INHIBITING HUMAN INTEGRIN α4ß7

RELATED APPLICATION

This application claims benefit of priority to U.S. Provisional Patent Application No. 62/916,062, filed October 16, 2019.

TECHNICAL FIELD

Disclosed are novel compounds and related methods useful for the inhibition of the $\alpha_4\beta_7$ integrin. The compounds and methods disclosed herein are applicable to the development of medicaments for the treatment of $\alpha_4\beta_7$ integrin-mediated conditions, such as inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease (CD).

BACKGROUND

Integrins are noncovalently associated α/β heterodimeric cell surface receptors involved in numerous cellular processes. Differential expression of integrins can regulate a cell's adhesive properties, allowing different leukocyte populations to be recruited to specific organs in response to different inflammatory signals. The α_4 integrins, including $\alpha_4\beta_7$, play a role in lymphocyte migration throughout the gastrointestinal tract. They are expressed on most leukocytes, including B and T lymphocytes, where they mediate cell adhesion via selective binding to its primary ligand, mucosal addressin cell adhesion molecule (MAdCAM). Memory T lymphocytes expressing the $\alpha_4\beta_7$ integrin preferentially migrate into the gastrointestinal tract via firm adhesion to mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1).

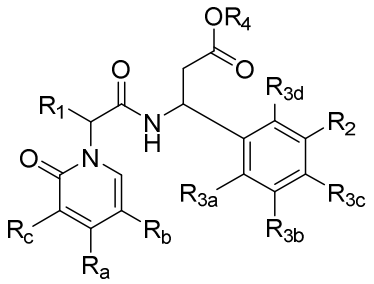
Inhibitors of specific integrin-ligand interactions have been used for the treatment of various diseases. For example, monoclonal antibodies displaying high binding affinity for $\alpha_4\beta_7$ have displayed therapeutic benefits for gastrointestinal auto-inflammatory/autoimmune diseases, such as Crohn's disease, and ulcerative colitis. However, these therapies also have certain undesirable properties for the patient. A monoclonal antibody $\alpha_4\beta_7$ integrin inhibitor is administered by parenteral administration, has a long half-life with inability to rapidly modify exposures, and a reduced activity due to anti-drug antibody formation. Monoclonal antibody therapies can be challenging to manufacture in comparison to small molecule therapies. In addition, some therapies that inhibit $\alpha_4\beta_7$ have also interfered with $\alpha_4\beta_1$ integrin-ligand interactions, thereby resulting in dangerous side effects to the patient. Activity at $\alpha_4\beta_1$ integrin

is implicated in emergence of progressive multifocal leukoencephalopathy (PML), a life-threatening and progressive brain infection, in immunosuppressed patients.

There remains a medical need for an effective and safe oral $\alpha_4\beta_7$ integrin inhibitor as an important addition to the therapeutic armamentarium for $\alpha_4\beta_7$integrin-mediated conditions, such as inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD).

SUMMARY

The disclosure relates to compounds of Formula (I):



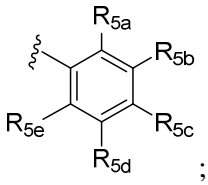
(I)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CN, - OCF_3, substituted or unsubstituted $(C_1\text{-}C_5)$-alkyl, substituted or unsubstituted $(C_1\text{-}C_5)$-alkoxy, $-CH_2CF_3$, and substituted or unsubstituted $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl, substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_3\text{-}C_6)$-cycloalkyl, or substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted $(C_1\text{-}C_5)$-alkyl, substituted or unsubstituted $(C_3\text{-}C_6)$-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -$(C_1$-

C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3 -CN, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_{3d} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, halide, and -(C_1-C_4)-alkoxy;

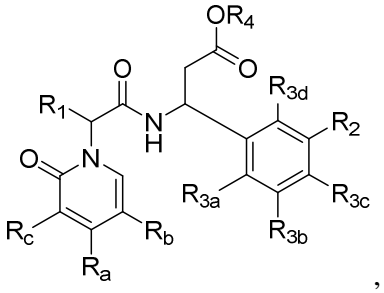
R_4 is H, or substituted or unsubstituted (C_1-C_4)-alkyl;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CH_2CF_3, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CH_2CF_3, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a compound of Formula (I):



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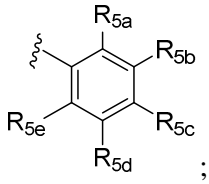
(I)

or a pharmaceutically acceptable salt thereof, wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that at least one of R_a, R_b, and R_c is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form an unsubstituted 4-6 membered ring or a substituted 4-6 membered ring, substituted with at least one halide, unsubstituted (C_1-C_4)-alkyl, or OMe;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl, substituted or unsubstituted (C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_2 is 

;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is H;

R_{3d} is H;

R_4 is H, or substituted or unsubstituted (C_1-C_4)-alkyl;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

wherein, unless otherwise specified, substituted means substituted with one or more substituents selected from alkyl, cycloalkyl, heterocyclylalkyl, halogen, OH, OMe, $C(H)F_2$, $C(F)H_2$, CF_3, $C(H)_2CF_3$, SF_5 $CHFCH_2$amine, CH_2amine, and CN.

In some examples of the disclosure, a compound of Formula (I) can be a compound wherein one and only one of R_a, R_b, and R_c is substituted or unsubstituted -(C_1-

C_5)alkylene-N-(R_x)(R_y); R_1 is (C_1-C_6) alkyl (e.g., isobutyl); R_{3a} and R_{3b} are independently selected from the group consisting of H, (C_1-C_4)-alkyl (e.g., methyl), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, provided that R_{3a} and R_{3b} are not both H; and R_4 is H.

In some examples, a compound of Formula (I) can be a compound wherein one and only one of R_a, R_b, and R_c is substituted or unsubstituted -(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are each independently unsubstituted (C_1-C_6)-alkyl (e.g., methyl) or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring; R_1 is unsubstituted (C_1-C_6) alkyl (e.g., isobutyl); R_{3a} and R_{3b} are independently selected from the group consisting of H, unsubstituted (C_1-C_4)-alkyl (e.g.,

methyl, ethyl, etc.), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, provided that R_{3a} and R_{3b} are not both H; R_{3c} is selected from the group consisting of: H, F, Cl, hydroxyl, substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl), substituted or unsubstituted (C_3-C_6)-cycloalkyl (e.g., cyclopropyl), (C_1-C_4)-alkoxy (e.g., methoxy); R_{3d} is selected from the group consisting of H, halide (e.g., F, or Cl), substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl), and hydroxyl; and R_4 is H. In some examples, a compound of Formula (I), Formula (Ia) and/or Formula (Ib) can be a compound wherein one and only one of R_a, R_b, and R_c is substituted or unsubstituted -(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y each independently unsubstituted methyl or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring; R_1 is isobutyl; R_{3a} and R_{3b} are independently selected from the group consisting of unsubstituted (C_1-C_4)-alkyl (e.g., methyl), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, R_{3c} and R_{3d} are both H; and R_4 is H. For instance, a compound of Formula (I), Formula (Ia) and/or Formula (Ib) can be a compound wherein R_1 is isobutyl; R_{3a} and R_{3b} are independently selected from the group consisting of unsubstituted (C_1-C_4)-alkyl (e.g., methyl), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, R_{3c} and R_{3d} are both H; R_4 is H; and R_{5a}, and R_{5e} are each substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl). A compound of Formula (I) can be a compound wherein one and only one of R_a, R_b, and R_c is substituted or unsubstituted -(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y each independently unsubstituted methyl or R_x and R_y taken together with the N to which they are attached form a 4-6 membered heterocyclyl ring optionally substituted with halide (e.g., F); R_1 is isobutyl; R_{3a} and R_{3b} are independently selected from the group consisting of unsubstituted (C_1-C_4)-alkyl (e.g., methyl), halide (e.g., F or Cl), CF_3, $C(H)F_2$, and $C(F)H_2$, R_{3c} and R_{3d} are both H; R_4 is H; R_{5a}, and R_{5e} are each substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl), and R_{5b}, R_{5c}, and R_{5d} are each independently selected from the group consisting of H, CN, halide (e.g., F, Cl), CF_3, $C(H)F_2$, $C(F)H_2$, (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy. In certain examples, the disclsoure relates to a method of treating auto-inflammatory/autoimmune diseases, such as Crohn's disease, and ulcerative colitis; comprising the step of: administering to a subject in need thereof a therapeutically effective amount of any one of the compounds described herein.

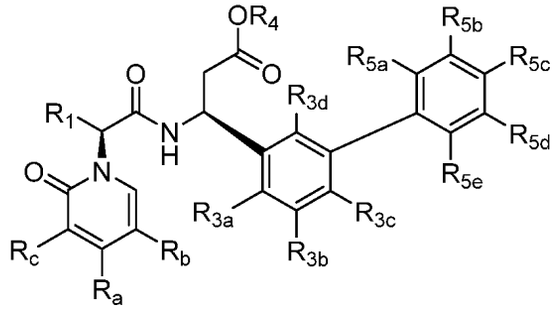
In another aspect, there is provided a pharmaceutical composition comprising a compound as described herein, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient.

In another aspect, there is provided use of the compound as described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

In another aspect, there is provided use of the pharmaceutical composition as described herein, in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

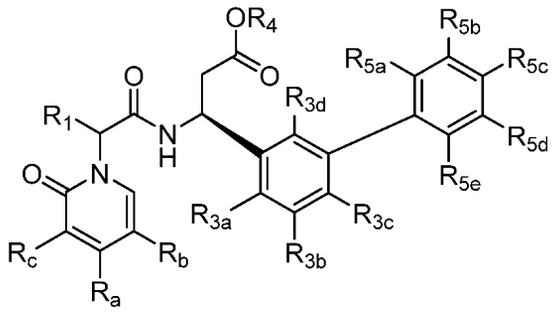
In another aspect, there is provided the compound as described herein, or a pharmaceutically acceptable salt thereof, for use as a medicament.

In some examples, a compound of Formula (I) can be a compound of Formula (Ia):



(Ia)

or a pharmaceutically acceptable salt thereof, wherein R_a, R_b, R_c, R_1, R_{3a}, R_{3b}, R_{3c}, R_{3d}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, R_{5e}, and R_4 in Formula (Ia) are each independently defined as above with respect to Formula (I).



(Ib)

or a pharmaceutically acceptable salt thereof, wherein R_a, R_b, R_c, R_1, R_{3a}, R_{3b}, R_{3c}, R_{3d}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, R_{5e}, and R_4 in Formula (Ia) are each independently defined as above with respect to Formula (I).

Methods of preparing and isolating the compounds of Formula (I), Formula (Ia) and/or Formula (Ib) are also provided herein.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 is a table (Table 1) summarizing *in vitro* inhibition of $\alpha_4\beta_7$ integrin by exemplary compounds (i.e., data obtained from the fluorescence polarization assay of Example 5, and the ligand binding assay of Example 6).

Figure 2 is a table (Table 2) providing additional exemplary compounds.

Figure 3 is a table (Table 5) summarizing *in vitro* inhibition of $\alpha_4\beta_7$ integrin by exemplary compounds (i.e., data obtained from the fluorescence polarization assay of Example 5, and the ligand binding assay of Example 6).

Figure 4 is a table (Table 6) summarizing *in vitro* inhibition of $\alpha_4\beta_7$ integrin by exemplary compounds (i.e., data obtained from the fluorescence polarization assay of Example 5, and the ligand binding assay of Example 6).

DETAILED DESCRIPTION

In certain embodiments, the invention relates to compounds that antagonize $\alpha_4\beta_7$ integrin. The compounds will be useful for the treatment of diseases that are treatable by the inhibition of $\alpha_4\beta_7$ integrin (e.g., Crohn's disease (CD), and ulcerative colitis (UC)).

DEFINITIONS

For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

The articles "a" and "an" are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The phrase "and/or," as used herein in the specification and in the claims, should be understood to mean "either or both" of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with "and/or" should be construed in the same fashion, i.e., "one or more" of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the "and/or" clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to "A and/or B", when used in conjunction with open-ended language such as "comprising" can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

As used herein in the specification and in the claims, "or" should be understood to have the same meaning as "and/or" as defined above. For example, when separating items in a list,

"or" or "and/or" shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as "only one of" or "exactly one of," or, when used in the claims, "consisting of," will refer to the inclusion of exactly one element of a number or list of elements. In general, the term "or" as used herein shall only be interpreted as indicating exclusive alternatives (i.e., "one or the other but not both") when preceded by terms of exclusivity, such as "either," "one of," "only one of," or "exactly one of." "Consisting essentially of," when used in the claims, shall have its ordinary meaning as used in the field of patent law.

As used herein in the specification and in the claims, the phrase "at least one," in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase "at least one" refers, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, "at least one of A and B" (or, equivalently, "at least one of A or B," or, equivalently "at least one of A and/or B") can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

In the claims, as well as in the specification above, all transitional phrases such as "comprising," "including," "carrying," "having," "containing," "involving," "holding," "composed of," and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases "consisting of" and "consisting essentially of" shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C- or ^{14}C-enriched carbon are within the scope of this invention.

The terms “α4β7”, “a4B7”, “a4b7”, “alpha-4 beta-7” and “alpha 4 beta 7” and the like as used herein all refer to $\alpha_4\beta_7$.

The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ or portion of the body, to another organ or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, not injurious to the patient, and substantially non-pyrogenic. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter; (9) oils, such as peanut oil, cottonseed oil,

safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term "pharmaceutically acceptable salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.)

In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

A "therapeutically effective amount" (or "effective amount") of a compound with respect to use in treatment, refers to an amount of the compound in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to

clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment.

The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

The term "patient" refers to a mammal in need of a particular treatment. In certain embodiments, a patient is a primate, canine, feline, or equine. In certain embodiments, a patient is a human.

An aliphatic chain comprises the classes of alkyl, alkenyl and alkynyl defined below. A straight aliphatic chain is limited to unbranched carbon chain moieties. As used herein, the term "aliphatic group" refers to a straight chain, branched-chain, or cyclic aliphatic hydrocarbon group and includes saturated and unsaturated aliphatic groups, such as an alkyl group, an alkenyl group, or an alkynyl group.

"Alkyl" refers to a fully saturated cyclic or acyclic, branched or unbranched carbon chain moiety having the number of carbon atoms specified, or 1 up to 30 carbon atoms if no specification is made. For example, alkyl of 1 to 8 carbon atoms refers to moieties such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl, and those moieties which are positional isomers of these moieties. Alkyl of 10 to 30 carbon atoms includes decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, heneicosyl, docosyl, tricosyl and tetracosyl. In certain embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (e.g., C_1-C_{30} for straight chains, C_3-C_{30} for branched chains), and more preferably 20 or fewer. Alkyl goups may be substituted or unsubstituted. As used herein, "Me" and $-CH_3$ both refer to methyl.

As used herein, the term "alkylene" refers to an alkyl group having the specified number of carbons, for example from 2 to 12 carbon atoms, that contains two points of attachment to the rest of the compound on its longest carbon chain. Non-limiting examples of alkylene groups include methylene $-(CH_2)-$, ethylene $-(CH_2CH_2)-$, n-propylene $-(CH_2CH_2CH_2)-$, isopropylene $-(CH_2CH(CH_3))-$, and the like. Alkylene groups can be cyclic or acyclic, branched or unbranched carbon chain moiety, and may be optionally substituted with one or more substituents.

"Cycloalkyl" means mono- or bicyclic or bridged or spirocyclic, or polycyclic saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 3-6 carbons in the ring structure. Cycloalkyl groups may be substituted or unsubstituted.

Unless the number of carbons is otherwise specified, "lower alkyl," as used herein, means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Throughout the application, preferred alkyl groups are lower alkyls. In certain embodiments, a substituent designated herein as alkyl is a lower alkyl.

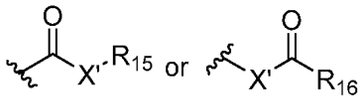
The term "aryl" as used herein includes 3- to 12-membered substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon (i.e., carbocyclic aryl) or where one or more atoms are heteroatoms (i.e., heteroaryl). Preferably, aryl groups include 5- to 12-membered rings, more preferably 6- to 10-membered rings The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Carbocyclic aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like. Heteroaryl groups include substituted or unsubstituted aromatic 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl and heteroaryl can be monocyclic, bicyclic, or polycyclic.

The term "halo", "halide", or "halogen" as used herein means halogen and includes, for example, and without being limited thereto, fluoro, chloro, bromo, iodo and the like, in both radioactive and non-radioactive forms. In a preferred embodiment, halo is selected from the group consisting of fluoro, chloro and bromo.

The terms "heterocyclyl" or "heterocyclic group" refer to 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can be monocyclic, bicyclic, spirocyclic, or polycyclic. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine,

indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, sulfamoyl, sulfinyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF_3, -CN, and the like.

The term "carbonyl" is art-recognized and includes such moieties as can be represented by the formula:



wherein X' is a bond or represents an oxygen or a sulfur, and R_{15} represents a hydrogen, an alkyl, an alkenyl, -$(CH_2)_m$-R_{10} or a pharmaceutically acceptable salt, R_{16} represents a hydrogen, an alkyl, an alkenyl or -$(CH_2)_m$-R_{10}, where m and R_{10} are as defined above. Where X' is an oxygen and R_{15} or R_{16} is not hydrogen, the formula represents an "ester." Where X' is an oxygen, and R_{15} is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R_{15} is a hydrogen, the formula represents a "carboxylic acid". Where X' is an oxygen, and R_{16} is a hydrogen, the formula represents a "formate." On the other hand, where X' is a bond, and R_{15} is not hydrogen, the above formula represents a "ketone" group. Where X' is a bond, and R_{15} is a hydrogen, the above formula represents an "aldehyde" group.

As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above, and for example substituted with one or more substituents selected from alkyl, cycloalkyl, heterocyclylakyl, halogen, OH, OMe, $C(H)F_2$, $C(F)H_2$, CF_3, $C(H)_2CF_3$, SF_5, $CHFCH_2$amine, CH_2amine, and CN. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of

the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

As used herein, the term "nitro" means -NO_2; the term "halogen" designates -F, -Cl, -Br, or -I; the term "hydroxyl" means -OH; and the term "cyano" means –CN;.

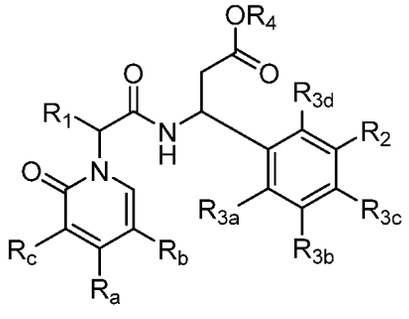
As used herein, the definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

The term "prodrug" as used herein encompasses compounds that, under physiological conditions, are converted into therapeutically active agents. A common method for making a prodrug is to include selected moieties that are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal.

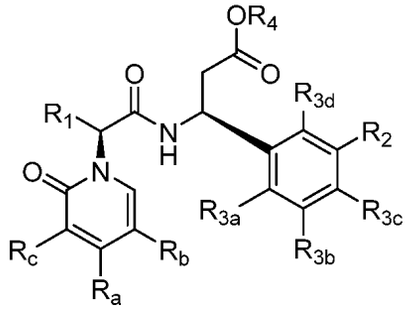
For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

EXEMPLARY COMPOUNDS

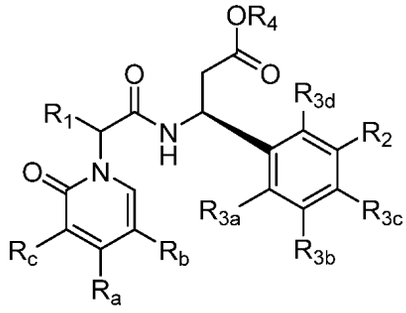
In some embodiments, the invention relates to a compound of Formula (I), Formula (Ia), or Formula (Ib):



(I)



(Ia)



(Ib)

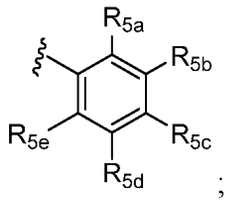
or a pharmaceutically acceptable salt thereof;

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CN, - OCF_3, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_1-C_5)-alkoxy, -CH_2CF_3, and substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that at least one of R_a, R_b, and R_c is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl, substituted or unsubstituted (C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, $-OCF_3$, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, $-OCF_3$ -CN, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_{3d} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, halide, and -(C_1-C_4)-alkoxy;

R_4 is H, or substituted or unsubstituted (C_1-C_4)-alkyl;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is Me; R_b, is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is H; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is (C_1-C_5)-alkyl; R_{3c} is H; R_{3d} is H; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected

from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is Me; R_b, is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is H; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is halide; R_{3c} is H; R_{3d} is H; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is H; R_b, is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is $CH(F)_2$; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is (C_1-C_5)-alkyl; R_{3c} is H; R_{3d} is H; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is H; R_b, is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is halide; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is (C_1-C_5)-alkyl; R_{3c} is H; R_{3d} is H; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl,

substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is CF_3; R_b, is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is H; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is (C_1-C_5)-alkyl; R_{3c} is H; R_{3d} is H; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is CF_3; R_b, is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is H; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is CF_3; R_{3c} is H; R_{3d} is H; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is CF_3; R_b, is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is H; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is halide; R_{3c} is H; R_{3d} is H; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is CF_3; R_b is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is H; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is (C_3-C_6)-cycloalkyl; R_{3c} is H; R_{3d} is halide; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

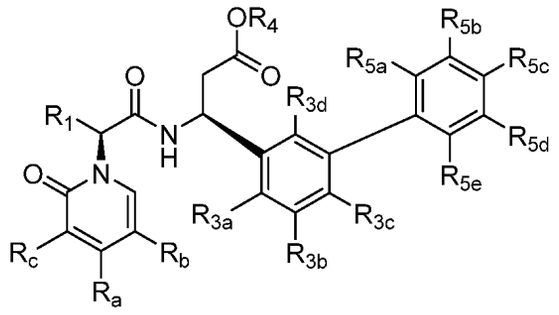
In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is CF_3; R_b is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is H; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is CF_3; R_{3c} is H; R_{3d} is halide; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia) can be a compound wherein: R_a is CF_3; R_b is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; R_c is H; R_1 is (C_1-C_6)-alkyl; R_{3a} is halide; R_{3b} is (C_1-C_5)-alkyl; R_{3c} is H; R_{3d} is halide; R_4 is H; R_{5a}, and R_{5e} are (C_1-C_5)-alkyl; and R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy, or a pharmaceutically acceptable salt thereof.

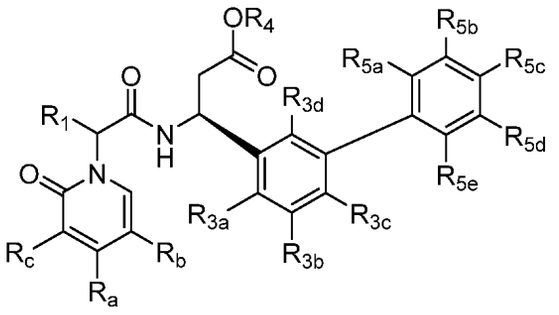
In some embodiments, a compound of Formula (Ia) can be a compound wherein R_{5a}, is halide or (C_1-C_5)-alkyl; R_{5b} is H, halide or substituted or unsubstituted (C_1-C_5)-alky; R_{5c} is

H, halide, substituted or unsubstituted (C_1-C_5)-alkyl, or substituted or unsubstituted (C_3-C_6)-cycloalkyl; and R_{5d} is selected from the group consisting of H, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CH_2CF_3, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy; and R5e is halide or or (C_1-C_5)-alkyl.

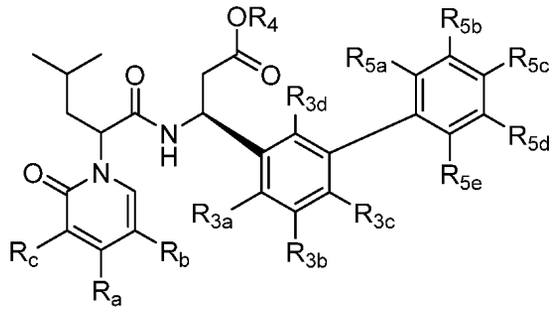
In some embodiments, a compound of Formula (I) can be a compound of Formula (Ia), Formula (Ib), Formula (Ic) and/or Formula (Id):



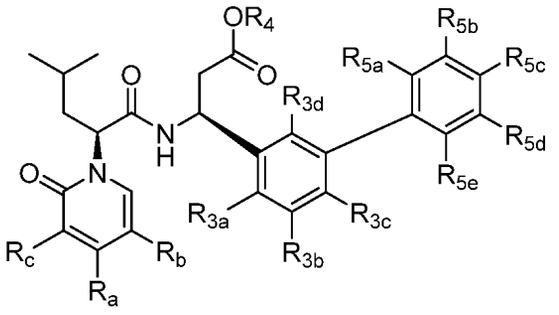
(Ia)



(Ib)



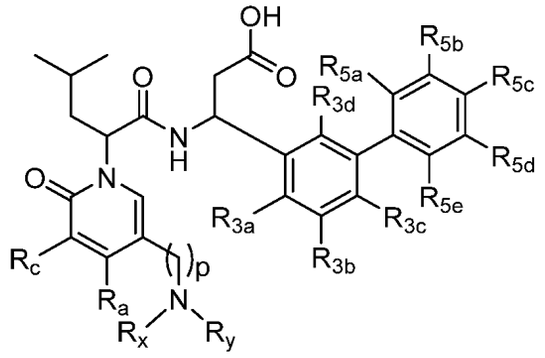
(Ic)



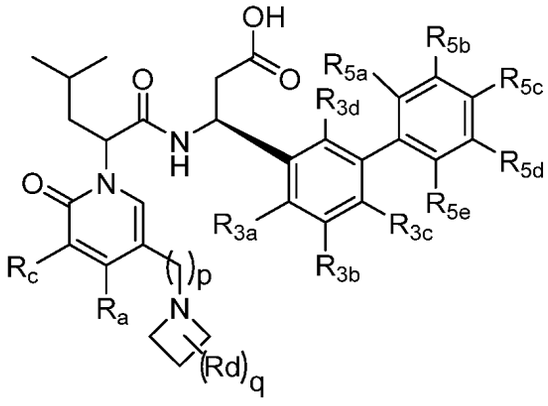
(Id)

wherein R_a, R_b, R_c, R_1, R_{3a}, R_{3b}, R_{3c}, R_{3d}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, R_{5e}, and R_4 in Formula (Ia), Formula (Ib), Formula (Ic) and Formula (Id) are each independently defined as above with respect to Formula (I).

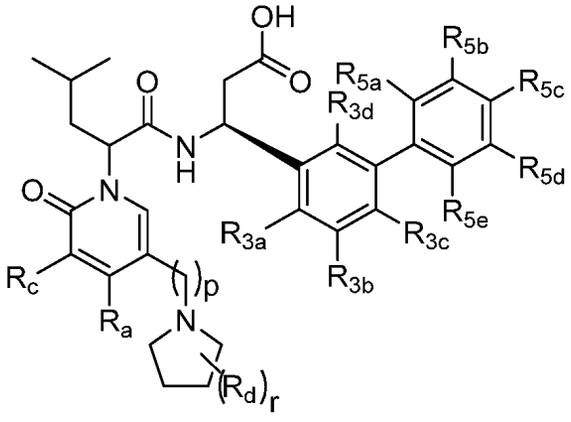
In some embodiments, a compound of Formula (I) can be a compound of Formula (II), including compounds of Formula (IIa), Formula (IIb) or Formula (IIc):



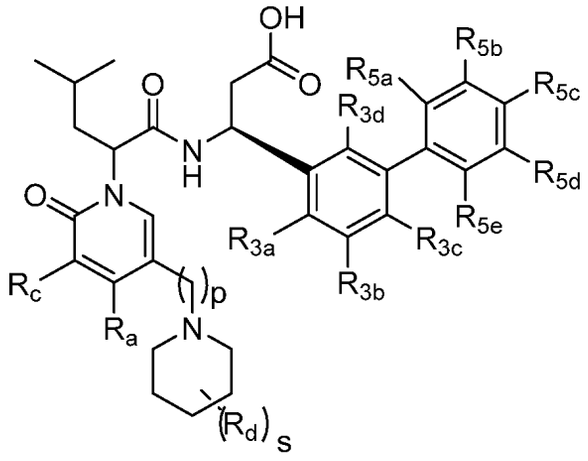
(II)



(IIa)

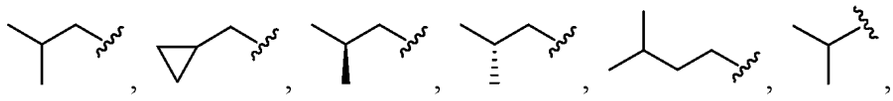
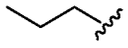


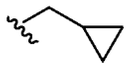
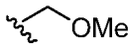
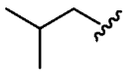
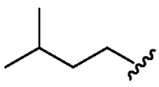
(IIb)



(IIc),

wherein R_a, R_c, R_{3a}, R_{3b}, R_{3c}, R_{3d}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, and R_{5e}, are as described in Formula (I); p is 1, 2, or 3; q is 0, 1, 2 or 3; r is an 0, 1, 2, 3 or 4; s is 0, 1, 2, 3, 4 or 5; and each R_d is independently selected from the group consisting of halide, (C_1-C_5)-alkyl, (C_1-C_4)-alkoxy, -CF_3, -C(H)F_2, -OCF_3, and -CN. In some embodiments, at least one instance of R_d is F or Cl. In some embodiments, at least one instance of R_d is methyl. In some embodiments, at least one instance of R_d is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds of Formula (IIa), wherein q is 1. In certain embodiments, the invention relates to any one of the aforementioned compounds of Formula (IIb), wherein r is 1. In certain embodiments, the invention relates to any one of the aforementioned compounds of Formula (IIc), wherein s is 1.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is unsubstituted (C_1-C_6)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is substituted (C_1-C_6)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is substituted or unsubstituted (C_1-C_4)-alkyl. In certain embodiments, R_1 is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, sec-butyl, or t-butyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is selected from the group consisting of  , and  . In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is substituted (C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1

is unsubstituted (C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl. In certain embodiments, R_1 is  . In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is substituted (C_1-C_4)-alkylene- (C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is unsubstituted (C_1-C_4)-alkylene- (C_1-C_4)-alkoxy. In certain embodiments, R_1 is  . In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is  . In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_1 is  .

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is H; provided that R_{3a} and R_{3b} are not both H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with a halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{3a} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is substituted or unsubstituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is substituted -(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is unsubstituted -(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is $-OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is substituted

(C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $-CH_2OMe$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3a} is F.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is H; provided that R_{3a} and R_{3b} are not both H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with a halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{3b} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is substituted or unsubstituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is substituted -(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is unsubstituted -(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is $-OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is substituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $-CH_2OMe$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one

or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is selected from the group consisting of methyl, cyclopropyl and CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is methyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is selected from the group consisting of halide, (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is selected from the group consisting of F, Cl, methyl, and CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is methyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is F. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is Cl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3b} is CF_3.

In certain embodiments, R_{3a} and R_{3b} are independently selected from the group consisting of H, (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, and $C(F)H_2$; provided that R_{3a} and R_{3b} are not both H. For example, R_{3a} and R_{3b} can be independently selected from the group consisting of H, methyl, Cl, F, CF_3, $C(H)F_2$, and $C(F)H_2$; provided that R_{3a} and R_{3b} are not both H. In certain embodiments, R_{3a} is halide and R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, R_{3a} is F and R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, R_{3a} is F and R_{3b} is selected from the group consisting of methyl, cyclopropyl and CF_3. In certain embodiments, R_{3a} is F and R_{3b} is selected from the group consisting of F, Cl, methyl, and CF_3. In certain embodiments, R_{3a} is F and R_{3b} is selected from the group consisting of F, Cl, methyl, cyclopropyl and CF_3.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is selected from the group consisting of: H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted cyclopropyl, hydroxyl, methoxy, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and –CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is unsubstituted

(C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with a halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{3c} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is substituted or unsubstituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is substituted -(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is unsubstituted -(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is $-OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is substituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $–CH_2OMe$.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is H; R_{3a} is halide; and R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, R_{3c} is H; R_{3a} is F; and R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, R_{3c} is H; R_{3a} is F; and R_{3b} is selected from the group consisting of methyl, cyclopropyl and CF_3. In certain embodiments, R_{3c} is H; R_{3a} is F; R_{3b} is selected from the group consisting of F, Cl, methyl, and CF_3. In certain embodiments, R_{3c} is H; R_{3a} is F; R_{3b} is selected from the group consisting of F, Cl, methyl, cyclopropyl and CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein

R_{3d} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, halide, methoxy, halide, CF_3, $C(H)F_2$, and $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with a halogen. In certain embodiments, the halogen is F. In certain embodiments, R_{3d} is methyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is substituted or unsubstituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is halide. In some embodiments, the halide is Cl or F In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is substituted -(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is unsubstituted -(C_1-C_4)-alkoxy. In certain embodiments, -(C_1-C_4)-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is -OCF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is substituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3d} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is –CH_2OMe.

In some embodiments, R_{3c} and R_{3d} are the same. In some embodiments, R_{3c} and R_{3d} are both H. In some embodiments, R_{3c} and R_{3d} are different. In some embodiments, R_{3c} is H and R_{3d} is H or halide. In some embodiments, R_{3c} is H and R_{3d} is F.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} and R_{3d} are both H; R_{3a} is halide; and R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, R_{3c} and R_{3d} are both H; R_{3a} is F; and R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, R_{3c} and R_{3d} are both H; R_{3a} is F; and R_{3b} is selected from the group consisting of methyl, cyclopropyl and CF_3. In certain embodiments, R_{3c} and R_{3d} are both H; R_{3a} is F; R_{3b} is selected from the group consisting of F, Cl, methyl, and CF_3. In certain embodiments, R_{3c} and R_{3d} are both H; R_{3a} is F; R_{3b} is selected from the group consisting of F, Cl, methyl, cyclopropyl and CF_3.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{3c} is H; R_{3d} is F; R_{3a} is halide; and R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, R_{3c} is H; R_{3d} is F; R_{3a} is F; and R_{3b} is selected from the group consisting of (C_1-C_4)-alkylene optionally substituted with one or more halide and (C_3-C_6)-cycloalkyl. In certain embodiments, R_{3c} is H; R_{3d} is F; R_{3a} is F; and R_{3b} is selected from the group consisting of methyl, cyclopropyl and CF_3. In certain embodiments, R_{3c} is H; R_{3d} is F; R_{3a} is F; R_{3b} is selected from the group consisting of F, Cl, methyl, and CF_3. In certain embodiments, R_{3c} is H; R_{3d} is F; R_{3a} is F; R_{3b} is selected from the group consisting of F, Cl, methyl, cyclopropyl and CF_3.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_4 is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_4 is substituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_4 is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_4 is methyl, ethyl, n-propyl, or i-propyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_4 is methyl or ethyl.

In certain embodiments, R_{5a} is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is substituted or unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is substituted

(C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with one or more halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5a} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, R_{5a} is methyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5a} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, R_{5a} is unsubstituted (C_3-C_6)-cycloalkyl. In some embodiments, (C_3-C_6)-cycloalkyl is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is (C_1-C_4)-alkoxy. In some embodiments, (C_1-C_4)-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is hydroxyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is $–OCF_3$. In certain embodiments, R_{5a} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is substituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $–CH_2OMe$. In certain embodiments, R_{5a} is CH_2OH.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with a halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5b} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, R_{5a} is methyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5b} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, R_{5b} is unsubstituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one

of the aforementioned compounds, wherein R_{5b} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is $(C_1\text{-}C_4)$-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is hydroxyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is $–OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is substituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy. In certain embodiments, $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy is $–CH_2OMe$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is hydrogen.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is unsubstituted $(C_1\text{-}C_4)$-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is substituted $(C_1\text{-}C_4)$-alkyl. In certain embodiments, the substituted $(C_1\text{-}C_5)$-alkyl, is substituted with a halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5c} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, R_{5c} is methyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5c} is substituted $(C_3\text{-}C_6)$-cycloalkyl. In certain embodiments, R_{5c} is cyclopropyl. In certain embodiments, R_{5c} is unsubstituted $(C_3\text{-}C_6)$-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is $(C_1\text{-}C_4)$-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is hydroxyl. In certain embodiments, the

invention relates to any one of the aforementioned compounds, wherein R_{5c} is $–OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is substituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $–CH_2OMe$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is hydrogen.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with a halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5d} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, R_{5d} is methyl In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5d} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, R_{5d} is unsubstituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is (C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is hydroxyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is $–OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is substituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $–CH_2OMe$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is hydrogen.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with a halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5e} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, R_{5e} is methyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5e} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, R_{5e} is unsubstituted (C_3-C_6)-cycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is (C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is hydroxyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is $–OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is substituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $–CH_2OMe$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is hydrogen.

