 $[\text{M}+\text{H}]^+$.

[684]

Step 6: Synthesis of 3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide

[685]



[686]

To a solution of 3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)propanamide (30mg, 1eq) in MeOH (1.5ml) was

added with HCl solution in MeOH (1.25N, 0.1ml, 2eq). The mixture was stirred for 2hr at room temperature. The solvent was removed under reduced pressure. The residue was diluted with water (6ml) and adjusted the pH to 7.0. The water was concentrated and the resulting residue was purified with column chromatography to prepare the title compound (10mg, 40%).

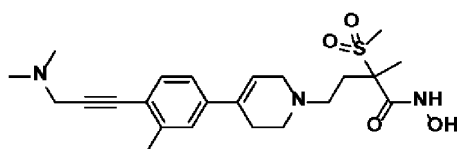
[687] ^1H NMR (600MHz, DMSO- d_6); δ 11.3 (bs, 1H), 9.51 (bs, 1H), 7.70-7.65 (m, 4H), 7.61-7.58 (m, 2H), 7.48-7.42 (m, 2H), 7.40-7.35 (m, 1H) 6.25 (s, 1H), 4.18-3.91 (m, 2H), 3.61-3.49 (m, 4H), 3.15 (s, 3H), 2.47-2.40 (m, 2H), 1.48 (s, 3H).

[688] MS (ESI, m/z): 415.1 [M+H] $^+$.

[689] **Example 77:** Synthesis of

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-methylphenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[690]



[691] The title compound was prepared the procedures described for the synthesis of Example 31 using 4-bromo-1-iodo-2-methylbenzene as a starting material.

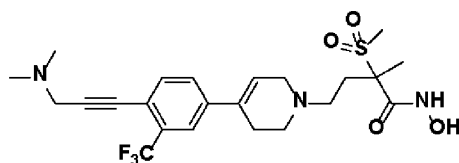
[692] ^1H NMR (600MHz, DMSO- d_6); δ 11.03 (bs, 1H), 9.13 (bs, 1H), 7.34-7.33 (m, 2H), 7.24-7.23 (m, 1H), 6.20 (s, 1H), 3.50 (s, 2H), 3.12-3.10 (m, 2H), 3.07 (s, 3H), 2.66-2.63 (m, 2H), 2.48-2.44 (m, 4H), 2.39 (s, 3H), 2.25 (s, 6H), 1.84-1.82 (m, 2H), 1.43 (s, 3H).

[693] MS (ESI, m/z): 448.2 [M+H] $^+$.

[694] **Example 78:** Synthesis of

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-(trifluoromethyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide

[695]



[696] The title compound was prepared the procedures described for the synthesis of Example 31 using 4-bromo-1-iodo-2-(trifluoromethyl)benzene as a starting material.

[697] ^1H NMR (600MHz, DMSO- d_6); δ 11.03 (bs, 1H), 9.11 (bs, 1H), 7.71-7.69 (m, 2H), 7.63-7.62 (m, 1H), 6.36 (s, 1H), 3.50 (s, 2H), 3.32 (s, 3H), 3.17-3.16 (m, 2H), 2.66-2.57 (m, 2H), 2.46-2.32 (m, 4H), 2.23 (s, 6H), 1.83-1.80 (m, 2H), 1.45 (s, 3H).

- [698] MS (ESI, m/z): 502.2 [M+H]⁺.
- [699] **Experimental** example 1: In vitro test for antibiotic activity
- [700] To measure the antibiotic activity of the compounds prepared by Examples, antibiotic activity test in vitro was performed by agar dilution method using Mueller-Hinton agar according to the NCCLS (National Committee for Clinical Laboratory Standards, 2000. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard, NCCLS document M7-M5, 5thed, vol 20, no 2. National Committee for Clinical Laboratory Standards, Wayne, PA.). The test strain was *Escherichia coli* (ATCC 25922), *Klebsiella pneumonia* (ATCC 29665) and *Pseudomonas aeruginosa* (PAO1). Their minimum Inhibitory Concentration (MIC, ug/ml) are summarized in Table 1.
- [701] <Table 1>

