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(71) Applicant: **VIIV HEALTHCARE UK LIMITED** [GB/GB]; 980 Great West Road, Brentford Middlesex TW8 (GS (GB).

(72) Inventors: **JOHNS, Brian Alvin**; c/o GlaxoSmithKline, Global Patents, Five Moore Drive, PO Box 13398, Research Triangle Park, North Carolina 27709 (US). **VELTHUISEN, Emile Johann**; c/o GlaxoSmithKline, Global Patents, Five Moore Drive, PO Box 13398, Research Triangle Park, North Carolina 27709 (US).

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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

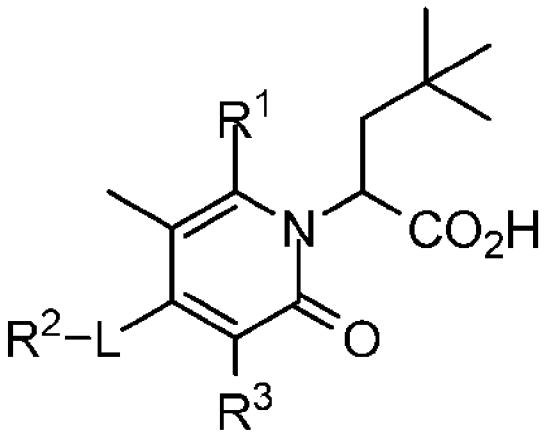
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(54) **Title**: PHENYL AND TERTBUTYLACETIC ACID SUBSTITUTED PYRIDINONES HAVING ANTI-HIV EFFECTS

(57) **Abstract**: Compounds of Formula I are disclosed and methods of treating viral invections with compositions comprising such compounds. Formula I



Formula I

WO 2016/012913 A1

PHENYL AND TERTBUTYLACETIC ACID SUBSTITUTED PYRIDINONES HAVING ANTI-HIV EFFECTS

FIELD OF THE INVENTION

The present invention relates to substituted pyridone compounds, pharmaceutical compositions, and methods of use thereof for (i) inhibiting HIV replication in a subject infected with HIV, or (ii) treating a subject infected with HIV, by administering such compounds.

BACKGROUND OF THE INVENTION

Human immunodeficiency virus type 1 (HIV-1) leads to the contraction of acquired immune deficiency disease (AIDS). The number of cases of HIV continues to rise, and currently over twenty-five million individuals worldwide suffer from the virus. Presently, long-term suppression of viral replication with antiretroviral drugs is the only option for treating HIV-1 infection. Indeed, the U.S. Food and Drug Administration has approved twenty-five drugs over six different inhibitor classes, which have been shown to greatly increase patient survival and quality of life. However, additional therapies are still required because of undesirable drug-drug interactions; drug-food interactions; non-adherence to therapy; and drug resistance due to mutation of the enzyme target.

Currently, almost all HIV positive patients are treated with therapeutic regimens of antiretroviral drug combinations termed, highly active antiretroviral therapy ("HAART"). However, HAART therapies are often complex because a combination of different drugs must be administered often daily to the patient to avoid the rapid emergence of drug-resistant HIV-1 variants. Despite the positive impact of HAART on patient survival, drug resistance can still occur. The emergence of multidrug-resistant HIV-1 isolates has serious clinical consequences and must be suppressed with a new drug regimen, known as salvage therapy.

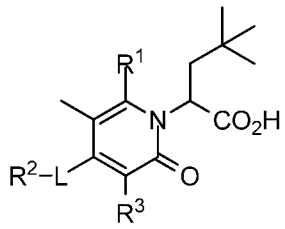
Current guidelines recommend that salvage therapy includes at least two, and preferably three, fully active drugs. Typically, first-line therapies combine three to four drugs targeting the viral enzymes reverse transcriptase and protease. One option for salvage therapy is to administer different combinations of drugs from the same mechanistic class that remain active against the resistant isolates. However, the options for this approach are often limited, as resistant mutations frequently confer broad cross-resistance to different drugs in the same class. Alternative therapeutic strategies have recently become available with the development of fusion, entry, and integrase inhibitors. However, resistance to all three new drug classes has already been reported both in the lab and in patients. Sustained successful treatment of HIV-1-

infected patients with antiretroviral drugs will therefore require the continued development of new and improved drugs with new targets and mechanisms of action.

For example, over the last decade HIV inhibitors have been reported to target the protein-protein interaction between HIV-1 integrase and Lens Epithelium Derived Growth Factor/p75 ("LEDGF"). LEDGF is a cellular transcriptional cofactor of HIV-1 integrase that promotes viral integration of reverse transcribed viral cDNA into the host cell's genome by tethering the preintegration complex to the chromatin. Because of its crucial role in the early steps of HIV replication, the interaction between LEDGF and integrase represents another attractive target for HIV drug therapy.

SUMMARY OF THE INVENTION

Briefly, in one aspect, the present invention discloses compounds of Formula I:



Formula I

wherein:

R^1 is phenyl optionally substituted by one to four substituents selected from $C_{1\text{-}3}$alkyl, halogen, or $–CH_2CH_2CH_2O-$ wherein this group is bonded to adjacent carbon atoms on the phenyl to form a ring;

L is a bond, $C_{1\text{-}3}$alkylene, $-SO_2-$, $-SO_2CH_2-$, $-NHSO_2-$, $-NHSO_2CH_2-$, -C(O)-, -C(O)NH-, $-C(O)NHCH_2-$, $-C(O)OCH_2-$, -C(O)C(O)-, $–CH_2C(O)-$, $C_{3\text{-}7}$heteroaryl, or $-C_{3\text{-}7}$heteroarylNH-, wherein each heteroaryl comprises one to three heteroatoms selected from S, N, and O;

R^2 is H, cyclohexyl, or phenyl wherein said cyclohexyl and phenyl are optionally substituted by one to three substituents selected from $C_{1\text{-}3}$alkyl and halogen

R^3 is H or $–NHSO_2R^4$ wherein R^4 is $C_{1\text{-}8}$alkyl and wherein said alkyl can include cycloalkyl portions.

In another aspect the present invention discloses pharmaceutically acceptable salts of the compounds of Formula I.

In another aspect, the present invention discloses pharmaceutical compositions comprising a compound of Formula I or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention discloses a method for treating a viral infection in a patient mediated at least in part by a virus in the *retrovirus* family of viruses, comprising administering to said patient a composition comprising a compound of Formula I, or a pharmaceutically acceptable salt thereof. In some embodiments, the viral infection is mediated by the HIV virus.

In another aspect, a particular embodiment of the present invention provides a method of treating a subject infected with HIV comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof.

In yet another aspect, a particular embodiment of the present invention provides a method of inhibiting progression of HIV infection in a subject at risk for infection with HIV comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt thereof. Those and other embodiments are further described in the text that follows.

In accordance with another embodiment of the present invention, there is provided a method for preventing or treating a viral infection in a mammal mediated at least in part by a virus in the *retrovirus* family of viruses which method comprises administering to a mammal, that has been diagnosed with said viral infection or is at risk of developing said viral infection, a compound as defined in Formula Iwherein said virus is an HIV virus and further comprising administration of a therapeutically effective amount of one or more agents active against an HIV virus, wherein said agent active against the HIV virus is selected from the group consisting of Nucleotide reverse transcriptase inhibitors; Non-nucleotide reverse transcriptase inhibitors; Protease inhibitors; Entry, attachment and fusion inhibitors; Integrase inhibitors; Maturation inhibitors; CXCR4 inhibitors; and CCR5 inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

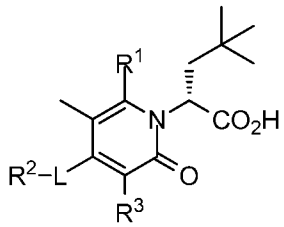
Preferably R^1 is phenyl optionally substituted by a methyl group.

Preferably L is a bond, -oxadiazolyl-NH-, -C(O)NH-, or -$C(O)NHCH_2$-.

Preferably R^2 is H, cyclohexyl, or phenyl wherein said cyclohexyl and phenyl are optionally substituted by 1 or 2 methyl groups.

Preferably R^3 is H, $–NHSO_2CH_3$, or $–NHSO_2CH_2$cyclohexyl.

Preferably the stereochemistry on the carbon to which the t-butyl group is bound is as depicted below.