In certain embodiments, R_{5b} is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is isubstituted or unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with one or more halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5b} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, the

invention relates to any one of the aforementioned compounds, wherein R_{5b} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5b} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, R_{5b} is unsubstituted (C_3-C_6)-cycloalkyl. In some embodiments, (C_3-C_6)-cycloalkyl is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is (C_1-C_4)-alkoxy. In some embodiments, (C_1-C_4)-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is hydroxyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is $–OCF_3$. In certain embodiments, R_{5b} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is substituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5b} is unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $–CH_2OMe$. In certain embodiments, R_{5b} is CH_2OH.

In certain embodiments, R_{5c} is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is isubstituted or unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is substituted (C_1-C_4)-alkyl. In certain embodiments, the substituted (C_1-C_5)-alkyl, is substituted with one or more halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5c} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5c} is substituted (C_3-C_6)-cycloalkyl. In certain embodiments, R_{5c} is unsubstituted (C_3-C_6)-cycloalkyl. In some embodiments, (C_3-C_6)-cycloalkyl is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein

R_{5c} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is $(C_1\text{-}C_4)$-alkoxy. In some embodiments, $(C_1\text{-}C_4)$-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is hydroxyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is $–OCF_3$. In certain embodiments, R_{5c} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5a} is substituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5c} is unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy. In certain embodiments, $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy is $–CH_2OMe$. In certain embodiments, R_{5c} is CH_2OH.

In certain embodiments, R_{5d} is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is substituted or unsubstituted $(C_1\text{-}C_4)$-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is unsubstituted $(C_1\text{-}C_4)$-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is substituted $(C_1\text{-}C_4)$-alkyl. In certain embodiments, the substituted $(C_1\text{-}C_5)$-alkyl, is substituted with one or more halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5d} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5d} is substituted $(C_3\text{-}C_6)$-cycloalkyl. In certain embodiments, R_{5d} is unsubstituted $(C_3\text{-}C_6)$-cycloalkyl. In some embodiments, $(C_3\text{-}C_6)$-cycloalkyl is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is $(C_1\text{-}C_4)$-alkoxy. In some embodiments, $(C_1\text{-}C_4)$-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is hydroxyl. In certain

embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is $-OCF_3$. In certain embodiments, R_{5d} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is substituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5d} is unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy. In certain embodiments, $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy is $-CH_2OMe$. In certain embodiments, R_{5d} is CH_2OH.

In certain embodiments, R_{5e} is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is substituted or unsubstituted $(C_1\text{-}C_4)$-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is unsubstituted $(C_1\text{-}C_4)$-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is substituted $(C_1\text{-}C_4)$-alkyl. In certain embodiments, the substituted $(C_1\text{-}C_5)$-alkyl, is substituted with one or more halogen. In certain embodiments, the halogen is Cl or F. In certain embodiments, R_{5e} is methyl, ethyl, isopropyl, n-propyl, i-butyl, n-butyl, or t-butyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is halide. In some embodiments, the halide is Cl or F. In certain embodiments, R_{5e} is substituted $(C_3\text{-}C_6)$-cycloalkyl. In certain embodiments, R_{5e} is unsubstituted $(C_3\text{-}C_6)$-cycloalkyl. In some embodiments, $(C_3\text{-}C_6)$-cycloalkyl is cyclopropyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is $(C_1\text{-}C_4)$-alkoxy. In some embodiments, $(C_1\text{-}C_4)$-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is hydroxyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is $-OCF_3$. In certain embodiments, R_{5e} is CN. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is substituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_{5e} is unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy. In

certain embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is –CH_2OMe. In certain embodiments, R_{5e} is CH_2OH.

In some embodiments, R_{5a} and R_{5e} are identical. For example, R_{5a} and R_{5e} can both be substituted or unsubstituted (C_1-C_4)-alkyl. In some examples, R_{5a} and R_{5e} are both unsubstituted (C_1-C_4)-alkyl (e.g., methyl). In some examples, R_{5a} and R_{5e} are both unsubstituted methyl.

In some embodiments, R_{5b} and R_{5d} are identical. For example, R_{5a} and R_{5e} can both be hydrogen.

In some embodiments, R_{5a} and R_{5e} are both substituted, and R_{5b} and R_{5d} are both hydrogen. For example, R_{5a} and R_{5e} can both be (the same or different) substituted or unsubstituted (C_1-C_4)-alkyl. In some examples, R_{5a} and R_{5e} can both be unsubstituted (C_1-C_4)-alkyl (e.g., methyl) and R_{5b} and R_{5d} are both hydrogen. In some examples, R_{5a} and R_{5e} are both unsubstituted methyl and R_{5b} and R_{5d} are both hydrogen. In some embodiments, R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy.

In some embodiments, R_{5c} is hydrogen, halide (e.g., F), substituted or unsubstituted (C_1-C_4)-alkoxy (e.g., methoxy), or substituted or unsubstituted (C_1-C_4)-alkyl (e.g., methyl).

In some embodiments, R_{5a} and R_{5e} are both substituted or unsubstituted (C_1-C_5)-alkyl, both R_{5b} and R_{5d} are hydrogen and R_{5c} is hydrogen, halide (e.g., F), substituted or unsubstituted (C_1-C_4)-alkoxy (e.g., methoxy), or substituted or unsubstituted (C_1-C_4)-alkyl (e.g, methyl). For example, R_{5a} and R_{5e} can both be methyl; R_{5b} and R_{5d} are both hydrogen; and R_{5c} is selected from the group consisting of hydrogen, halide (e.g., F), substituted or unsubstituted (C_1-C_4)-alkoxy (e.g., methoxy), and substituted or unsubstituted (C_1-C_4)-alkyl (e.g, methyl). In some examples, R_{5a} and R_{5e} can both be methyl; R_{5b} and R_{5d} are both hydrogen; and R_{5c} is selected from the group consisting of hydrogen, F, Cl, methoxy, and methyl. In some examples, R_{5a}, R_{5c} and R_{5e} are each methyl; and R_{5b} and R_{5d} are both hydrogen. In some embodiments, R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a, R_b and R_c comprise a charged amine. At least one of R_a, R_b and R_c can be a substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); wherein R_x and R_y are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_6)-alkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring.

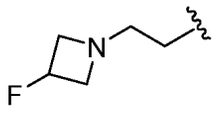
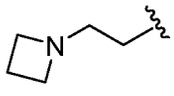
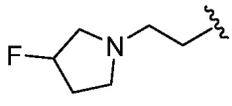
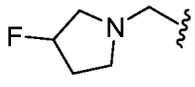
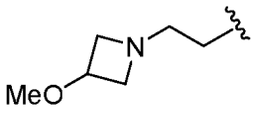
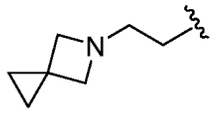
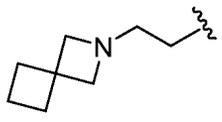
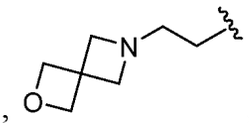
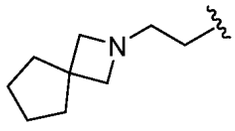
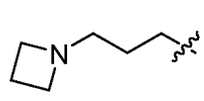
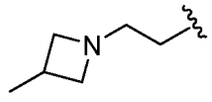
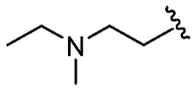
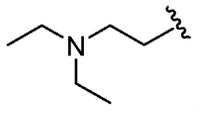
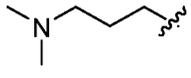
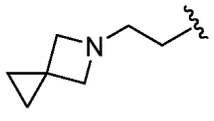
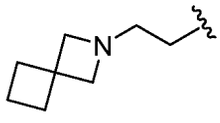
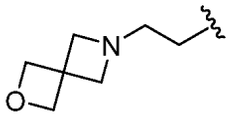
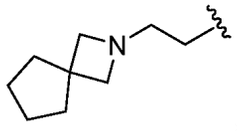
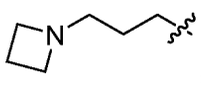
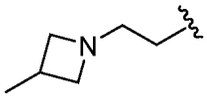
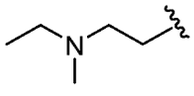
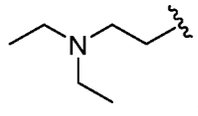
In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein only one of R_a, R_b and R_c is a substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); wherein R_x and R_y are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_6)-alkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein only one of R_a, R_b and R_c is a substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); wherein R_x and R_y are independently selected from the group consisting of substituted or unsubstituted (C_1-C_6)-alkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein only one of R_a, R_b and R_c is a substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); wherein R_x and R_y are independently selected from the group consisting of substituted or unsubstituted (C_1-C_6)-alkyl.

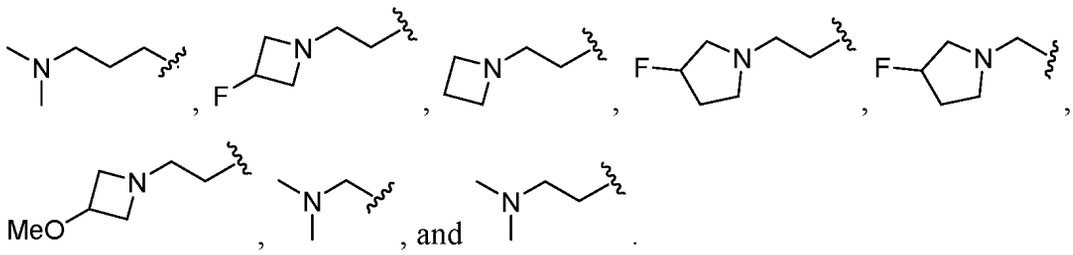
In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein only one of R_a, R_b and R_c is a substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); wherein R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein only one of R_a, R_b and R_c is a substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); wherein R_x and R_y taken together with the N to which they are attached form a 4-6 membered heterocyclyl ring optionally substituted with one or more halide (e.g., F, Cl).

In some embodiments, R_a, R_b, and R_c are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_4)-alkoxy, -OCF_3, and at least one of R_a, R_b, and R_c is –-–(C_1-C_3)alkylene-N-(R_x)(R_y) wherein R_x and R_y are independently selected from the group

consisting of H and (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered heterocyclyl ring optionally substituted with one or more halide (e.g., F, or Cl).

In some embodiments, R_a, R_b, and R_c are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_4)-alkoxy, -OCF_3, and at least one of R_a, R_b, and R_c is ---(C_1-C_3)alkylene-N-(R_x)(R_y) wherein R_x and R_y are independently selected from the group consisting of (C_1-C_6)-alkyl (e.g., methyl); or R_x and R_y taken together with the N to which they are attached form a 4-6 membered heterocyclyl ring optionally substituted with one or more halide (e.g., F, or Cl).

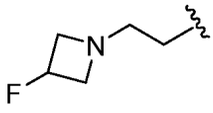
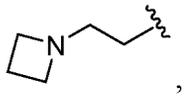
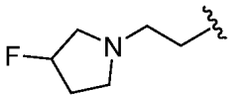
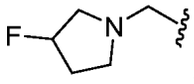
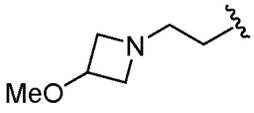
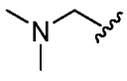
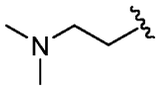
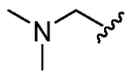
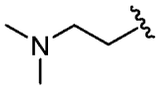
In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein only one of R_a, R_b and R_c is selected from the group consisting of  ,  ,  ,  , and  . In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein only one of R_a, R_b and R_c is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  , and  . In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein only one of R_a, R_b and R_c is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,  , .



In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_4)-alkoxy, and $-OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_4)-alkoxy, and $-OCF_3$; and one of R_b and R_c is a substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); wherein R_x and R_y are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_6)-alkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is Me. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is halide. In some embodiments, halide is Cl or F. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is substituted (C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is unsubstituted (C_1-C_4)-alkoxy. In some embodiments, (C_1-C_4)-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is $-OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is substituted –(C_1-C_5)alkylene-N-(R_x)(R_y). In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y). In some embodiments, –(C_1-C_5)alkylene of –(C_1-C_5)alkylene-N-(R_x)(R_y) is substituted with one

or more halide or –(C_1-C_4)alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein —(C_1-C_5)alkylene-N-(R_x)(R_y) is —(C_1-C_4)alkylene-N-(R_x)(R_y).

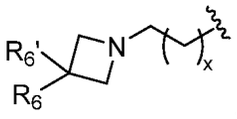
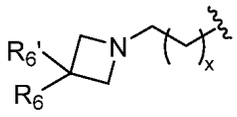
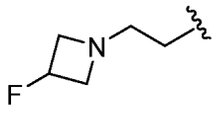
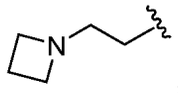
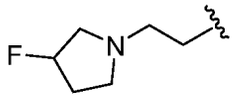
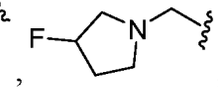
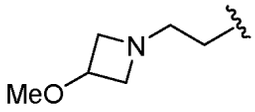
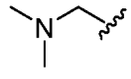
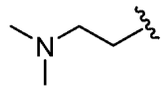
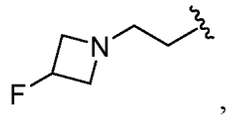
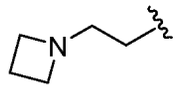
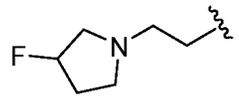
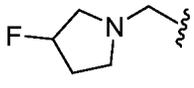
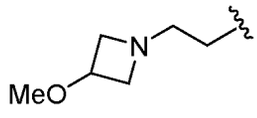
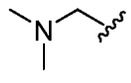
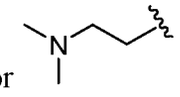
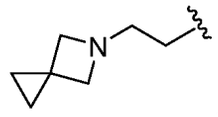
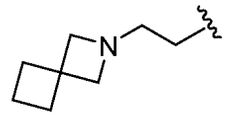
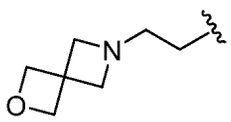
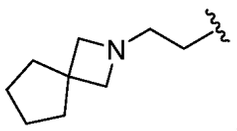
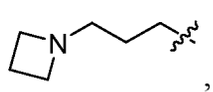
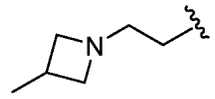
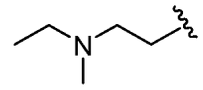
In some embodiments, R_a is substituted (C_1-C_5)-alkyl, substituted (C_1-C_4)-alkoxy, or substituted –(C_1-C_5)alkylene-N-(R_x)(R_y), wherein substituted means substituted with halide or (C_1-C_4)-alkoxy. In some embodiments, R_a is substituted (C_1-C_5)-alkyl, substituted (C_1-C_4)-alkoxy, or substituted –(C_1-C_5)alkylene-N-(R_x)(R_y), wherein substituted means substituted with F or methoxy. In some embodiments, R_a is selected from the group consisting of  ,  ,  ,  , and  . In some embodiments, R_a  , and  . In some embodiments, R_a is  , or  . In some embodiments, R_a is CF_3.

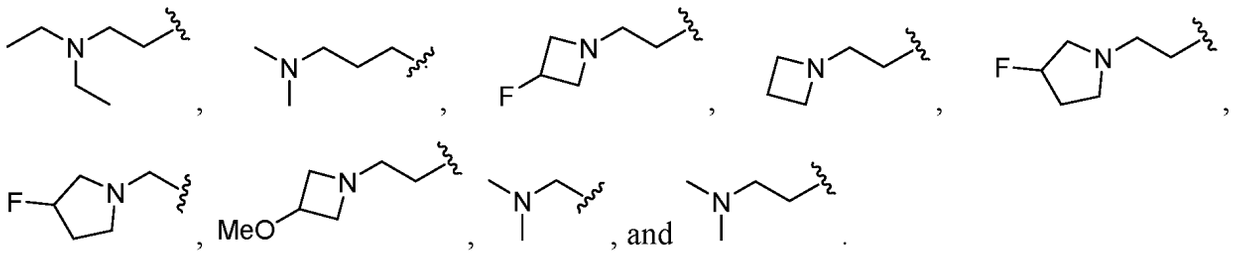
In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_a is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_4)-alkoxy, and -OCF_3; and R_b is a substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); wherein R_x and R_y are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_6)-alkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is Me. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is halide. In some embodiments, halide is Cl or F. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b

is substituted (C_1-C_4)-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is unsubstituted (C_1-C_4)-alkoxy. In some embodiments, (C_1-C_4)-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is -OCF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is substituted –(C_1-C_5)alkylene-N-(R_x)(R_y). In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y). In some embodiments, –(C_1-C_5)alkylene of –(C_1-C_5)alkylene-N-(R_x)(R_y) is substituted with one or more halide or –(C_1-C_4)alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein —(C_1-C_5)alkylene-N-(R_x)(R_y) is —(C_1-C_4)alkylene-N-(R_x)(R_y).

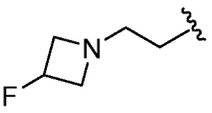
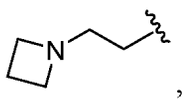
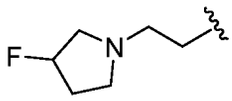
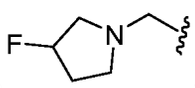
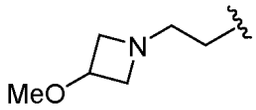
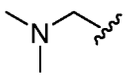
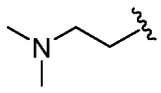
In some embodiments, R_b is substituted (C_1-C_5)-alkyl, substituted (C_1-C_4)-alkoxy, or substituted –(C_1-C_5)alkylene-N-(R_x)(R_y), wherein substituted means substituted with halide or (C_1-C_4)-alkoxy. In some embodiments, R_b is substituted (C_1-C_5)-alkyl, substituted (C_1-C_4)-alkoxy, or substituted –(C_1-C_5)alkylene-N-(R_x)(R_y), wherein substituted means substituted with F or methoxy. In some embodiments, R_b is–(C_1-C_5)alkylene-N-(R_x)(R_y) wherein R_x and R_y are each methyl, or wherein R_x and R_y taken together with the N to which they are attached form a 4-6 membered heterocyclyl ring optionally substituted with one or more halide (e.g., F, or Cl). In some embodiments, R_b is–(C_2-C_3)alkylene-N-(R_x)(R_y) wherein R_x and R_y are each methyl, or wherein R_x and R_y taken together with the N to which they are attached form a 4-6 membered heterocyclyl ring optionally substituted with one or more halide (e.g., F, or Cl). In some embodiments, R_b is–(C_2-C_3)alkylene-N-(R_x)(R_y) wherein R_x and R_y are each methyl, or wherein R_x and R_y taken together with the N to which they are attached form a 4-membered heterocyclyl ring optionally substituted with one or more halide (e.g., F, or Cl). In some embodiments, R_b is–(C_2-C_3)alkylene-N-(R_x)(R_y) wherein R_x and R_y are each methyl, or wherein R_x and R_y taken together with the N to which they are attached form a 4-6 membered heterocyclyl ring optionally substituted with one or more halide (e.g., F, or Cl). In some embodiments, R_b is–(C_2-C_3)alkylene-N-(R_x)(R_y) wherein R_x and R_y are each methyl, or wherein R_x and R_y taken together with the N to which they are attached form a 4-membered heterocyclyl ring optionally substituted with one or more halide (e.g., F, or Cl).

In certain embodiments, the invention relates to any one of the aforementioned compounds, R_b is  , wherein x is 1 or 2; R_6 is H and R_6' is (C_1-C_4)alkyl optionally substituted with one or more halide (e.g., CF_3), or R_6 and R_6' together form a substituted or unsubstituted 3-6 member cycloalkyl or heterocycloalkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, R_b is  , wherein x is 1 or 2; R_6 is H and R_6' is (C_1-C_4)alkyl optionally substituted with one or more halide (e.g., CF_3), or R_6 and R_6' together form a 3-6 member cycloalkyl or heterocycloalkyl optionally substituted with halide (e.g., F), (C_1-C_4)alkyl (e.g., methyl), (C_1-C_4)alkoxy (e.g., methoxy), (C_3-C_6)cycloalkyl (e.g., spirocyclopropyl) or (C_3-C_6)heterocycloalkyl (e.g., azaspiro[3.3]heptyl). In some embodiments, R_b is selected from the group consisting of  ,  ,  ,  , and  . In some embodiments, R_b  , and  . In certain embodiments, the invention relates to any one of the aforementioned compounds, R_b is selected from the group consisting of:  ,  ,  ,  , and  . In some embodiments, R_b is  , or  . In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_b is selected from the group consisting of:  ,  ,  ,  ,  ,  ,  ,



In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is Me. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is halide. In some embodiments, halide is Cl or F. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is CF_3. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is $C(H)F_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is $C(F)H_2$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is substituted $(C_1\text{-}C_4)$-alkoxy. In some embodiments, $(C_1\text{-}C_4)$-alkoxy is methoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is unsubstituted $(C_1\text{-}C_4)$-alkoxy. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is $-OCF_3$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is substituted $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_c is unsubstituted $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$. In some embodiments, $-(C_1\text{-}C_5)$alkylene of $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$ is substituted with one or more halide or $-(C_1\text{-}C_4)$alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein $—(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$ is $—(C_1\text{-}C_4)$alkylene-N-$(R_x)(R_y)$.

In some embodiments, R_c is substituted $(C_1\text{-}C_5)$-alkyl, substituted $(C_1\text{-}C_4)$-alkoxy, or substituted $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$, wherein substituted means substituted with halide or $(C_1\text{-}C_4)$-alkoxy. In some embodiments, R_c is substituted $(C_1\text{-}C_5)$-alkyl, substituted $(C_1\text{-}C_4)$-alkoxy, or substituted $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$, wherein substituted means substituted with F or methoxy.

In some embodiments, R_c is selected from the group consisting of  ,  ,  ,  , and  . In some embodiments, R_c  , and  .

In some embodiments, at least one of R_a, R_b, and R_c is H.

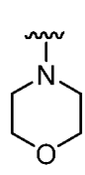
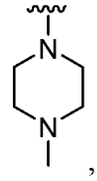
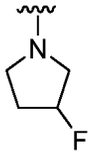
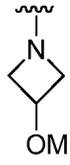
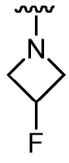
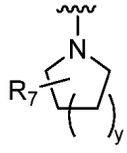
In some embodiments, at least one of R_a, R_b, and R_c is a charged amine; and at least one of R_a, R_b, and R_c is H.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x is substituted (C_1-C_6)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x is unsubstituted (C_1-C_6)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x is substituted (C_1-C_4)-alkyl. In some embodiments (C_1-C_6)-alkyl is substituted with OMe, CN, or halide. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x is (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In some embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is $-(CH_2)_2OMe$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x is Me.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_y is H. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_y is substituted (C_1-C_6)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_y is unsubstituted (C_1-C_6)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_y is substituted (C_1-C_4)-alkyl. In some embodiments, (C_1-C_6)-alkyl is substituted with OMe, CN, or halide. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_y is unsubstituted (C_1-C_4)-alkyl. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_y is (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy. In some embodiments, (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy is

–$(CH_2)_2OMe$. In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_y is Me.

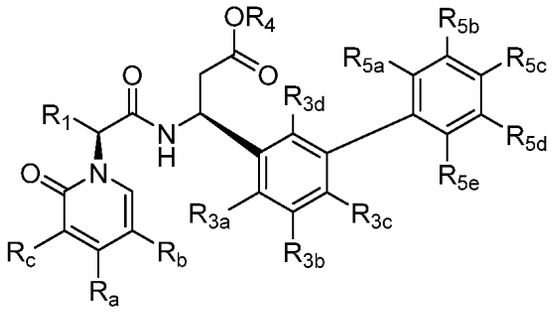
In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x is Me; and R_y is Me.

In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered ring. In some embodiments, the 4-6 membered ring is a substituted or unsubstituted heterocycloalkyl. In some embodiments, the substituted 4-6 membered heterocyclalkyl is substituted with halide of (C_1-C_6)alkyl. In some embodiments, the 4-6 membered ring is a substituted or unsubstituted heteroaryl. In some embodiments, the substituted 4-6 membered heteroaryl is substituted with halide of (C_1-C_6)alkyl. In some embodiments, the 4-6 membered ring is selected from  ,  ,  ,  , and  . In some embodiments, R_x and R_y taken together with the N to which they are attached form  . In some embodiments, R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered ring of the formula  , wherein y is 0, 1 or 2; and R_7 is H, halide, alkoxy, spirocyclic 3-5 member cycloalkyl, and spirocyclic 3-5 member heterocycloalkyl.

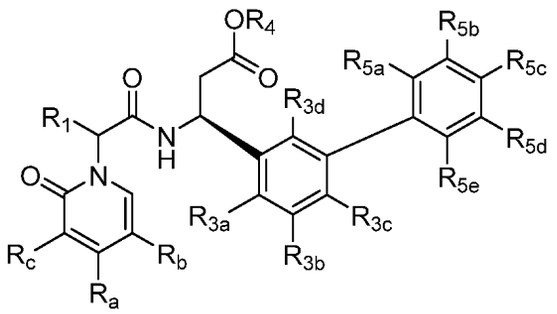
In some embodiments, R_a is (C_1-C_5)-alkyl optionally substituted with halide; R_b is –(C_1-C_5)alkylene-N-(R_x)(R_y) wherein R_x and R_y are each methyl, or wherein R_x and R_y taken together with the N to which they are attached form a 4-5 membered heterocyclyl ring optionally substituted with one or more halide or alkoxy (e.g., methoxy); and R_c is hydrogen, halide or (C_1-C_5)-alkyl optionally substituted with halide. In some embodiments, R_a is methyl optionally substituted with halide; R_b is –(C_2-C_3)alkylene-N-(R_x)(R_y) wherein R_x and R_y are each methyl, or wherein R_x and R_y taken together with the N to which they are attached form

a 4-5 membered heterocyclyl ring optionally substituted with one or more halide (e.g., F); and R_c is hydrogen, halide or methyl optionally substituted with halide. In some embodiments, R_a is methyl or CF_3; R_b is $-(C_2\text{-}C_3)$alkylene-N-$(R_x)(R_y)$ wherein R_x and R_y are each methyl, or wherein R_x and R_y taken together with the N to which they are attached form a 4-5 membered heterocyclyl ring optionally substituted with one or more F or methoxy; and R_c is hydrogen, F, CH_2F, CHF_2, CF_3.

In certain embodiments, the invention relates to a compound of Formula (Ia) or (Ib):



(Ia)



(Ib)

wherein

R_1, R_{3c}, R_{3d}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, R_{5e}, R_a, R_b, and R_c are as defined above with respect to Formula (I);

R_4 is H; and

at least one of R_a, R_b, and R_c is $-(C_1\text{-}C_3)$alkylene-N$(R_x)(R_y)$;

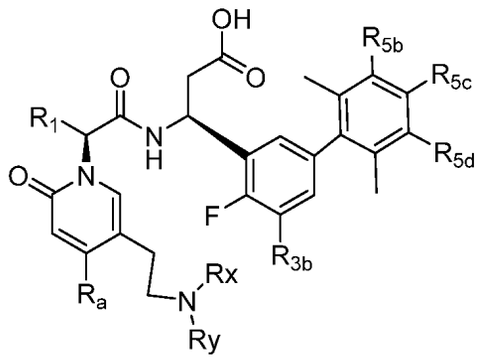
R_x and R_y are independently selected from the group consisting of H and methyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring; and

R_{3a}, and R_{3b} are each independently selected from the group consisting of methyl and F.

In certain embodiments, the invention relates to any one of the compounds depicted in Figure 1. In certain embodiments, the invention relates to any one of the compounds depicted in Figure 2. In certain embodiments, the invention relates to any one of the compounds depicted in Figure 3. In certain embodiments, the invention relates to any one of the compounds depicted in Figure 4.

In certain embodiments, a compound is a compound of Formula (I) that is not a compound depicted in Figure 1. In certain embodiments, a compound is a compound of Formula (I) that is not a compound depicted in Figure 2. In certain embodiments, a compound is a compound of Formula (I) that is not a compound depicted in Figure 3. In certain embodiments, a compound is a compound of Formula (I) that is not a compound depicted in Figure 4. In certain embodiments, a compound is a compound of Formula (I) that is not a compound depicted in Figure 2, Figure 3 or Figure 4.

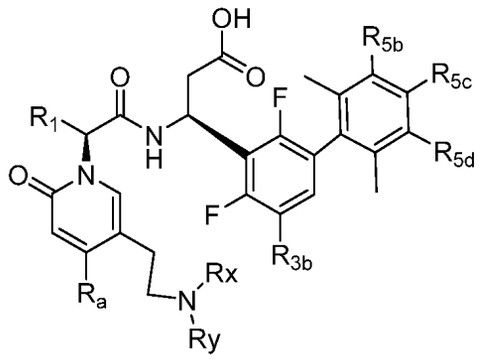
In certain embodiments, the invention relates to a compound of Formula (IIIa):



(IIIa),

wherein R_1, R_a, R_x, R_y, R_{3b}, R_{5b}, R_{5c}, R_{5d}, are as defined above with respect to Formula (I).

In certain embodiments, the invention relates to a compound of Formula (IVa):



(IVa),

wherein R_1, R_a, R_x, R_y, R_{3b}, R_{5b}, R_{5c}, R_{5d}, are as defined above with respect to Formula (I).

In certain embodiments, the invention relates to a compound selected from the group consisting of:

(3S)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid;

(3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

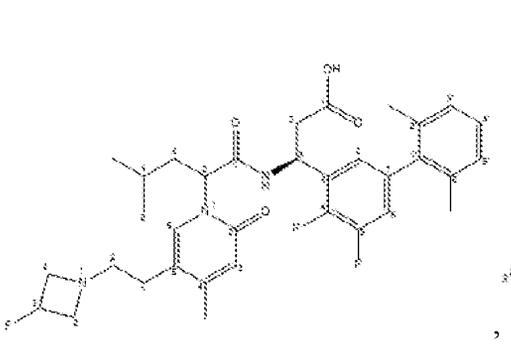
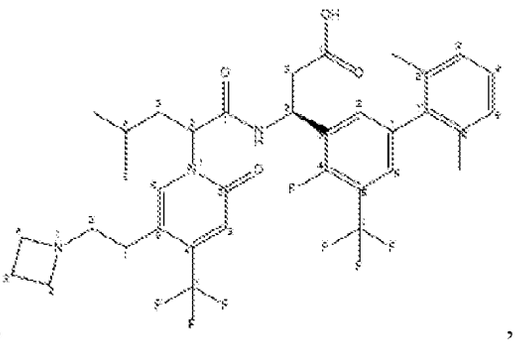
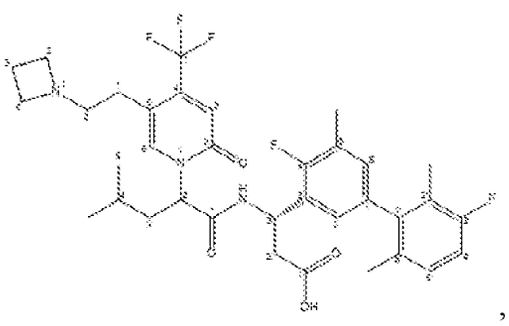
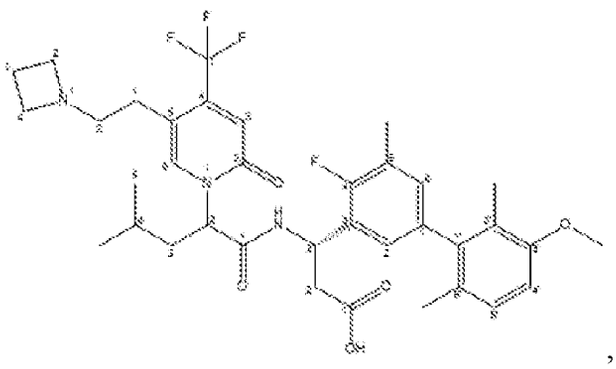
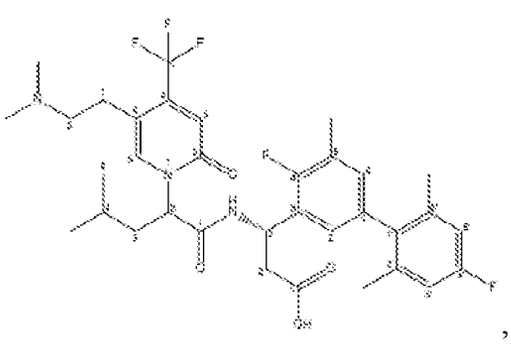
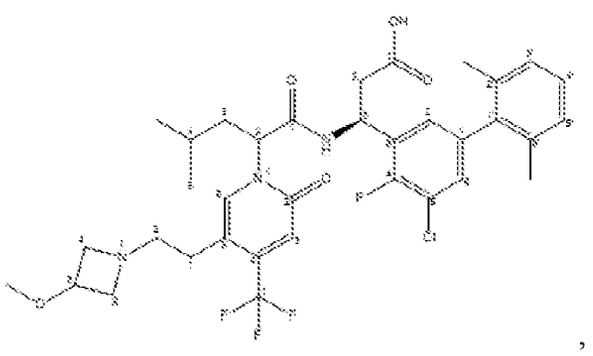
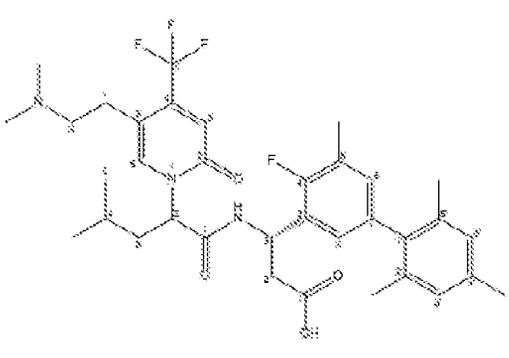
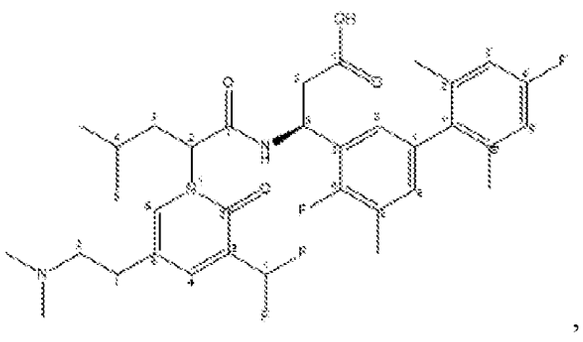
(3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid;

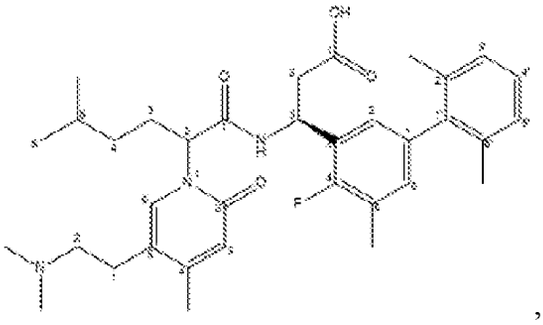
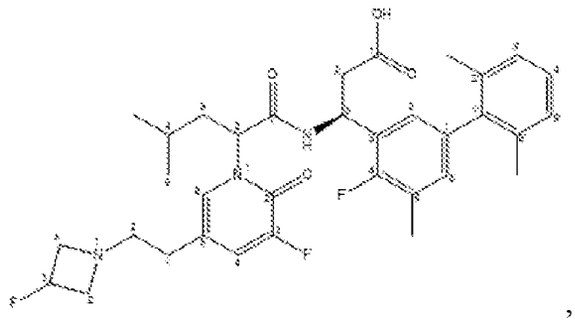
(3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid; and

(3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid.

