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] **Methodsforpreparationofthe**tetrahydropyidine 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.

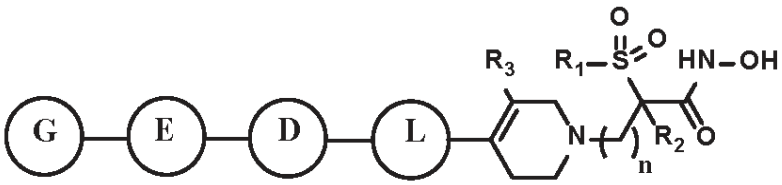
[154] These methods can be used either directly or with obvious variations to trained chemists to prepare key intermediates and certain compounds of this invention

[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 Elesvier 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 disclosureare illustrated below.

[157] [General Procedure 1]

[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 pneumoniae (including those encoding extended-spectrum beta-lactamases (hereinafter "ESBLs")), *Legionella* pneumophila, Moraxella catarrhalis (beta-lactamase positive and negative), *Morganella* morganii, Neisseria gonorrhoeae, Neisseria meningitides, 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 marcescenes, Treponema spp., Burkholderia cepacia, Vibrio spp., Yersinia spp., and *Stenotrophomonas maltophilia*.

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 pneumoniae, 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.

added with CuI (20mg, 0.1eq), $Pd(PPh_3)_2Cl_2$ (74mg, 0.1eq), Et_3N (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 $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (225mg, 43%).

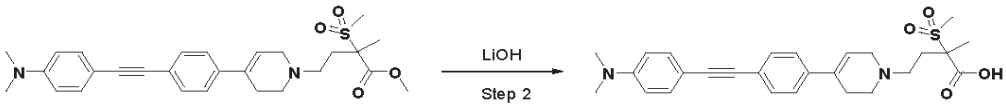
[206] ^{1}H NMR (600MHz, $CDCl_3$-d1);δ7.43 (d, *J*=8.4Hz, 2H), 7.39 (d, *J*=9Hz, 2H), 7.32 (d, *J*=9Hz, 2H), 6.65 (d, *J*=8.4Hz, 2H), 6.08 (s, 1H), 3.87 (s, 3H), 3.24-3.22 (m, 1H), 3.07-3.05 (m, 1H), 3.04 (s, 3H), 2.98 (s, 6H), 2.82-2.76 (m, 1H), 2.67-2.56 (m, 4H), 2.62-2.58 (m, 2H), 2.03-2.00 (m, 1H), 1.63 (s, 3H).

[207] MS (ESI, m/z): 495.3 $[M+H]^+$.

[208] Step 2: Synthesis of

To a solution of 4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-m ethyl-2-(methylsulfonyl)butanoic acid

[209]



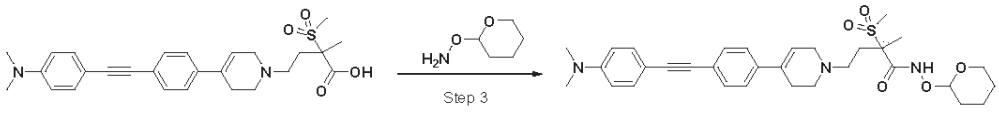
[210] To a solution of methyl 4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-m ethyl-2-(methylsulfonyl)butanoate (225mg, 1eq) in a mixture of THF (8ml)/ MeOH (2ml) was added with 2N-LiOH (0.68mL, 3eq) solution and stirred for 2hr at room temperature. The solvent was 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

To a solution of 4-(4-(4-((4-(dimethylamino)phenyl)ethynyl)phenyl)-3,6-dihydropyridin-1(2H)-yl)-2-m ethyl-2-(methylsulfonyl)-N-((tetrahydro-2H-pyran-2-yl)oxy)butanamide

[213]



[214] To a solution of 4-(4-(4-((4-(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), Et_3N (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

[522] ^{1}H NMR (600MHz, $CDCl_3$-d1): δ7.39-7.37 (m, 1H), 7.11-7.09 (m, 1H), 7.07-7.05 (m, 1H), 6.13 (s, 1H), 3.78 (t, *J*=6Hz, 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*=6.6Hz, 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

[524] 

[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 $[M+H]^+$.

[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

[528] 

[529] 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)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 $[M+H]^+$.

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

[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)butano ate (Intermediate 2) (1.27g, 1eq) in a mixture of 1,4-dioxane (12ml)/water (3ml) was added with $Pd(PPh_3)_2Cl_2$ (0.21g, 0.1eq), K_2CO_3 (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 $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography to prepare the title compound (536mg, 41%).

[603] ^{1}H NMR (600MHz, $CDCl_3$-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 of 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 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), Et_3N (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 $MgSO_4$ and concentrated in vacuo. The residue was purified with column chromatography to prepare

[698] MS (ESI, m/z): 502.2 $[M+H]^+$.

[699] **Experimantal** 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 aerobiocally. 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* pneumoniae (ATCC 29665) and *Pseudomonas* aeruginosa (PAO1). Their Minimum Inhibitory Concentration (MIC, ug/ml) are summarized in Table 1.

[701] <Table 1>