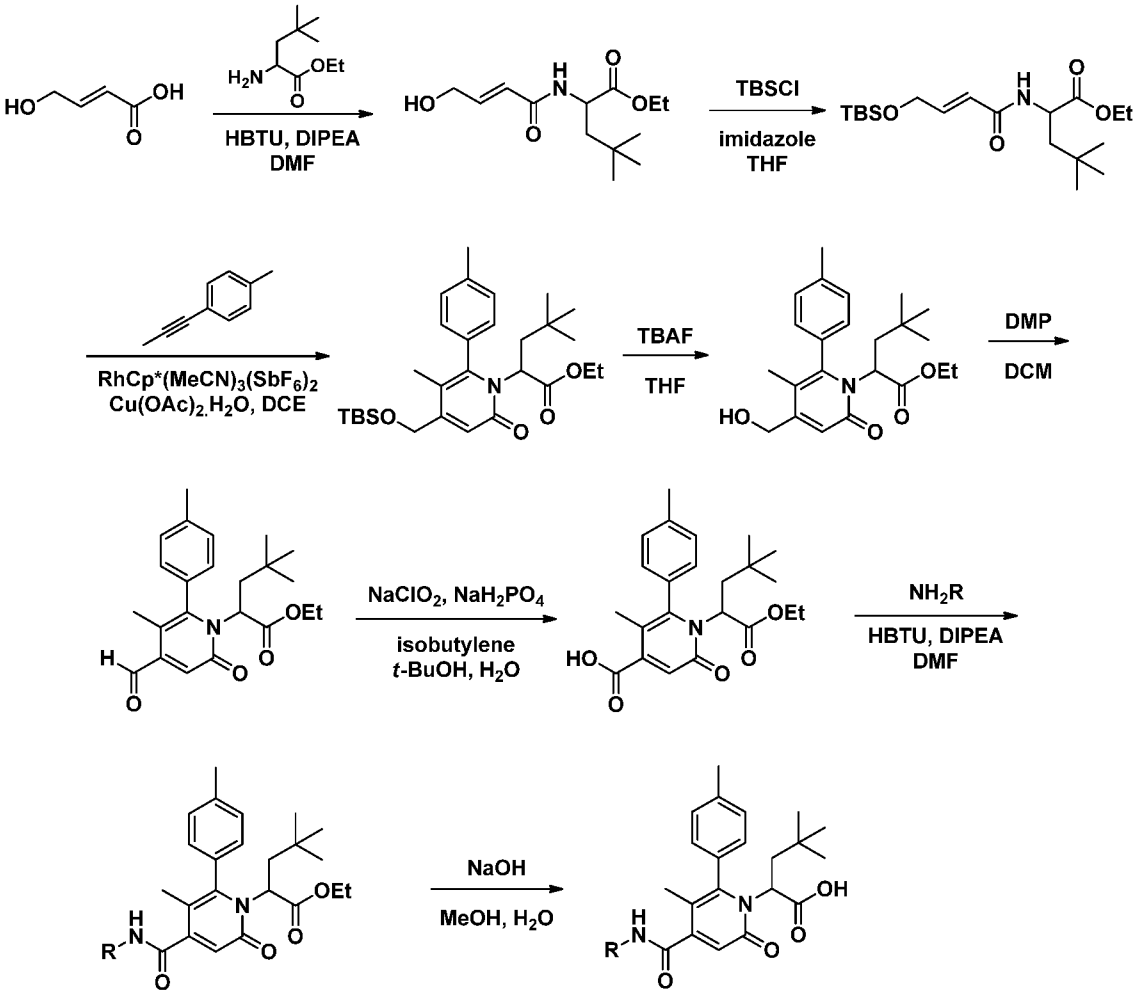


"Pharmaceutically acceptable salt" refers to pharmaceutically acceptable salts derived from a variety of organic and inorganic counter ions well known in the art and include, by way of example only, sodium, potassium, calcium, magnesium, ammonium, and tetraalkylammonium, and when the molecule contains a basic functionality, salts of organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, and oxalate. Suitable salts include those described in P. Heinrich Stahl, Camille G. Wermuth (Eds.), Handbook of Pharmaceutical Salts Properties, Selection, and Use; 2002.

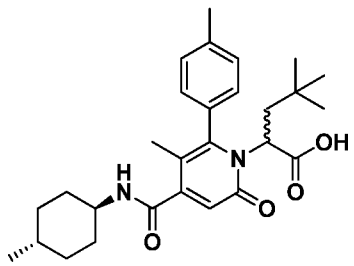
Examples

The compounds of this invention may be made by a variety of methods, including well-known standard synthetic methods. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working examples.

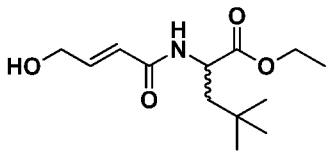
Scheme 1



Example 1: *4,4-Dimethyl-2-(5-methyl-4-(((1r,4r)-4-methylcyclohexyl)carbamoyl)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoic acid*

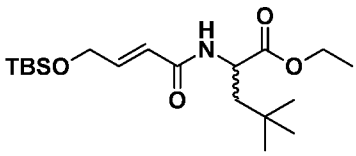


Step 1: *(E)-Ethyl 2-(4-hydroxybut-2-enamido)-4,4-dimethylpentanoate*



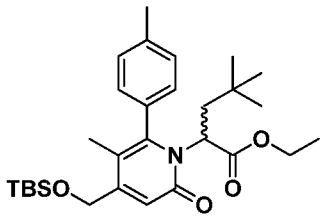
To a solution of (*E*)-4-hydroxybut-2-enoic acid (418 mg, 4.09 mmol) in DMF (5 mL) were added DIPEA (3.5 mL, 20.5 mmol), HBTU (3.2 g, 8.2 mmol) and ethyl 2-amino-4,4-dimethylpentanoate (1.05 g, 6.1 mmol). After 30 min, the reaction mixture was partitioned between DCM and water. The layers were separated and the aqueous layer was extracted with DCM (20 mL X 2). The combined organic layers was washed with $NaHCO_3$ (aq.) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 1:1) to afford the title compound as a yellow solid (1.05 g, 64% yield). LC-MS (ESI): m/z (M+1) = 258.23.

Step 2: *(E)-ethyl 2-(4-(tert-butyldimethylsilyloxy)but-2-enamido)-4,4-dimethylpentanoate*



To a solution of (*E*)-ethyl 2-(4-hydroxybut-2-enamido)-4,4-dimethylpentanoate (1.05 g, 4.1 mmol) in DCM (10 mL) were added DMAP (498 mg, 4.1 mmol), imidazole (833 mg, 12.3 mmol) and TBSCl (922 mg, 6.2 mmol). After 2 h, the reaction mixture was quenched with H_2O and extracted with DCM (20 ml X 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 5:1) to afford the title compound as a yellow oil (800 mg, 53% yield). LC-MS (ESI): m/z (M+1) = 372.24.

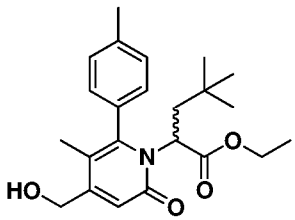
Step 3: *Ethyl 2-(4-((tert-butyldimethylsilyloxy)methyl)-5-methyl-2-oxo-6-p-tolylpyridin-1(2H)-yl)-4,4-dimethylpentanoate*



1-Methyl-4-(prop-1-yn-1-yl)benzene was prepared from the known procedure as described in *Angew. Chem. Int. Edit.*, **2012** 51, 1287–1294.

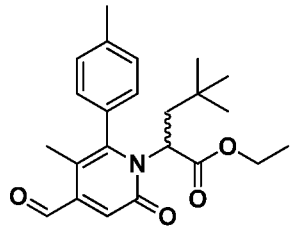
A mixture of (*E*)-ethyl 2-(4-(tert-butyl dimethylsilyloxy)but-2-enamido)-4,4-adimethyl pentanoate (300 mg, 0.81 mmol), 1-methyl-4-(prop-1-ynyl)benzene (132 mg, 1.0 mmol), $RhCp^*(MeCN)_3(SbF_6)_2$ (33.7 mg, 0.04 mmol) and $Cu(OAc)_2.H_2O$ (340 mg, 1.7 mmol) in DCE (10 mL) was stirred at 80°. After 18h, the mixture was cooled down to ambient temperature and quenched with 10% $NH_3.H_2O$ in saturated NH_4Cl (aq.) and extracted with DCM (20 mL x 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, 2% MeOH in DCM) to afford the title compound as a yellow solid (114 mg, 28% yield). LC-MS (ESI): m/z (M+1) = 500.31

Step 4: *Ethyl 2-(4-(hydroxymethyl)-5-methyl-2-oxo-6-p-tolylpyridin-1(2H)-yl)-4,4-dimethylpentanoate*



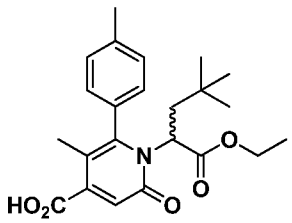
To a solution of ethyl 2-(4-((tert-butyldimethylsilyloxy)methyl)-5-methyl-2-oxo-6-p-tolyl pyridin-1(2H)-yl)-4,4-dimethylpentanoate (114 mg, 0.23 mmol) in THF (3 mL) was added TBAF (120 mg, 0.46 mmol). After 1 h, the reaction mixture was partitioned between EtOAc and water. The layers were separated and the organic layer was washed with H2O and brine, dried over Na2SO4, filtered and concentrated under reduced pressure to give the title compound as a yellow oil (108 mg, quant. yield) which was used in next step without further purification. LC-MS (ESI): m/z (M+1) 386.18.

Step 5: *Ethyl 2-(4-formyl-5-methyl-2-oxo-6-p-tolylpyridin-1(2H)-yl)-4,4-dimethylpentanoate*



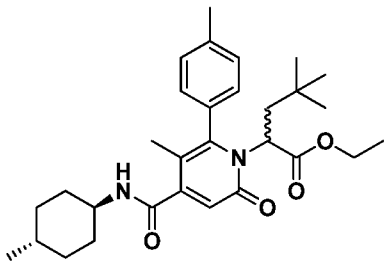
A solution of ethyl 2-(4-(hydroxymethyl)-5-methyl-2-*oxo*-6-*p*-tolylpyridin-1(2*H*) -yl)-4,4-dimethylpentanoate (108 mg ,0.28 mmol) in DCM (5 mL) was added DMP (214 mg , 0.50 mmol). After 1 h, the reaction mixture was quenched with $NaHCO_3$ (aq.) and extracted with DCM (20 ml X 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 2:1) to afford the title compound as a yellow solid (63 mg, 58% yield). LC-MS (ESI): m/z (M+1) = 384.3.