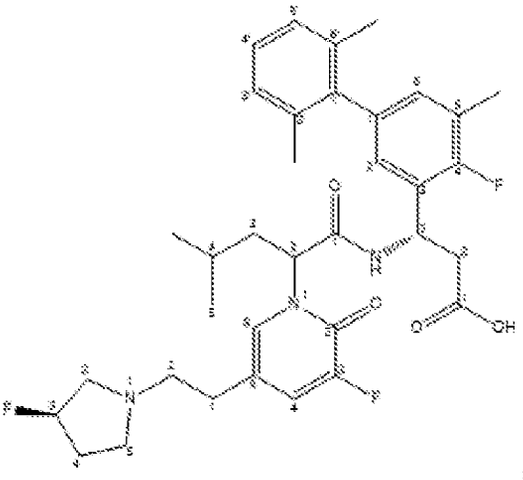
or a pharmaceutically acceptable salt thereof.

In certain embodiments, the invention relates to a compound selected from the group consisting of:

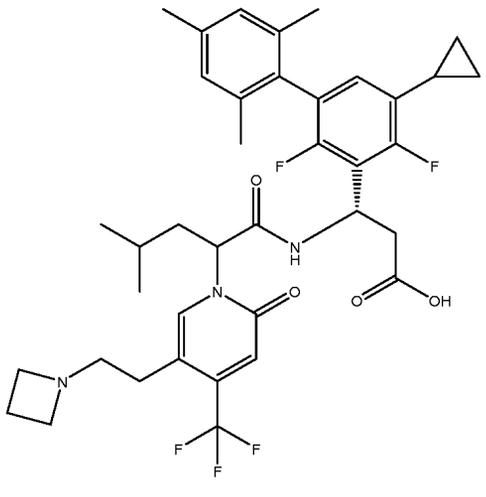
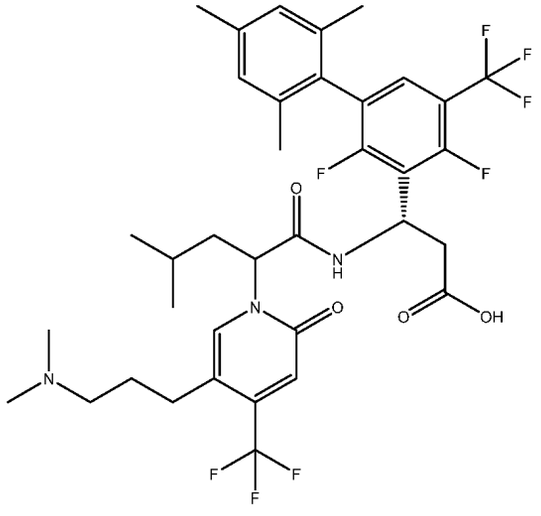

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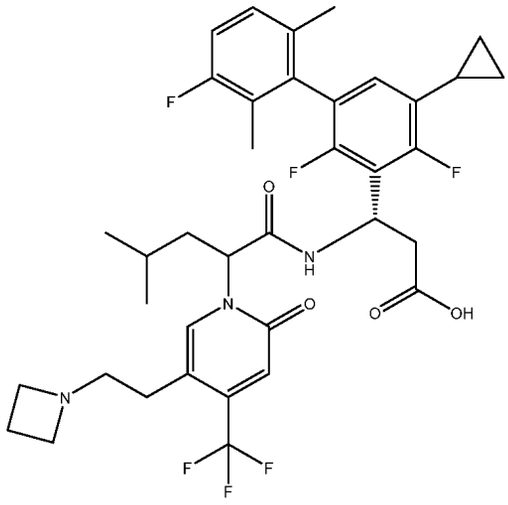

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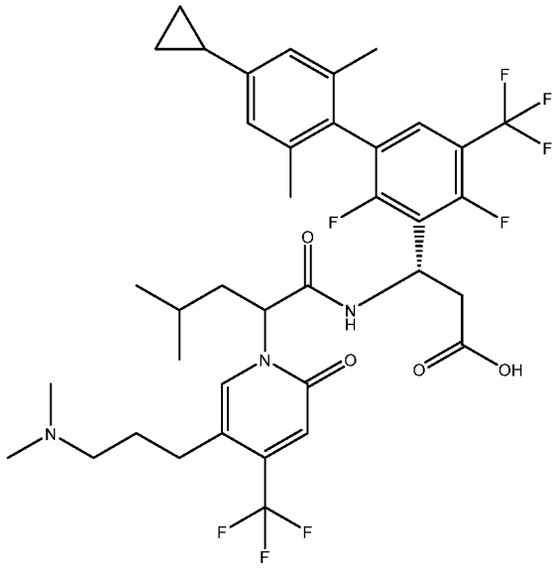
and

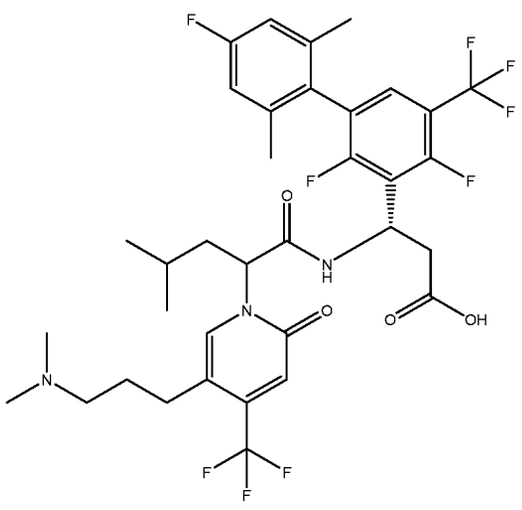

, or a pharmaceutically acceptable salt thereof.

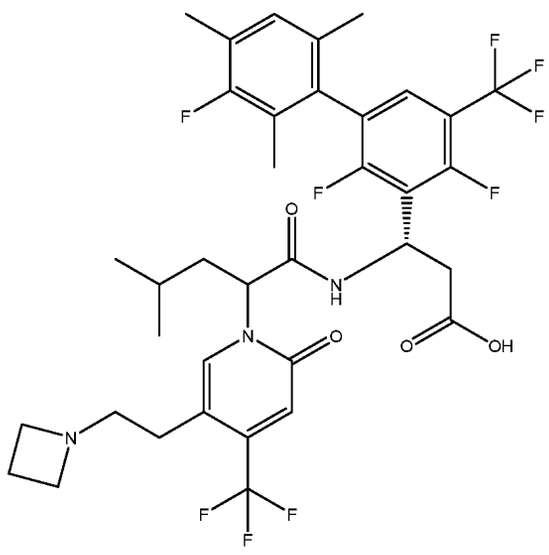
In certain embodiments, the invention relates to a compound selected from the group consisting of:

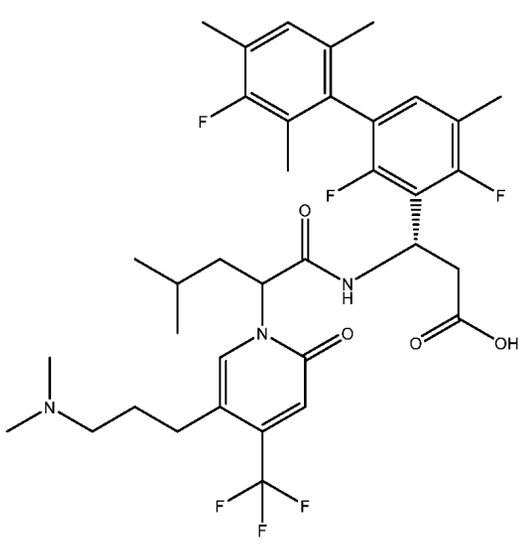



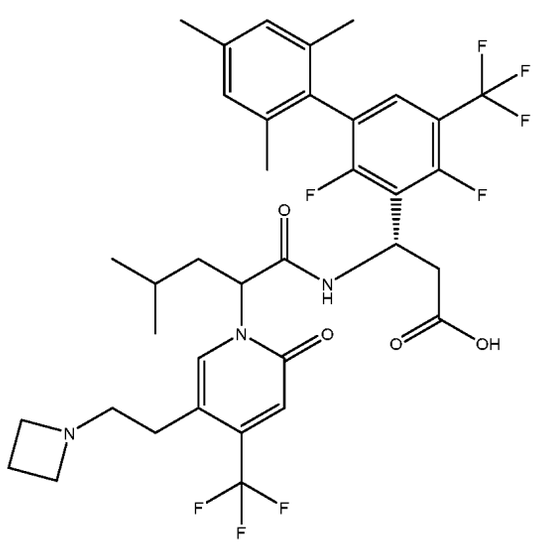


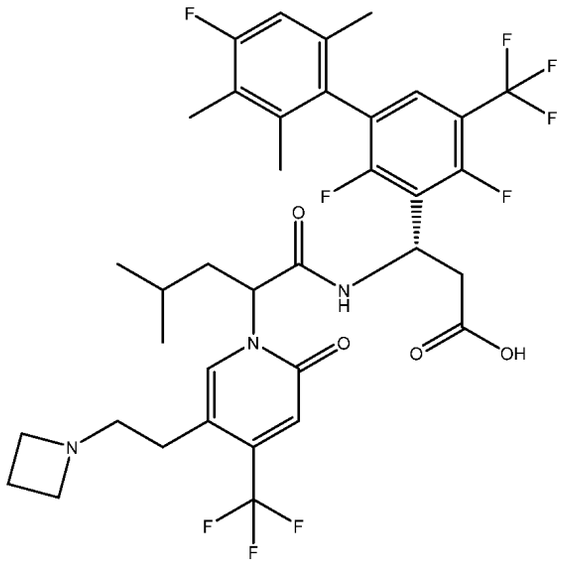


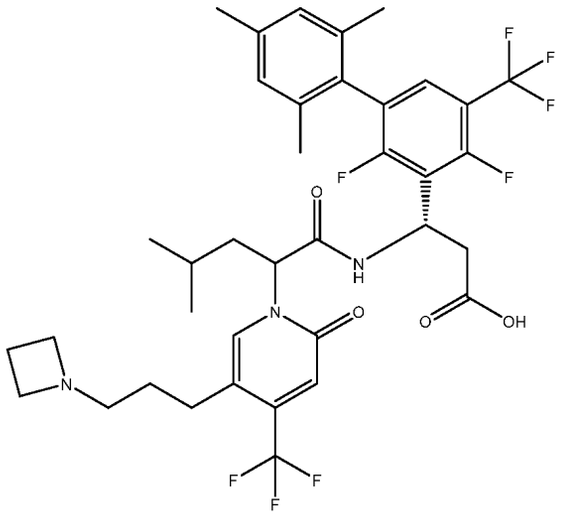


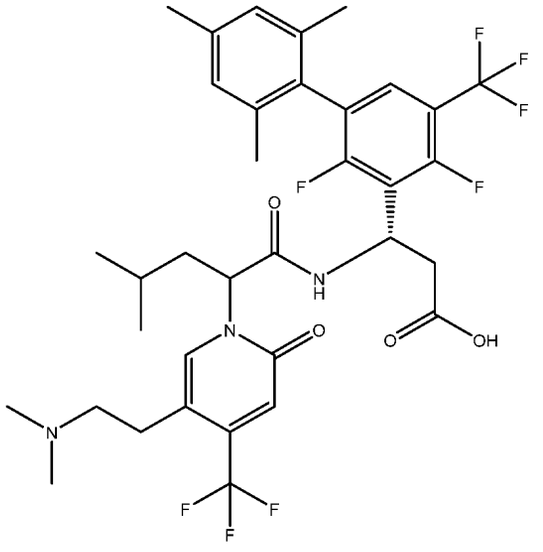












In certain embodiments, the invention relates to a compound selected from the group consisting of:

(S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid;

(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

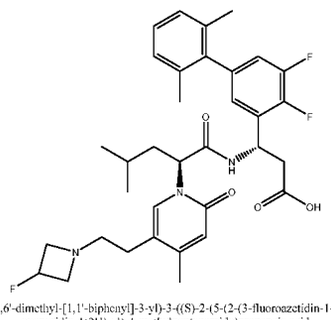
(S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid; and

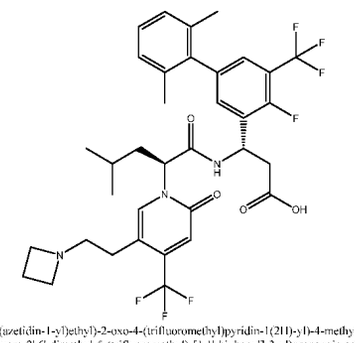
(S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

or a pharmaceutically acceptable salt thereof.

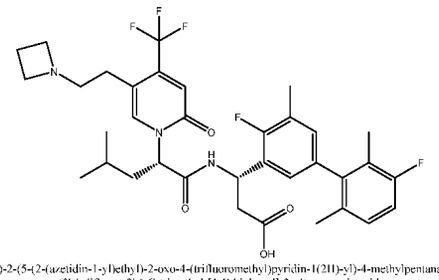
In certain embodiments, the invention relates to a compound selected from the group consisting of:



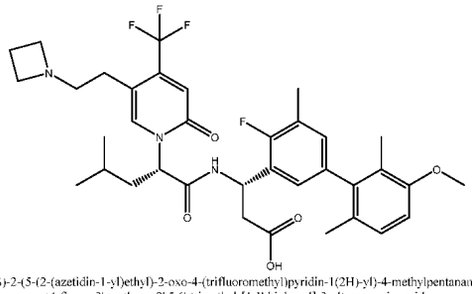
(S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;



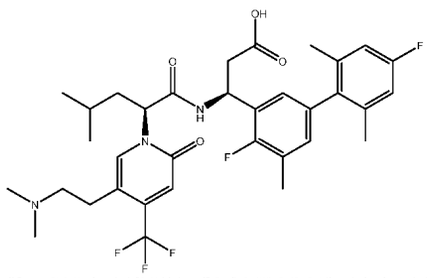
(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid;



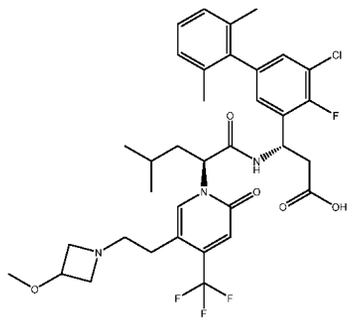
(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;



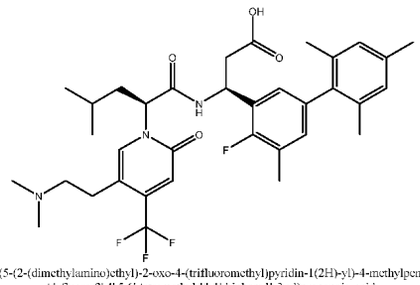
(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;



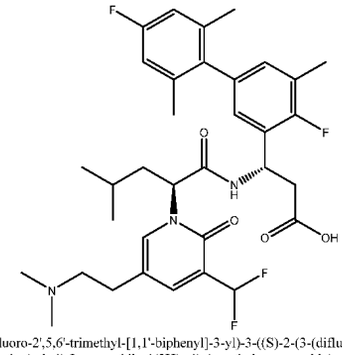
(S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;



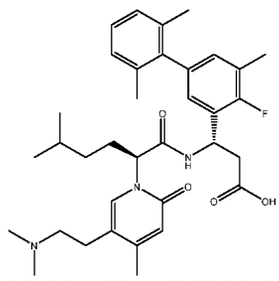
(S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;



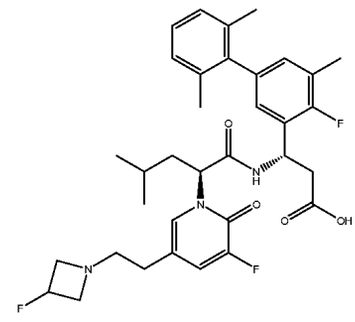
(S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid;



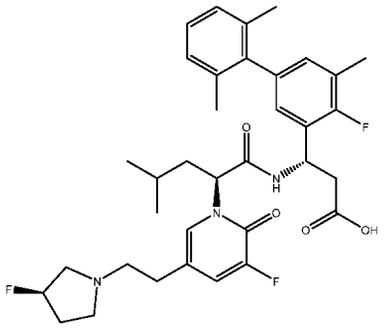
(S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;



(S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;



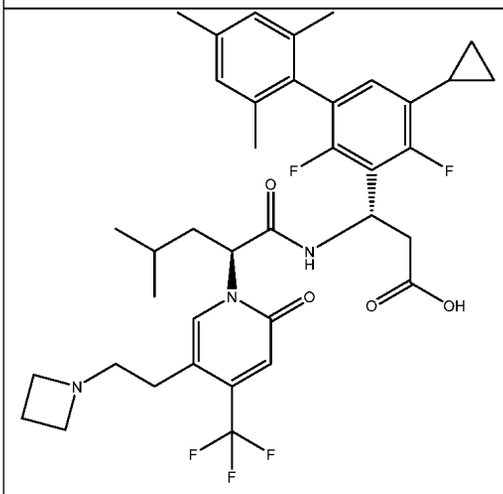
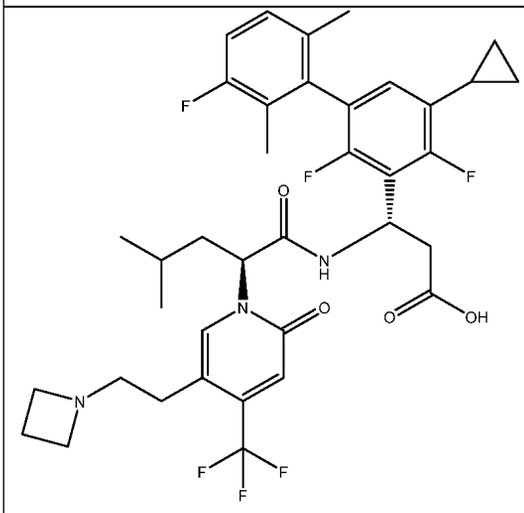
(S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid

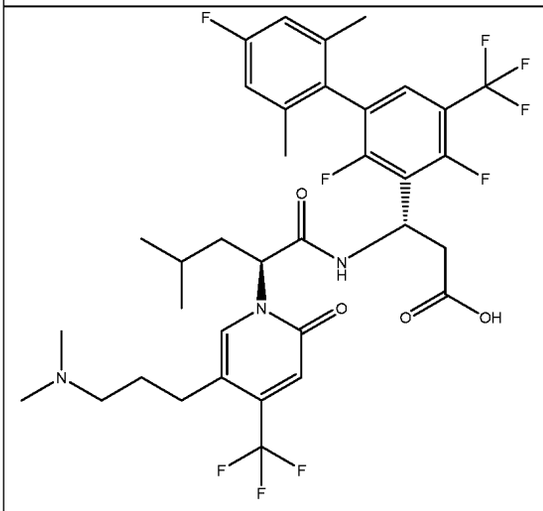
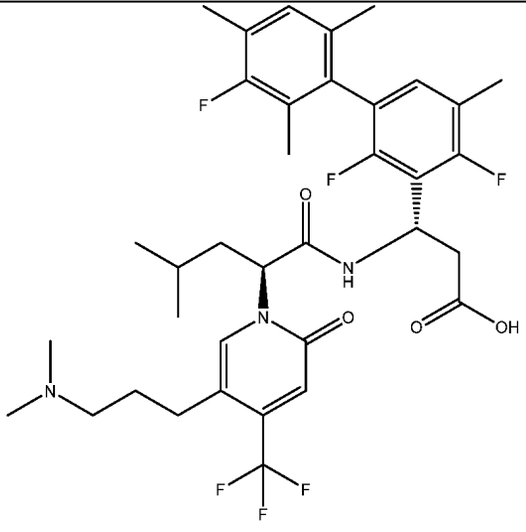
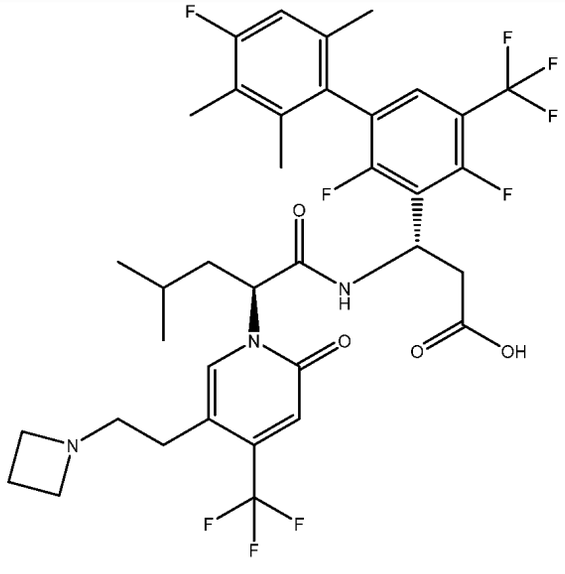


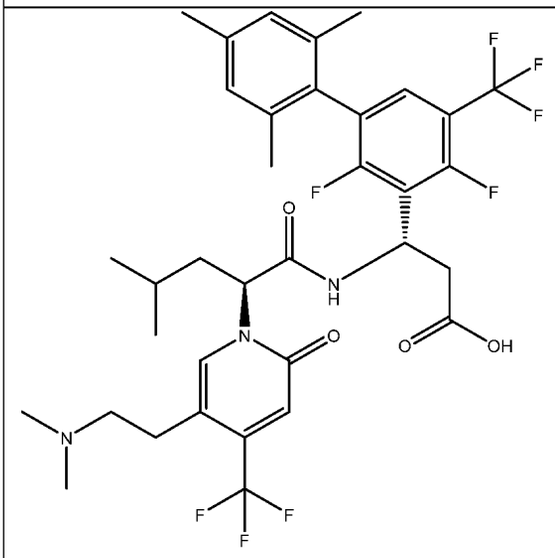
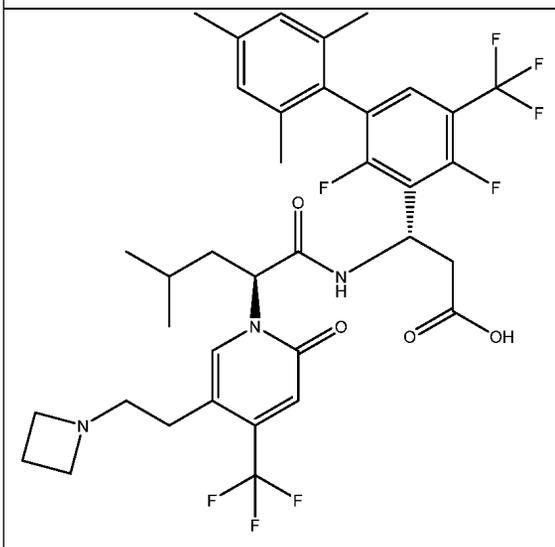
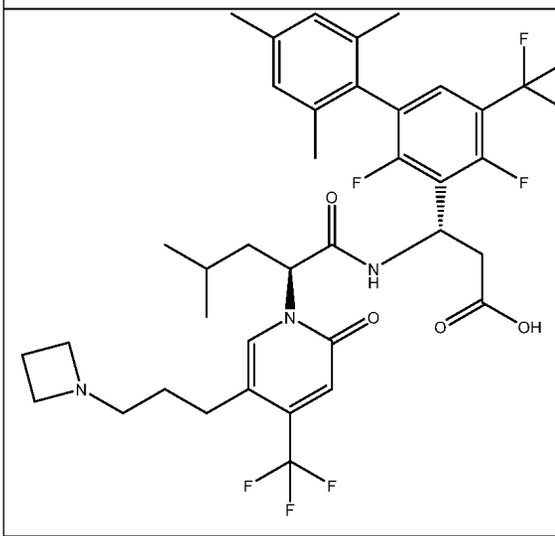
and (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

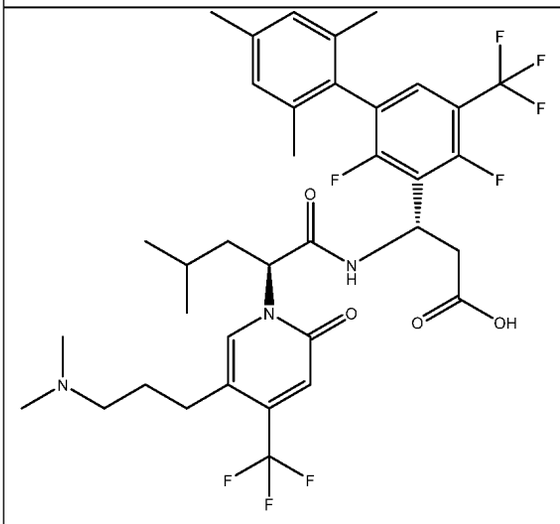
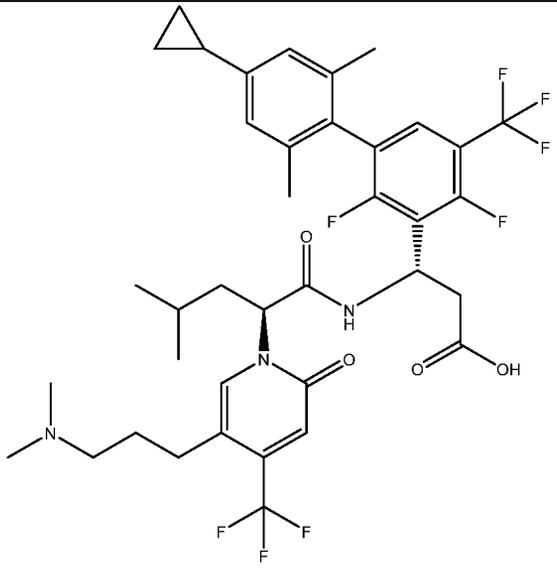
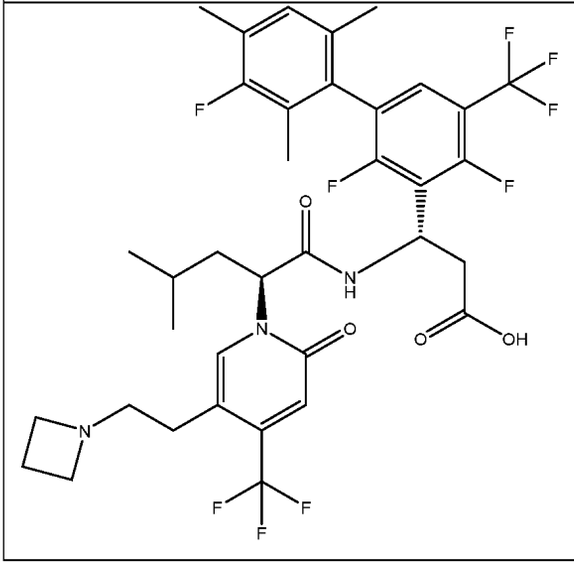
In certain embodiments, the invention relates to any one of the aforementioned compounds, wherein the compound is in the form of a pharmaceutically acceptable salt.

In certain embodiments, the invention relates to a compound selected from the group consisting of:

Structure	Name
	(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;
	(3S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid

Structure	Name
	(S)-3-((S)-2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid
	(3S)-3-((S)-2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid
	(3S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid

Structure	Name
	(S)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid
	(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid
	(S)-3-((S)-2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid

Structure	Name
	(S)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid
	(S)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid
	(3S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid

EXEMPLARY PHARMACEUTICAL COMPOSITIONS

Compounds of Formula (I) can be formulated in various pharmaceutical compositions. A compound of Formula (I) (including compounds of Formula (Ia) and Formula (Ib) as provided herein), as well as pharmaceutically acceptable salts thereof, may be the active pharmaceutical ingredient (API) combined with one or more other ingredients to form a drug substance pharmaceutical composition. The drug substance (DS) pharmaceutical composition can comprise the API (i.e., a compound of Formula (I) or pharmaceutically acceptable salt thereof) and one or more pharmaceutically acceptable carriers, diluents, and/or excipients. The carrier(s), diluent(s) or excipient(s) can be selected to be compatible with the other ingredients of the formulation and appropriately safe and effective for an intended therapy. A desired weight concentration of the compound of Formula (I) as the active pharmaceutical ingredient (API) can be combined with the other inactive ingredients to form a drug substance (DS) in a formulation batch. Pharmaceutically acceptable compositions can be formulated for administration by an appropriate route, for example by the oral delivery (including as a capsule or tablet) in unit dosage forms. Such compositions may be prepared by bringing into association the active pharmaceutical ingredient (API) comprising a compound of Formula (I) with the carrier(s) or excipient(s).

In certain embodiments, the invention provides a pharmaceutical composition formulated for oral delivery of an $\alpha_4\beta_7$ integrin integrin inhibitor, the composition comprising the $\alpha_4\beta_7$ integrin inhibitor compound of formula (I) as an API and a pharmaceutically acceptable carrier formulated for oral therapeutic administration of the $\alpha_4\beta_7$ integrin inhibitor compound.

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound of Formula (I), or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound of Formula (Ia), or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound of Formula (Ib), or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-

(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

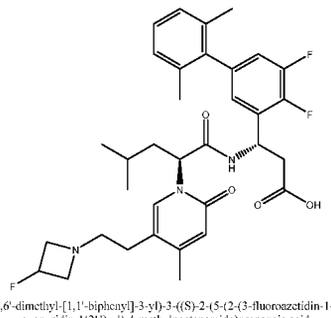
In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-

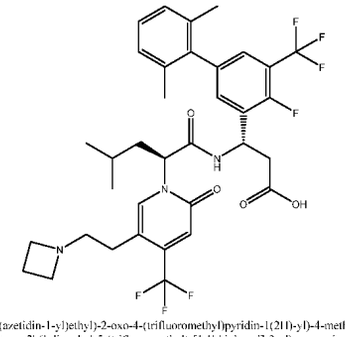
fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

In certain embodiments, the invention provides a pharmaceutical composition comprising the compound (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient (API).

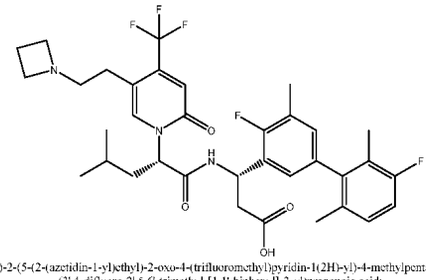
In certain embodiments, the invention relates to a pharmaceutical composition comprising a compound selected from the group consisting of:



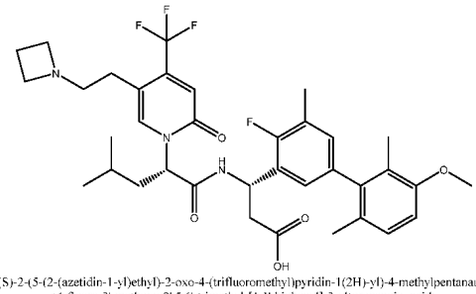
(S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;



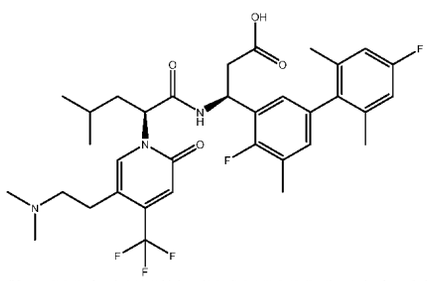
(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid;



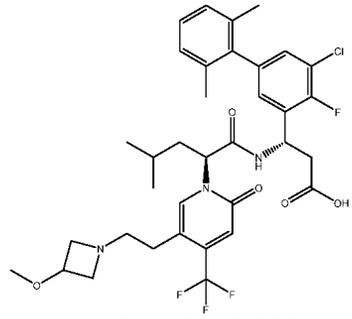
(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;



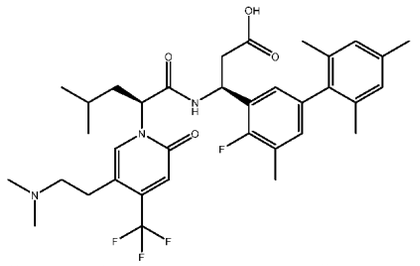
(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;



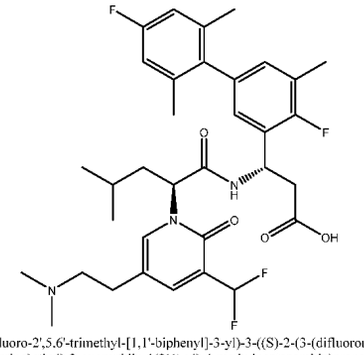
(S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;



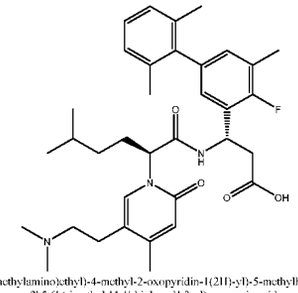
(S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;



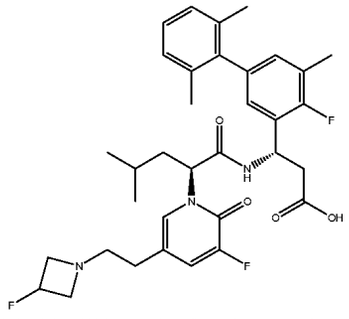
(S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid;



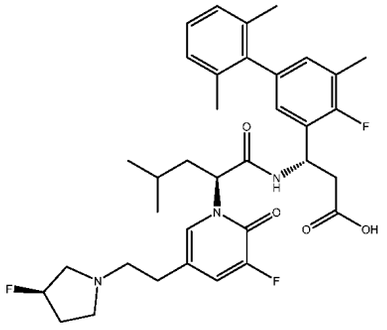
(S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;



(S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

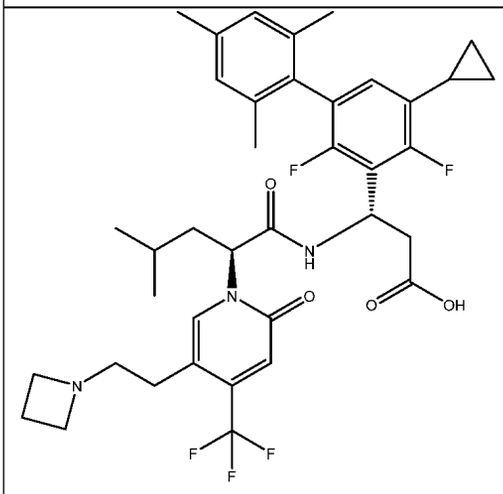
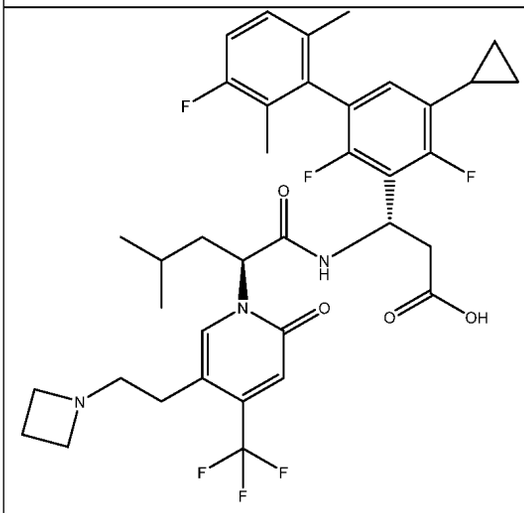
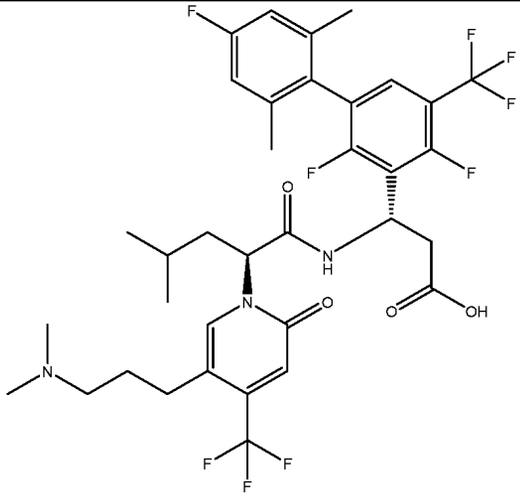