[702]

Example	MIC for <i>E.coli</i> ATCC 25922	MIC for <i>K.pneumoniae</i> ATCC 29665	MIC for <i>P.aeruginosa</i> PAO1
1	D	D	D
2	A	B	B
3	D	B	D
4	A	A	B
5	B	C	B
6	A	B	C
7	B	B	B
8	D	D	D
9	A	B	D
10	B	C	C
11	A	B	B
12	C	C	D
13	A	B	C
14	A	B	B
15	B	C	B
16	B	B	B
17	D	C	B
18	A	B	B
19	A	B	B
20	B	C	C
21	C	D	D
22	B	D	B
23	A	B	B
24	B	B	B
25	B	B	B

[703]

26	B	C	B
27	A	B	B
28	A	A	B
29	A	B	B
30	A	B	B
31	A	B	B
32	A	B	B
33	B	C	B
34	A	B	B
35	D	D	D
36	A	B	B
37	A	D	D
38	A	B	B
39	C	C	C
40	B	B	B
41	B	C	C
42	A	B	B
43	A	B	B
44	A	B	B
45	A	B	B
46	A	B	B
47	A	B	A
48	A	B	A
49	A	B	A
50	A	B	A
51	D	D	D
52	C	D	D
53	B	B	D
54	C	D	D
55	B	B	B
56	A	A	C
57	B	D	D
58	A	B	D

[704]

59	A	C	C
60	A	C	D
61	B	D	B
62	A	B	B
63	A	A	C
64	A	B	B
65	A	C	D
66	A	B	D
67	C	D	D
68	A	B	B
69	A	A	C
70	A	A	D
71	A	A	D
72	A	A	D
73	A	B	B
74	A	A	B
75	D	D	D
76	D	D	D

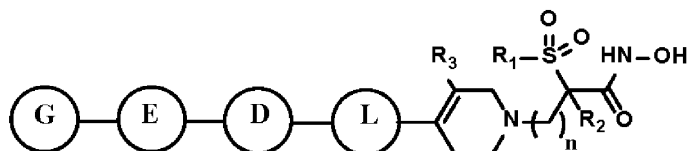
[705] MIC key:

[706] A = MIC's of 1.0 $\mu\text{g/mL}$ or less[707] B = MIC's of greater than 1.0 $\mu\text{g/mL}$ to 8.0 $\mu\text{g/mL}$ [708] C = MIC's of greater than 8.0 $\mu\text{g/mL}$ to 16.0 $\mu\text{g/mL}$ [709] D = MIC's of greater than 16 $\mu\text{g/mL}$

Claims

[Claim 1]

A tetrahydropyridine compound represented by the following formula I, a stereoisomer thereof or a pharmaceutically acceptable salt thereof:
[Formula I]



wherein,

n is 1, 2 or 3;

R₁ is C1-C6 alkyl or C1-C6 haloalkyl;

R₂ is hydrogen or C1-C6 alkyl;

R₃ is hydrogen, C1-C6 alkyl, C1-C6 alkoxy, -OH or halogen;

L is C3-C7 cycloalkyl, aryl, heteroaryl or null, wherein at least one H of C3-C7 cycloalkyl, aryl or heteroaryl may be substituted with halogen, C1-C6 alkyl, C1-C6 haloalkyl, -NR_AR_B or -OH;

D is C≡C, C3-C7 cycloalkyl, aryl, heteroaryl or null, wherein at least one H of C3-C7 cycloalkyl, aryl or heteroaryl may be substituted with halogen, C1-C6 alkyl, C1-C6 haloalkyl, -NR_AR_B or -OH;

E is C≡C, C3-C7 cycloalkyl, aryl, heteroaryl or null, wherein at least one H of C3-C7 cycloalkyl, aryl or heteroaryl may be substituted with halogen, C1-C6 alkyl, C1-C6 haloalkyl, -NR_AR_B or -OH;