Step 6: *1-(1-Ethoxy-4,4-dimethyl-1-oxopentan-2-yl)-5-methyl-2-oxo-6-p-tolyl-1,2-dihydropyridine-4-carboxylic acid*



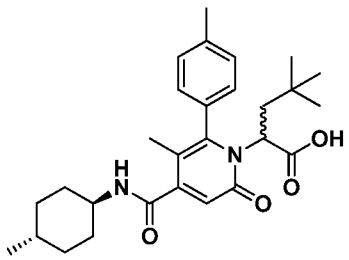
To a solution of ethyl 2-(4-formyl-5-methyl-2-*oxo*-6-*p*-tolylpyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (63 mg, 0.16 mmol) in THF (2.2 mL), *t*-BuOH (2.2 mL) and isobutylene (4.5 ml) in a sealed tube was added a solution of NaH_2PO_4 and $NaClO_2$ in H_2O (5 mL). After 18h, the reaction mixture was acidified with 1N HCl (0.5 mL) and extracted with ethyl acetate (20 ml X 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a yellow solid (51 mg, 80% yield) which was used in next step without further purification. LC-MS (ESI): m/z (M+1) = 400.1

Step 7: *Ethyl 4,4-dimethyl-2-(5-methyl-4-((1r,4r)-4-methylcyclohexylcarba moyl)-2-oxo-6-p-tolylpyridin-1(2H)-yl)pentanoate*



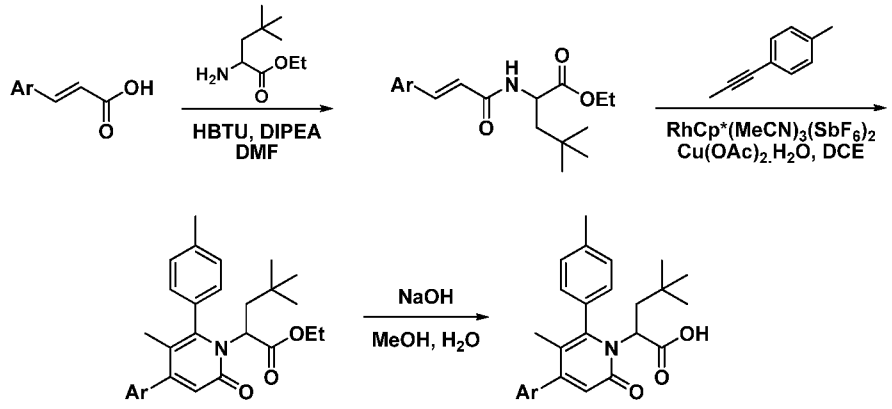
A solution of 1-(1-ethoxy-4,4-dimethyl-1-oxopentan-2-yl)-5-methyl-2-*oxo*-6-*p*-tolyl- 1,2-dihydropyridine-4-carboxylic acid (28 mg, 0.07 mmol) in DMF (2 mL) was treated with DIPEA (0.06 ml , 0.35 mmol), HBTU (54.2 mg, 0.14 mmol) and *trans*-4-methyl cyclohexyl amine (0.02 ml, 0.14 mmol). After 18h, the reaction mixture was diluted with water and extracted with DCM (20 ml X 3). The combined organic layers was washed with $NaHCO_3$ (aq.) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by prep. TLC (PE:EA = 1:1) to afford the title compound as a yellow solid (30 mg, 86%). LC-MS (ESI): m/z (M+1) = 495.37.

Step 8: *4,4-Dimethyl-2-(5-methyl-4-((1r,4r)-4-methylcyclohexylcarbamoyl)-2-oxo-6-p-tolylpyridin-1(2H)-yl)pentanoic acid*

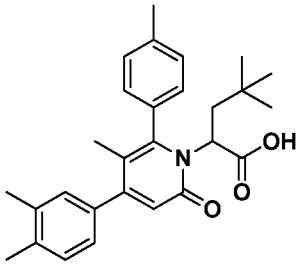


To a solution of ethyl 4,4-dimethyl-2-(5-methyl-4-((1*r*,4*r*)-4-methylcyclohexylcarbamo yl)-2-*oxo*-6-*p*-tolylpyridin-1(2*H*)-yl)pentanoate (30 mg, 0.06 mmol) in MeOH (2 mL) was added 1 N NaOH (0.6 mL) and heated to reflux. After 18h, the reaction mixture was cooled to ambient temperature, acidified with 1 N HCl (0.6 mL) (pH = 6~7) and concentrated under reduced pressure to give the crude product which was purified by reverse phase HPLC (C_{18} 70~100% CH_3CN in H_2O with 0.1% formic acid) to afford the title compound as a white powder (12 mg, 40% yield). ^1H NMR (400 MHz, DMSO) δ 8.43 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.31 (m, 3H), 7.28 (d, *J* = 8.1 Hz, 1H), 6.24 (s, 1H), 4.19 (s, 1H), 3.63 – 3.58 (m, 1H), 2.39 (s, 3H), 2.31 – 2.23 (m, 1H), 1.92 – 1.77 (m, 3H), 1.76 – 1.60 (m, 5H), 1.32 – 1.23 (m, 3H), 1.05 – 0.95 (m, 2H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.58 (s, 9H). LC-MS (ESI): m/z (M+1) = 467.33.

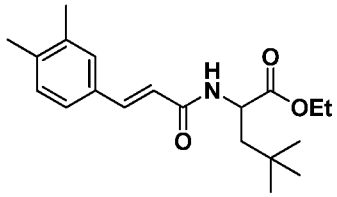
Scheme 2



Example 2: *2-(4-(3,4-Dimethylphenyl)-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid*

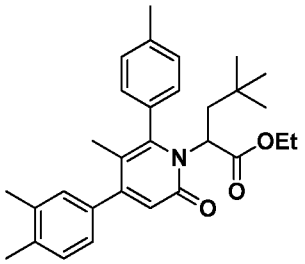


Step 1: *(E)-Ethyl 2-(3-(3,4-dimethylphenyl)acrylamido)-4,4-dimethylpentanoate.*



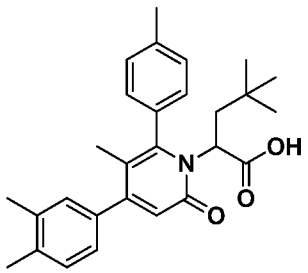
A mixture of (*E*)-3-(3,4-dimethylphenyl)acrylic acid (200 mg, 1.14 mmol), ethyl 2-amino-4,4-dimethylpentanoate (240 mg, 1.4 mmol), HBTU (880 mg, 2.3 mmol) and DIPEA (733 mg, 5.7 mmol) in DCM (10 mL) was stirred at r.t. for 40min. The reaction mixture was diluted with sat. $NaHCO_3$ (aq.) and extracted with DCM (20 ml X 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 3:1) to afford the title compound as a yellow oil (288 mg, 77% yield). LC-MS (ESI): m/z (M+1) = 332.3.

Step 2: *Ethyl 2-(4-(3,4-dimethylphenyl)-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



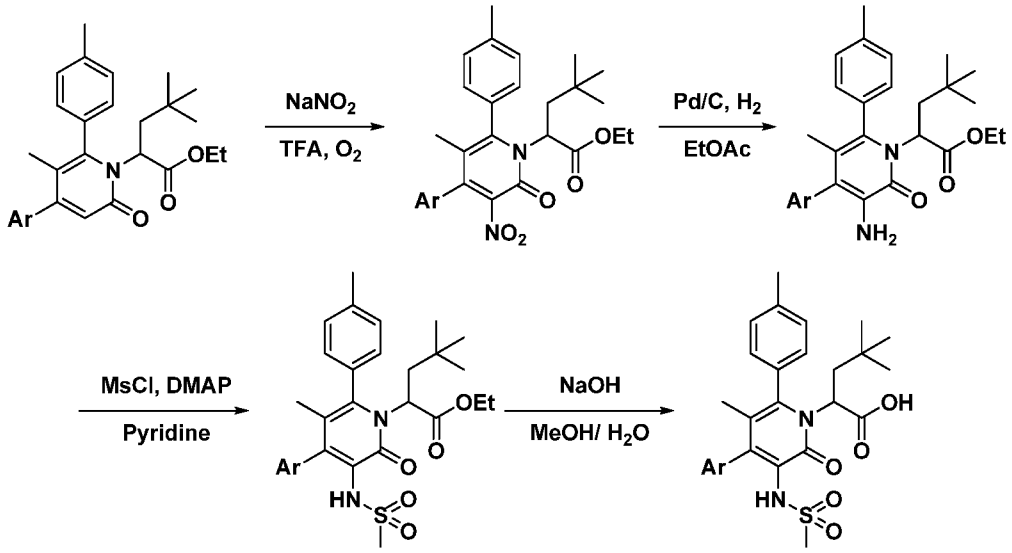
A mixture of (*E*)-Ethyl 2-(3-(3,4-dimethylphenyl)acrylamido)-4,4-dimethylpentanoate (60 mg, 0.18 mmol), 1-methyl-4-(prop-1-ynyl)benzene (24 mg, 0.18 mmol), $RhCp^*(MeCN)_3(SbF_6)_2$ (7.5 mg, 0.01 mmol) and $Cu(OAc)_2 \cdot H_2O$ (152 mg, 0.76 mmol) in DCE (2 mL) was stirred at 100°C. After 24h, the mixture was cooled down to ambient temperature and quenched with 10% $NH_3 \cdot H_2O$ in saturated NH_4Cl (aq.) and extracted with DCM (10 mL x 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 3:1) to afford the title compound as a yellow oil (50 mg, 60% yield). LC-MS (ESI): m/z (M+1) = 460.5.