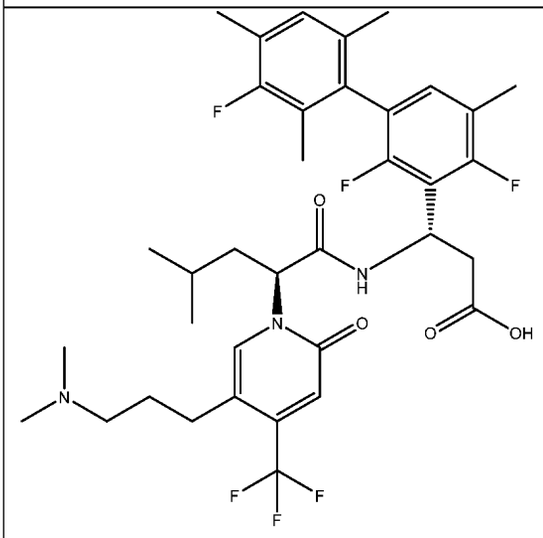
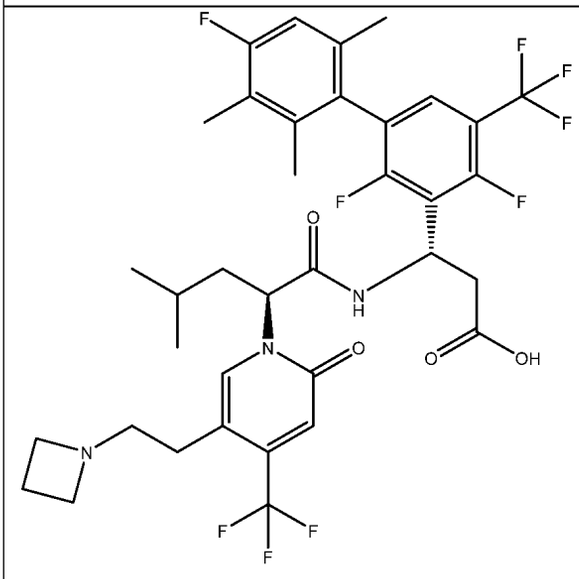
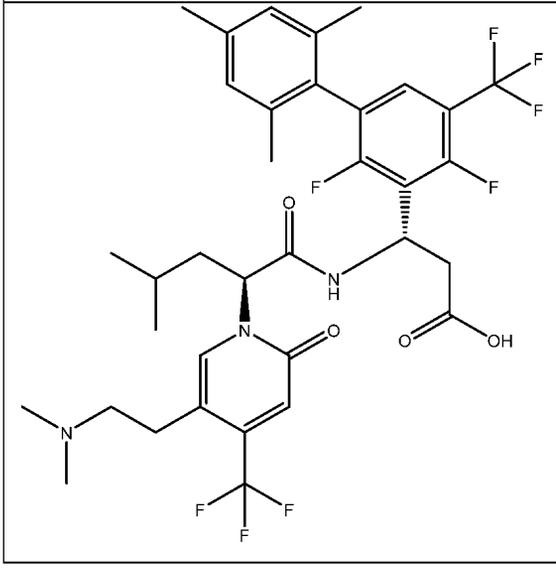
(S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

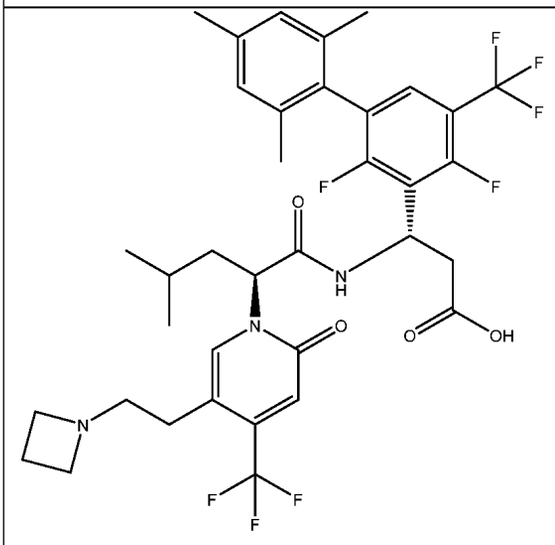
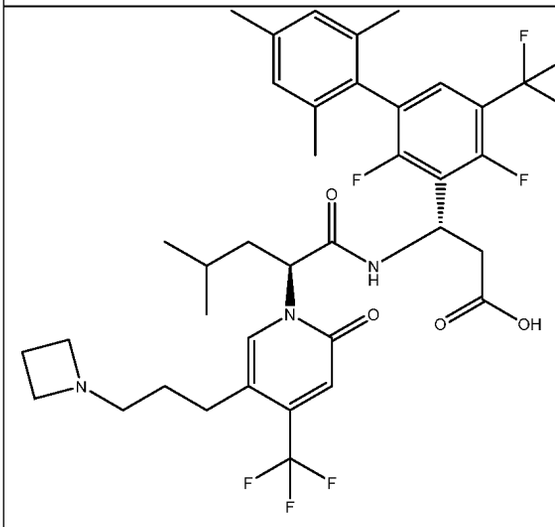
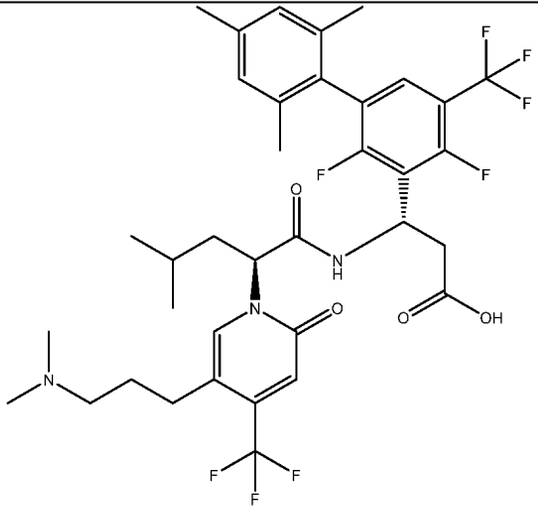


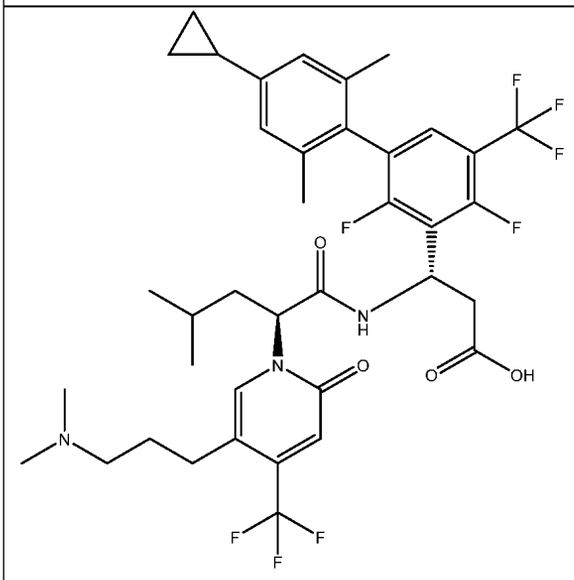
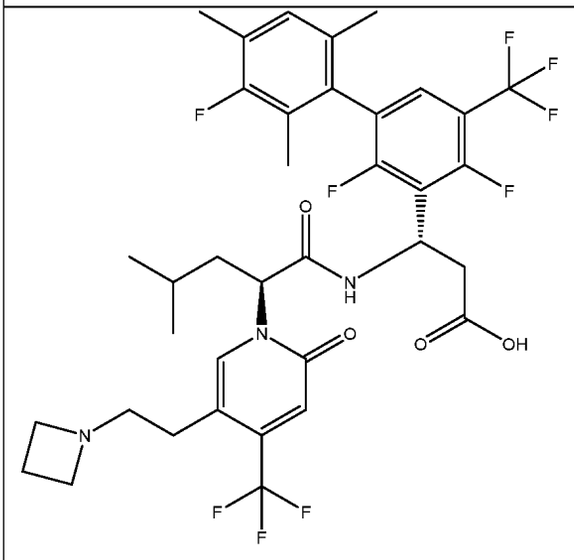
and (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the invention relates to a pharmaceutical composition comprising a compound selected from the group consisting of, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingrediend (API):

Structure	Name
	(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;
	(3S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid
	(S)-3-((S)-2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid

Structure	Name
	(3S)-3-((S)-2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid
	(3S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid
	(S)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid

Structure	Name
	(S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid
	(S)-3-((S)-2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid
	(S)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid

Structure	Name
	(S)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid
	(3S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid.

Pharmaceutically acceptable compositions comprising the compound of Formula (I) can be prepared by various procedures. For example, the compounds of Formula (I) can be formulated with suitable excipients, diluents, or carriers, and formed into tablets, or capsules, and other suitable dosage forms.

Pharmaceutical compositions can be provided in unit dose forms containing a predetermined amount of API comprising a compound of Formula (I) per unit dose. Such a unit may contain, a desired amount of a compound of the Formula (I) or pharmaceutically acceptable salt thereof, depending on the condition being treated, the route of administration and the age, weight and condition of the patient. Such unit doses may therefore be administered at a desired dose interval. The concentration of active compound in the drug composition will depend on various applicable parameters and considerations such as the absorption, inactivation and excretion rates of the drug as well as other factors known to those of skill in

the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient can be administered at once, or can be divided into a number of smaller doses to be administered at varying intervals of time.

In certain embodiments, the mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. Pharmaceutical compositions comprising a compound of Formula (I) formulated for oral delivery can be prepared in a unit dosage form, such as a capsule at a desired dosage strength of the compound of Formula (I). For oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. For oral administration in the form of a tablet or capsule, the compound of Formula (I) can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier. Other examples of excipients, diluents, and carriers that are suitable for such formulations include the following: fillers and extenders such as starch, and sugars; and binding agents such as cellulose derivatives. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, natural sugars, natural and synthetic gums, and the like. Lubricants and/or glidants can be used in these dosage forms.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, unit dosage forms can contain various other materials that

modify the physical form of the dosage unit, for example, coatings of sugar, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, or the like. A syrup can contain, in addition to the active compound(s), sucrose or sweetener as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compounds can be formulated as solutions appropriate for parenteral administration, for example, by intramuscular, subcutaneous or intravenous routes. For example, a compound of Formula (I) can be dissolved in a suitable buffer. A pharmaceutical composition comprising a desired concentration of a compound of Formula (I) can be formulated as an injectable drug solution in (useful, e.g., in preclinical animal studies).

EXEMPLARY METHODS

Compounds inhibiting $\alpha_4\beta_7$ are useful for development of medicaments to treat ulcerative colitis and Crohn's disease patients. Ulcerative colitis (UC) and Crohn's disease (CD) patients suffer from autoimmune inflammation in the digestive tract and for many of these patients, the $CD4^+$ memory T cells drive the progression and flare ups of the disease via their ability to secrete pro-inflammatory, effector cytokines within the gut, impacting the surrounding immune cells and tissue. The progression and flare ups of these disease conditions are believed to include extravasation of T cells leaving the blood to enter tissue in the gut leading to inflammatory conditions found in UC and CD via integrin related mechanisms. The inhibition of $\alpha_4\beta_7$ can disrupt this mechanism, thereby preventing the localization of T cells to the tissue and effectively treating and preventing disease such as UC and CD. T cell homing to the gut requires surface expression of integrin $\alpha_4\beta_7$ and chemokine receptor CCR9. While CCR9 is utilized by the cell to migrate against the gradient of CCL25 expressed in the small intestine, $\alpha_4\beta_7$ is a tethering molecule which binds the ligand, mucosal addressin cell adhesion molecule 1 (MAdCAM-1). Integrin $\alpha_4\beta_7$ binds MAdCAM-1 with high affinity facilitating rolling and firm adhesion of cells followed by extravasation into tissue.

Pharmaceutical compositions can comprise compounds that inhibit the $\alpha_4\beta_7$ integrin on inflammatory cells that enables adhesion of these cells to mucosal addressin cell adhesion molecule-1 (MAdCAM-1), and inhibiting or preventing these cells from entering the gut lamina propria and gut associated lymphoid tissue.

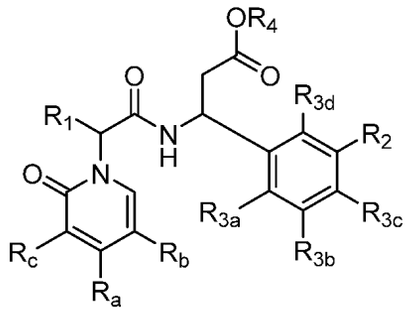
Compounds of Formula (I) were evaluated using a fluorescent polarization (FP) assay, as described in Example 5. FP assays are used to evaluate potency of compounds on purified protein. The FP assays consists of measuring purified integrin $\alpha\beta$ heterodimer ecto domains

or headpiece binding to surrogate or truncated ligands. Results of the FP assay for exemplary compounds of Formula (I) are provided herein.

Compounds of Formula (I) were further evaluated using a Ligand binding assay (LBA) as described in Example 6 to examine compound potency of free ligand binding to receptors expressed on cells. The MAdCAM ligand binding assay uses flow cytometry to measure the binding of fluorescently-labeled MAdCAM-1-Fc to RPMI 8866 cells in the presence of Mn++. This assay assesses the binding of compounds to native full-length receptors on the cell surface. One advantage of the MAdCAM ligand binding assay is its ability to quantify and discriminate the activity of potent compounds that exceed the FP assay's functional sensitivity limit [~10nM in Mn]. Ligand binding assays (LBA) are used to examine compound potency and selectivity of free ligand binding to receptors expressed on cells.

In some embodiments, compounds of the invention can be selected from one or more of the following numbered embodiments:

1. A compound of Formula (I):



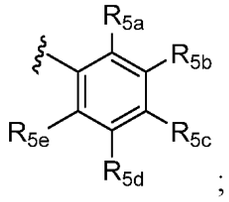
(I)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and –$(C_1$-$C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is -$(C_1$-$C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1$-$C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl, substituted or unsubstituted (C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, or substituted or unsubstituted (C_1-C_4)-alkylene- (C_1-C_4)-alkoxy;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c}, and R_{3d} are H;

R_4 is H, or substituted or unsubstituted (C_1-C_4)-alkyl;

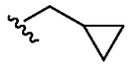
R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

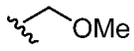
R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof.

2. The compound of embodiment 1, wherein R_1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl.

3. The compound of embodiment 2, wherein R_1 is iso-butyl.

4. The compound of embodiment 1, wherein R_1 is  .

5. The compound of embodiment 1, wherein R_1 is  .

6. The compound of any one of embodiments 1-5, wherein R_{3a} and R_{3b} are independently selected from the group consisting of halide, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_4)-alkoxy, CF_3, $C(H)F_2$, and $C(F)H_2$.

7. The compound of embodiment 6, wherein R_{3a} and R_{3b} are independently selected from the group consisting of halide and (C_1-C_4)-alkyl.

8. The compound of embodiment 7, wherein halide is Cl or F.

9. The compound of embodiment 7 or 8, wherein (C_1-C_4)-alkyl is methyl.

10. The compound of any one of embodiments 1-7, wherein R_{3a} is methyl; and R_{3b} is F.

11. The compound of any one of embodiments 1-7, wherein R_{3a} is F; and R_{3b} is methyl.

12. The compound of any one of embodiments 1-11, wherein R_4 is H.

13. The compound of any one of embodiments 1-11, wherein R_4 is methyl, ethyl, n-propyl, iso-propyl.

14. The compound of any one of embodiments 1-13, wherein R_{5a} and R_{5e} are independently selected from the group consisting of halide, CF_3, $C(H)F_2$, $C(F)H_2$, and substituted or unsubstituted (C_1-C_4)-alkyl.

15. The compound of any one of embodiments 1-14, wherein R_{5a} is halide.

16. The compound of embodiment 15, wherein R_{5a} is F or Cl.

17. The compound of any one of embodiments 1-14, wherein R_{5a} is CF_3.

18. The compound of any one of embodiments 1-14, wherein R_{5a} is $C(H)F_2$.

19. The compound of any one of embodiments 1-14, wherein R_{5a} is $C(F)H_2$.

20. The compound of any one of embodiments 1-14, wherein R_{5a} is unsubstituted (C_1-C_4)-alkyl.

21. The compound of embodiment 20, wherein R_{5a} is methyl.

22. The compound of any one of embodiments 1-14, wherein R_{5a} is substituted (C_1-C_5)-alkyl, substituted with at least one halide.

23. The compound of any one of embodiments 1-14, wherein R_{5a} is unsubstituted (C_1-C_4)-alkoxy.

24. The compound of embodiment 23, wherein R_{5a} is OMe.

25. The compound of any one of embodiments 1-24, wherein R_{5e} is halide.

26. The compound of embodiment 25, wherein R_{5e} is F or Cl.

27. The compound of any one of embodiments 1-24, wherein R_{5e} is CF_3.

28. The compound of any one of embodiments 1-24, wherein R_{5e} is $C(H)F_2$.

29. The compound of any one of embodiments 1-24, wherein R_{5e} is $C(F)H_2$.

30. The compound of any one of embodiments 1-24, wherein R_{5e} is unsubstituted (C_1-C_4)-alkyl.

31. The compound of embodiment 30, wherein R_{5e} is methyl.

32. The compound of any one of embodiments 1-24, wherein R_{5e} is substituted (C_1-C_5)-alkyl, substituted with at least one halide.

33. The compound of any one of embodiments 1-24, wherein R_{5e} is unsubstituted (C_1-C_4)-alkoxy.

34. The compound of embodiment 33, wherein R_{5e} is OMe.

35. The compound of any one of embodiments 1-34, wherein R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, and substituted or unsubstituted (C_1-C_4)-alkoxy.

36. The compound of any one of embodiments 1-35, wherein R_{5b} is H.

37. The compound of any one of embodiments 1-35, wherein R_{5b} is halide.

38. The compound of embodiment 37, wherein R_{5b} is Cl or F.

39. The compound of any one of embodiments 1-35, wherein R_{5b} is CF_3.

40. The compound of any one of embodiments 1-35, wherein R_{5b} is $C(H)F_2$.

41. The compound of any one of embodiments 1-35, wherein R_{5b} is $C(F)H_2$.

42. The compound of any one of embodiments 1-35, wherein R_{5b} is unsubstituted (C_1-C_4)-alkyl.

43. The compound of embodiment 37, wherein R_{5b} is methyl.

44. The compound of any one of embodiments 1-35, wherein R_{5b} is unsubstituted (C_1-C_4)-alkoxy.

45. The compound of embodiment 44, wherein R_{5b} is OMe.

46. The compound of any one of embodiments 1-35, wherein R_{5b} is unsubstituted (C_3-C_6)-cycloalkyl.

47. The compound of embodiment 46, wherein R_{5b} is cyclopropyl.

48. The compound of any one of embodiments 1-47, wherein R_{5c} is H.

49. The compound of any one of embodiments 1-47, wherein R_{5c} is halide.

50. The compound of embodiment 49, wherein R_{5c} is Cl or F.

51. The compound of any one of embodiments 1-47, wherein R_{5c} is CF_3.

52. The compound of any one of embodiments 1-47, wherein R_{5c} is $C(H)F_2$.

53. The compound of any one of embodiments 1-47, wherein R_{5c} is $C(F)H_2$.

54. The compound of any one of embodiments 1-47, wherein R_{5c} is unsubstituted (C_1-C_4)-alkyl.

55. The compound of embodiment 54, wherein R_{5c} is methyl.

56. The compound of any one of embodiments 1-47, wherein R_{5c} is unsubstituted (C_1-C_4)-alkoxy.

57. The compound of embodiment 56, wherein R_{5c} is OMe.

58. The compound of any one of embodiments 1-47, wherein R_{5c} is unsubstituted (C_3-C_6)-cycloalkyl.

59. The compound of embodiment 58, wherein R_{5b} is cyclopropyl.

60. The compound of any one of embodiments 1-59, wherein R_{5d} is H.

61. The compound of any one of embodiments 1-59, wherein R_{5d} is halide.

62. The compound of embodiment 61, wherein R_{5d} is Cl or F.

63. The compound of any one of embodiments 1-59, wherein R_{5d} is CF_3.

64. The compound of any one of embodiments 1-59, wherein R_{5d} is $C(H)F_2$.

65. The compound of any one of embodiments 1-59, wherein R_{5d} is $C(F)H_2$.

66. The compound of any one of embodiments 1-59, wherein R_{5d} is unsubstituted (C_1-C_4)-alkyl.

67. The compound of embodiment 66, wherein R_{5d} is methyl.

68. The compound of any one of embodiments 1-67, wherein R_{5d} is unsubstituted (C_1-C_4)-alkoxy.

69. The compound of embodiment 68, wherein R_{5d} is OMe.

70. The compound of any one of embodiments 1-67, wherein R_{5d} is unsubstituted (C_3-C_6)-cycloalkyl.

71. The compound of embodiment 70, wherein R_{5d} is cyclopropyl.

72. The compound of any one of embodiments 1-35, wherein R_{5b}, and R_{5d} are each H.

73. The compound of any one of embodiments 1-72, wherein R_a is H.

74. The compound of any one of embodiments 1-72, wherein R_a is Me.

75. The compound of any one of embodiments 1-72, wherein R_a is halide.

76. The compound of embodiment 75, wherein R_a is Cl or F.

77. The compound of any one of embodiments 1-72, wherein R_a is CF_3.

78. The compound of any one of embodiments 1-72, wherein R_a is $C(H)F_2$.

79. The compound of any one of embodiments 1-72, wherein R_a is $C(F)H_2$.

80. The compound of any one of embodiments 1-72, wherein R_a is unsubstituted –(C_1-C_3)alkylene-N-(R_x)(R_y).

81. The compound of any one of embodiments 1-72, wherein R_a is substituted –(C_1-C_3)alkylene-N-(R_x)(R_y), substituted with F or OMe.

82. The compound of any one of embodiments 1-81, wherein R_b is H.

83. The compound of any one of embodiments 1-81, wherein R_b is Me.

84. The compound of any one of embodiments 1-81, wherein R_b is halide.

85. The compound of embodiment 84, wherein R_b is Cl or F.

86. The compound of any one of embodiments 1-81, wherein R_b is CF_3.

87. The compound of any one of embodiments 1-81, wherein R_b is $C(H)F_2$.

88. The compound of any one of embodiments 1-81, wherein R_b is $C(F)H_2$.

89. The compound of any one of embodiments 1-81, wherein R_b is unsubstituted –(C_1-C_3)alkylene-N-(R_x)(R_y).

90. The compound of any one of embodiments 1-81, wherein R_b is substituted –(C_1-C_3)alkylene-N-(R_x)(R_y), substituted with F or OMe.

91. The compound of any one of embodiments 1-90, wherein R_c is H.

92. The compound of any one of embodiments 1-90, wherein R_c is Me.

93. The compound of any one of embodiments 1-90, wherein R_c is halide.

94. The compound of embodiment 93, wherein R_c is Cl or F.

95. The compound of any one of embodiments 1-90, wherein R_c is CF_3.

96. The compound of any one of embodiments 1-90, wherein R_c is $C(H)F_2$.

97. The compound of any one of embodiments 1-90, wherein R_c is $C(F)H_2$.

98. The compound of any one of embodiments 1-90, wherein R_c is unsubstituted –(C_1-C_3)alkylene-N-(R_x)(R_y).

99. The compound of any one of embodiments 1-90, wherein R_c is substituted –(C_1-C_3)alkylene-N-(R_x)(R_y), substituted with F or OMe.

100. The compound of any one of embodiments 1-99, wherein R_x is H.

101. The compound of any one of embodiments 1-99, wherein R_x is unsubstituted (C_1-C_6)-alkyl.

102. The compound of any one of embodiments 1-100, wherein R_y is H.

103. The compound of any one of embodiments 1-100, wherein R_y is unsubstituted (C_1-C_6)-alkyl.

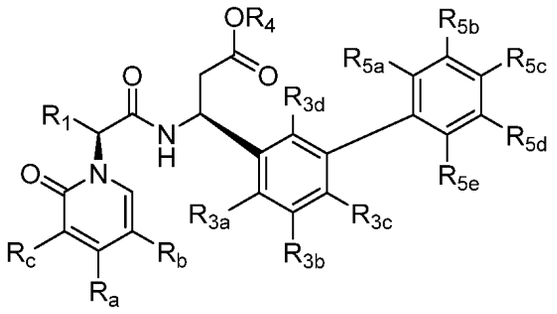
104. The compound of any one of embodiments 1-72, 80-81, 89-90, and 98-99, wherein R_x and R_y taken together with the N to which they are attached form a unsubstituted 4-6 membered ring.

105. The compound of any one of embodiments 1-72, 80-81, 89-90, and 98-99, wherein R_x and R_y taken together with the N to which they are attached form a substituted 4-6 membered ring, substituted with at least one halide, substituted or unsubstituted (C_1-C_4) alkyl, or OMe.

106. The compound of embodiment 104 or 105, wherein the 4-6 membered ring is a 3-6 membered heterocycloalkyl.

107. The compound of embodiment 104 or 105, wherein the 4-6 membered ring is a 4-5 membered heterocycloalkyl.

108. The compound of embodiment 1, wherein the compound is a compound of Formula (Ia):



(Ia)

wherein

at least one of R_a, R_b, and R_c is $-(C_1\text{-}C_3)$alkylene-$N(R_x)(R_y)$;

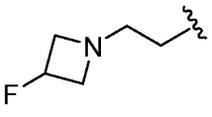
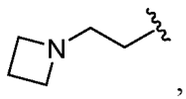
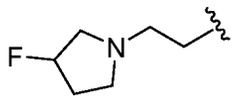
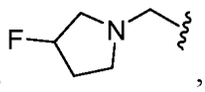
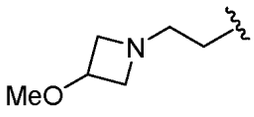
R_x and R_y are independently selected from the group consisting of H and methyl; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered ring ; and

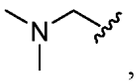
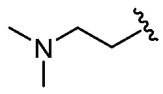
R_{3a}, and R_{3b} are each independently selected from the group consisting of methyl and F.

109. The compound of embodiment 108, wherein R_{5a}, and R_{5e} are independently unsubstituted $(C_1\text{-}C_4)$ alkyl.

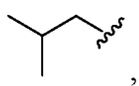
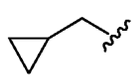
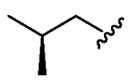
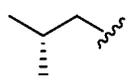
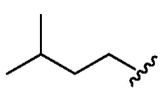
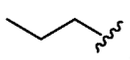
110. The compound of embodiment 108 or 109, wherein R_b is unsubstituted $-(C_1\text{-}C_3)$alkylene-$N(R_x)(R_y)$.

111. The compound of embodiment 1 or 108, wherein R_a is selected from the group consisting of H, $C(H)F_2$, CF_3, and Me.

112. The compound of embodiment 1 or 108, wherein R_b is selected from the group consisting of  ,  ,  ,  , and  .

113. The compound of embodiment 1 or 108, wherein R_b is selected from the group consisting of  , and  .

114. The compound of embodiment 1 or 108, wherein R_c is H or F.

115. The compound of any one of embodiments 1 and 108-114, wherein R_1 is selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

116. The compound of any one of embodiments 108-115, wherein R_{5a} is CF_3.

117. The compound of any one of embodiments 108-115, wherein R_{5a} is $C(H)F_2$.

118. The compound of any one of embodiments 108-115, wherein R_{5a} is $C(F)H_2$.

119. The compound of any one of embodiments 108-115, wherein R_{5a} is methyl.

120. The compound of any one of embodiments 108-115, wherein R_{5a} is OMe.

121. The compound of any one of embodiments 108-115, wherein R_{5a} is F or Cl.

122. The compound of any one of embodiments 108-121, wherein R_{5b} is H.

123. The compound of any one of embodiments 108-121, wherein R_{5b} is CF_3.

124. The compound of any one of embodiments 108-121, wherein R_{5b} is $C(H)F_2$.

125. The compound of any one of embodiments 108-121, wherein R_{5b} is $C(F)H_2$.

126. The compound of any one of embodiments 108-121, wherein R_{5b} is methyl.

127. The compound of any one of embodiments 108-121, wherein R_{5b} is OMe.

128. The compound of any one of embodiments 108-121, wherein R_{5b} is F or Cl.

129. The compound of any one of embodiments 108-128, wherein R_{5c} is H.

130. The compound of any one of embodiments 108-128, wherein R_{5c} is CF_3.

131. The compound of any one of embodiments 108-128, wherein R_{5c} is $C(H)F_2$.

132. The compound of any one of embodiments 108-128, wherein R_{5c} is $C(F)H_2$.

133. The compound of any one of embodiments 108-128, wherein R_{5c} is methyl.

134. The compound of any one of embodiments 108-128, wherein R_{5c} is OMe.

135. The compound of any one of embodiments 108-128, wherein R_{5c} is F or Cl.

136. The compound of any one of embodiments 108-135, wherein R_{5d} is H.

137. The compound of any one of embodiments 108-135, wherein R_{5d} is CF_3.

138. The compound of any one of embodiments 108-135, wherein R_{5d} is $C(H)F_2$.

139. The compound of any one of embodiments 108-135, wherein R_{5d} is $C(F)H_2$.

140. The compound of any one of embodiments 108-135, wherein R_{5d} is methyl.

141. The compound of any one of embodiments 108-135, wherein R_{5d} is OMe.

142. The compound of any one of embodiments 108-135, wherein R_{5d} is F or Cl.

143. The compound of any one of embodiments 108-142, wherein R_{5e} is CF_3.

144. The compound of any one of embodiments 108-142, wherein R_{5e} is $C(H)F_2$.

145. The compound of any one of embodiments 108-142, wherein R_{5e} is $C(F)H_2$.

146. The compound of any one of embodiments 108-142, wherein R_{5e} is methyl.

147. The compound of any one of embodiments 108-142, wherein R_{5e} is OMe.

148. The compound of any one of embodiments 108-142, wherein R_{5e} is F or Cl.

149. The compound of any one of embodiments 1, and 108-121, wherein at least one of R_{5b}, R_{5c}, and R_{5d} is H.

150. The compound of any one of embodiments 1, and 108-121, wherein at least two of R_{5b}, R_{5c}, and R_{5d} is H.

151. The compound of any one of embodiments 1, and 108-121, wherein R_{5b}, R_{5c}, and R_{5d} are H.

152. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is H.

153. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is methyl.

154. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is halide.

155. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is CF_3.

156. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is $C(H)F_2$.

157. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is $C(F)H_2$.

158. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is OMe.

159. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is H.

160. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is methyl.

161. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is halide.

162. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is CF_3.

163. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is $C(H)F_2$.

164. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is $C(F)H_2$.

165. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is OMe.

166. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is OCF_3.

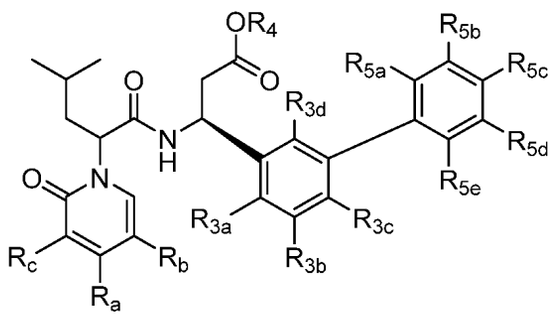
167. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is cyclopropyl.

168. The compound of any one of embodiments 108-151, wherein R_{3a} is methyl and R_{3b} is F.

169. The compound of any one of embodiments 108-151, wherein R_{3a} is F and R_{3b} is methyl.

170. The compound of embodiment 1, wherein the compound is selected from any one of the compounds of Figure 1, or an enantiomer thereof.

171. The compound of embodiment 1, wherein the compound is a compound of Formula (Ic)



(Ic)

or a pharmaceutically acceptable salt thereof, wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that one of R_a, R_b, and R_c is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_6)-alkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3 -CN, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_{3d} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, halide, and -(C_1-C_4)-alkoxy;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof.

172. A compound selected from the group consisting of:

(3S)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid;

(3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid;

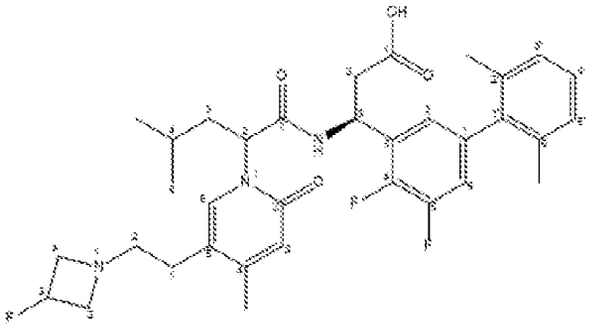
(3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid; and

(3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid,

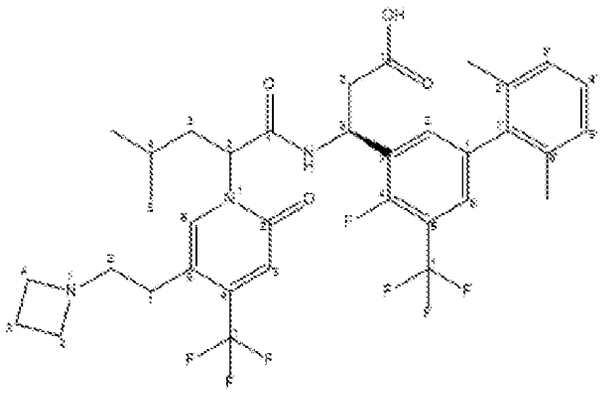
or a pharmaceutically acceptable salt thereof.

173. The compound of embodiment 1, wherein the compound is the compound:



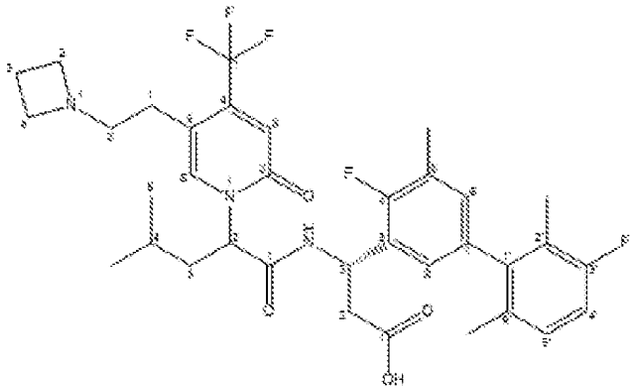
or a pharmaceutically acceptable salt thereof.

174. The compound of embodiment 1, wherein the compound is the compound:



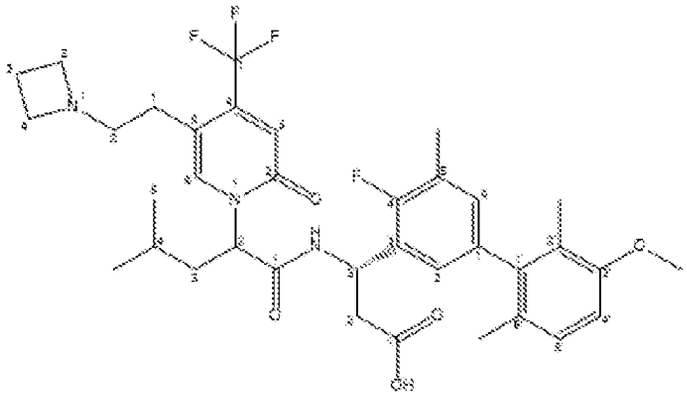
or a pharmaceutically acceptable salt thereof.

175. The compound of embodiment 1, wherein the compound is the compound:



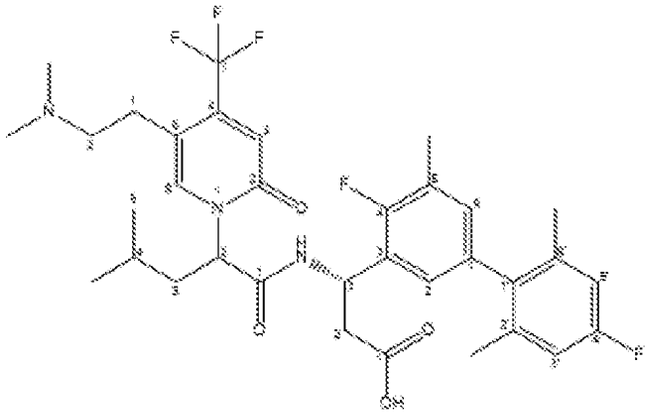
or a pharmaceutically acceptable salt thereof.

176. The compound of embodiment 1, wherein the compound is the compound:



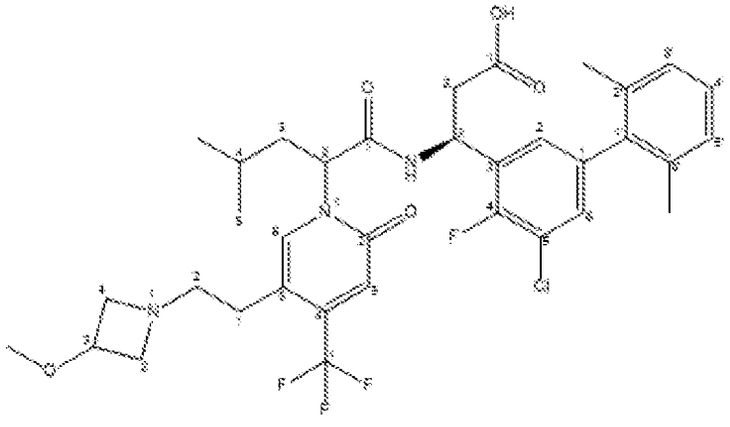
or a pharmaceutically acceptable salt thereof.