G is C1-C6 alkyl, C3-C7 cycloalkyl, 4-6 membered heterocycloalkyl, aryl or heteroaryl,

wherein at least one H of C1-C6 alkyl may be substituted with halogen, -NR_AR_B, -OH or -OR_C,

at least one H of C3-C7 cycloalkyl or 4-6 membered heterocycloalkyl may be substituted with C1-C6 alkyl, C1-C6 alkyl-NR_AR_B, C1-C6 hydroxyalkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 alkyl-OR_C, -NR_AR_B, -OH, -(C=O)-C1-C6 alkyl or -S(=O)₂-C1-C6 alkyl,

at least one H of aryl or heteroaryl may be substituted with C1-C6 alkyl, C1-C6 hydroxyalkyl, C1-C6 alkyl-NR_AR_B, halogen, nitro, cyano, -NR_AR_B, -OH, -OR_C, -S(=O)₂-C1-C6 alkyl, -S(=O)₂-NR_AR_B or -N-S(=O)₂-C1-C6 alkyl;

R_A and R_B are each independently hydrogen or C1-C6 alkyl, or R_A and R_B may be linked together to form 4-6 membered ring, wherein the 4-6 membered ring may have O or S atom and at least one H of the 4-6

- membered ring may be substituted with halogen, -OH or C1-C6 hydroxyalkyl;
 R_C is C1-C6 alkyl, C1-C6 hydroxyalkyl, $-(C=O)-NR_D R_E$ or $-S(=O)_2$ -C1-C6 alkyl; and
 R_D and R_E are each independently hydrogen or C1-C6 alkyl.
- [Claim 2] The tetrahydropyridine compound, a stereoisomer thereof or a pharmaceutically acceptable salt thereof according to claim 1:
 wherein,
 n is 1 or 2;
 R_1 is C1-C6 alkyl;
 R_2 is C1-C6 alkyl;
 R_3 is hydrogen;
 L is aryl, heteroaryl or null, wherein at least one H of aryl or heteroaryl may be substituted with halogen, C1-C6 alkyl or C1-C6 haloalkyl;
 D is $C\equiv C$ or null;
 E is $C\equiv C$ or null;
 G is C1-C6 alkyl, C3-C7 cycloalkyl, 4-6 membered heterocycloalkyl, aryl or heteroaryl,
 wherein at least one H of C1-C6 alkyl may be substituted with halogen, $-NR_A R_B$, -OH or $-OR_C$,
 at least one H of 4-6 membered heterocycloalkyl may be substituted with C1-C6 alkyl, $-(C=O)-C1-C6$ alkyl or $-S(=O)_2-C1-C6$ alkyl,
 at least one H of aryl or heteroaryl may be substituted with C1-C6 alkyl, C1-C6 hydroxyalkyl, C1-C6 alkyl- $NR_A R_B$, halogen, nitro, cyano, $-NR_A R_B$, -OH, $-OR_C$, $-S(=O)_2-C1-C6$ alkyl or $-S(=O)_2-NR_A R_B$;
 R_A and R_B are each independently hydrogen or C1-C6 alkyl, or R_A and R_B may be linked together to form 4-6 membered ring, wherein the 4-6 membered ring may have O atom and at least one H of the 4-6 membered ring may be substituted with C1-C6 hydroxyalkyl;
 R_C is C1-C6 alkyl, C1-C6 hydroxyalkyl, $-(C=O)-NR_D R_E$ or $-S(=O)_2$ -C1-C6 alkyl; and
 R_D and R_E are each independently hydrogen.
- [Claim 3] The tetrahydropyridine compound, a stereoisomer thereof or a pharmaceutically acceptable salt thereof according to claim 2:
 wherein,
 n is 1 or 2;
 R_1 is C1-C6 alkyl;
 R_2 is C1-C6 alkyl;

R₃ is hydrogen;

L is phenyl, pyridinyl or null, wherein at least one H of phenyl or pyridinyl may be substituted with halogen, C1-C6 alkyl or C1-C6 haloalkyl;

D is C≡C or null;

E is C≡C or null;