Step 3: *2-(4-(3,4-dimethylphenyl)-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid*

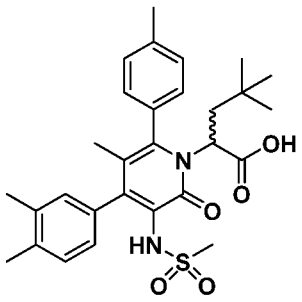


To a solution of Ethyl 2-(4-(3,4-dimethylphenyl)-5-methyl-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (50 mg, 0.11 mmol) in MeOH (2 mL) was added 1 N NaOH (1.0 mL) and heated to reflux. After 12h, the reaction mixture was cooled to ambient temperature, acidified with 1 N HCl (1.0 mL) (pH = 6~7) and concentrated under reduced pressure to give the crude product which was purified by reverse phase HPLC (C_{18} 50~100% CH_3CN in H_2O with 0.1% formic acid) to afford the title compound as a white powder (37 mg, 77% yield). ^1H NMR (400 MHz, DMSO) δ 12.86 (br, 1H), 7.57 – 6.99 (m, 7H), 6.24 (s, 1H), 4.27 (s, 1H), 2.39 (s, 3H), 2.36 – 2.15 (m, 7H), 1.96 – 1.79 (m, 1H), 1.58 (s, 3H), 0.61 (s, 9H). LC-MS (ESI): m/z (M+1) = 432.4.

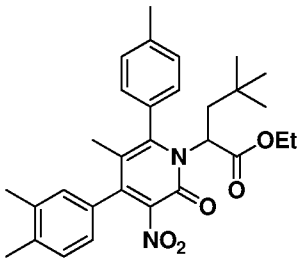
Scheme 3



Example 3: *2-(4-(3,4-dimethylphenyl)-5-methyl-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid*



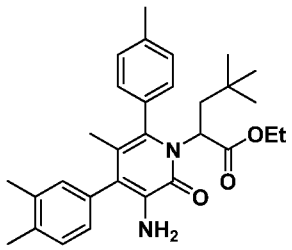
Step 1: *Ethyl 2-(4-(3,4-dimethylphenyl)-5-methyl-3-nitro-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



To a mixture of Ethyl 2-(4-(3,4-dimethylphenyl)-5-methyl-2-oxo-6-*p*-tolylpyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (153 mg, 0.33 mmol) and $NaNO_2$ (28 mg, 0.37 mmol) in DCM (5 mL) was added TFA (0.5 mL) under O_2 atmosphere. After 12h, the reaction mixture was quenched with sat. $NaHCO_3$ (aq.) and extracted with DCM (20 ml X 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give

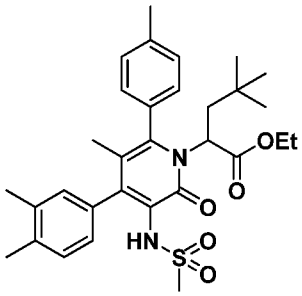
the crude product which was purified by column chromatography (silica gel, PE:EA = 3:1) to afford the title compound as a yellow oil (140 mg, 83% yield). LC-MS (ESI): m/z (M+1) = 505.3.

Step 2: *Ethyl 2-(3-amino-4-(3,4-dimethylphenyl)-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



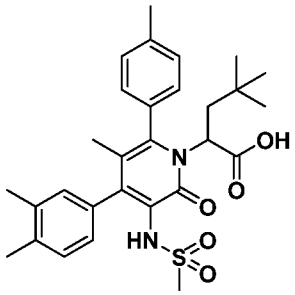
A mixture of Ethyl 2-(4-(3,4-dimethylphenyl)-5-methyl-3-nitro-2-oxo-6-*p*-tolylpyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (140 mg, 0.28 mmol) and Pd/C (130 mg) in EtOAc (5 mL) was purged with H_2 three times. After 2h, the reaction mixture was filtered through Celite pad and the filtrate was concentrated under reduced pressure to afford the title compound as a yellow solid (133 mg, 99% yield). LC-MS (ESI): m/z (M+1) = 475.4.

Step 3: *Ethyl 2-(4-(3,4-dimethylphenyl)-5-methyl-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



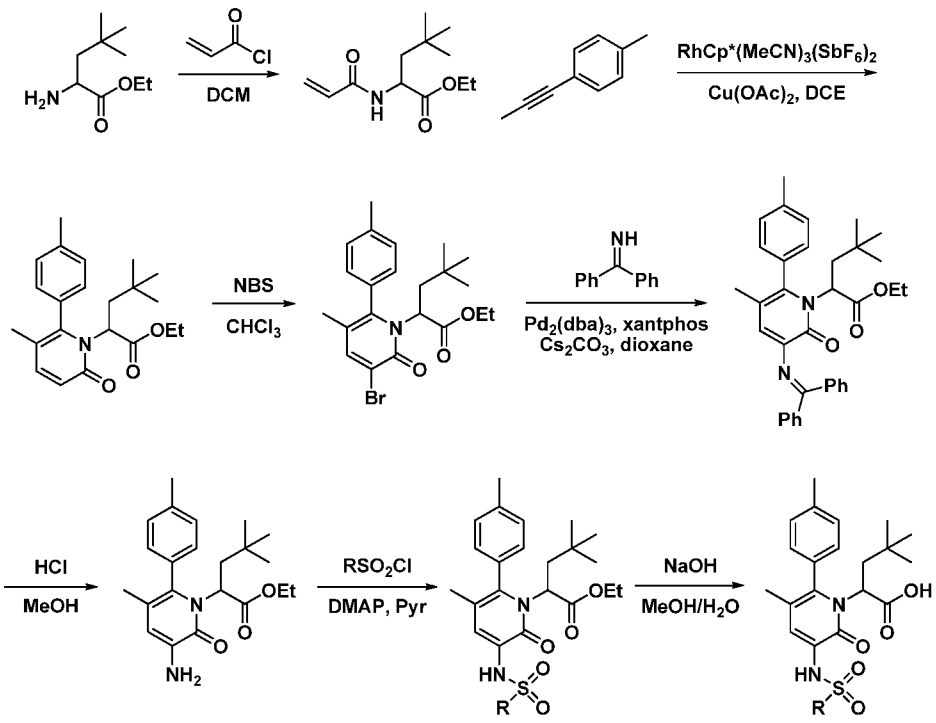
To a solution of Ethyl 2-(4-(3,4-dimethylphenyl)-5-methyl-3-(methylsulfonamido)-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (36 mg, 0.076 mmol) and DMAP (5 mg, 0.003 mmol) in pyridine (1 mL) was added MsCl (44 mg, 0.38 mmol). After 12h, the reaction mixture was diluted with sat. NH_4Cl (aq.) and extracted with EtOAc (10 ml X 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 2:1) to afford the title compound as a yellow oil (24 mg, 57% yield). LC-MS (ESI): m/z (M+1) = 553.4.

Step 4: *2-(4-(3,4-Dimethylphenyl)-5-methyl-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid*

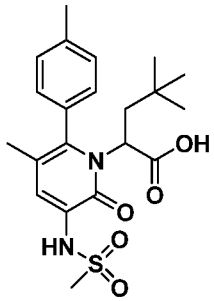


To a solution of Ethyl 2-(4-(3,4-dimethylphenyl)-5-methyl-3-(methylsulfonamido)-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (30 mg, 0.054 mmol) in MeOH (2 mL) was added 1 N NaOH (0.6 mL) and heated to reflux. After 12h, the reaction mixture was cooled to ambient temperature, acidified with 1 N HCl (0.6 mL) (pH = 6~7) and concentrated under reduced pressure to give the crude product which was purified by reverse phase HPLC (C_{18} 60~100% CH_3CN in H_2O with 0.1% formic acid) to afford the title compound as a white powder (14 mg, 49% yield). ^{1}H NMR (400 MHz, DMSO) δ 12.93 (br, 1H), 8.30 (s, 1H), 7.51 – 7.27 (m, 4H), 7.28 – 7.16 (m, H), 7.08 – 6.92 (m, 2H), 4.31 (s, 1H), 2.91 (d, *J* = 4.6Hz, 3H), 2.41 – 2.31 (m, 4H), 2.31 – 2.18 (m, 6H), 1.94 – 1.86 (m, 1H), 1.41 (s, 3H), 0.61 (s, 9H). LC-MS (ESI): m/z (M+1) = 525.8.