177. The compound of embodiment 1, wherein the compound is the compound:



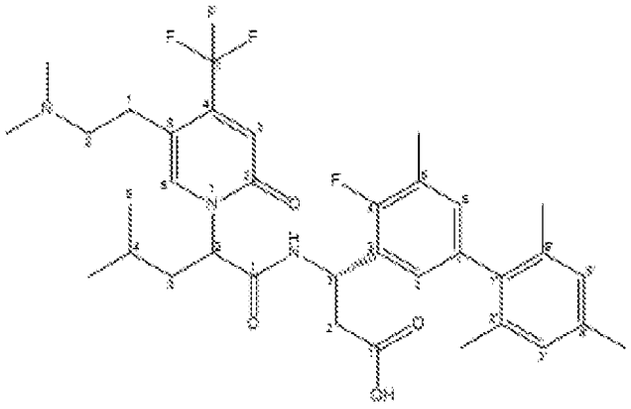
or a pharmaceutically acceptable salt thereof.

178. The compound of embodiment 1, wherein the compound is the compound:



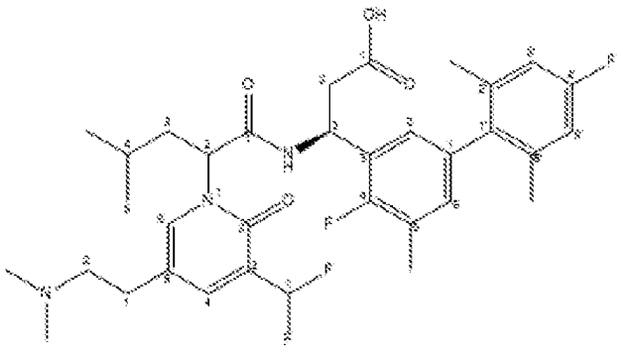
or a pharmaceutically acceptable salt thereof.

179. The compound of embodiment 1, wherein the compound is the compound:



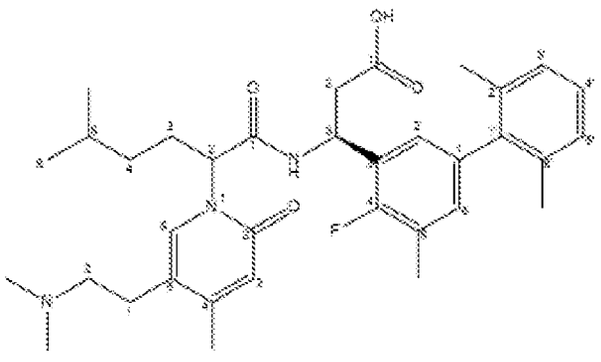
or a pharmaceutically acceptable salt thereof.

180. The compound of embodiment 1, wherein the compound is the compound:



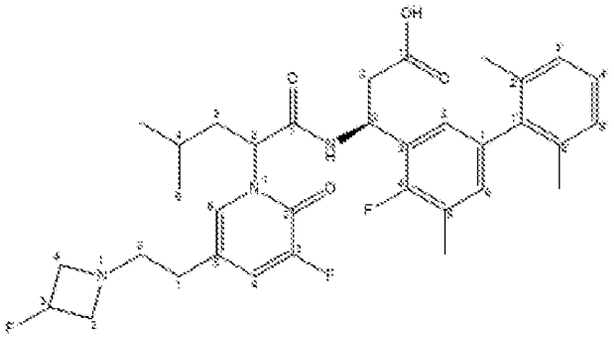
or a pharmaceutically acceptable salt thereof.

181. The compound of embodiment 1, wherein the compound is the compound:



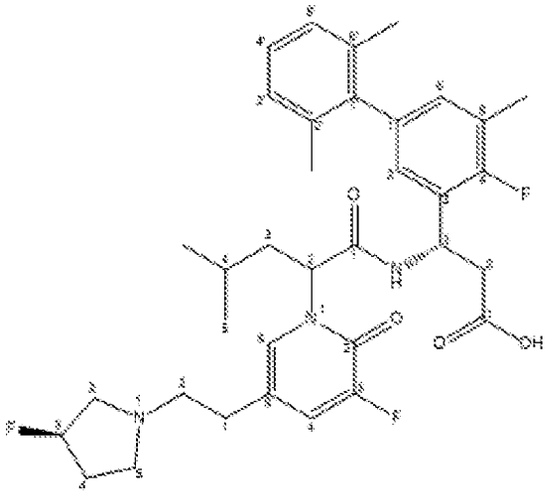
or a pharmaceutically acceptable salt thereof.

182. The compound of embodiment 1, wherein the compound is the compound:



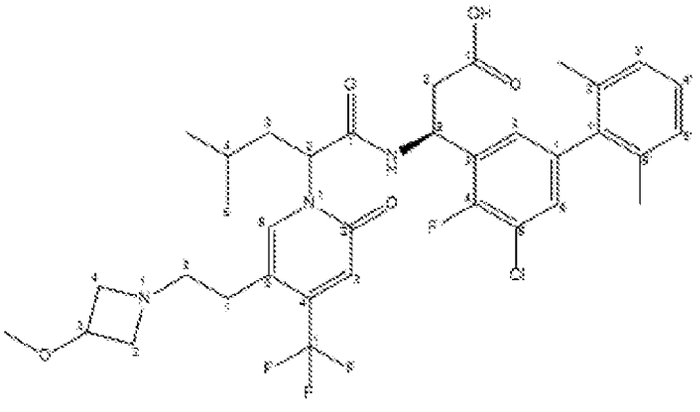
or a pharmaceutically acceptable salt thereof.

183. The compound of embodiment 1, wherein the compound is the compound:



or a pharmaceutically acceptable salt thereof.

184. The compound of embodiment 1, wherein the compound is the compound:



or a pharmaceutically acceptable salt thereof.

185. The compound of embodiment 1, wherein the compound is (3S)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

186. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

187. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

188. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

189. The compound of embodiment 1, wherein the compound is (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

190. The compound of embodiment 1, wherein the compound is (3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

191. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

192. The compound of embodiment 1, wherein the compound is (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

193. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

194. The compound of embodiment 1, wherein the compound is (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

195. The compound of embodiment 1, wherein the compound is (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

196. The compound of embodiment 1, wherein the compound is (3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

197. The compound of embodiment 1, wherein the compound is (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

198. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

199. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

200. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

201. The compound of embodiment 1, wherein the compound is (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

202. The compound of embodiment 1, wherein the compound is (S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

203. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

204. The compound of embodiment 1, wherein the compound is (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

205. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

206. The compound of embodiment 1, wherein the compound is (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

207. The compound of embodiment 1, wherein the compound is (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

208. The compound of embodiment 1, wherein the compound is (S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

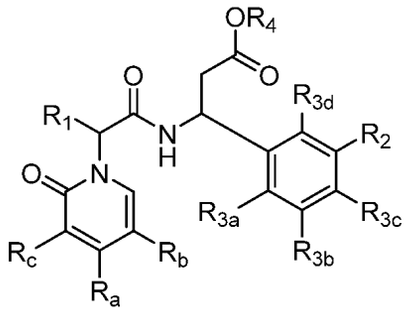
209. A pharmaceutical composition, comprising a compound of any one of embodiments 1-208; and a pharmaceutically acceptable excipient.

210. A method of inhibiting $\alpha_4\beta_7$ integrin in a cell, comprising contacting the cell with a compound of any one of embodiments 1-208 under conditions effective to reduce the adhesion of the cell to MAdCAM-1.

211. A method of reducing the adhesion of a cell comprising an $\alpha_4\beta_7$ integrin to MAdCAM-1, the method comprising contacting the cell with a compound of any one of embodiments 1-208 under conditions effective to reduce the adhesion of the cell to MAdCAM-1.

212. A method of treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments 1-208

In some embodiments, compounds of the invention can be a compound of Formula (I):



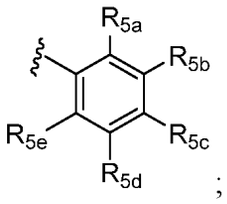
(I)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is -$(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of halide, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_4)-alkoxy, CF_3, $C(H)F_2$, and $C(F)H_2$;

R_{3c}, and R_{3d} are H;

R_4 is H;

R_{5a} is methyl;

R_{5b} is selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

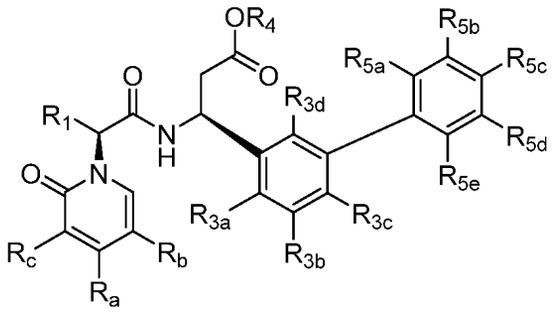
R_{5c} is methyl;

R_{5d} is H;

R_{5e} is selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof.

In some embodiments, compounds of the invention can be a compound of Formula (Ia):



(Ia)

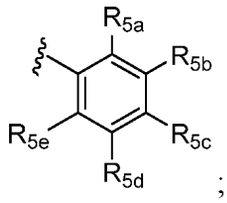
wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and –$(C_1$-$C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is -$(C_1$-$C_5)$alkylene-N-$(R_x)(R_y)$;

at least one of R_a, R_b, and R_c is –$(C_1$-$C_3)$alkylene-N$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and methyl; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered ring ;

R_1 is substituted or unsubstituted $(C_1$-$C_6)$-alkyl, substituted or unsubstituted $(C_1$-$C_4)$-alkylene-$(C_3$-$C_6)$-cycloalkyl, or substituted or unsubstituted $(C_1$-$C_4)$-alkylene- $(C_1$-$C_4)$-alkoxy;

R_2 is 

;

R_{3a}, and R_{3b} are each independently selected from the group consisting of methyl and F, and R_{3a} is halide;

R_{3c}, and R_{3d} are H;

R_4 is H, or substituted or unsubstituted $(C_1$-$C_4)$-alkyl;

R_{5a} is selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted $(C_3$-$C_6)$-cycloalkyl, substituted or unsubstituted $(C_1$-$C_5)$-alkyl, hydroxyl, and $(C_1$-$C_4)$-alkoxy; and

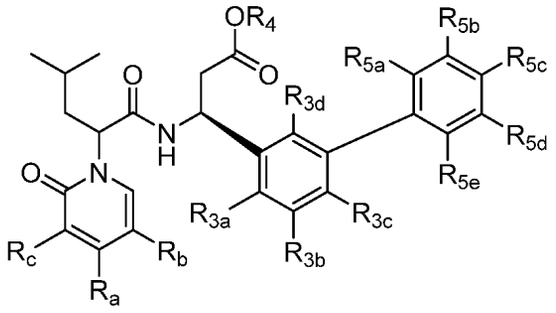
R_{5b}, and R_{5c} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted $(C_1$-$C_5)$-alkyl, substituted or unsubstituted $(C_3$-$C_6)$-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and $(C_1$-$C_4)$-alkoxy; and

R_{5d} is H;

R_{5e} is methyl;

or a pharmaceutically acceptable salt thereof.

In some embodiments, compounds of the invention can be a compound of Formula (Ic)



(Ic)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that one of R_a, R_b, and R_c is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_6)-alkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring;

R_{3a} is halide and R_{3b} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_{3c} is H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, halide,

CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3 -CN, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

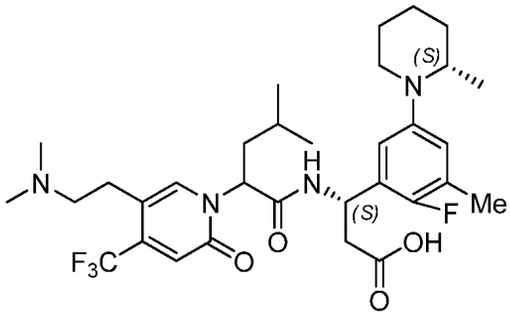
R_{3d} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, halide, and -(C_1-C_4)-alkoxy;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof.

In some embodiments, compounds of the invention can be a compound (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2-fluoro-3-methyl-5-((S)-2-methylpiperidin-1-yl)phenyl)propanoic acid



, or a pharmaceutically acceptable salt thereof.

In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the subject is a mammal. In certain embodiments, the invention relates to any one of the aforementioned methods, wherein the subject is human.

EXAMPLES

The invention now being generally described, it will be more readily understood by reference to the following examples, which are included merely for purposes of illustration of

certain aspects and embodiments of the present invention, and are not intended to limit the invention.

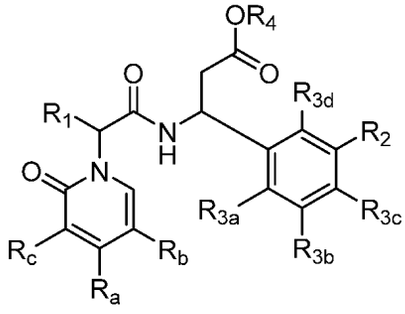
Examples 1-4 describe the synthesis of certain compounds presented in Figure 1, including compounds of Formula (Ia) and Formula (Ib). Compounds in Figure 1 can be prepared as a mixture of diastereomeric compounds (e.g., as disclosed in Examples 1-4) having a (3*S*) configuration (i.e., at the stereocenter *beta* to the carboxylic acid moiety), and a mixture of diastereomers at the chiral center covalently bound to the pyridone ring nitrogen atom of Formula (I) (e.g., as shown in Formula (Ib)).

In Figure 1, compounds having greater activity in the fluorescence polarization (FP) assay of Example 5 are shown with the stereochemistry of Formula (Ia). Example 5 describes a fluorescence polarization (FP) assay. Example 6 describes a ligand binding (LB) assay. Example 7 describes a cell adhesion (CA) assay.

Additional Embodiments

In some embodiments, a compound can be selected from one or more of the enumerated embodiments provided below:

1. A compound of Formula (I):



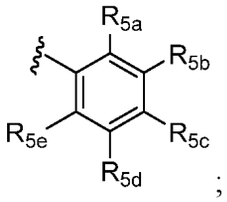
(I)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is -$(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl, substituted or unsubstituted (C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, or substituted or unsubstituted (C_1-C_4)-alkylene- (C_1-C_4)-alkoxy;

R_2 is 

;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c}, and R_{3d} are H;

R_4 is H, or substituted or unsubstituted (C_1-C_4)-alkyl;

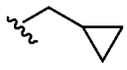
R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

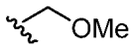
R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof.

2. The compound of embodiment 1, wherein R_1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl.

3. The compound of embodiment 2, wherein R_1 is iso-butyl.

4. The compound of embodiment 1, wherein R_1 is  .

5. The compound of embodiment 1, wherein R_1 is 
.

6. The compound of any one of embodiments 1-5, wherein R_{3a} and R_{3b} are independently selected from the group consisting of halide, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_4)-alkoxy, CF_3, $C(H)F_2$, and $C(F)H_2$.

7. The compound of embodiment 6, wherein R_{3a} and R_{3b} are independently selected from the group consisting of halide and (C_1-C_4)-alkyl.

8. The compound of embodiment 7, wherein halide is Cl or F.

9. The compound of embodiment 7 or 8, wherein (C_1-C_4)-alkyl is methyl.

10. The compound of any one of embodiments 1-7, wherein R_{3a} is methyl; and R_{3b} is F.

11. The compound of any one of embodiments 1-7, wherein R_{3a} is F; and R_{3b} is methyl.

12. The compound of any one of embodiments 1-11, wherein R_4 is H.

13. The compound of any one of embodiments 1-11, wherein R_4 is methyl, ethyl, n-propyl, iso-propyl.

14. The compound of any one of embodiments 1-13, wherein R_{5a} and R_{5e} are independently selected from the group consisting of halide, CF_3, $C(H)F_2$, $C(F)H_2$, and substituted or unsubstituted (C_1-C_4)-alkyl.

15. The compound of any one of embodiments 1-14, wherein R_{5a} is halide.

16. The compound of embodiment 15, wherein R_{5a} is F or Cl.

17. The compound of any one of embodiments 1-14, wherein R_{5a} is CF_3.

18. The compound of any one of embodiments 1-14, wherein R_{5a} is $C(H)F_2$.

19. The compound of any one of embodiments 1-14, wherein R_{5a} is $C(F)H_2$.

20. The compound of any one of embodiments 1-14, wherein R_{5a} is unsubstituted (C_1-C_4)-alkyl.

21. The compound of embodiment 20, wherein R_{5a} is methyl.

22. The compound of any one of embodiments 1-14, wherein R_{5a} is substituted (C_1-C_5)-alkyl, substituted with at least one halide.

23. The compound of any one of embodiments 1-14, wherein R_{5a} is unsubstituted (C_1-C_4)-alkoxy.

24. The compound of embodiment 23, wherein R_{5a} is OMe.

25. The compound of any one of embodiments 1-24, wherein R_{5e} is halide.

26. The compound of embodiment 25, wherein R_{5e} is F or Cl.

27. The compound of any one of embodiments 1-24, wherein R_{5e} is CF_3.

28. The compound of any one of embodiments 1-24, wherein R_{5e} is $C(H)F_2$.

29. The compound of any one of embodiments 1-24, wherein R_{5e} is $C(F)H_2$.

30. The compound of any one of embodiments 1-24, wherein R_{5e} is unsubstituted (C_1-C_4)-alkyl.

31. The compound of embodiment 30, wherein R_{5e} is methyl.

32. The compound of any one of embodiments 1-24, wherein R_{5e} is substituted (C_1-C_5)-alkyl, substituted with at least one halide.

33. The compound of any one of embodiments 1-24, wherein R_{5e} is unsubstituted (C_1-C_4)-alkoxy.

34. The compound of embodiment 33, wherein R_{5e} is OMe.

35. The compound of any one of embodiments 1-34, wherein R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, and substituted or unsubstituted (C_1-C_4)-alkoxy.

36. The compound of any one of embodiments 1-35, wherein R_{5b} is H.

37. The compound of any one of embodiments 1-35, wherein R_{5b} is halide.

38. The compound of embodiment 37, wherein R_{5b} is Cl or F.

39. The compound of any one of embodiments 1-35, wherein R_{5b} is CF_3.

40. The compound of any one of embodiments 1-35, wherein R_{5b} is $C(H)F_2$.

41. The compound of any one of embodiments 1-35, wherein R_{5b} is $C(F)H_2$.

42. The compound of any one of embodiments 1-35, wherein R_{5b} is unsubstituted (C_1-C_4)-alkyl.

43. The compound of embodiment 37, wherein R_{5b} is methyl.

44. The compound of any one of embodiments 1-35, wherein R_{5b} is unsubstituted (C_1-C_4)-alkoxy.

45. The compound of embodiment 44, wherein R_{5b} is OMe.

46. The compound of any one of embodiments 1-35, wherein R_{5b} is unsubstituted (C_3-C_6)-cycloalkyl.

47. The compound of embodiment 46, wherein R_{5b} is cyclopropyl.

48. The compound of any one of embodiments 1-47, wherein R_{5c} is H.

49. The compound of any one of embodiments 1-47, wherein R_{5c} is halide.

50. The compound of embodiment 49, wherein R_{5c} is Cl or F.

51. The compound of any one of embodiments 1-47, wherein R_{5c} is CF_3.

52. The compound of any one of embodiments 1-47, wherein R_{5c} is $C(H)F_2$.

53. The compound of any one of embodiments 1-47, wherein R_{5c} is $C(F)H_2$.

54. The compound of any one of embodiments 1-47, wherein R_{5c} is unsubstituted (C_1-C_4)-alkyl.

55. The compound of embodiment 54, wherein R_{5c} is methyl.

56. The compound of any one of embodiments 1-47, wherein R_{5c} is unsubstituted (C_1-C_4)-alkoxy.

57. The compound of embodiment 56, wherein R_{5c} is OMe.

58. The compound of any one of embodiments 1-47, wherein R_{5c} is unsubstituted (C_3-C_6)-cycloalkyl.

59. The compound of embodiment 58, wherein R_{5b} is cyclopropyl.

60. The compound of any one of embodiments 1-59, wherein R_{5d} is H.

61. The compound of any one of embodiments 1-59, wherein R_{5d} is halide.

62. The compound of embodiment 61, wherein R_{5d} is Cl or F.

63. The compound of any one of embodiments 1-59, wherein R_{5d} is CF_3.

64. The compound of any one of embodiments 1-59, wherein R_{5d} is $C(H)F_2$.

65. The compound of any one of embodiments 1-59, wherein R_{5d} is $C(F)H_2$.

66. The compound of any one of embodiments 1-59, wherein R_{5d} is unsubstituted (C_1-C_4)-alkyl.

67. The compound of embodiment 66, wherein R_{5d} is methyl.

68. The compound of any one of embodiments 1-67, wherein R_{5d} is unsubstituted (C_1-C_4)-alkoxy.

69. The compound of embodiment 68, wherein R_{5d} is OMe.

70. The compound of any one of embodiments 1-67, wherein R_{5d} is unsubstituted (C_3-C_6)-cycloalkyl.

71. The compound of embodiment 70, wherein R_{5d} is cyclopropyl.

72. The compound of any one of embodiments 1-35, wherein R_{5b}, and R_{5d} are each H.

73. The compound of any one of embodiments 1-72, wherein R_a is H.

74. The compound of any one of embodiments 1-72, wherein R_a is Me.

75. The compound of any one of embodiments 1-72, wherein R_a is halide.

76. The compound of embodiment 75, wherein R_a is Cl or F.

77. The compound of any one of embodiments 1-72, wherein R_a is CF_3.

78. The compound of any one of embodiments 1-72, wherein R_a is $C(H)F_2$.

79. The compound of any one of embodiments 1-72, wherein R_a is $C(F)H_2$.

80. The compound of any one of embodiments 1-72, wherein R_a is unsubstituted –(C_1-C_3)alkylene-N-(R_x)(R_y).

81. The compound of any one of embodiments 1-72, wherein R_a is substituted –(C_1-C_3)alkylene-N-(R_x)(R_y), substituted with F or OMe.

82. The compound of any one of embodiments 1-81, wherein R_b is H.

83. The compound of any one of embodiments 1-81, wherein R_b is Me.

84. The compound of any one of embodiments 1-81, wherein R_b is halide.

85. The compound of embodiment 84, wherein R_b is Cl or F.

86. The compound of any one of embodiments 1-81, wherein R_b is CF_3.

87. The compound of any one of embodiments 1-81, wherein R_b is $C(H)F_2$.

88. The compound of any one of embodiments 1-81, wherein R_b is $C(F)H_2$.

89. The compound of any one of embodiments 1-81, wherein R_b is unsubstituted –(C_1-C_3)alkylene-N-(R_x)(R_y).

90. The compound of any one of embodiments 1-81, wherein R_b is substituted –(C_1-C_3)alkylene-N-(R_x)(R_y), substituted with F or OMe.

91. The compound of any one of embodiments 1-90, wherein R_c is H.

92. The compound of any one of embodiments 1-90, wherein R_c is Me.

93. The compound of any one of embodiments 1-90, wherein R_c is halide.

94. The compound of embodiment 93, wherein R_c is Cl or F.

95. The compound of any one of embodiments 1-90, wherein R_c is CF_3.

96. The compound of any one of embodiments 1-90, wherein R_c is $C(H)F_2$.

97. The compound of any one of embodiments 1-90, wherein R_c is $C(F)H_2$.

98. The compound of any one of embodiments 1-90, wherein R_c is unsubstituted –(C_1-C_3)alkylene-N-(R_x)(R_y).

99. The compound of any one of embodiments 1-90, wherein R_c is substituted –(C_1-C_3)alkylene-N-(R_x)(R_y), substituted with F or OMe.

100. The compound of any one of embodiments 1-99, wherein R_x is H.

101. The compound of any one of embodiments 1-99, wherein R_x is unsubstituted (C_1-C_6)-alkyl.

102. The compound of any one of embodiments 1-100, wherein R_y is H.

103. The compound of any one of embodiments 1-100, wherein R_y is unsubstituted (C_1-C_6)-alkyl.

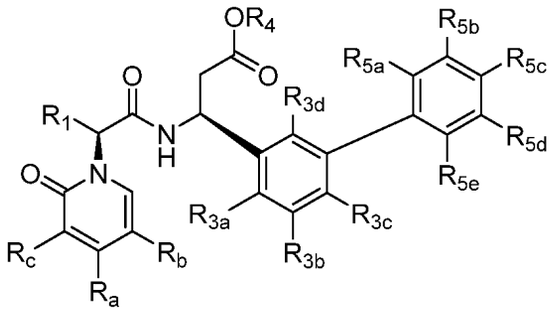
104. The compound of any one of embodiments 1-72, 80-81, 89-90, and 98-99, wherein R_x and R_y taken together with the N to which they are attached form a unsubstituted 4-6 membered ring.

105. The compound of any one of embodiments 1-72, 80-81, 89-90, and 98-99, wherein R_x and R_y taken together with the N to which they are attached form a substituted 4-6 membered ring, substituted with at least one halide, substituted or unsubstituted (C_1-C_4) alkyl, or OMe.

106. The compound of embodiment 104 or 105, wherein the 4-6 membered ring is a 3-6 membered heterocycloalkyl.

107. The compound of embodiment 104 or 105, wherein the 4-6 membered ring is a 4-5 membered heterocycloalkyl.

108. The compound of embodiment 1, wherein the compound is a compound of Formula (Ia):



(Ia)

wherein

at least one of R_a, R_b, and R_c is –(C_1-C_3)alkylene-N(R_x)(R_y);

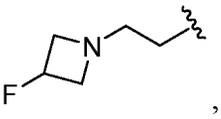
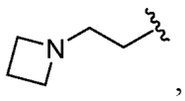
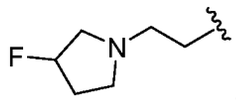
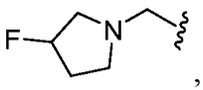
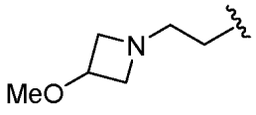
R_x and R_y are independently selected from the group consisting of H and methyl; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered ring ; and

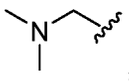
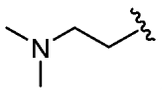
R_{3a}, and R_{3b} are each independently selected from the group consisting of methyl and F.

109. The compound of embodiment 108, wherein R_{5a}, and R_{5e} are independently unsubstituted (C_1-C_4) alkyl.

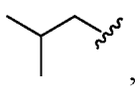
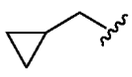
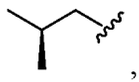
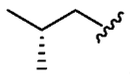
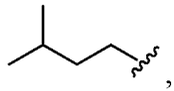
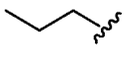
110. The compound of embodiment 108 or 109, wherein R_b is unsubstituted –(C_1-C_3)alkylene-N(R_x)(R_y).

111. The compound of embodiment 1 or 108, wherein R_a is selected from the group consisting of H, C(H)F_2, CF_3, and Me.

112. The compound of embodiment 1 or 108, wherein R_b is selected from the group consisting of  ,  ,  ,  , and  .

113. The compound of embodiment 1 or 108, wherein R_b is selected from the group consisting of  , and  .

114. The compound of embodiment 1 or 108, wherein R_c is H or F.

115. The compound of any one of embodiments 1 and 108-114, wherein R_1 is selected from the group consisting of  ,  ,  ,  ,  ,  , and  .

116. The compound of any one of embodiments 108-115, wherein R_{5a} is CF_3.

117. The compound of any one of embodiments 108-115, wherein R_{5a} is $C(H)F_2$.

118. The compound of any one of embodiments 108-115, wherein R_{5a} is $C(F)H_2$.

119. The compound of any one of embodiments 108-115, wherein R_{5a} is methyl.

120. The compound of any one of embodiments 108-115, wherein R_{5a} is OMe.

121. The compound of any one of embodiments 108-115, wherein R_{5a} is F or Cl.

122. The compound of any one of embodiments 108-121, wherein R_{5b} is H.

123. The compound of any one of embodiments 108-121, wherein R_{5b} is CF_3.

124. The compound of any one of embodiments 108-121, wherein R_{5b} is $C(H)F_2$.

125. The compound of any one of embodiments 108-121, wherein R_{5b} is $C(F)H_2$.

126. The compound of any one of embodiments 108-121, wherein R_{5b} is methyl.

127. The compound of any one of embodiments 108-121, wherein R_{5b} is OMe.

128. The compound of any one of embodiments 108-121, wherein R_{5b} is F or Cl.

129. The compound of any one of embodiments 108-128, wherein R_{5c} is H.

130. The compound of any one of embodiments 108-128, wherein R_{5c} is CF_3.

131. The compound of any one of embodiments 108-128, wherein R_{5c} is $C(H)F_2$.

132. The compound of any one of embodiments 108-128, wherein R_{5c} is $C(F)H_2$.

133. The compound of any one of embodiments 108-128, wherein R_{5c} is methyl.

134. The compound of any one of embodiments 108-128, wherein R_{5c} is OMe.

135. The compound of any one of embodiments 108-128, wherein R_{5c} is F or Cl.

136. The compound of any one of embodiments 108-135, wherein R_{5d} is H.

137. The compound of any one of embodiments 108-135, wherein R_{5d} is CF_3.

138. The compound of any one of embodiments 108-135, wherein R_{5d} is $C(H)F_2$.

139. The compound of any one of embodiments 108-135, wherein R_{5d} is $C(F)H_2$.

140. The compound of any one of embodiments 108-135, wherein R_{5d} is methyl.

141. The compound of any one of embodiments 108-135, wherein R_{5d} is OMe.

142. The compound of any one of embodiments 108-135, wherein R_{5d} is F or Cl.

143. The compound of any one of embodiments 108-142, wherein R_{5e} is CF_3.

144. The compound of any one of embodiments 108-142, wherein R_{5e} is $C(H)F_2$.

145. The compound of any one of embodiments 108-142, wherein R_{5e} is $C(F)H_2$.

146. The compound of any one of embodiments 108-142, wherein R_{5e} is methyl.

147. The compound of any one of embodiments 108-142, wherein R_{5e} is OMe.

148. The compound of any one of embodiments 108-142, wherein R_{5e} is F or Cl.

149. The compound of any one of embodiments 1, and 108-121, wherein at least one of R_{5b}, R_{5c}, and R_{5d} is H.

150. The compound of any one of embodiments 1, and 108-121, wherein at least two of R_{5b}, R_{5c}, and R_{5d} is H.

151. The compound of any one of embodiments 1, and 108-121, wherein R_{5b}, R_{5c}, and R_{5d} are H.

152. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is H.

153. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is methyl.

154. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is halide.

155. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is CF_3.

156. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is $C(H)F_2$.

157. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is $C(F)H_2$.

158. The compound of any one of embodiments 1, and 108-151, wherein R_{3a} is OMe.

159. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is H.

160. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is methyl.

161. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is halide.

162. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is CF_3.

163. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is $C(H)F_2$.

164. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is $C(F)H_2$.

165. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is OMe.

166. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is OCF_3.

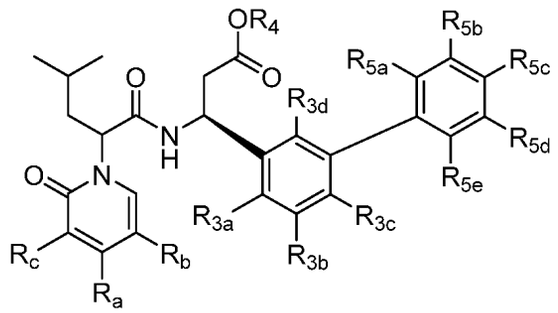
167. The compound of any one of embodiments 1, and 108-158, wherein R_{3b} is cyclopropyl.

168. The compound of any one of embodiments 108-151, wherein R_{3a} is methyl and R_{3b} is F.

169. The compound of any one of embodiments 108-151, wherein R_{3a} is F and R_{3b} is methyl.

170. The compound of embodiment 1, wherein the compound is selected from any one of the compounds of Figure 1, or an enantiomer thereof.

171. The compound of embodiment 1, wherein the compound is a compound of Formula (Ic)



(Ic)

or a pharmaceutically acceptable salt thereof, wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that one of R_a, R_b, and R_c is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_6)-alkyl, or substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; or R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered heterocyclyl ring;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or

unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, $-OCF_3$, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, $-OCF_3$ -CN, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_{3d} is selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, halide, and -(C_1-C_4)-alkoxy;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof.

172. A compound selected from the group consisting of:

(3S)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

(3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid;

(3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid;

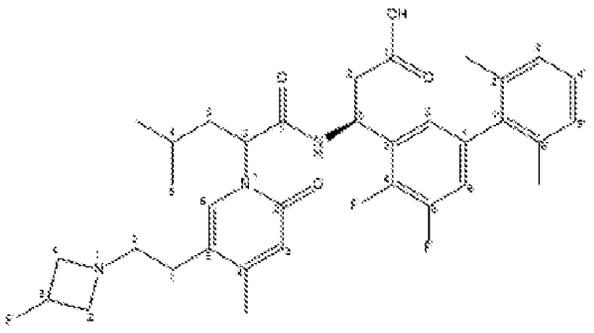
(3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

(3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid; and

(3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid,

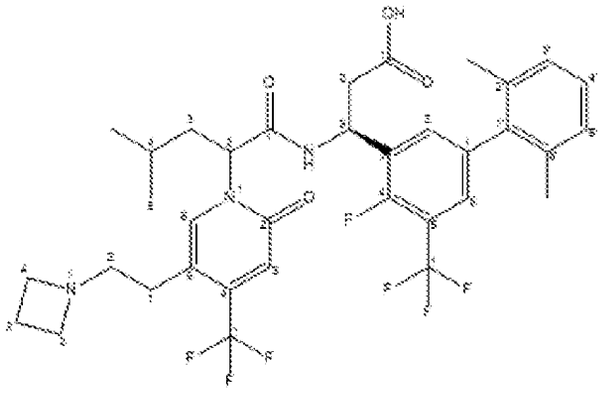
or a pharmaceutically acceptable salt thereof.

173. The compound of embodiment 1, wherein the compound is the compound:



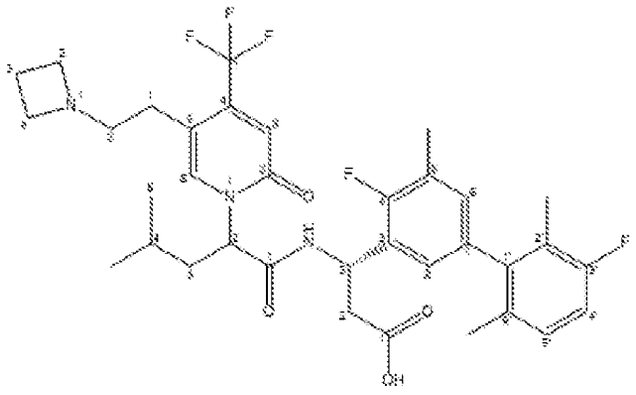
or a pharmaceutically acceptable salt thereof.

174. The compound of embodiment 1, wherein the compound is the compound:



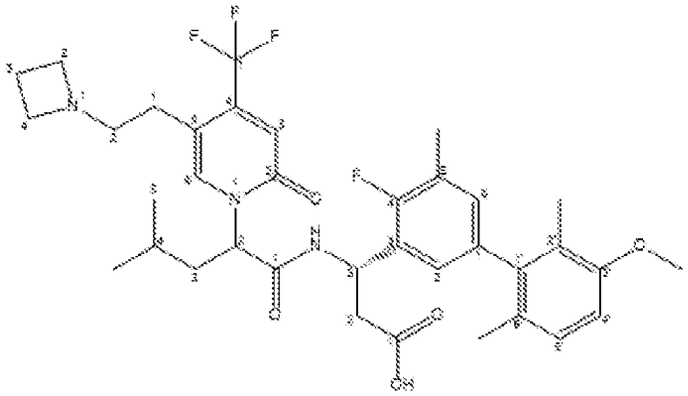
or a pharmaceutically acceptable salt thereof.