G is C1-C6 alkyl, C3-C6 cycloalkyl, 4-6 membered heterocycloalkyl, phenyl, pyridinyl, furanyl, thiophenyl or imidazolyl, wherein at least one H of C1-C6 alkyl may be substituted with halogen, -NR_AR_B, -OH or -OR_C,

at least one H of 4-6 membered heterocycloalkyl may be substituted with C1-C6 alkyl, -(C=O)-C1-C6 alkyl or -S(=O)₂-C1-C6 alkyl,

at least one H of phenyl, pyridinyl, furanyl, thiophenyl or imidazolyl may be substituted with C1-C6 alkyl, C1-C6 hydroxyalkyl, C1-C6 alkyl-NR_AR_B, halogen, nitro, cyano, -NR_AR_B, -OH, -OR_C, -S(=O)₂-C1-C6 alkyl or -S(=O)₂-NR_AR_B;

R_A and R_B are each independently hydrogen or C1-C6 alkyl, or R_A and R_B may be linked together to form 4-6 membered ring, wherein the 4-6 membered ring may have O atom and at least one H of the 4-6 membered ring may be substituted with C1-C6 hydroxyalkyl;

R_C is C1-C6 alkyl, C1-C6 hydroxyalkyl, -(C=O)-NR_DR_E or -S(=O)₂-C1-C6 alkyl; and

R_D and R_E are each independently hydrogen.

[Claim 4]

The tetrahydropyridine compound, a stereoisomer thereof or a pharmaceutically acceptable salt thereof according to claim 3, wherein the compound is selected from the group consisting of compounds described in the following table:

1)

4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

2) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(phenylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

3) N-

hydroxy-4-(4-(4-((4-methoxyphenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

4)

4-(4-(4-(cyclopropylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-h

ydroxy-2-methyl-2-(methylsulfonyl)butanamide;

5) N-

hydroxy-4-(4-(4-(4-hydroxybut-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

6)

4-(4-(4-(hex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

7)

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

8) N-

hydroxy-4-(4-(4-(3-hydroxybut-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

9)

4-(4-(4-(cyclopentylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

10)

4-(4-(4-(cyclohexylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

11) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

12)

4-(4-(4-(3-cyclohexylprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

13) N-

hydroxy-2-methyl-4-(4-(4-(4-methylpent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide;

14)

4-(4-(4-(5-chloropent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

15) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-(pyrrolidin-1-yl)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

16)

4-(4-(4-(3-(diethylamino)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

17) N-

hydroxy-4-(4-(4-(3-((S)-2-(hydroxymethyl)pyrrolidin-1-yl)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

18) N-

hydroxy-4-(4-(4-(5-hydroxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

19)

5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl methanesulfonate;

20)

4-(4-(4-(5-(dimethylamino)pent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

21)

4-(4-(4-(5-aminopent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

22) N-

hydroxy-4-(4-(4-(3-hydroxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

23) N-

hydroxy-4-(4-(4-(3-methoxyprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

24) N-

hydroxy-4-(4-(4-(3-(3-hydroxypropoxy)prop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

25) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(3-morpholinoprop-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

26)

3-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)prop-2-yn-1-yl carbamate;

27)

5-(4-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)pent-4-yn-1-yl carbamate;

28) N-

hydroxy-4-(4-(4-(5-methoxypent-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

29) N-

hydroxy-4-(4-(4-(6-hydroxyhex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-

- 1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- 30) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(6-morpholinohex-1-yn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- 31) 4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- 32) 4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3,5-difluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- 33) 4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-2-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- 34) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(thiophen-2-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- 35) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-((4-nitrophenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- 36) N-hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-3-ylethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
- 37) N-hydroxy-4-(4-(4-((4-hydroxyphenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
- 38) N-hydroxy-2-methyl-4-(4-(4-((1-methyl-1H-imidazol-4-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide;
- 39) N-hydroxy-2-methyl-4-(4-(4-((1-methylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-(methylsulfonyl)butanamide;
- 40) 4-(4-(4-((1-acetylazetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
- 41) N-

- hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-((1-(methylsulfonyl)azetidin-3-yl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
42)
- 4-(4-(3-fluoro-4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
43)
- 4-(4-(3-fluoro-4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
44)
- 4-(4-(4-(cyclopropylbuta-1,3-diyn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
45)
- 4-(4-(4-(5-(dimethylamino)penta-1,3-diyn-1-yl)-3-fluorophenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
46) N-
- hydroxy-4-(4-(4-(7-hydroxyhepta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
47) N-
- hydroxy-4-(4-(4-(6-hydroxyhexa-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
48) N-
- hydroxy-4-(4-(4-(5-hydroxypenta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
49)
- 4-(4-(4-(5-(dimethylamino)penta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;
50) N-
- hydroxy-4-(4-(4-(5-methoxypenta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;
51) N-
- hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(phenylbuta-1,3-diyn-1-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
52) N-
- hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(pyridin-4-ylethynyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;
53)
- 4-(4-((4-bromophenyl)ethynyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydrox

y-2-methyl-2-(methylsulfonyl)butanamide;

54) N-

hydroxy-4-(4-(7-hydroxyhepta-1,3-diyne-1-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

55) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-4-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

56)

4-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

57)

4-(4-(4'-chloro-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

58)

4-(4-(4'-fluoro-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

59) N-

hydroxy-4-(4-(4'-hydroxy-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

60)

4-(4-(3'-fluoro-4'-methoxy-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

61) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(pyridin-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

62)

4-(4-(4-(6-fluoropyridin-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

63)

4-(4-(4-(furan-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

64) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

65) N-

hydroxy-4-(4-(4'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

66)

4-(4-(4'-cyano-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

67) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-pentyl-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

68)

4-(4-(4'-(azetidin-1-ylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

69)

4'-(1-(4-(hydroxyamino)-3-methyl-3-(methylsulfonyl)-4-oxobutyl)-1,2,3,6-tetrahydropyridin-4-yl)-[1,1'-biphenyl]-4-yl methanesulfonate;

70) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(thiophen-3-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

71) N-

hydroxy-4-(4-(4-(3-methoxythiophen-2-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

72) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4-(4-methylthiophen-2-yl)phenyl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

73)

4-(4-(4'-(ethylsulfonyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide;

74) N-

hydroxy-2-methyl-2-(methylsulfonyl)-4-(4-(4'-(morpholinomethyl)-[1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)butanamide;

75) N-

hydroxy-4-(6-(3-methoxyprop-1-yn-1-yl)-3',6'-dihydro-[3,4'-bipyridin]-1'(2'H)-yl)-2-methyl-2-(methylsulfonyl)butanamide;

76)

3-(4-([1,1'-biphenyl]-4-yl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)propanamide;

77)

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-methylphenyl)-3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide; and

78)

4-(4-(4-(3-(dimethylamino)prop-1-yn-1-yl)-3-(trifluoromethyl)phenyl)-

- 3,6-dihydropyridin-1(2H)-yl)-N-hydroxy-2-methyl-2-(methylsulfonyl)butanamide.
- [Claim 5] A method for inhibiting UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase (LpxC), comprising administering to a patient in need thereof a therapeutically effective amount of the compound represented by formula I, stereoisomer thereof or pharmaceutically acceptable salt thereof according to claim 1.
- [Claim 6] A method for treating bacterial infections, comprising administering to a patient in need thereof a therapeutically effective amount of the compound represented by formula I, stereoisomer thereof or pharmaceutically acceptable salt thereof according to claim 1.
- [Claim 7] The method of claim 6, wherein the bacterial infections are caused by Gram-negative bacteria.
- [Claim 8] The method of claim 7, wherein the bacterial infections are selected from the group consisting of nosocomial pneumonia, urinary tract infections, systemic infections, skin and soft tissue infections, surgical infections, intraabdominal infections, lung infections, endocarditis, diabetic foot infection, osteomyelitis, and central nervous system infections.
- [Claim 9] Use of the compound represented by formula I, stereoisomer thereof or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4 in preparation of a medicament for treating bacterial infections.
- [Claim 10] A pharmaceutical composition for preventing or treating bacterial infections, comprising, as an active ingredient, the compound represented by formula I, stereoisomer thereof or pharmaceutically acceptable salt thereof according to any one of claims 1 to 4.