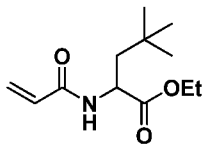
Scheme 4



Example 4: *4,4-Dimethyl-2-(5-methyl-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoic acid*

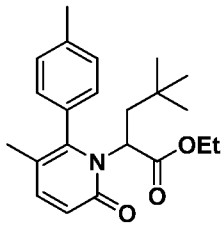


Step 1: *Ethyl 2-acrylamido-4,4-dimethylpentanoate*



To a solution of Ethyl 2-amino-4,4-dimethylpentanoate (150 mg, 0.86 mmol) in DCM (4 mL) was added acryloyl chloride (156 mg, 1.72 mmol). After 1h, the reaction mixture was diluted with sat. $NaHCO_3$ (aq.) and extracted with DCM (20 ml X 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, DCM:MeOH = 20:1) to afford the title compound as a yellow solid (190 mg, 96% yield). LC-MS (ESI): m/z (M+1) = 228.3.

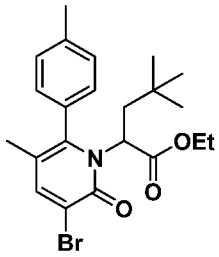
Step 2: *Ethyl 4,4-dimethyl-2-(5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoate*



A mixture of Ethyl 2-acrylamido-4,4-dimethylpentanoate (200 mg, 0.18 mmol), 1-methyl-4-(prop-1-ynyl)benzene (250 mg, 0.35 mmol), $RhCp^*(MeCN)_3(SbF_6)_2$ (30 mg, 0.01 mmol) and $Cu(OAc)_2 \cdot H_2O$ (365 mg, 0.37 mmol) in DCE (4 mL) was stirred at 100°C. After 24h, the mixture was cooled down to ambient temperature and quenched with 10% $NH_3 \cdot H_2O$ in saturated NH_4Cl (aq.) and extracted with DCM (10 mL x 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product

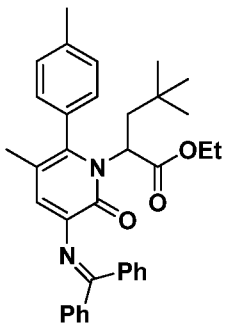
which was purified by column chromatography (silica gel, PE:EA = 2:1) to afford the title compound as a yellow oil (50 mg, 16% yield). LC-MS (ESI): m/z (M+1) = 356.2.

Step 3: *Ethyl 2-(3-bromo-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



To a solution of Ethyl 4,4-dimethyl-2-(5-methyl-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)pentanoate (105 mg, 0.3 mmol) in $CHCl_3$ (4 mL) was added NBS (61 mg, 0.33 mmol) and heated to 40°C. After 12h, the reaction mixture was diluted with water and extracted with DCM (20 ml X 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 5:1) to afford the title compound as a yellow oil (115 mg, 90% yield). LC-MS (ESI): m/z (M/M+2) = 434.2/436.2.

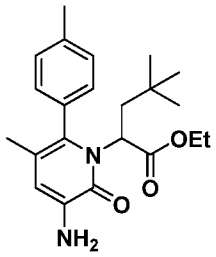
Step 4: *Ethyl 2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



A mixture of Ethyl 2-(3-bromo-5-methyl-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (130 mg, 0.30 mmol), diphenylmethanimine (165 mg, 0.90 mmol), $Pd_2(dba)_3$ (30 mg, 0.03 mmol), Xantphos (17 mg, 0.03 mmol) and Cs_2CO_3 (292 mg, 0.90 mmol) in dioxane (3 mL) was stirred at 90°C under N_2 atmosphere. After 20h, the mixture was cooled down to ambient temperature, diluted with water and extracted with EtOAc (20 mL x 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column

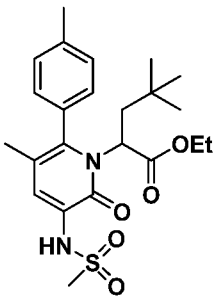
chromatography (silica gel, PE:EA = 3:1) to afford the title compound as a yellow oil (100 mg, 63% yield). LC-MS (ESI): m/z (M+1) = 535.3.

Step 5: *Ethyl 2-(3-amino-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



To a solution of Ethyl 2-(3-((diphenylmethylene)amino)-5-methyl-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (100 mg, 0.19 mmol) in MeOH (5 mL) was added 1 N HCl (1 mL). After 1h, the reaction mixture was neutralized with sat. $NaHCO_3$ (aq.) and extracted with DCM (20 ml X 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 2:1) to afford the title compound as a yellow oil (53 mg, 77% yield). ^{1}H NMR (400 MHz, DMSO) δ 7.31 (t, *J* = 6.9 Hz, 2H), 7.23 (dd, *J* = 8.7, 7.1 Hz, 2H), 6.40 (s, 1H), 5.13 (s, 2H), 4.32 (s, 1H), 4.22 – 4.11 (m, 1H), 4.10 – 3.95 (m, 2H), 2.36 (s, 3H), 2.28 – 2.19 (m, 1H), 1.89 – 1.79 (m, 1H), 1.74 (s, 3H), 1.17 (q, *J* = 7.1 Hz, 3H), 0.56 (s, 9H). LC-MS (ESI): m/z (M+1) = 371.2.

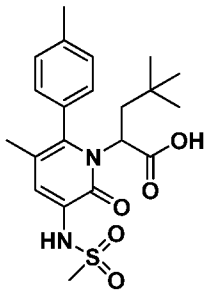
Step 6: *Ethyl 4,4-dimethyl-2-(5-methyl-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoate*



To a solution of Ethyl 2-(3-amino-5-methyl-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpenta noate (13 mg, 0.035 mmol) and DMAP (1 mg, 0.008 mmol) in pyridine (2 mL) was added MsCl (12 mg, 0.105 mmol). After 1h, the reaction mixture was quenched with sat. NH_4Cl (aq.) and extracted with DCM (20 ml X 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the

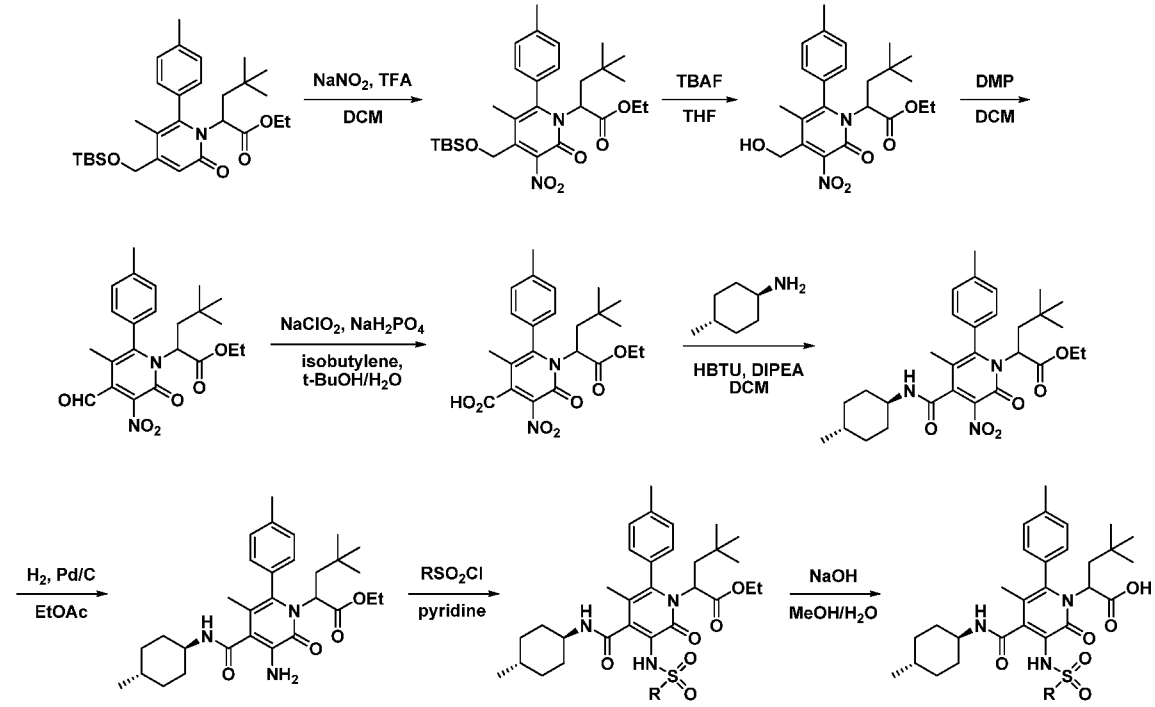
title compound as a yellow oil (53 mg, 77% yield) which was used in next step without further purification. LC-MS (ESI): m/z (M+1) = 449.3.

Step 7: *4,4-Dimethyl-2-(5-methyl-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoic acid*

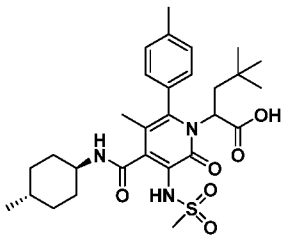


To a solution of Ethyl 4,4-dimethyl-2-(5-methyl-3-(methylsulfonamido)-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)pentanoate (15 mg, 0.033 mmol) in MeOH (3 mL) was added 1 N NaOH (0.3 mL) and heated to reflux. After 6h, the reaction mixture was cooled to ambient temperature, acidified with 1 N HCl (0.3 mL) (pH = 6~7) and concentrated under reduced pressure to give the crude product which was purified by reverse phase HPLC (C_{18} 60~100% CH_3CN in H_2O with 0.1% formic acid) to afford the title compound as a white powder (7 mg, 50% yield). ^1H NMR (400 MHz, DMSO) δ 12.93 (br, 1H), 8.88 (s, 1H), 7.45 – 7.22 (m, 5H), 4.34 (s, 1H), 3.09 (s, 3H), 2.39 (s, 3H), 2.23 (dd, *J* = 15.1, 3.7 Hz,1H), 1.98 – 1.91 (m, 1H), 1.81 (s, 3H), 0.57 (s, 9H). LC-MS (ESI): m/z (M+1) = 421.2.