175. The compound of embodiment 1, wherein the compound is the compound:



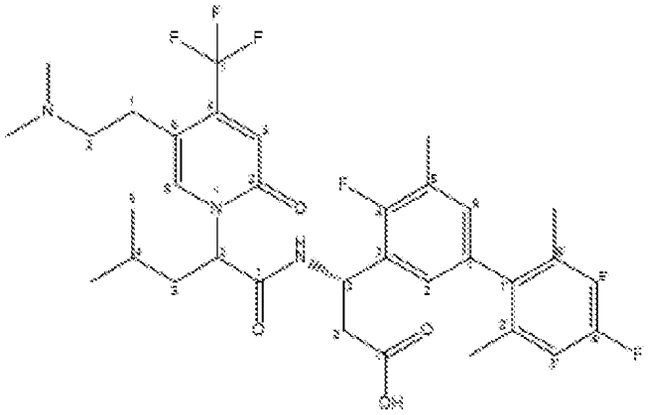
or a pharmaceutically acceptable salt thereof.

176. The compound of embodiment 1, wherein the compound is the compound:



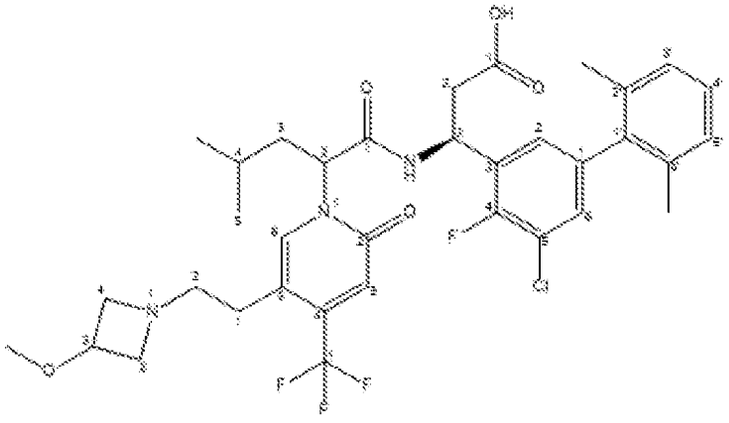
or a pharmaceutically acceptable salt thereof.

177. The compound of embodiment 1, wherein the compound is the compound:



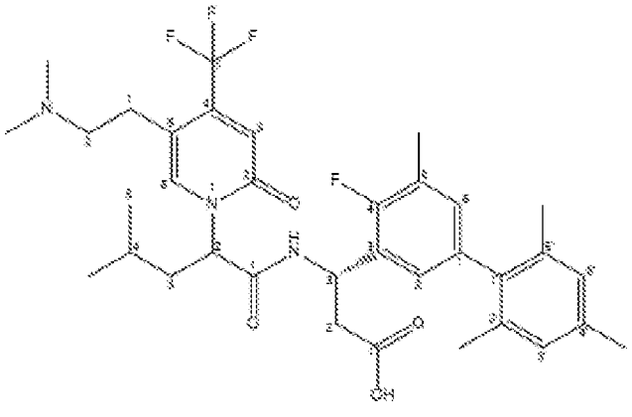
or a pharmaceutically acceptable salt thereof.

178. The compound of embodiment 1, wherein the compound is the compound:



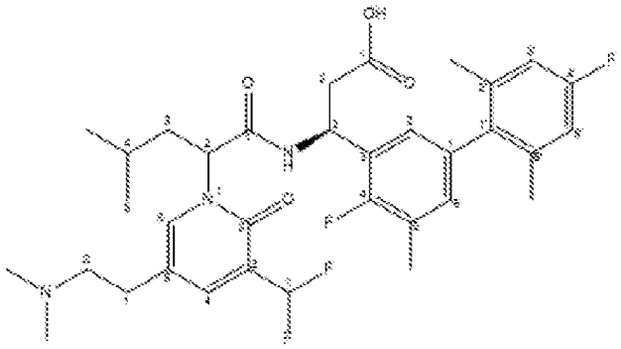
or a pharmaceutically acceptable salt thereof.

179. The compound of embodiment 1, wherein the compound is the compound:



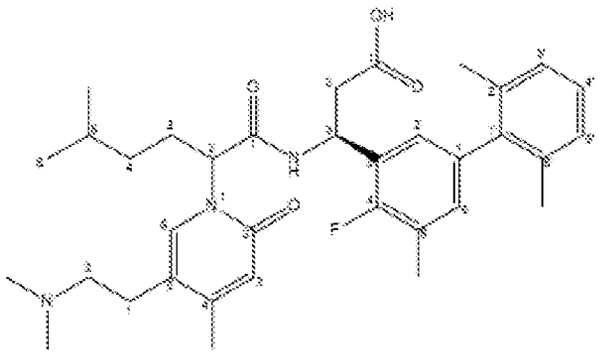
or a pharmaceutically acceptable salt thereof.

180. The compound of embodiment 1, wherein the compound is the compound:



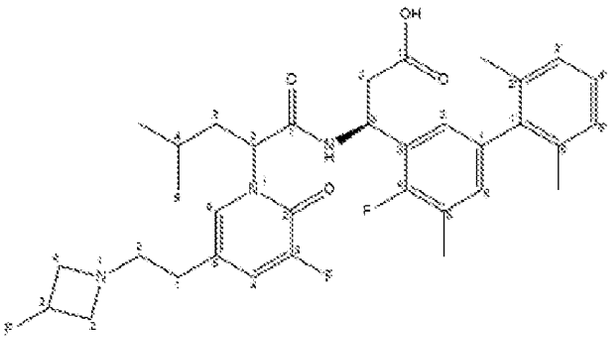
or a pharmaceutically acceptable salt thereof.

181. The compound of embodiment 1, wherein the compound is the compound:



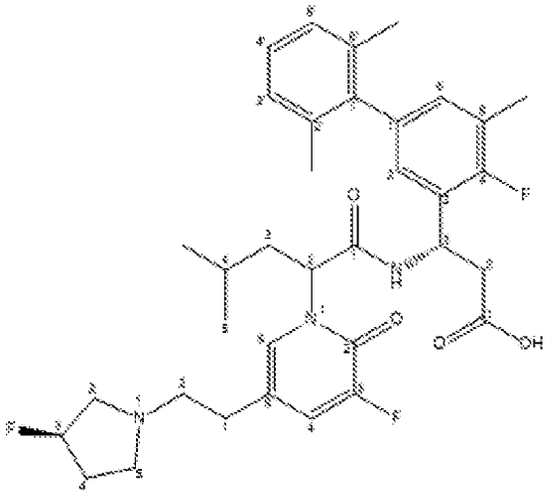
or a pharmaceutically acceptable salt thereof.

182. The compound of embodiment 1, wherein the compound is the compound:



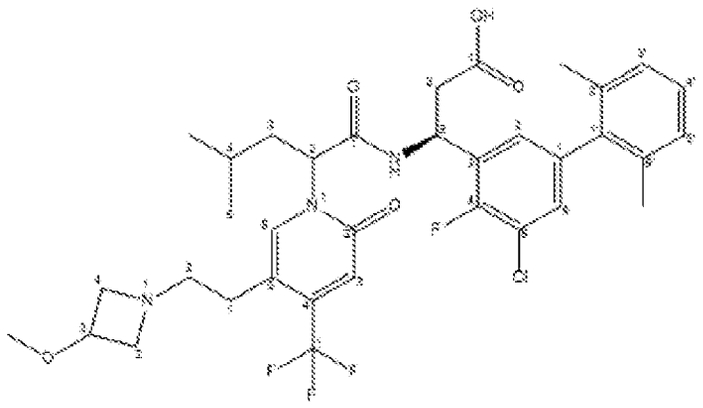
or a pharmaceutically acceptable salt thereof.

183. The compound of embodiment 1, wherein the compound is the compound:



or a pharmaceutically acceptable salt thereof.

184. The compound of embodiment 1, wherein the compound is the compound:



or a pharmaceutically acceptable salt thereof.

185. The compound of embodiment 1, wherein the compound is (3S)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

186. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

187. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-

difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

188. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

189. The compound of embodiment 1, wherein the compound is (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

190. The compound of embodiment 1, wherein the compound is (3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

191. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

192. The compound of embodiment 1, wherein the compound is (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

193. The compound of embodiment 1, wherein the compound is (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

194. The compound of embodiment 1, wherein the compound is (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

195. The compound of embodiment 1, wherein the compound is (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

196. The compound of embodiment 1, wherein the compound is (3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

197. The compound of embodiment 1, wherein the compound is (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

198. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

199. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

200. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

201. The compound of embodiment 1, wherein the compound is (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

202. The compound of embodiment 1, wherein the compound is (S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

203. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

204. The compound of embodiment 1, wherein the compound is (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

205. The compound of embodiment 1, wherein the compound is (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

206. The compound of embodiment 1, wherein the compound is (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

207. The compound of embodiment 1, wherein the compound is (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

208. The compound of embodiment 1, wherein the compound is (S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

209. A pharmaceutical composition, comprising a compound of any one of embodiments 1-208; and a pharmaceutically acceptable excipient.

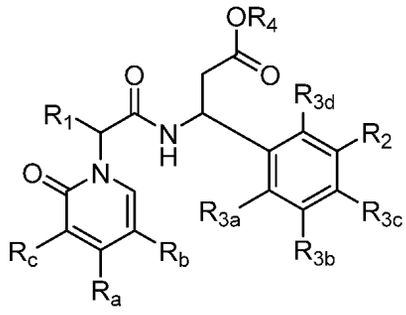
210. A method of inhibiting $\alpha_4\beta_7$ integrin in a cell, comprising contacting the cell with a compound of any one of embodiments 1-208 under conditions effective to reduce the adhesion of the cell to MAdCAM-1.

211. A method of reducing the adhesion of a cell comprising an $\alpha_4\beta_7$ integrin to MAdCAM-1, the method comprising contacting the cell with a compound of any one of

embodiments 1-208 under conditions effective to reduce the adhesion of the cell to MAdCAM-1.

212. A method of treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of embodiments 1-208

In some embodiments, the following compound of Formula (I):



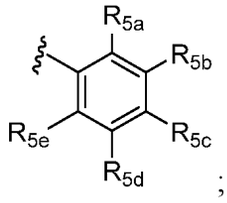
(I)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is -$(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, $(C_1\text{-}C_5)$-alkyl, $(C_3\text{-}C_6)$-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN,

halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c}, and R_{3d} are H;

R_4 is H;

R_{5a}, and R_{5e} are independently methyl;

R_{5b}, and R_{5c} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

R_{5d} is H; and

wherein the compound of Formula (I) is selected from the group consisting of:

a. (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

b. (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid;

c. (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

d. (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

e. (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

f. (S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

g. (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

h. (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

i. (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

j. (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid; and

k. (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-

1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

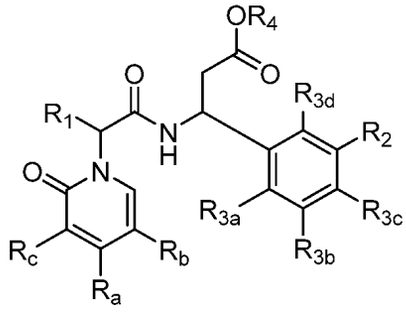
In some embodiments, wherein the compound is (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid, or a pharmaceutically acceptable salt thereof.

In some embodiments, a pharmaceutical composition comprising a compound of Formula (I) as the active pharmaceutical ingredient:



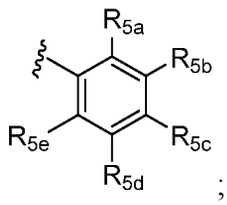
(I)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is -$(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted $(C_1\text{-}C_5)$-alkyl, substituted or unsubstituted $(C_3\text{-}C_6)$-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -$(C_1\text{-}C_4)$-alkoxy, $-OCF_3$, and substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c}, and R_{3d} are H;

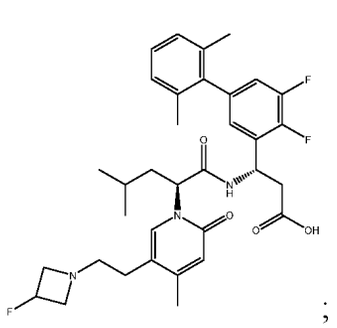
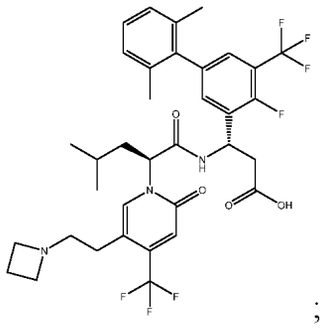
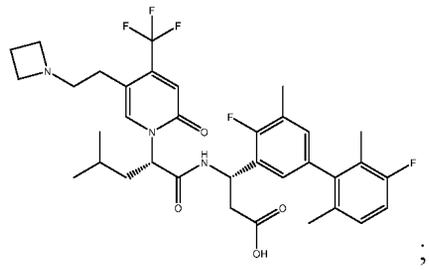
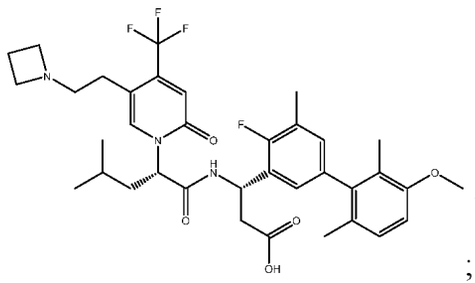
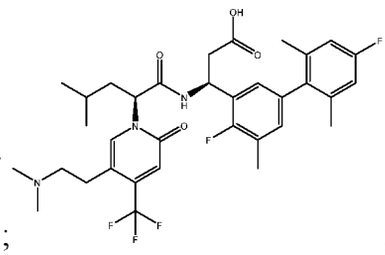
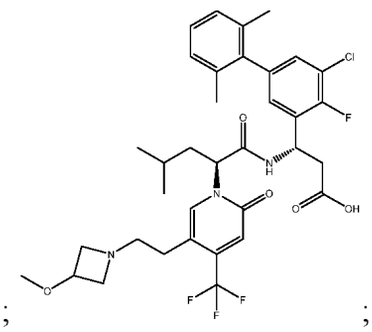
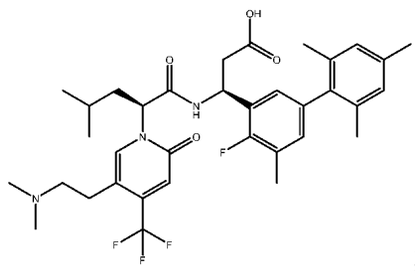
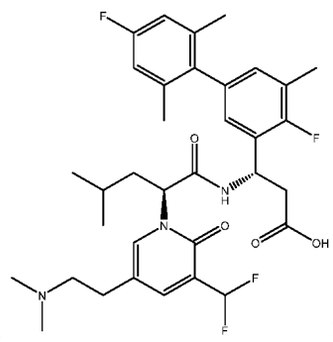
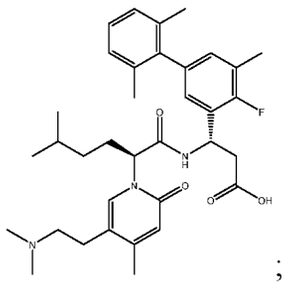
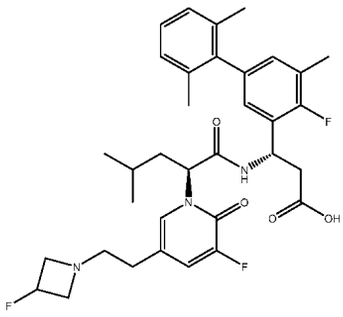
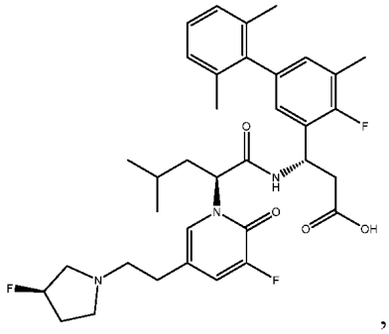
R_4 is H;

R_{5a}, and R_{5e} are independently methyl;

R_{5b}, and R_{5c} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

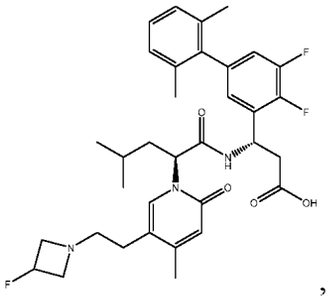
R_{5d} is H; and

wherein the compound of Formula (I) is selected from the group consisting of:


;

;

;

;

;

;

;

;

;

, and

,

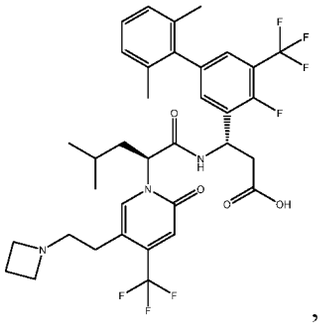
or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



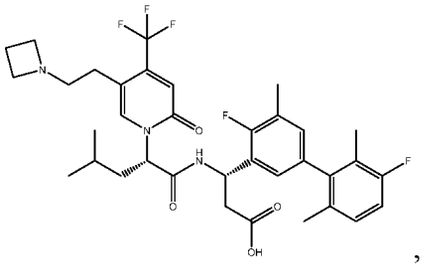
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



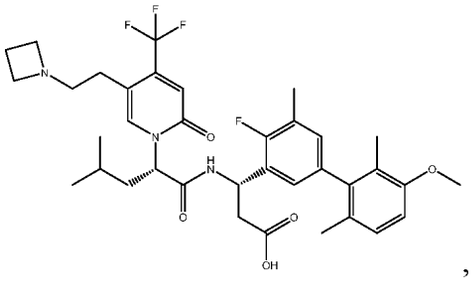
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



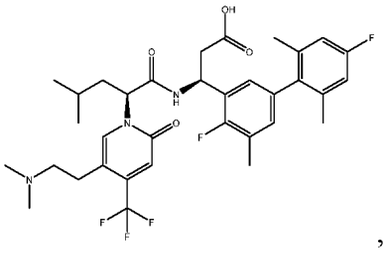
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



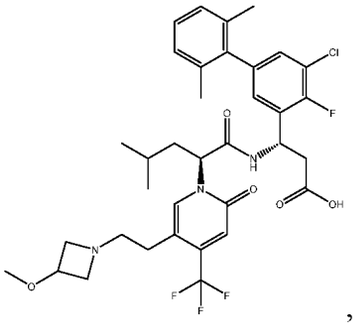
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



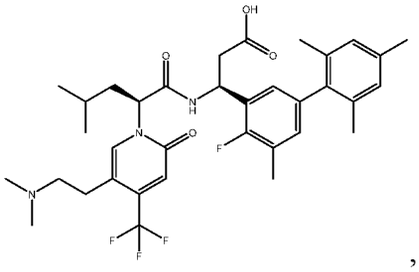
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



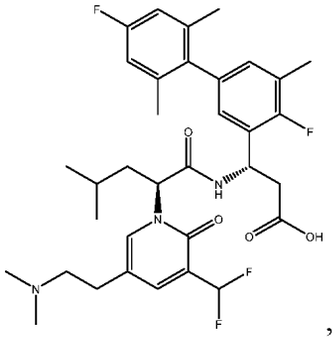
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



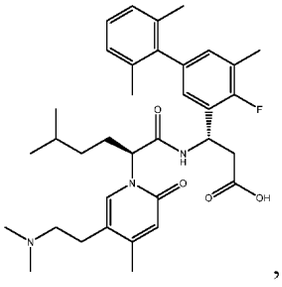
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



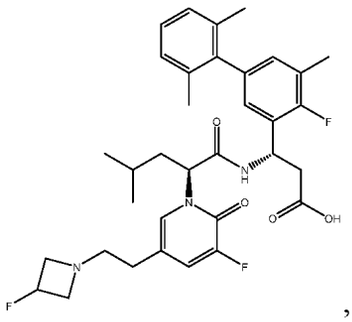
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



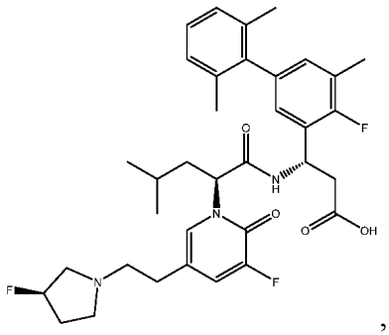
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



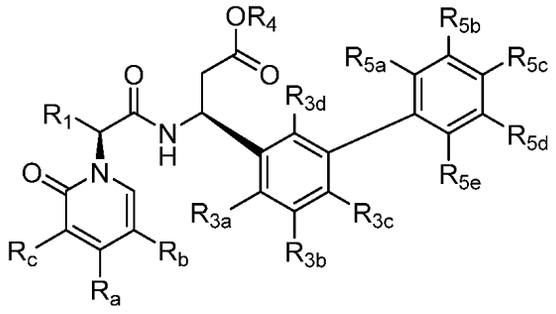
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



, or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound of Formula (Ia):



(Ia),

wherein:

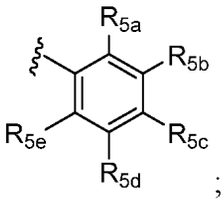
R_a, is CF_3;

R_b is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_c is H;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl;

R_2 is 

;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, $-OCF_3$, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is H;

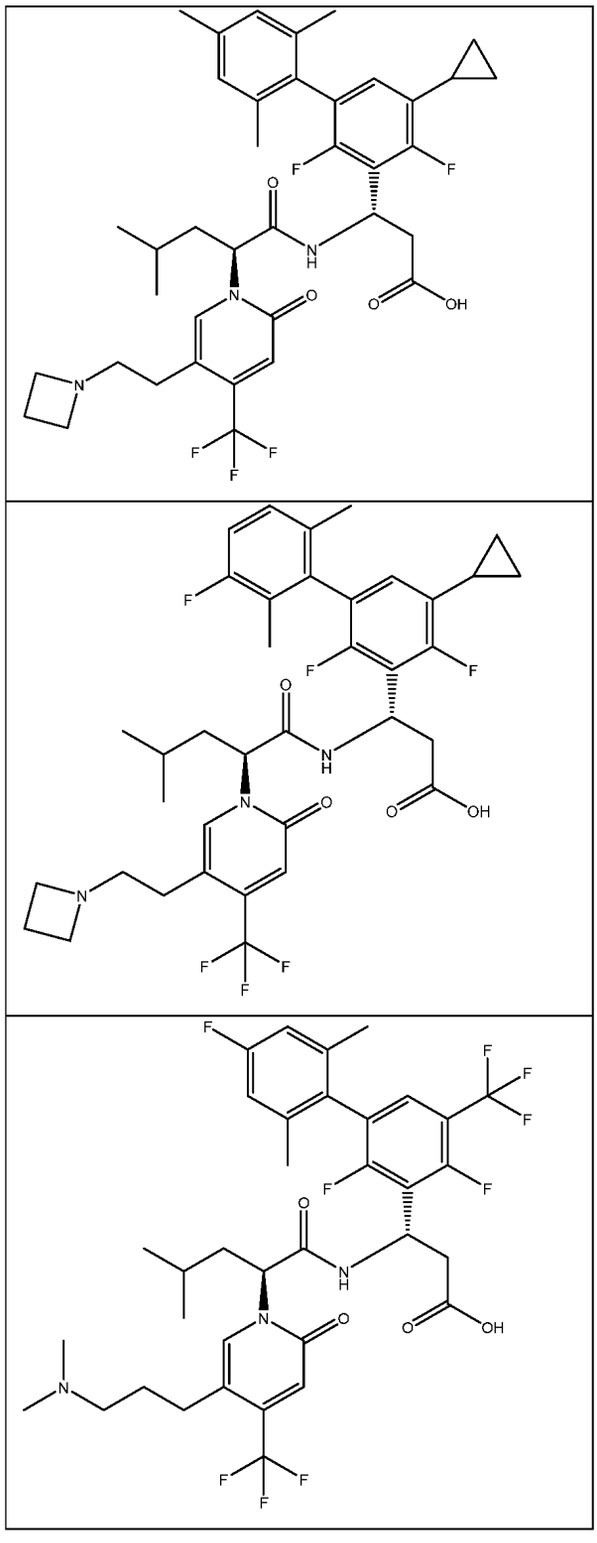
R_{3d} is halide;

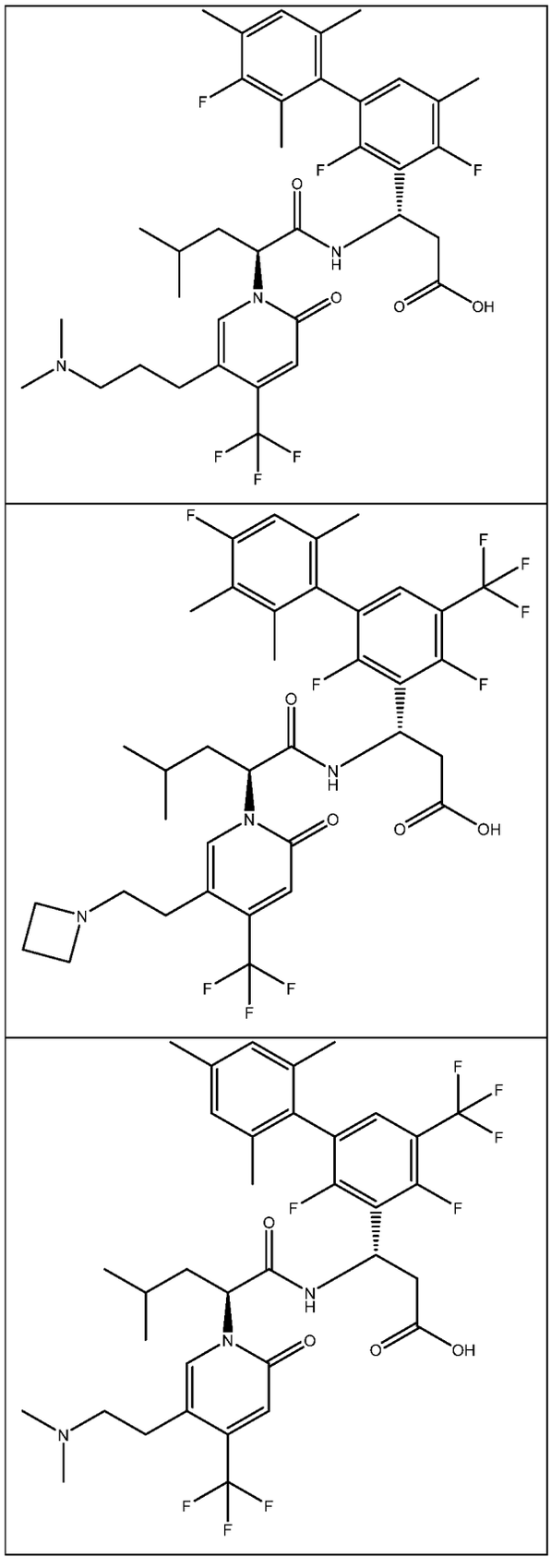
R_4 is H;

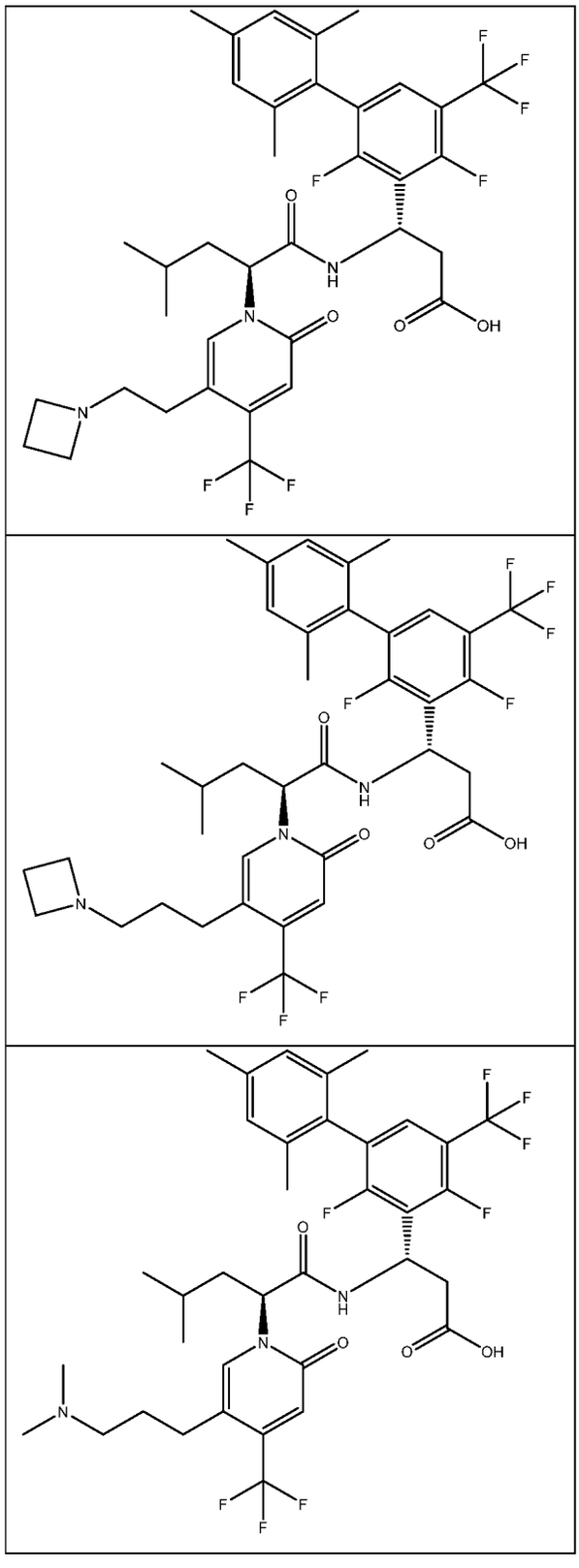
R_{5a}, and R_{5e} are each independently selected from (C_1-C_5)-alkyl; and

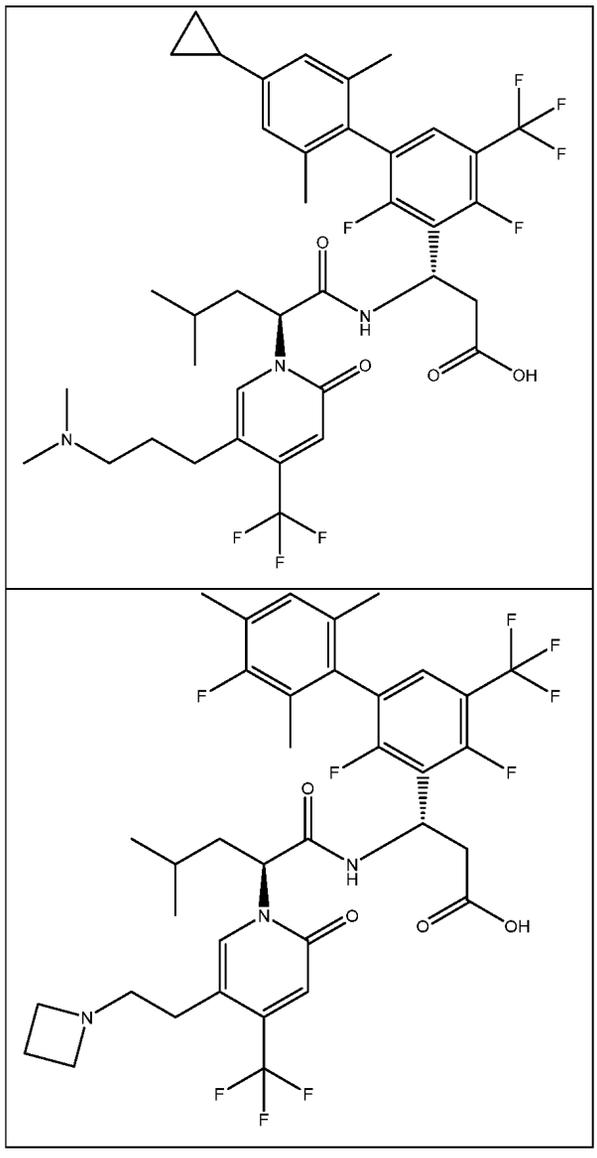
R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

wherein the compound of Formula (I) is selected from the group consisting of:

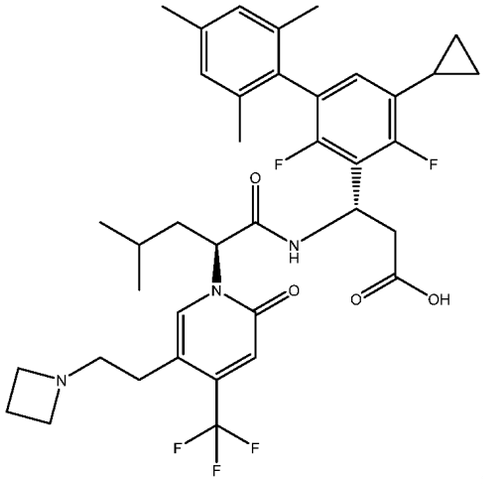






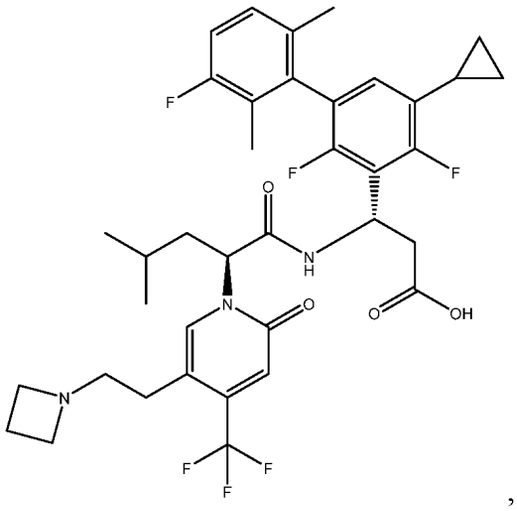


In some embodiments, wherein the compound is



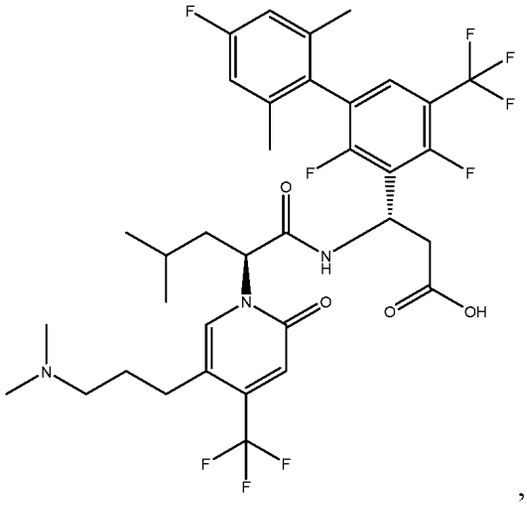
, or a pharmaceutically acceptable salt thereof.

In some embodiments,, wherein the compound is



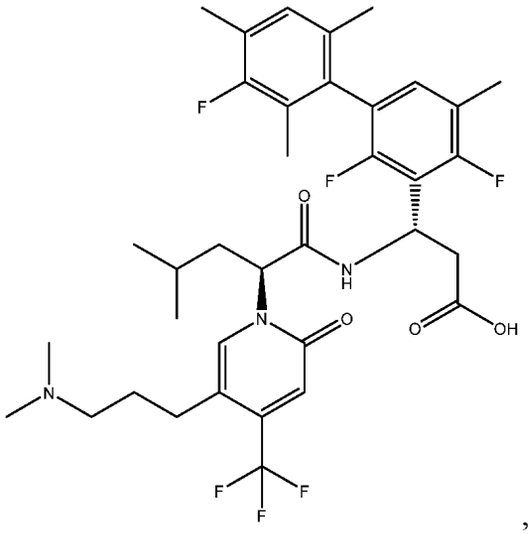
, or a pharmaceutically acceptable salt thereof.