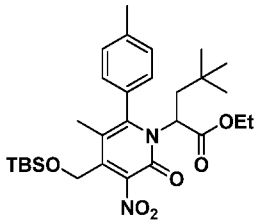
Scheme 5



Example 5: 4,4-dimethyl-2-(5-methyl-4-(((1s,4s)-4-methylcyclohexyl)carbamoyl)-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoic acid



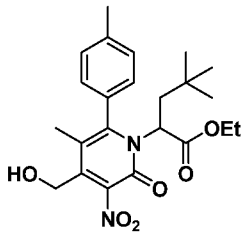
Step 1: *Ethyl 2-(4-(((tert-butyldimethylsilyl)oxy)methyl)-5-methyl-3-nitro-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



To a mixture of Ethyl 2-(4-((tert-butyldimethylsilyloxy)methyl)-5-methyl-2-oxo-6-*p*-tolylpyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (50 mg, 0.10 mmol), $NaNO_2$ (7.5 mg, 0.11 mmol) in DCM (5 mL) was added TFA (0.05 mL) under O_2 atmosphere. After 12h, the reaction mixture was quenched with sat. $NaHCO_3$ (aq.) and extracted with DCM (20 ml X 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under

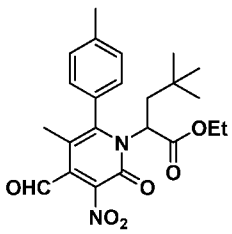
reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 5:1) to afford the title compound as a yellow oil (54 mg, 92% yield). LC-MS (ESI): m/z (M+1) = 545.6.

Step 2: *Ethyl 2-(4-(hydroxymethyl)-5-methyl-3-nitro-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



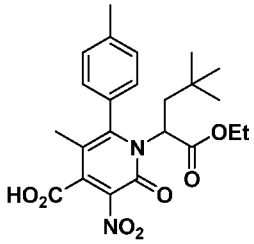
To a solution of Ethyl 2-(4-(((tert-butyldimethylsilyl)oxy)methyl)-5-methyl-3-nitro-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (138 mg, 0.25 mmol) in THF (10 mL) was added TBAF (133 mg, 0.51 mmol). After 30min, the reaction mixture was partitioned between EtOAc and water. The layers were separated and the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 2:1) to afford the title compound as a yellow oil (104 mg, 95% yield). LC-MS (ESI): m/z (M+1) 431.4.

Step 3: *Ethyl 2-(4-formyl-5-methyl-3-nitro-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



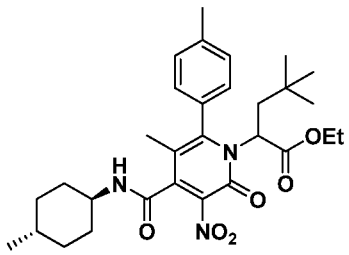
To a solution of Ethyl 2-(4-(hydroxymethyl)-5-methyl-3-nitro-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (33 mg ,0.08 mmol) in DCM (5 mL) was added DMP (49 mg , 0.12 mmol). After 1h, the reaction mixture was quenched with $NaHCO_3$ (aq.) and extracted with DCM (20 ml X 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, DCM) to afford the title compound as a yellow solid (27 mg, 82% yield). LC-MS (ESI): m/z (M+1) = 429.5.

Step 4: *1-(1-Ethoxy-4,4-dimethyl-1-oxopentan-2-yl)-5-methyl-3-nitro-2-oxo-6-(p-tolyl)-1,2-dihydropyridine-4-carboxylic acid*



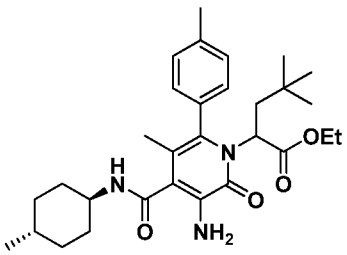
To a solution of Ethyl 2-(4-formyl-5-methyl-3-nitro-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethyl pentanoate (27 mg, 0.06 mmol) in THF (1 mL), *t*-BuOH (1 mL) and isobutylene (1 ml) in a sealed tube was added a solution of NaH_2PO_4 (59 mg, 0.38 mmol) and $NaClO_2$ (46 mg, 0.50 mmol) in H_2O (1 mL). After 12h, the reaction mixture was acidified with 1 N HCl and extracted with EtOAc (20 ml X 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the title compound as a yellow solid (30 mg, 99% yield) which was used in next step without further purification. LC-MS (ESI): m/z (M+1) = 445.5

Step 6: *Ethyl 4,4-dimethyl-2-(5-methyl-4-(((1s,4s)-4-methylcyclohexyl)carbamoyl)-3-nitro-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoate*



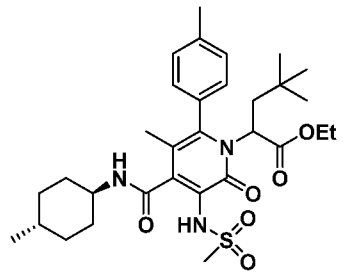
A solution of 1-(1-ethoxy-4,4-dimethyl-1-oxopentan-2-yl)-5-methyl-3-nitro-2-oxo-6-(*p*-tolyl)-1,2-dihydropyridine-4-carboxylic acid (30 mg, 0.067 mmol) in DMF (3 mL) was treated with DIPEA (35 mg, 0.27 mmol), HBTU (52 mg, 0.13 mmol) and *trans*-4-methyl cyclohexyl amine (15 mg, 0.14 mmol). After 30min, the reaction mixture was diluted with water and extracted with EtOAc (20 ml X 3). The combined organic layers was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 2:1) to afford the title compound as a yellow oil (18 mg, 50%). LC-MS (ESI): m/z (M+1) = 540.8.

Step 7: *Ethyl 2-(3-amino-5-methyl-4-(((1s,4s)-4-methylcyclohexyl)carbamoyl)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



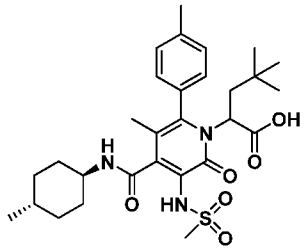
A mixture of Ethyl 4,4-dimethyl-2-(5-methyl-4-(((1*s*,4*s*)-4-methylcyclohexyl)carbamoyl)-3-nitro-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)pentanoate (18 mg, 0.03 mmol) and Pd/C (10 mg) in EtOAc (5 mL) was purged with H_2 three times. After 12h, the reaction mixture was filtered through Celite pad and the filtrate was concentrated under reduced pressure to afford the title compound as a yellow solid (10 mg, 65% yield). LC-MS (ESI): m/z (M+1) = 510.6.

Step 8: *Ethyl 4,4-dimethyl-2-(5-methyl-4-(((1s,4s)-4-methylcyclohexyl)carbamoyl)-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoate*



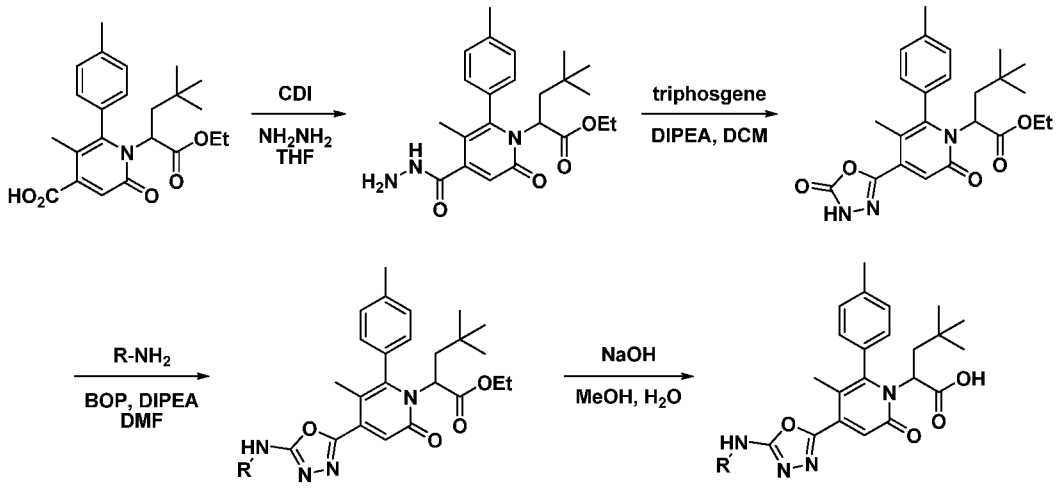
To a solution of Ethyl 2-(3-amino-5-methyl-4-(((1*s*,4*s*)-4-methylcyclohexyl)carbamoyl)-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (19 mg, 0.037 mmol) and DMAP (1 mg, 0.008 mmol) in pyridine (2 mL) was added MsCl (0.03 mL, 0.37 mmol). After 2h, the reaction mixture was diluted with water and extracted with EtOAc (20 ml X 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 2:1) to afford the title compound as a yellow oil (5 mg, 23% yield). LC-MS (ESI): m/z (M+1) = 588.7.

Step 9: *4,4-Dimethyl-2-(5-methyl-4-(((1s,4s)-4-methylcyclohexyl)carbamoyl)-3-(methylsulfonamido)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoic acid*

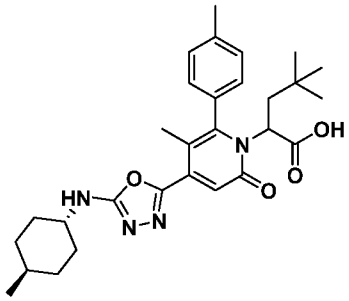


To a solution of Ethyl 4,4-dimethyl-2-(5-methyl-4-(((1*s*,4*s*)-4-methylcyclohexyl)carbamoyl)-3-(methylsulfonamido)-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)pentanoate (5 mg, 0.008 mmol) in MeOH (2 mL) was added 1 N NaOH (0.2 mL) and heated to reflux. After 12h, the reaction mixture was cooled to ambient temperature, acidified with 1 N HCl (0.2 mL) (pH = 6~7) and concentrated under reduced pressure to give the crude product which was purified by reverse phase HPLC (C_{18} 10~100% CH_3CN in H_2O with 0.1% formic acid) to afford the title compound as a white powder (3 mg, 67% yield). ^{1}H NMR (400 MHz, DMSO) δ 8.33 (s, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.48 – 7.34 (m, 3H), 7.26 (d, *J* = 7.6 Hz, 1H), 4.19 (s, 1H), 3.65 – 3.61 (m, 1H), 3.14 (s, 3H), 2.39 (s, 3H), 2.31 – 2.26 (m, 1H), 1.93 – 1.80 (m, 3H), 1.75 – 1.56 (m, 5H), 1.32 – 1.20 (m, 3H), 1.03 – 0.94 (m, 2H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.57 (s, 9H). LC-MS (ESI): m/z (M+1) = 560.6.

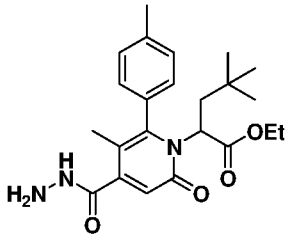
Scheme 6



Example 6: *4,4-Dimethyl-2-(5-methyl-4-(5-(((1r,4r)-4-methylcyclohexyl)amino)-1,3,4-oxadiazol-2-yl)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoic acid*

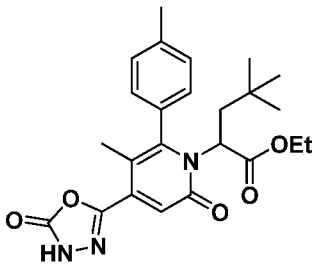


Step 1: *Ethyl 2-(4-(hydrazinecarbonyl)-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate*



To a solution of 1-(1-ethoxy-4,4-dimethyl-1-oxopentan-2-yl)-5-methyl-2-oxo-6-*p*-tolyl-1,2-dihydropyridine-4-carboxylic acid (66 mg, 0.165 mmol) in THF (3 mL) was added CDI (107 mg, 0.66 mmol). After 30min, hydrazine (0.1 mL, 1.65 mmol) was added and stirred for 1h. The reaction mixture was concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, DCM:MeOH = 10:1) to afford the title compound as a colorless oil (44 mg, 64% yield). LC-MS (ESI): m/z (M+1) = 414.4.

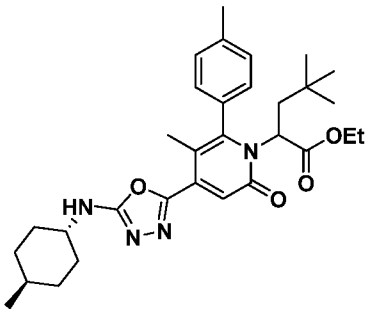
Step 2: *Ethyl 4,4-dimethyl-2-(5-methyl-2-oxo-4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-6-(p-tolyl)pyridin-1(2H)-yl)pentanoate*



To a solution of Ethyl 2-(4-(hydrazinecarbonyl)-5-methyl-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoate (44 mg, 0.11 mmol) and DIPEA (0.04 mL, 0.22 mmol) in DCM (2 mL) was added triphosgene (13 mg, 0.04 mmol). After 30min, the reaction mixture was quenched with water and extracted with DCM (20 ml X 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give

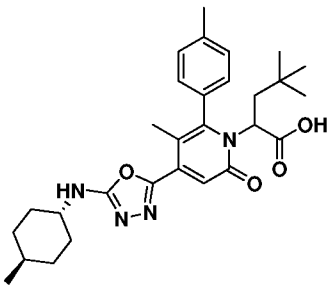
the crude product which was purified by column chromatography (silica gel, PE:EA = 1:1) to afford the title compound as a yellow oil (46 mg, 100% yield). LC-MS (ESI): m/z (M+1) = 440.4.

Step 3: *Ethyl 4,4-dimethyl-2-(5-methyl-4-(5-(((1r,4r)-4-methylcyclohexyl)amino)-1,3,4-oxadiazol-2-yl)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoate*



A mixture of Ethyl 4,4-dimethyl-2-(5-methyl-2-oxo-4-(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-6-(*p*-tolyl)pyridin-1(2*H*)-yl)pentanoate (25 mg, 0.06 mmol), (1*r*,4*r*)-4-methylcyclohexanamine (0.015 mL, 0.11 mmol), BOP (28 mg, 0.063 mmol) and DIPEA (0.02 mL, 0.11 mmol) in DMF (2 mL) was stirred at ambient temperature for 12h. The reaction mixture was diluted with water and extracted with EtOAc (20 ml X 2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by column chromatography (silica gel, PE:EA = 1:1) to afford the title compound as a yellow oil (20 mg, 66% yield). LC-MS (ESI): m/z (M+1) = 535.6.

Step 4: *4,4-Dimethyl-2-(5-methyl-4-(5-(((1r,4r)-4-methylcyclohexyl)amino)-1,3,4-oxadiazol-2-yl)-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)pentanoic acid*

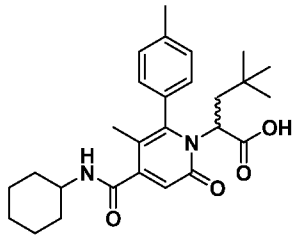


To a solution of Ethyl 4,4-dimethyl-2-(5-methyl-4-(5-(((1*r*,4*r*)-4-methylcyclohexyl)amino)-1,3,4-oxadiazol-2-yl)-2-oxo-6-(*p*-tolyl)pyridin-1(2*H*)-yl)pentanoate (20 mg, 0.037 mmol) in MeOH (2 mL) was added 1 N NaOH (0.4 mL) and heated to reflux. After 12h, the reaction mixture was cooled to ambient temperature, acidified with 1 N HCl (0.4 mL) (pH = 6~7) and concentrated under reduced pressure to give the crude product which was purified by reverse phase HPLC

(C_{18} 60~100% CH_3CN in H_2O with 0.1% formic acid) to afford the title compound as a white powder (8 mg, 42% yield). ^{1}H NMR (400 MHz, DMSO) δ 12.86 (s, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.45 – 7.30 (m, 4H), 6.75 (s, 1H), 4.28 (s, 1H), 3.39 – 3.36 (m, 1H), 2.41 (s, 3H), 2.26 – 2.22 (m, 1H), 2.06 – 1.93 (m, 5H), 1.92 – 1.87 (m, 1H), 1.75 – 1.68 (m, 2H), 1.37 – 1.27 (m, 3H), 1.08 – 1.01 (m, 2H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.59 (s, 9H). LC-MS (ESI): m/z (M+1) = 507.6.

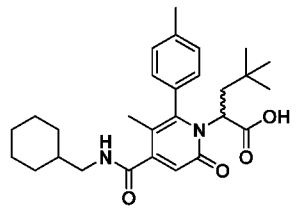
The following compounds were prepared in a manner simialar to the procedures described above for examples 1-6.

Example 7: 2-(4-(cyclohexylcarbamoyl)-5-methyl-2-oxo-6-p-tolylpyridin-1(2H)-yl)-4,4-dimethylpentanoic acid



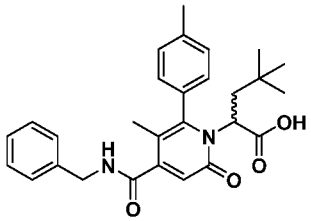
^{1}H NMR (400 MHz, DMSO) δ = 12.78 (br, 1H), 8.47 (d, J = 8.0 Hz, 1H), 7.36 (m, 4H), 6.27 (s, 1H), 4.22 (s, 1H), 3.71 – 3.63 (m, 1H), 2.39 (s, 3H), 2.32 – 2.26 (m, 1H), 1.84 – 1.64 (m, 7H), 1.60 – 1.54 (m, 1H), 1.34 – 1.06 (m, 6H), 0.58 (s, 9H). LC-MS (ESI): m/z (M+1) = 453.6

Example 8: 2-(4-(cyclohexylmethylcarbamoyl)-5-methyl-2-oxo-6-p-tolylpyridin-1(2H)-yl)-4,4-dimethylpentanoic acid