In some embodiments,, wherein the compound is



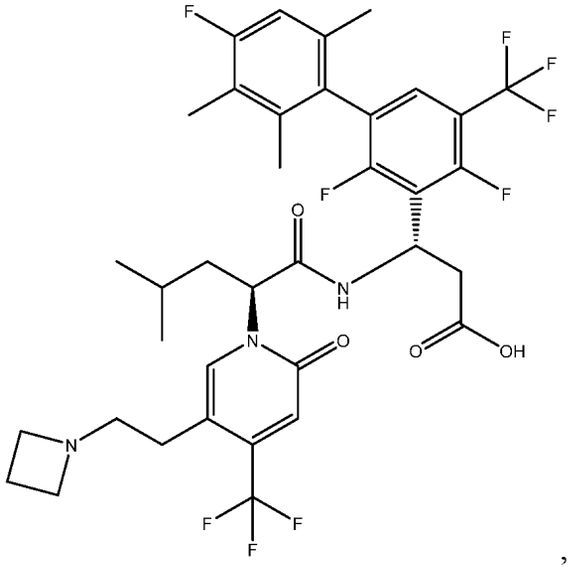
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



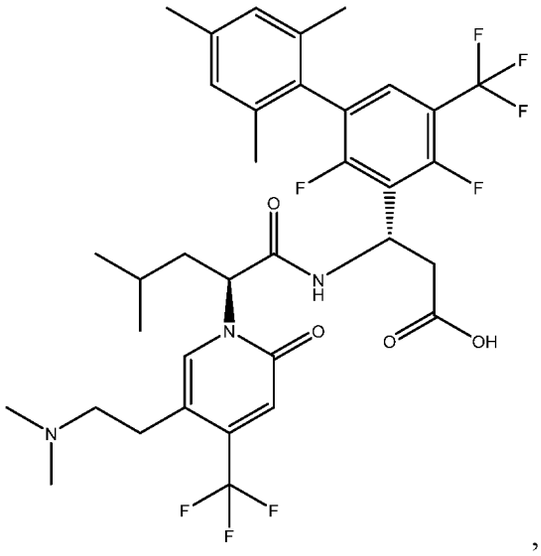
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



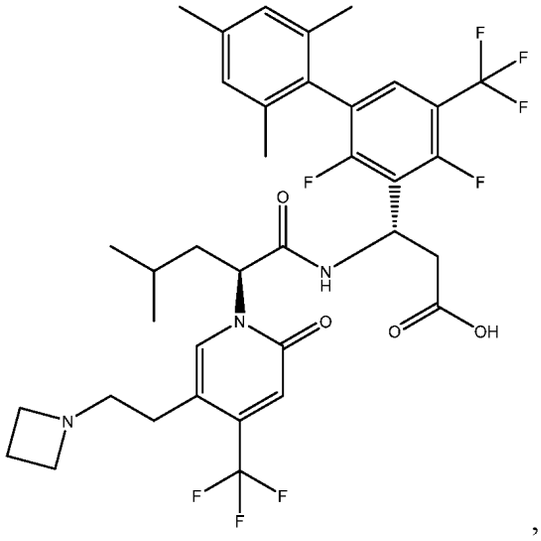
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



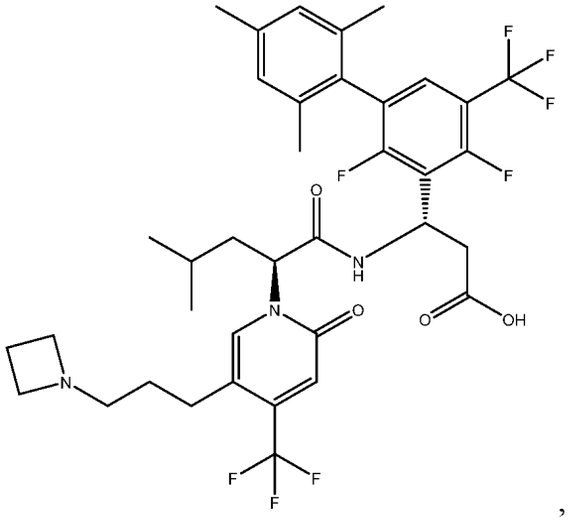
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



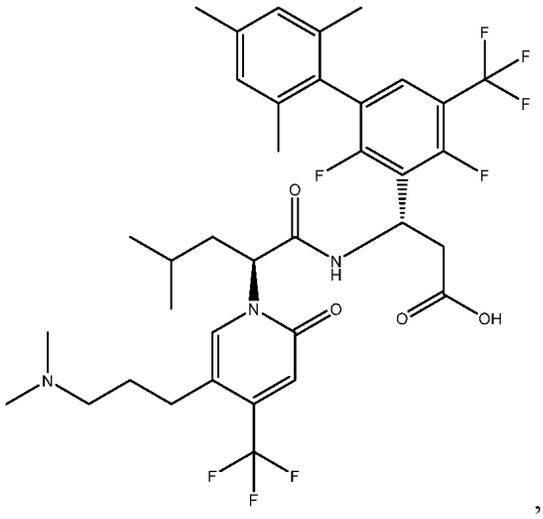
, or a pharmaceutically acceptable salt thereof.

The compound of claim 25, wherein the compound is



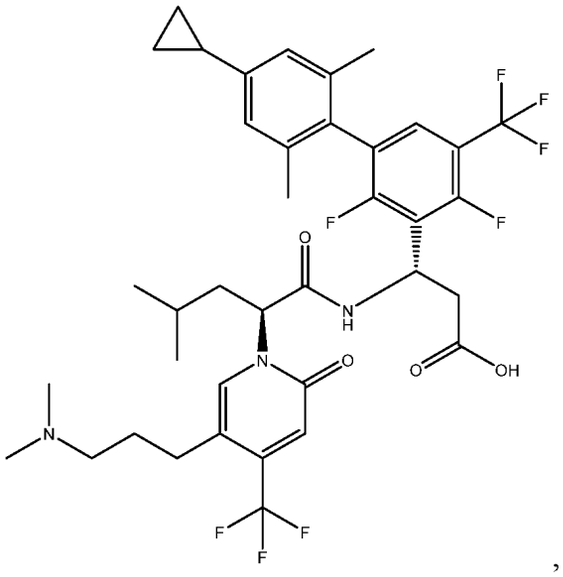
, or a pharmaceutically acceptable salt thereof.

The compound of claim 25, wherein the compound is



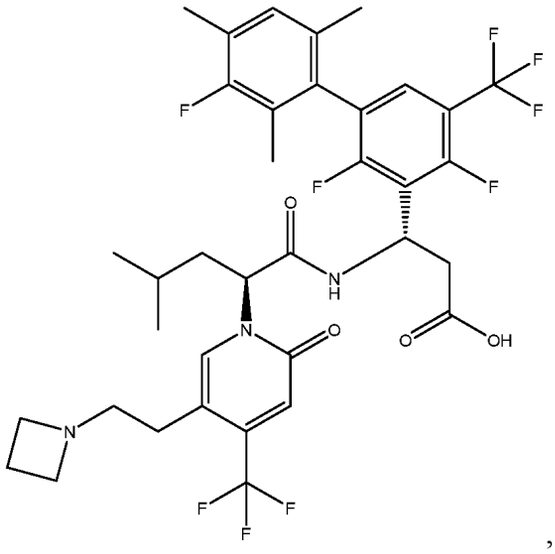
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is



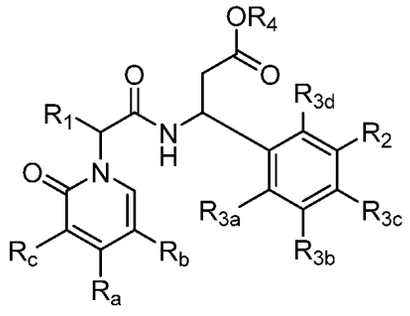
, or a pharmaceutically acceptable salt thereof.

In some embodiments, wherein the compound is

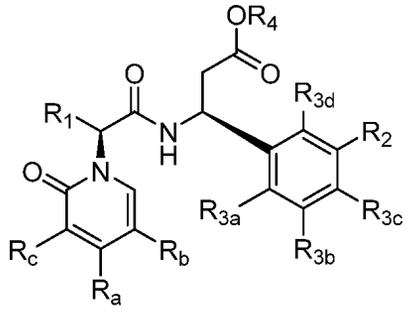


, or a pharmaceutically acceptable salt thereof.

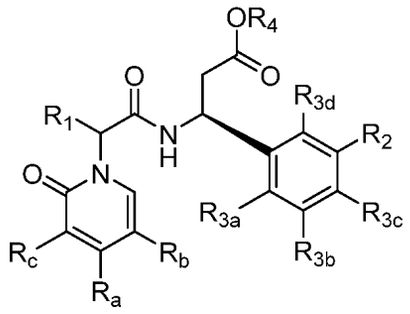
In some embodiments, a pharmaceutical composition comprising a compound of the present application or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient. In some embodiments, the the invention relates to a compound of Formula (I), Formula (Ia), or Formula (Ib):



(I)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

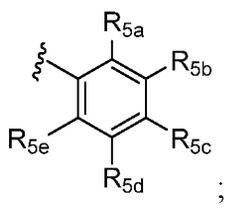
wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CN, - OCF_3, substituted or unsubstituted $(C_1$-$C_5)$-alkyl, $(C_1$-$C_5)$-alkoxy, $-CH_2CF_3$, and substituted or unsubstituted $-(C_1$-$C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is $-(C_1$-$C_5)$alkylene-N-$(R_x)(R_y)$,

wherein the substituted $(C_1$-$C_5)$-alkyl is substituted with halide, amino, or $(C_1$-$C_4)$-alkylamino; and the substituted $-(C_1$-$C_5)$alkylene-N-$(R_x)(R_y)$ is substituted with halide or $(C_1$-$C_4)$-alkoxy;

R_x and R_y are independently selected from the group consisting of H and $(C_1$-$C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is $(C_1$-$C_6)$-alkyl, $(C_1$-$C_4)$-alkylene-$(C_3$-$C_6)$-cycloalkyl, or $(C_1$-$C_4)$-alkylene-$(C_1$-$C_4)$-alkoxy;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, $(C_1$-$C_5)$-alkyl, $(C_3$-$C_6)$-cycloalkyl, 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$,

-(C_1-C_4)-alkoxy, -OCF_3, and (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is selected from the group consisting of H, (C_1-C_5)-alkyl, (C_3-C_6)-cycloalkyl, 3-6 membered heterocycloalkyl, hydroxyl, halide, CF_3, C(H)F_2, C(F)H_2, -(C_1-C_4)-alkoxy, -OCF_3 -CN, and (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_{3d} is selected from the group consisting of H, (C_1-C_5)-alkyl, hydroxyl, halide, and -(C_1-C_4)-alkoxy;

R_4 is H, or (C_1-C_4)-alkyl;

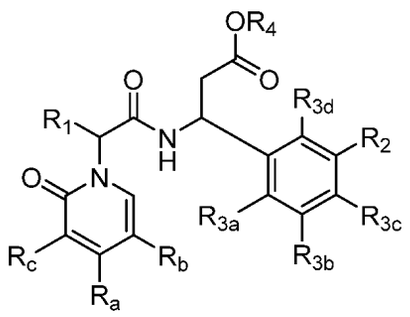
R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, C(H)F_2, C(F)H_2, -CH_2CF_3, (C_3-C_6)-cycloalkyl, (C_1-C_5)-alkyl, 3-6 membered heterocycloalkyl hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, C(H)F_2, C(F)H_2, -CH_2CF_3, (C_1-C_5)-alkyl, (C_3-C_6)-cycloalkyl, 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy.

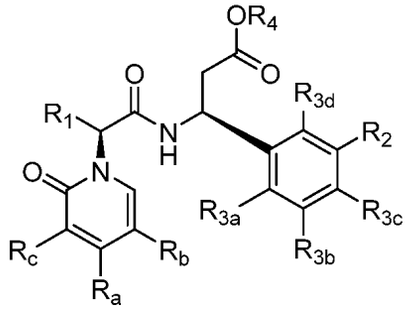
In one embodiment of the above Formula (Ib), the compound is not a compound recited in Figure 1.

In one embodiment of the above Formula (Ib), the compound is a compound recited in Figure 2 and/or 3.

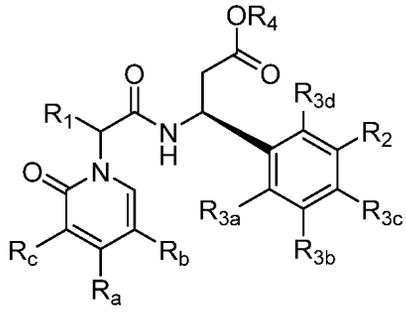
In some embodiments, the the invention relates to a compound of Formula (I), Formula (Ia), or Formula (Ib):



(I)



(Ia)



(Ib)

or a pharmaceutically acceptable salt thereof;

wherein

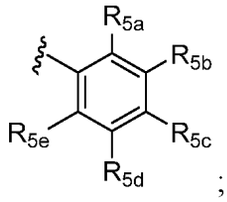
R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CN, - OCF_3, substituted or unsubstituted (C_1-C_5)-alkyl, (C_1-C_5)-alkoxy, -CH_2CF_3, and substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that at least one of R_a, R_b, and R_c is –(C_1-C_5)alkylene-N-(R_x)(R_y),

wherein the substituted (C_1-C_5)-alkyl is substituted with halide, amino, or (C_1-C_4)-alkylamino; and the substituted –(C_1-C_5)alkylene-N-(R_x)(R_y) is substituted with halide, (C_1-C_5)-alkyl, (C_1-C_5)-alkyl-OCH_3, (C_1-C_4)-haloalkyl, (C_3-C_6)-cycloalkyl, (C_1- C_4)-alkoxy, or heterocyclyl;

R_x and R_y are independently selected from the group consisting of H and (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl, (C_1-C_4)-alkylene-(C_3-C_6)-cycloalkyl, or (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy,

wherein the substituted (C_1-C_6)-alkyl is substituted with halide or (C_3-C_6)-cycloalkyl;

R_2 is 

;

R_{3a} and R_{3b} are independently selected from the group consisting (C_1-C_5)-alkyl, (C_3-C_6)-cycloalkyl, 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is selected from the group consisting of H, (C_1-C_5)-alkyl, (C_3-C_6)-cycloalkyl, 3-6 membered heterocycloalkyl, hydroxyl, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3 -CN, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy;

R_{3d} is selected from the group consisting of H, (C_1-C_5)-alkyl, hydroxyl, halide, and -(C_1-C_4)-alkoxy;

R_4 is H, or (C_1-C_4)-alkyl;

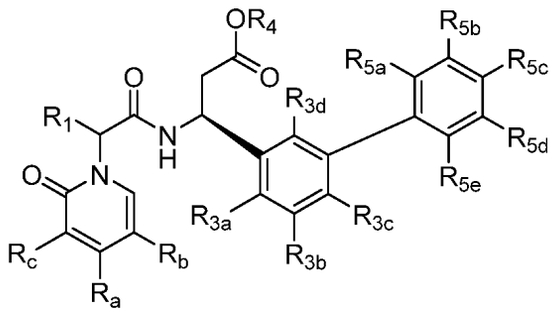
R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CH_2CF_3, (C_3-C_6)-cycloalkyl (C_1-C_5)-alkyl, 3-6 membered heterocycloalkyl hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -CH_2CF_3, (C_1-C_5)-alkyl, (C_3-C_6)-cycloalkyl, 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy.

In one embodiment of the above Formula (Ib), the compound is not a compound recited in Figure 1.

In one embodiment of the above Formula (Ib), the compound is a compound recited in Figure 2 and/or 3.

In some embodiments, a compound of Formula (I) can be a compound of Formula (Ib),



(Ib),

wherein

R_a is selected from the group consisting of hydrogen, and (C_1-C_5)-alkyl optionally substituted with halide;

R_b is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring optionally substituted with halide or (C_1-C_4)-alkoxy;

R_c are is selected from the group consisting of hydrogen and (C_1-C_5)-alkyl optionally substituted with halide;

R_1 is (C_1-C_6)-alkyl;

R_{3a} is halide;

R_{3b} is selected from the group consisting of (C_1-C_5)-alkyl optionally substituted with halide, and (C_3-C_6)-cycloalkyl;

R_{3c} is hydrogen;

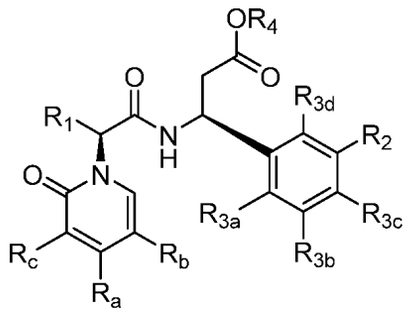
R_{3d} is selected from the group consisting of H and halide;

R_4 is hydrogen;

R_{5a}, and R_{5e} are each (C_1-C_5)-alkyl; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, (C_1-C_5)-alkyl optionally substituted with halide (e.g., CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$), (C_3-C_6)-cycloalkyl, 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy.

In some embodiments, a compound of Formula (I) can be a compound of Formula (Ia),



(Ia)

wherein

R_a is selected from the group consisting of hydrogen, and methyl optionally substituted with halide;

R_b is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of methyl and ethyl; or R_x and R_y taken together with the N to which they are attached form a 4-5 membered ring optionally substituted with F or methoxy;

R_c are is selected from the group consisting of hydrogen and methyl optionally substituted with halide;

R_1 is selected from the group consisting of isobutyl and isopentyl;

R_{3a} is F;

R_{3b} is selected from the group consisting of (C_1-C_5)-alkyl optionally substituted with F, and (C_3-C_6)-cycloalkyl;

R_{3c} is hydrogen;

R_{3d} is selected from the group consisting of H and F;

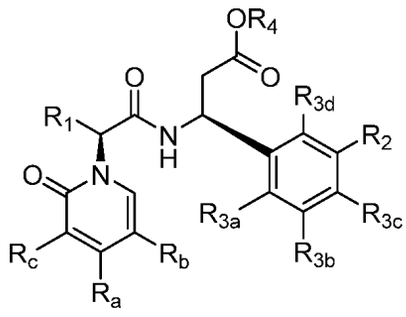
R_4 is hydrogen;

R_{5a}, and R_{5e} are each methyl;

R_{5b} and R_{5d} are independently selected from the group consisting of H, F, methyl and methoxy; and

R_{5c} is selected from the group consisting of F, methyl and cyclopropyl.

In some embodiments, a compound of Formula (I) can be a compound of Formula (Ia),



(Ia)

wherein

R_a is selected from the group consisting of hydrogen, and methyl optionally substituted with halide;

R_b is –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are methyl; or R_x and R_y taken together with the N to which they are attached form a 4-5 membered ring optionally substituted with F or methoxy;

R_c are is selected from the group consisting of hydrogen and methyl optionally substituted with halide;

R_1 is selected from the group consisting of isobutyl and isopentyl;

R_{3a} is F;

R_{3b} is selected from the group consisting of (C_1-C_5)-alkyl optionally substituted with F, and (C_3-C_6)-cycloalkyl;

R_{3c} is hydrogen;

R_{3d} is F;

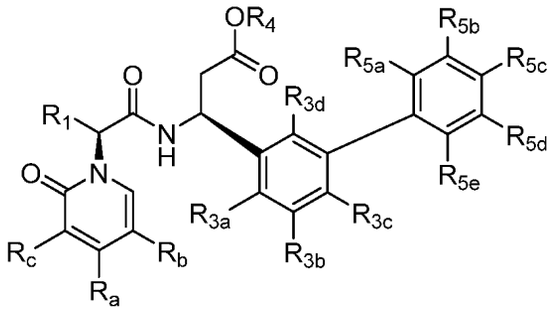
R_4 is hydrogen;

R_{5a}, and R_{5e} are each methyl;

R_{5b} and R_{5d} are independently selected from the group consisting of H, F, methyl and methoxy; and

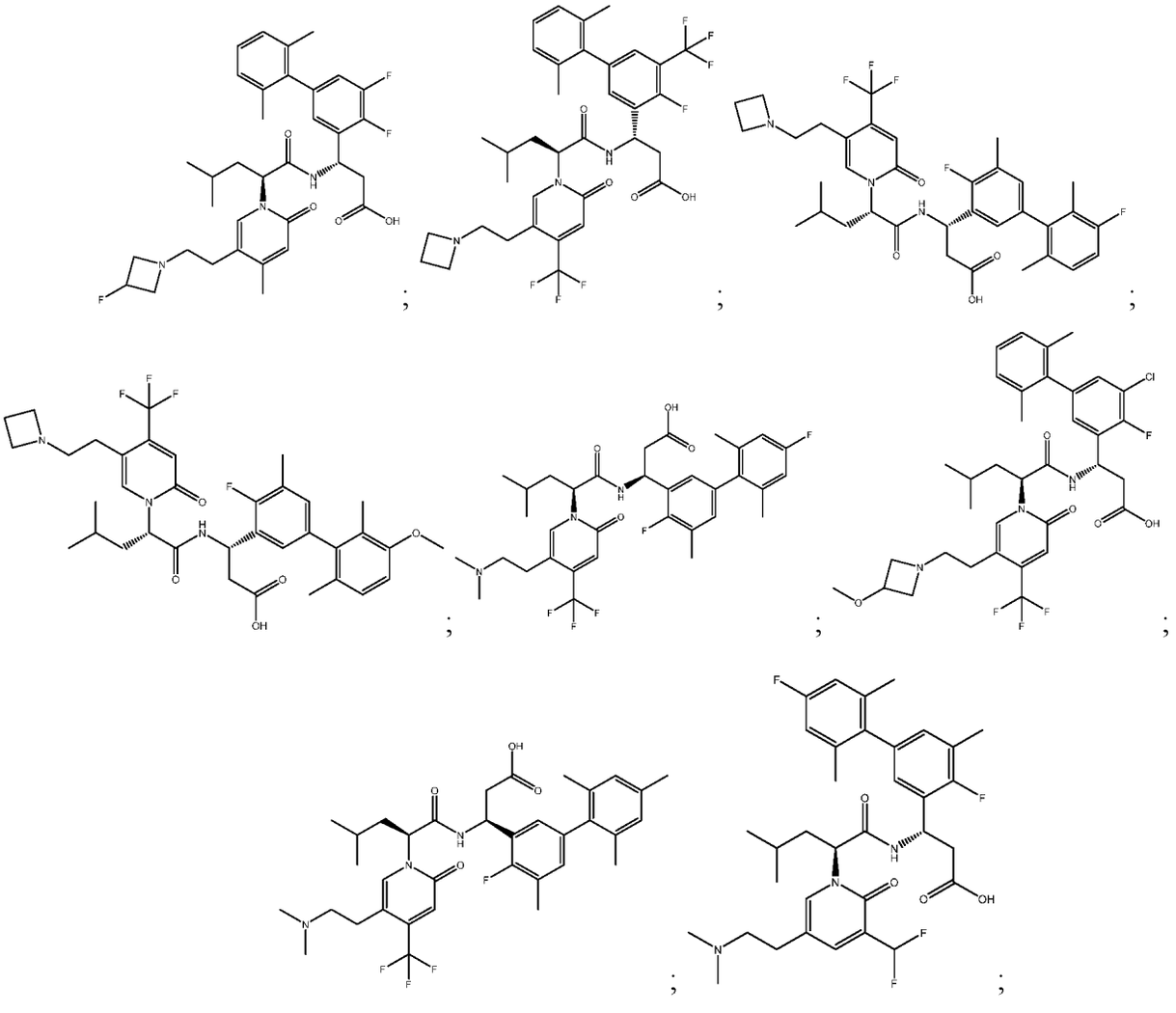
R_{5c} is selected from the group consisting of F, methyl and cyclopropyl.

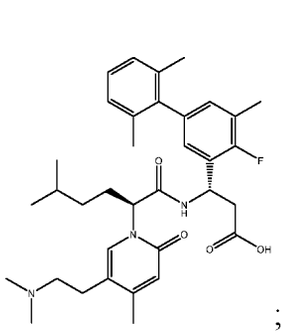
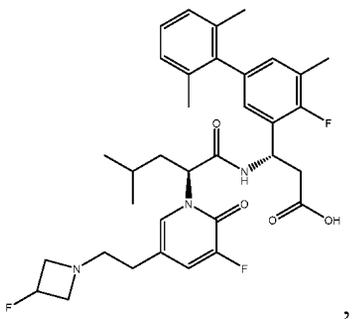
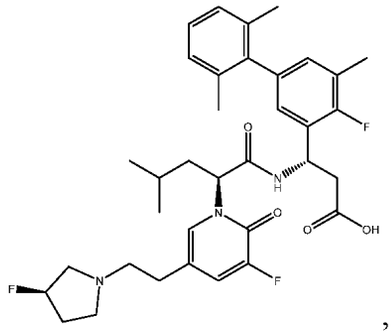
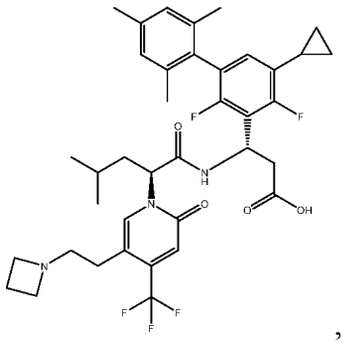
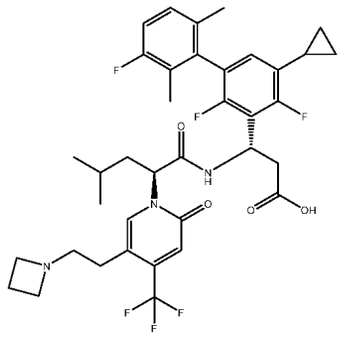
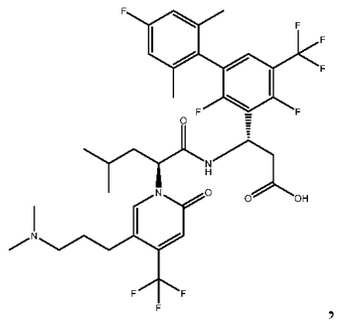
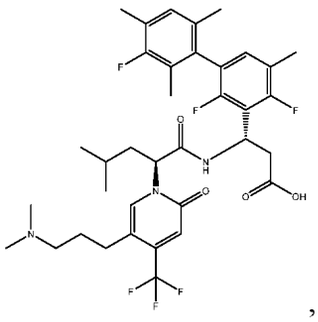
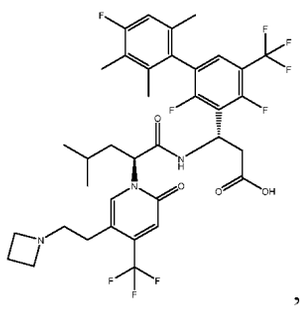
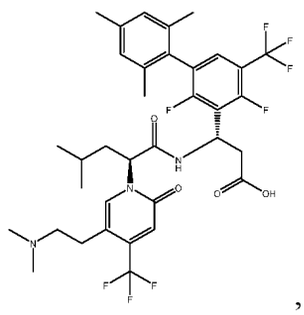
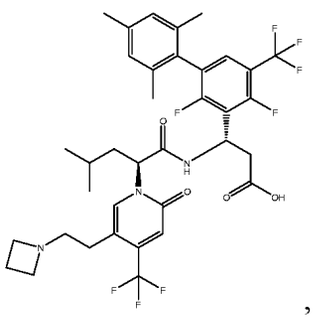
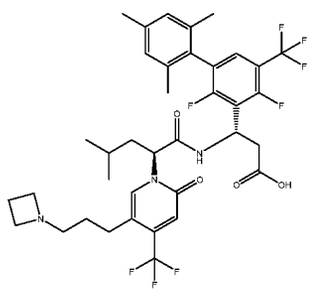
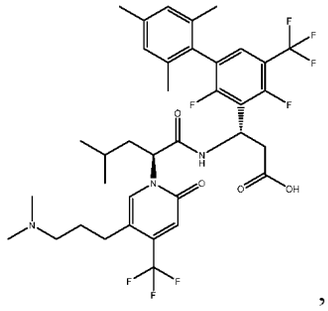
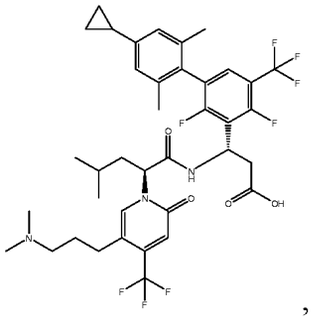
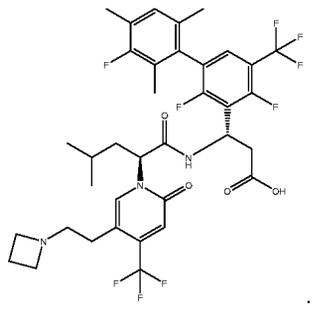
In some embodiments, a compound of Formula (I) can be a compound of Formula (Ia):



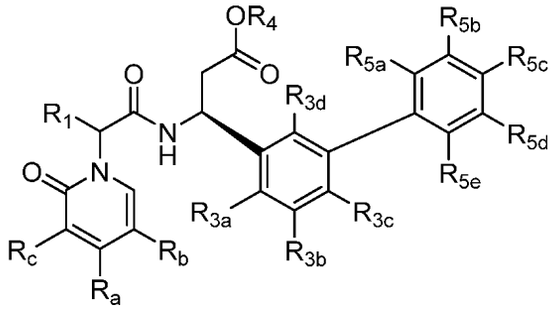
(Ia)

or a pharmaceutically acceptable salt thereof, wherein R_a, R_b, R_c, R_1, R_{3a}, R_{3b}, R_{3c}, R_{3d}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, R_{5e}, and R_4 in Formula (Ia) are each independently defined as above with respect to Formula (I), and provided that the compound of Formula (Ia) is not a compound selected from the group consisting of:



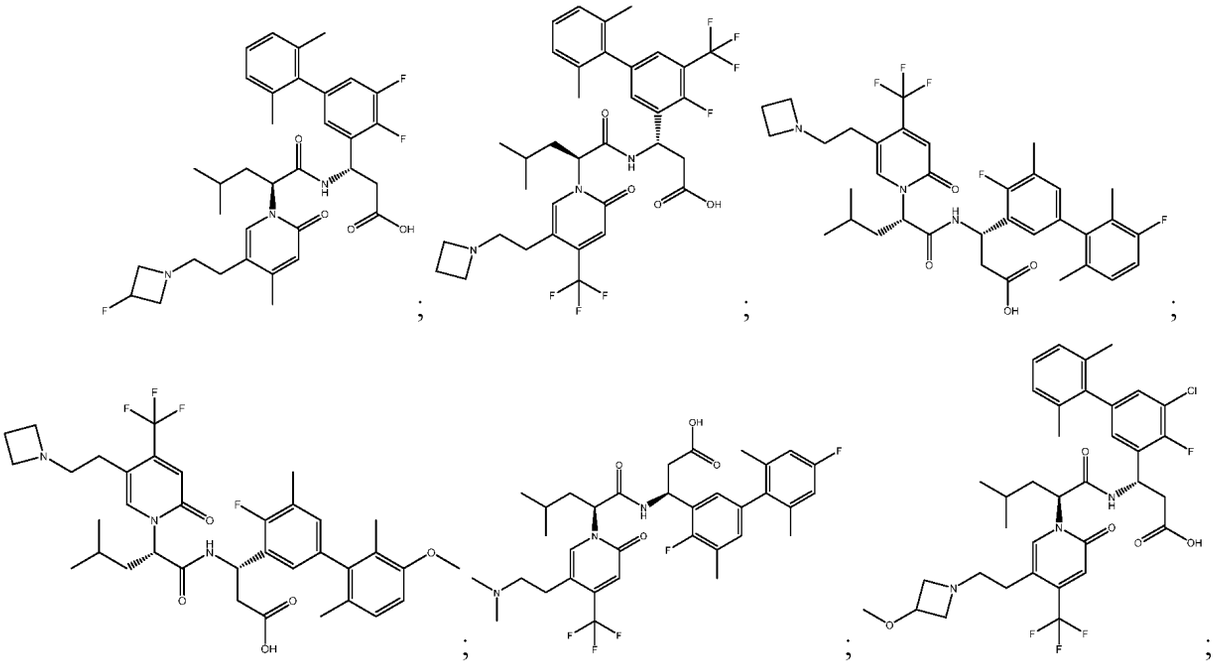

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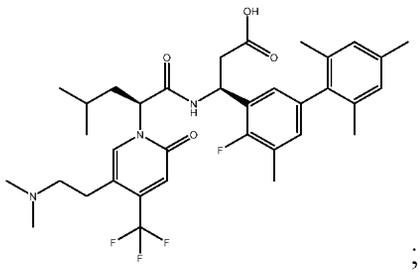
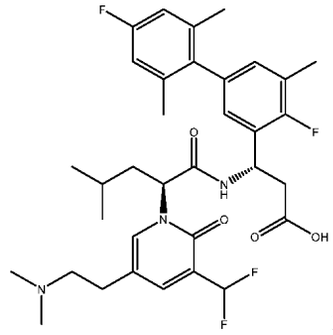
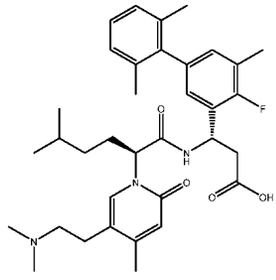
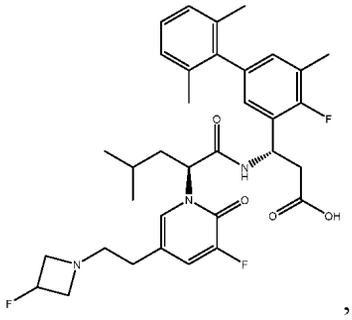
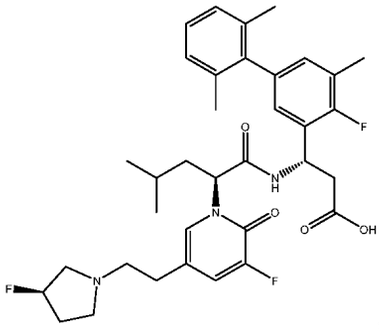
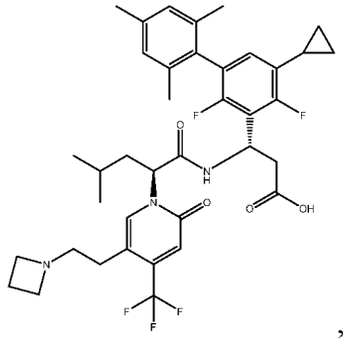
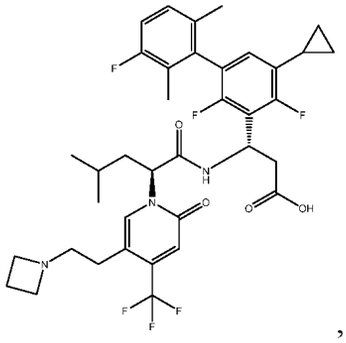
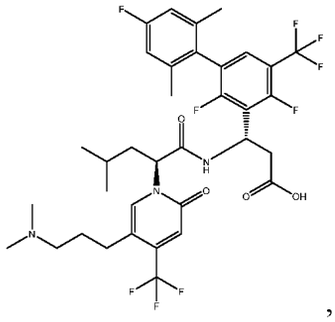
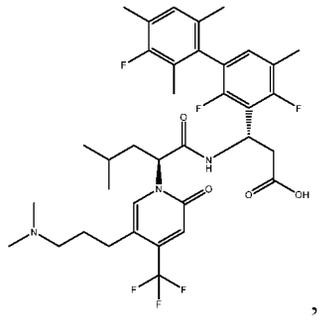
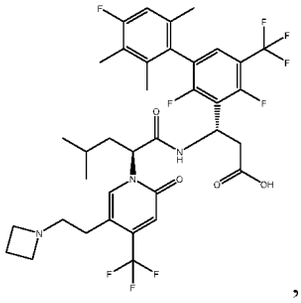
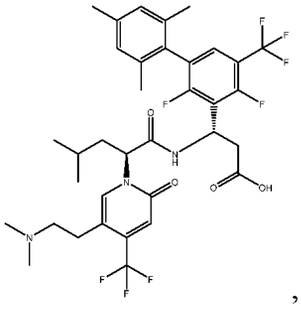
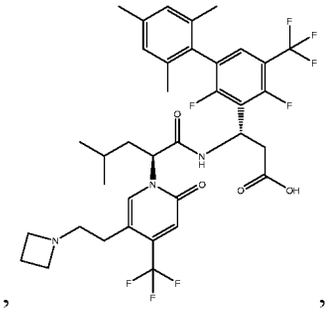
In some embodiments, a compound of Formula (I) can be a compound of Formula (Ib):



(Ib)

or a pharmaceutically acceptable salt thereof, wherein R_a, R_b, R_c, R_1, R_{3a}, R_{3b}, R_{3c}, R_{3d}, R_{5a}, R_{5b}, R_{5c}, R_{5d}, R_{5e}, and R_4 in Formula (Ia) are each independently defined as above with respect to Formula (I), and provided that the compound of Formula (Ia) is not a compound selected from the group consisting of:

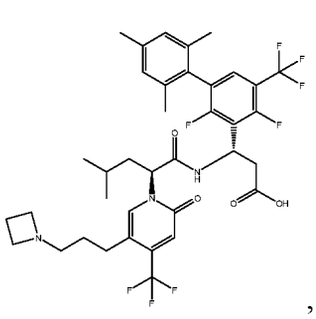
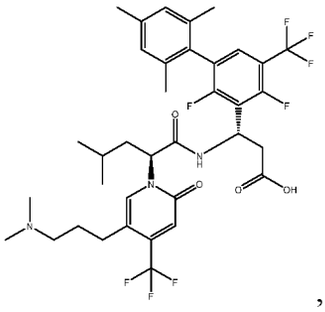
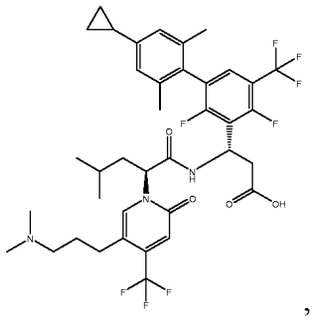
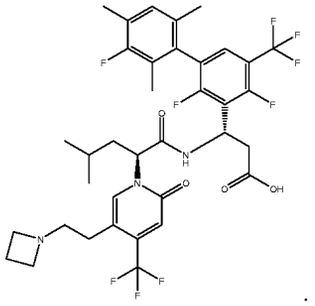



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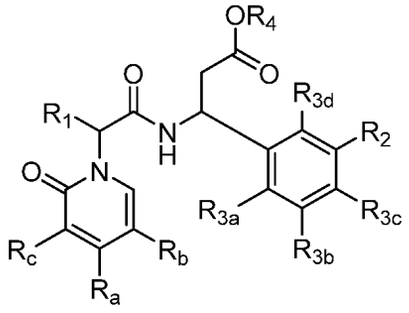
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In some embodiments, a compound can be a compound of Formula (I)



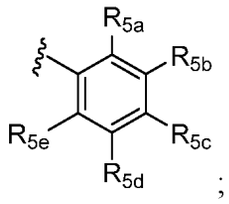
(I)

wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is -$(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl;

R_2 is 

;

R_{3a} and R_{3b} are independently selected from the group consisting of H, (C_1-C_5)-alkyl, (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, -OCF_3, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c}, and R_{3d} are H;

R_4 is H;

R_{5a}, and R_{5e} are independently methyl;

R_{5b}, and R_{5c} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

R_{5d} is H; and

provided the compound of Formula (I) is not a compound selected from the group consisting of:

a. (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

b. (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid;

c. (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

d. (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

e. (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

f. (S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

g. (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

h. (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

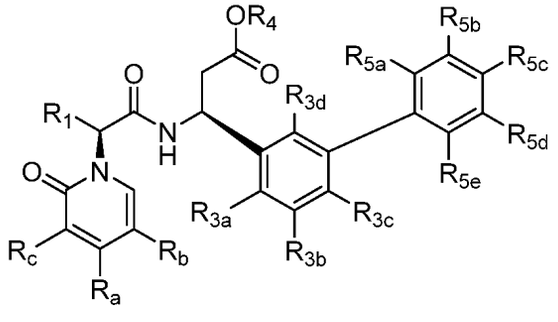
i. (S)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid;

j. (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid; and

k. (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid;

or a pharmaceutically acceptable salt thereof.