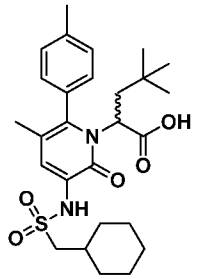
^{1}H NMR (400 MHz, DMSO) δ = 12.92 (br, 1H), 8.57 (t, J = 5.9 Hz, 1H), 7.42 – 7.28 (m, 4H), 6.29 (s, 1H), 4.23 (s, 1H), 3.08 – 3.01 (m, 2H), 2.39 (s,3H), 2.32 – 2.24 (m, 1H), 1.90 – 1.80 (m, 1H), 1.74 – 1.58 (m, 8H), 1.52 – 1.44 (m, 1H), 1.24 – 1.13 (m, 3H), 0.96 – 0.86 (m, 2H), 0.59 (s, 9H). LC-MS (ESI): m/z (M+1) = 467.6

Example 9: 2-(4-(benzylcarbamoyl)-5-methyl-2-oxo-6-p-tolylpyridin-1(2H)-yl)-4,4-dimethylpentanoic acid



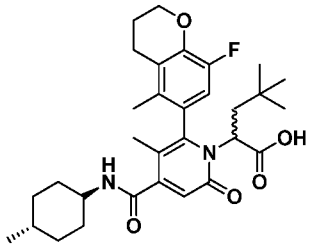
^{1}H NMR (400 MHz, DMSO) δ 12.86 (br, 1H), 9.15 (t, J = 5.8 Hz, 1H), 7.67 – 6.96 (m, 9H), 6.38 (s, 1H), 4.41 (d, J = 4.7 Hz, 2H), 4.25 (s, 1H), 2.39 (s, 3H), 2.32 – 2.22 (m, 1H), 1.92 – 1.78 (m, 1H), 1.67 (s, 3H), 0.59 (s, 9H). LC-MS (ESI): m/z (M+1) = 461.3

Example 10: 2-(3-(cyclohexylmethylsulfonamido)-5-methyl-2-oxo-6-(p-tolyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid



1H NMR (400 MHz, DMSO) δ 12.93 (br, 1H), 8.82 (s, 1H), 7.46 – 7.25 (m, 5H), 4.31 (s, 1H), 3.05 (d, J = 6.1 Hz, 2H), 2.39 (s, 3H), 2.25 – 2.19 (m, 1H), 2.04 – 1.97 (m, 1H), 1.92 – 1.78 (m, 5H), 1.68 – 1.56 (m, 3H), 1.24 – 0.99 (m, 5H), 0.56 (s, 9H). LC-MS (ESI): m/z (M+1) = 503.3

Example 11: 2-(6-(8-fluoro-5-methylchroman-6-yl)-5-methyl-4-(((1s,4s)-4-methylcyclohexyl)carbamoyl)-2-oxopyridin-1(2H)-yl)-4,4-dimethylpentanoic acid



1H NMR (400 MHz, DMSO) δ 8.45 (d, J = 8.1 Hz, 1H), 7.03 – 6.84 (m, 1H), 6.23 (s, 1H), 4.23 – 4.15 (m, 3H), 3.61 – 3.55 (m, 1H), 2.72 – 2.56 (m, 2H), 2.42 – 2.32 (m, 1H), 2.05 – 1.88 (m, 5H), 1.85 – 1.75 (m, 2H), 1.71 – 1.62 (m,2H), 1.55 (d, J = 24.2 Hz, 3H), 1.33 – 1.16 (m, 4H), 1.03 – 0.91 (m, 2H), 0.85 (d, J = 6.5 Hz, 3H), 0.61 (d, J = 33.7 Hz, 9H). LC-MS (ESI): m/z (M+1) = 541.9

Biological Examples

ANTI-HIV ACTIVITY

MT4 Assay

Antiviral HIV activity and cytotoxicity values for compounds of the invention from Table 1 were measured in parallel in the HTLV-1 transformed cell line MT-4 based on the method previously described (Hazen et al., 2007, *In vitro* antiviral activity of the novel, tyrosyl-based human immunodeficiency virus (HIV) type 1 protease inhibitor brecanavir (GW640385) in combination with other antiretrovirals and against a panel of protease inhibitor-resistant HIV (Hazen et al., "In vitro antiviral activity of the novel, tyrosyl-based human immunodeficiency virus (HIV) type 1 protease inhibitor brecanavir (GW640385) in combination with other antiretrovirals and against a panel of protease inhibitor-resistant HIV", *Antimicrob. Agents Chemother*. 2007, 51: 3147-3154; and Pauwels et al., "Sensitive and rapid assay on MT-4 cells for the detection of antiviral compounds against the AIDS virus", *J. of Virological Methods* 1987, 16: 171-185).

Luciferase activity was measured 96 hours later by adding a cell titer glo (Promega, Madison, Wis.). Percent inhibition of cell protection data was plotted relative to no compound control. Under the same condition, cytotoxicity of the compounds was determined using cell titer Glo™ (Promega, Madison, Wis). IC_{50}s were determined from a 10 point dose response curve using 3-4-fold serial dilution for each compound, which spans a concentration range > 1000 fold.

These values are plotted against the molar compound concentrations using the standard four parameter logistic equation:

y = ((Vmax * x^n) / (K^n + x^n)) + Y2

where:

Y2 = minimum y n = slope factor

Vmax= maximum y x = compound concentration [M]

K = EC_{50}

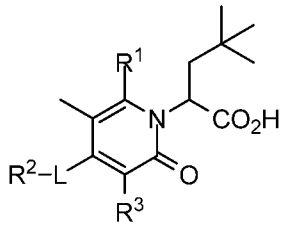
When tested in the MT4 assay compounds were found to have IC_{50} values listed in Table 2.

Table 2

Example	HIV MT4 Assay IC_{50} (uM)
1	0.35
2	1.09
3	0.31
4	33
5	
6	5.6
7	0.43
8	0.84
9	3.29
10	1.56
11	

What is claimed is:

1. A compound of Formula I:



Formula I

wherein:

R^1 is phenyl optionally substituted by one to four substituents selected from C_{1-3}alkyl, halogen, or $–CH_2CH_2CH_2O-$ wherein this group is bonded to adjacent carbon atoms on the phenyl to form a ring;

L is a bond, C_{1-3}alkylene, $-SO_2-$, $-SO_2CH_2-$, $-NHSO_2-$, $-NHSO_2CH_2-$, -C(O)-, -C(O)NH-, $-C(O)NHCH_2-$, $-C(O)OCH_2-$, -C(O)C(O)-, $–CH_2C(O)-$, C_{3-7}heteroaryl, or $-C_{3-7}$heteroarylNH-, wherein each heteroaryl comprises one to three heteroatoms selected from S, N, and O;

R^2 is H, cyclohexyl, or phenyl wherein said cyclohexyl and phenyl are optionally substituted by one to three substituents selected from C_{1-3}alkyl and halogen

R^3 is H or $–NHSO_2R^4$ wherein R^4 is C_{1-8}alkyl and wherein said alkyl can include cycloalkyl portions.

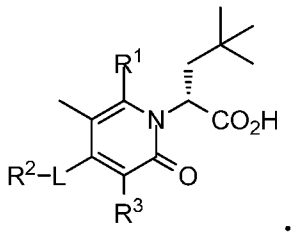
2. A compound according to Claim 1 wherein R^1 is phenyl optionally substituted by a methyl group.

3. A compound according to Claim 1 or 2 wherein L is a bond, -oxadiazolyl-NH-, -C(O)NH-, or $-C(O)NHCH_2-$.

4. A compound according to any of Claims 1-3 wherein R^2 is H, cyclohexyl, or phenyl wherein said cyclohexyl and phenyl are optionally substituted by 1 or 2 methyl groups.

5. A compound according to any of Claims 1-4 wherein R^3 is H, $–NHSO_2CH_3$, or $–NHSO_2CH_2$cyclohexyl.

6. A compound according to any of Claim 1-5 wherein the stereochemistry on the carbon to which the t-butyl group is bound is as depicted below.



7. A pharmaceutically acceptable salt of a compound according to any of Claims 1-6.

8. A pharmaceutical composition comprising a compound or salt according to any of Claims 1-7.

9. A method for treating a viral infection in a patient mediated at least in part by a virus in the *retrovirus* family of viruses, comprising administering to said patient a composition according to Claim 8.

10. The method of Claim 9 wherein said viral infection is mediated by the HIV virus.

11. A compound or salt as defined in any of Claims 1-7 for use in medical therapy.

12. A compound or salt as defined in any of Claims 1-7 for use in the treatment of a viral infection in a human.

13. The use of a compound or salt as defined in any of Claims 1-7 In the manufacture of a medicament for use in the treatment of a viral infection in a human.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/055385

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/75 A61K31/4418 A61K31/4439 C07D213/81 C07D213/64
A61P31/18
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2013/002357 A1 (SHIONOGI & CO [JP]; HATTORI KAZUNARI [JP]; KURIHARA NAOKO [JP]; IWAKI) 3 January 2013 (2013-01-03) claims 1, 46	1-13
Y	WO 2007/131350 A1 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; TSANT) 22 November 2007 (2007-11-22) claims 1-13, 22, 24-38	1-13
Y	WO 2005/018557 A2 (PHARMACIA CORP [US]; DEVADAS BALEKUDRU [US]; WALKER JOHN [US]; SELNESS) 3 March 2005 (2005-03-03) page 108, line 8 - page 110, line 26; claim 1	1-13

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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

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18 August 2015	31/08/2015

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INTERNATIONAL SEARCH REPORT

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Information on patent family members

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