In some embodiments, a compound can be a compound of Formula (Ia)



(Ia),

wherein:

R_a, is CF_3;

R_b is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_c is H;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, $-OCF_3$, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is H;

R_{3d} is halide;

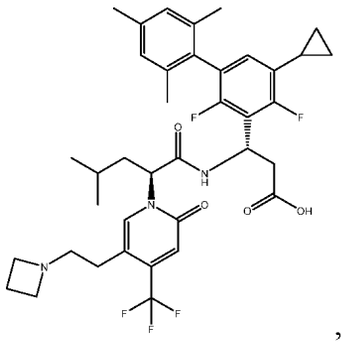
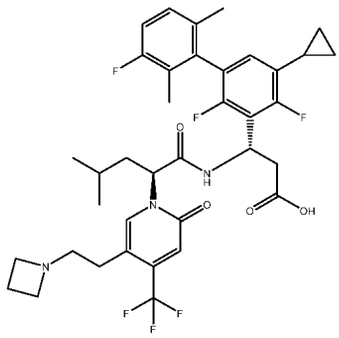
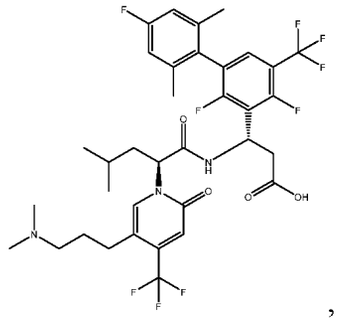
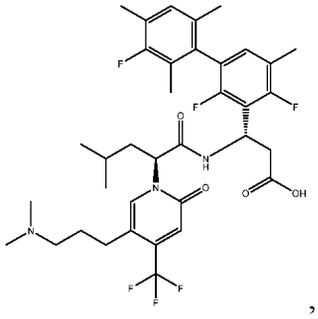
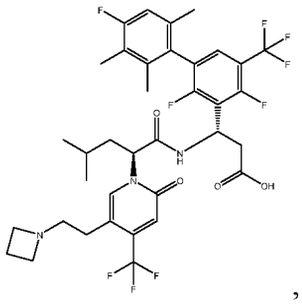
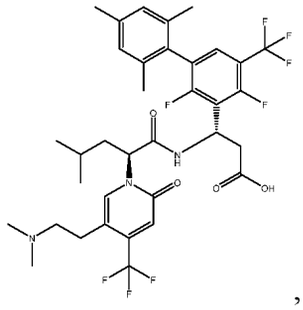
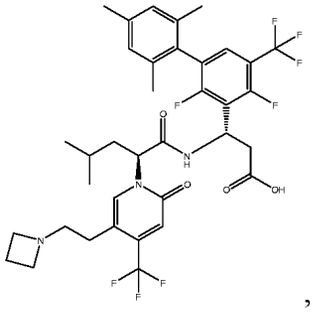
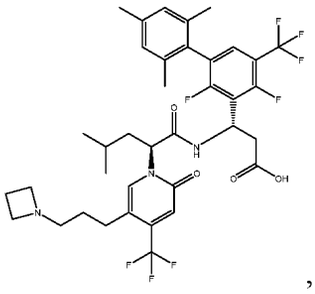
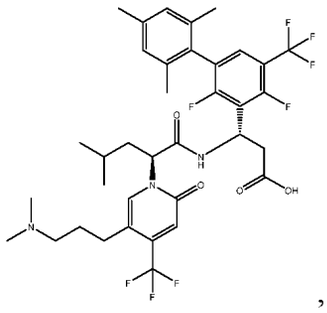
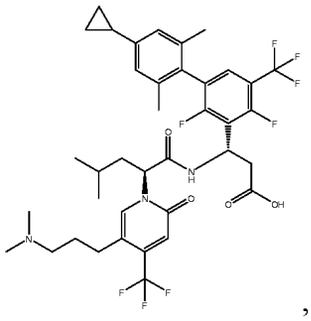
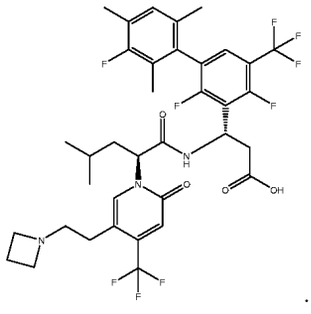
R_4 is H;

R_{5a}, and R_{5e} are each independently selected from (C_1-C_5)-alkyl; and

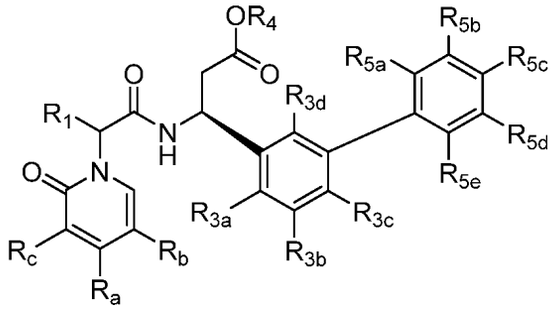
R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof;

provided the compound of Formula (Ia) is not selected from the group consisting of:


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In some embodiments, a compound can be a compound of Formula (Ib)



(Ib),

wherein:

R_a, is CF_3;

R_b is substituted or unsubstituted –(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_c is H;

R_1 is substituted or unsubstituted (C_1-C_6)-alkyl;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, -(C_1-C_4)-alkoxy, $-OCF_3$, and substituted or unsubstituted (C_1-C_4)-alkylene-(C_1-C_4)-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is H;

R_{3d} is halide;

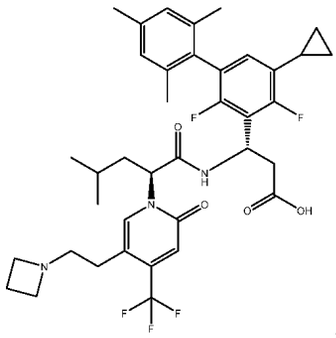
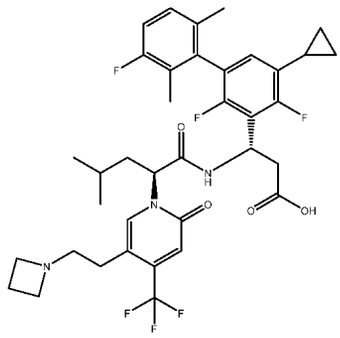
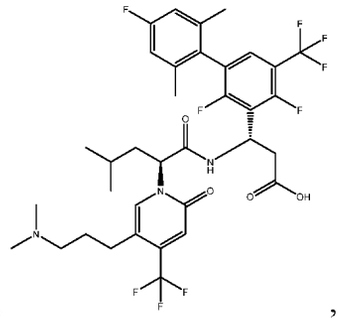
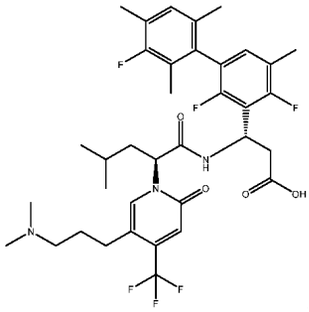
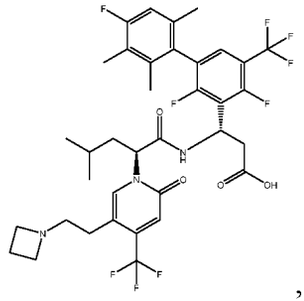
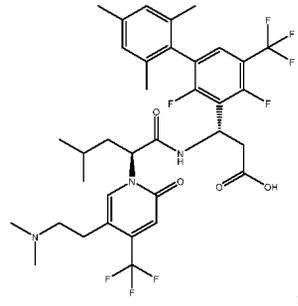
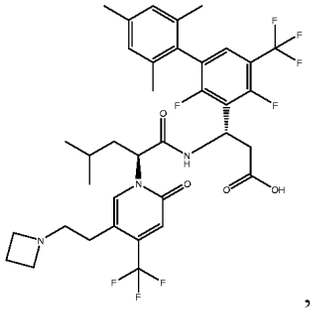
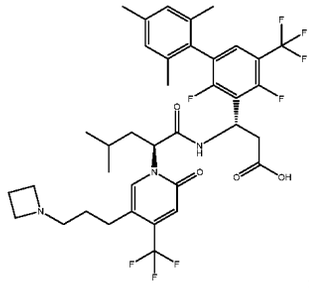
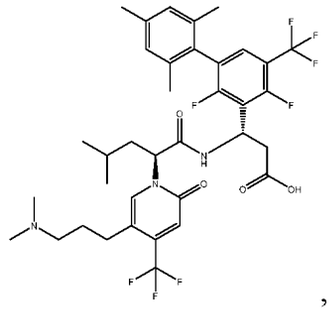
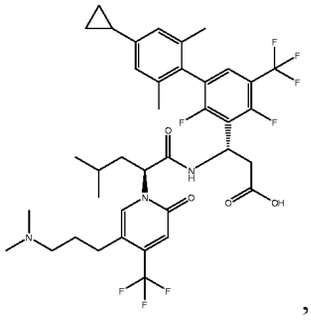
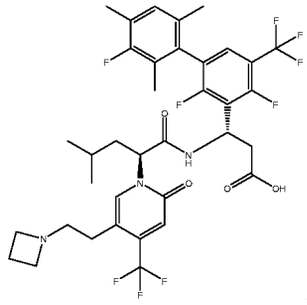
R_4 is H;

R_{5a}, and R_{5e} are each independently selected from (C_1-C_5)-alkyl; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-CH_2CF_3$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

or a pharmaceutically acceptable salt thereof;

provided the compound of Formula (Ib) is not selected from the group consisting of:


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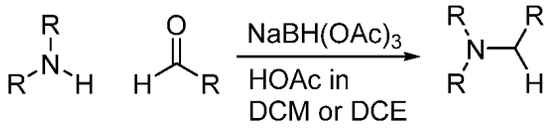
Example 1. General Schemes for the synthesis of α4β7 inhibitors

β-amino acid synthesis

The synthesis of β-amino acids can be achieved using well known procedures described in the literature, such as but not limited to "Enantioselective Synthesis of β-Amino Acids,"

Second Edition, Editors: Eusebio Juaristi, Vadim A. Soloshonok, First published:27 January 2005, John Wiley & Sons, Inc.; Ellman et. Al Acc. Chem. Res.2002. 35, 984-995; Franklin A. Davis and Bang-Chi Chen Chem. Soc. Rev., 1998, 27, 13-18; Jacobsen, M. F.; Skrydstrup, T. J. Org. Chem. 2003, 68, 7122; Tang, T. P.; Ellman, J. A. J. Org. Chem. 2002, 67, 7819 ;and Tang, T. P.; Ellman, J. A. J. Org. Chem. 1999, 64, 12.

Reductive Aminations

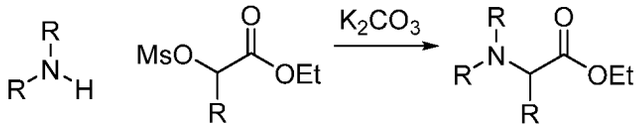


Procedure A: A mixture of amine (1 equiv.), aldehyde (1.2 equiv.) in DCM (1-2 mL/mmol amine) was stirred at room temperature for 30 min. Then $NaBH(OAc)_3$ (1.5 equiv.) was added portion-wise and stirred at room temperature overnight. The solvent was concentrated *in vacuo* and the residue was purified by silica gel chromatography to provide the desired amine.

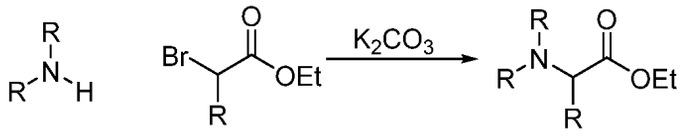
Procedure B: A mixture of aldehyde (1 equiv.), amine (1.05-2 equiv.) in DCE (3-4 mL/mmol of aldehyde) was stirred at room temperature for 10-30 mins. Then $NaBH(OAc)_3$ (3-4 equiv.) was added portion-wise and stirred at room temperature 1-16 until complete by LC/MS. The solvent was concentrated *in vacuo* and the residue was purified by silica gel chromatography to provide the desired amine.

Procedure C: A mixture of aldehyde (1 equiv.), AcOH (1.2 equiv), amine (1.05-2 equiv.) in DCM (2-3 mL/mmol aldehyde) and MeOH (0.5 mL/mmol aldehyde) was stirred at room temperature for 15-30 mins Then $NaBH(OAc)_3$ (2 equiv.) was added portion-wise and stirred at room temperature 1-16 until complete by LC/MS. The solvent was concentrated *in vacuo* and the residue was purified by silica gel chromatography to provide the desired amine.

Alkylations

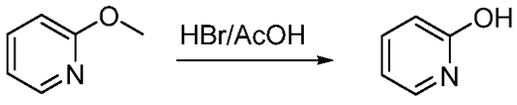


Procedure A: To a solution of amine (1 equiv.) in MeCN (3-4 mL/mmol amine) was added mesylate (1.5 equiv.) and K_2CO_3 (3 equiv.). The reaction mixture was stirred at 80°C for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC to give the alkylated product.



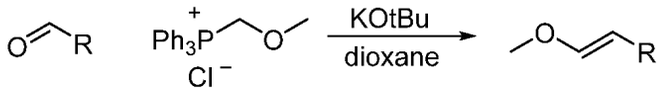
Procedure B: To a solution of amine (1 equiv.) in MeCN (3-4 mL/mmol amine) was added alkylbromide (2 equiv.) and K_2CO_3 (2 equiv.). The reaction mixture was stirred at 80°C for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC to give the alkylated product.

Phenol Deprotections



A mixture of methoxypyridine (1 equiv.) in 44% HBr/AcOH (10 mL/mmol of substrate) was heated at 55-75°C for 5-16 hours until complete by LCMS. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC to give the phenol product.

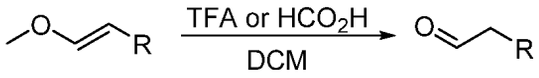
Wittig Reactions



Procedure A: A mixture of (methoxymethyl)triphenylphosphonium chloride (1.5 equiv.), t-BuOK (2.5 equiv.) in dioxane (2 mL/mmol phosphonium salt) was stirred at room temperature for 15 minutes. Then aldehyde (1 equiv.) in THF (1 mL/mmol aldehyde) was added. The mixture was stirred for 2-16 h at room temperature. The reaction mixture was worked up (diluted with water and extracted with EtOAc; combined extacts dried over Na_2SO_4, filtered and concentrated) and purified by silica gel chromatography to give the enol ether product.

Procedure B: A mixture of (methoxymethyl)triphenylphosphonium chloride (1.1equiv.), t-BuOK (2.5 equiv.) in THF (4 mL/mmol phosphonium salt) was stirred at 0°C for 1 h. Then aldehyde (1 equiv.) in THF (2 mL/mmol aldehyde) was added. The mixture was stirred for 16 h at room temperature. The reaction mixture was worked up (diluted with water and extracted with EtOAc; combined extacts dried over Na_2SO_4, filtered, and concentrated) and purified by silica gel chromatography to give the enol ether product.

Enol Ether to Aldehyde

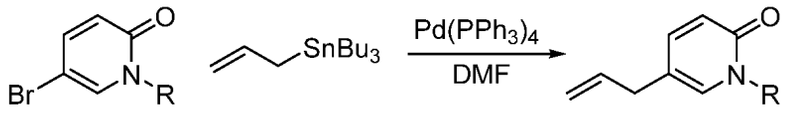


Procedure A: Enol ether (1 equiv.) was treated with TFA (2 mL/mmol) at room temperature for 4 hours. The solvent was removed *in vacuo* to provide the desired aldehyde.

Procedure B: Enol ether (1 equiv.) was treated with HCOOH (2 mL/mmol) at 70°C for 2 hours. The solvent was removed *in vacuo* to provide the desired aldehyde.

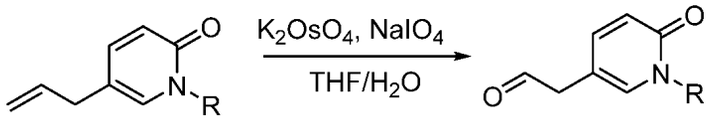
Procedure C: To a solution of enol ether (1 equiv.) in DCM (15 mL/mmol enol ether) was added TFA (2 mL/mmol) and water (0.25 mL/ mmol enol ether). The reaction was stirred at 45°C for 18 h. The reaction was worked up (quenched with $NaHCO_3$, extracted with DCM; combined extracts dried over Na_2SO_4, filtered, and concentrated) to provide the desired aldehyde.

Stille Reaction



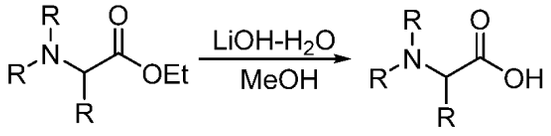
To a solution of arylbromide (1 equiv.) and allylstannane (1.2 equiv.) under N_2 in DMF (3 mL/mmol arylbromide) was added $Pd(PPh_3)_4$ (0.1 equiv.). The reaction was stirred at 100°C for 16 hours. The reaction was concentration *in vacuo* then diluted with EtOAc, poured into 20% aq. KF and stirred for 1 h and extracted. The combined organic layers were dried over Na_2SO_4, filtered and concentrated, and purified by silica gel chromatography to provide the desired product.

Alkene to Aldehyde



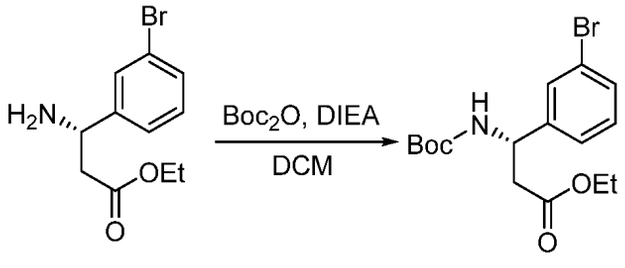
To a solution of alkene (1 equiv.) in THF/H_2O (1:1) (10 mL/mmol of alkene) at 0°C was added K_2OsO_4-$2H_2O$ (0.01 equiv.). The mixture was stirred at 0°C for 5 min then $NaIO_4$ (3 equiv.) in H_2O (1 mL/mmol alkene) was added dropwise and stirred at 0°C for 1 h then warmed to room temperature and stirred until complete by LCMS. The reaction was worked up (dilute with water and extract with EtOAc; combined organic layers were dried over Na_2SO_4, filtered, and concentrated) to give the desired aldehyde.

Ester to Acid



The ester (1 equiv.) was treated with LiOH-H_2O (3-5 equiv.) in MeOH (1-3 mL/mmol ester) and water (1-3 mL/mmol ester) at room temperature for 1-5 h. The reaction was acidified with 1N HCl to pH=3 and concentrated. The residue was purified by prep HPLC to give the desired carboxylic acid product.

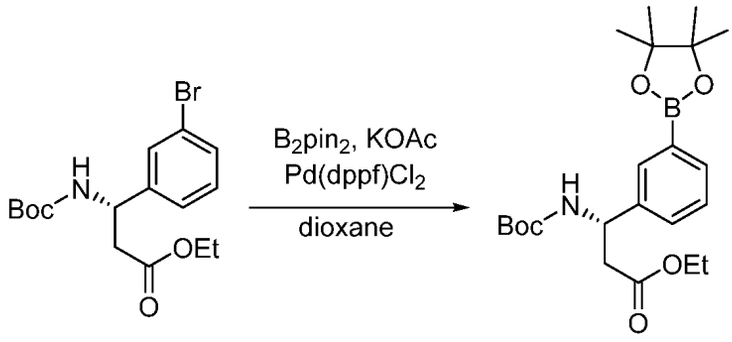
Amine protection



A mixture of amine (1 equiv.), DIEA (3 equiv.), and Boc_2O (2 equiv.) was stirred in DCM (5 mL/mmole amine) at room temperature for 16 h until complete by LCMS. The reaction was worked up (wash with 0.5 N HCl, sat. $NaHCO_3$, brine, extract with DCM; combined organic

layers were dried over Na_2SO_4, filtered, and concentrated) and purified by silica gel chromatography.

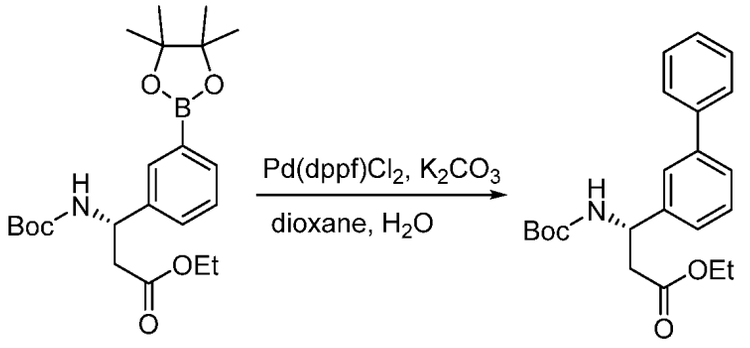
Preparation of arylborane



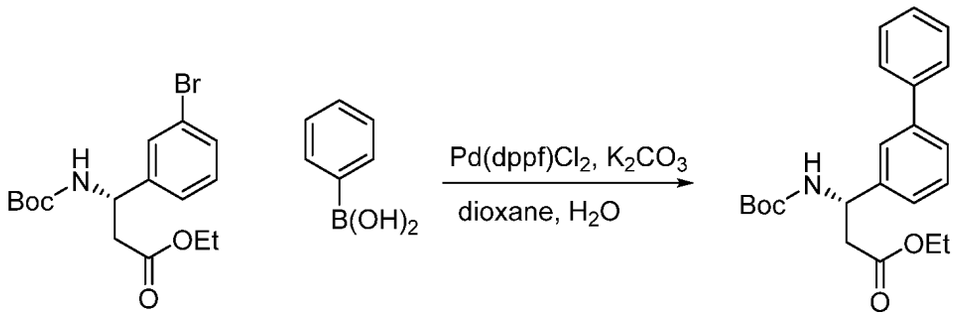
A mixture of arylbromide (1 equiv.), B_2pin_2 (1.2 equiv.), $Pd(dppf)Cl_2$ (0.05 equiv.), and KOAc (3 equiv.) in dioxane (10 mL/mmol arylbromide) was stirred at 110 °C for 2-5 h under N_2 until complete by LCMS. The reaction was filtered, concentrated in vacuo, and purified by silica gel chromotagraphy to provide the desired arylborane.

Suzuki Coupling

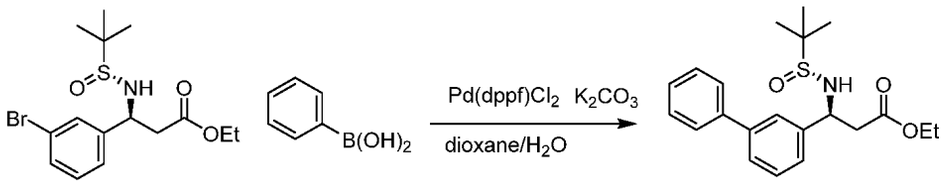
"Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds" N. Miyaura; A. Suzuki *Chem. Rev.* 1995, 957, 2457-2483.



Procedure A: To a solution of arylborane (1 equiv.) in dioxane (10 mL/mmol arylborane) was added arylbromide (1.2 equiv.), $Pd(dppf)Cl_2$ (0.1 equiv.), K_2CO_3 (2 equiv.), and water (2 mL/mmol). The reaction was stirred at 110 °C for 3 h under N_2. The reaction was worked up (washed with brine and extracted with EtOAc; combined extracts dried over Na_2SO_4, filtered, and concentrated) and purified by silica gel chromatography to provide the desired biaryl product.

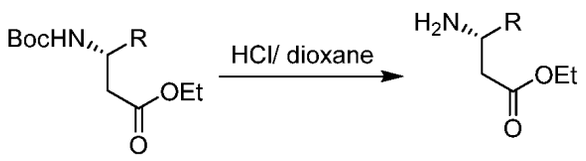


Procedure B: To a solution of arylbromide (1 equiv.) and arylborane (1.1 equiv.) in dioxane (10 mL/mmol arylbromide) was added K_2CO_3 (2 equiv.) in water (2 mL/mmol) and $Pd(dppf)Cl_2$ (0.1 equiv.). The reaction was stirred at 110 °C for 2 h under N_2. The reaction was worked up (washed with brine and extracted with EtOAc; combined extracts dried over Na_2SO_4, filtered, and concentrated) and purified by silica gel chromatography to provide the desired biaryl product.



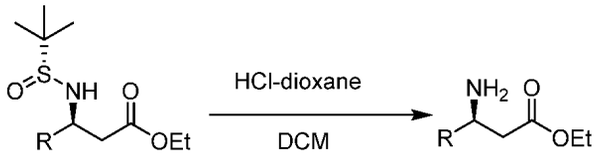
Procedure C: A mixture of arylbromide (1 equiv.), arylborane (2.0 equiv), K_2CO_3 (3 equiv.), and $Pd(dppf)Cl_2$ (0.05 equiv.) in dioxane (10 mL/mmol arylbromide) and water (1 mL/mmol) was stirred at 110°C for 2 h under N_2 until complete by LCMS. The reaction was worked up (washed with brine and extracted with EtOAc; combined extracts dried over Na_2SO_4, filtered, and concentrated) and purified by silica gel chromatography to provide the desired biaryl product.

Boc deprotection



Boc-protected amine (1 equiv.) in DCM (4 mL/mmol amine) was added 4M HCl-dioxane (12 equiv.). The reaction was stirred for 1-2 h until complete by LCMS. The reaction was concentrated in vacuo to give the desired amine.

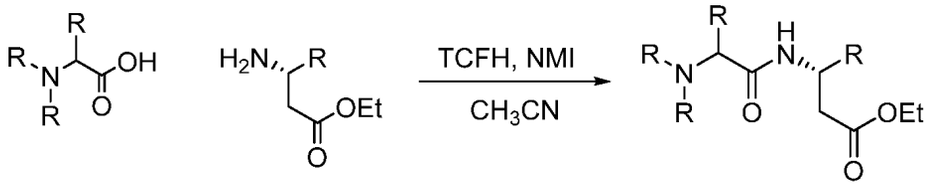
t-butylsulfinyl deprotection



To a solution of t-butylsulfinylamine (1 equiv.) in DCM (0.5 mL/mmol amine) was added 4M HCl-dioxane (1.7 equiv.). The reaction was stirred for 0.5-1 h until complete by LCMS. The reaction was concentrated and purified by prep HPLC to give the desired amine.

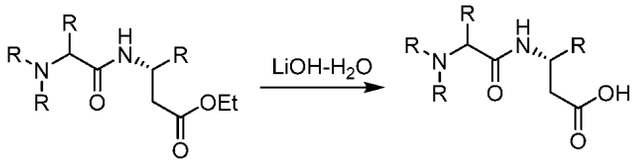
Amide Bond Formation

"Peptide Coupling Reagents, More than a Letter Soup" A. El-Faham, F. Albericio *Chem. Rev.* 2011, 111, 11, 6557-6602; "Amide bond formation and peptide coupling" C. A. G. N. Montalbetti; V. Falque *Tetrahedron* 2005, 61, 10827-10852.



A mixture of amine (1 equiv.), carboxylic acid (1 equiv.), TCFH (2 equiv.), and NMI (4 equiv.) in CH_3CN (10 mL/mmol amine) was stirred at room temperature for 1-2 h until complete by LCMS. The reaction was concentrated in vacuo and purified by silica gel chromatography to give the desired amide product.

Ester Hydrolysis



The ester (1 equiv.) was treated with LiOH-H_2O (3-5 equiv.) in MeOH (1-3 mL/mmol ester) and water (1-3 mL/mmol ester) at room temperature for 1-5 h. The reaction was acidified with 1N HCl to pH=4-5 and concentrated. The residue was purified by prep HPLC to give the desired carboxylic acid product.

Analytical Methods

LCMS Analytical Methods

Final compounds were analyzed using LC/MS conditions, with UV detector monitoring at 214 nm and 254 nm, and mass spectrometry scanning 110-800 amu in ESI+ ionization mode.

LC/MS A**:** column: XBridge C18, 4.6 X 50 mm, 3.5 µm; mobile phase: A water (10 mM ammonium hydrogen carbonate), B CH_3CN; gradient: 5%-95% B in 1.4 min, then 1.6 min hold; flow rate: 1.8 mL/min; oven temperature 50 °C.

LC/MS B**:** column: SunFire C18, 4.6 X 50 mm, 3.5 µm; mobile phase: A water (0.01% TFA), B CH_3CN; gradient: 5%-95% B in 1.5 min, then 1.5 min hold; flow rate: 2.0 mL/min; oven temperature 50 °C.

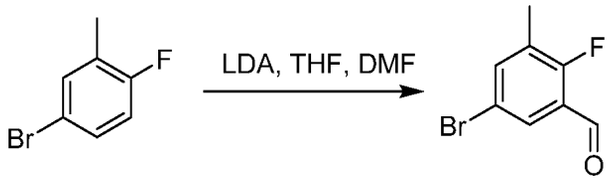
LC/MS C: column: XBridge C18, 4.6 X 50 mm, 3.5 µm; mobile phase: A water (10 mM ammonium hydrogen carbonate), B CH3CN; gradient: 5%-95%B in 1.5min, then 1.5 min hold; flow rate: 1.8 mL/min; oven temperature 50 °C.

LC/MS D**:** column: Poroshell 120 EC-C138, 4.6 X 30 mm, 2.7 µm; mobile phase: A water (0.01% TFA), B CH_3CN (0.01% TFA); gradient: 5%-95% B in 1.2 min, then 1.8 min hold; flow rate: 2.2 mL/min; oven temperature 50 °C.

Example 2A. Preparation of Intermediates

Preparation of ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate

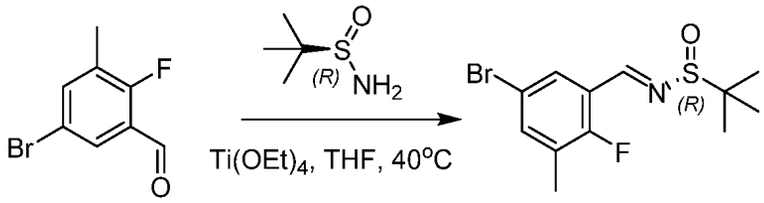
Step 1: 5-bromo-2-fluoro-3-methylbenzaldehyde



To a mixture of 4-bromo-1-fluoro-2-methylbenzene (10.0 g, 52.9 mmol, 1.0 *eq*) in anhydrous THF (100.0 mL) under nitrogen atmosphere at -78 °C was added Lithium diisopropylamide

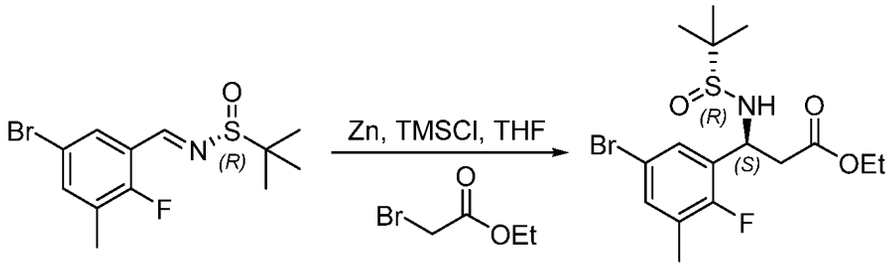
(2.0 M, 39.7 mL, 79.4 mmol, 1.5 *eq*) dropwise over the period of 10 mins and stirred at -78°C for 1 hour. DMF (15.0 mL) was added dropwise and the mixture was stirred at -78°C for 2 hours. LCMS showed that the reaction was completed. The reaction mixture was quenched with a saturated NH_4Cl solution (aq) (100 mL) at 0 °C, extracted with EtOAc (100 mL x 2). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified by silica gel column (pet ether: EtOAc 9:1) to provide 5-bromo-2-fluoro-3-methylbenzaldehyde as a white solid (8.0 g). Yield 70% (ESI 218.9 $[M+H]^+$).

Step 2: (*R*, *E*)-*N*-(5-bromo-2-fluoro-3-methylbenzylidene)-2-methylpropane-2-sulfinamide



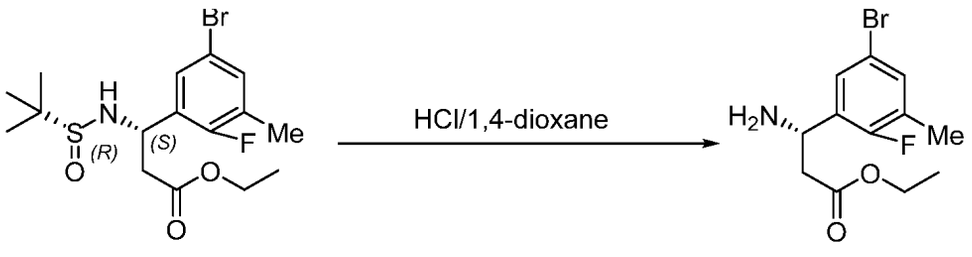
To a mixture of 5-bromo-2-fluoro-3-methylbenzaldehyde (8.0 g, 36.9 mmol, 1.00 *eq*) and (*R*)-2-methylpropane-2-sulfinamide (5.4 g, 44.3 mmol, 1.2 *eq*) in anhydrous THF (80 mL) under nitrogen atmosphere was added $Ti(OEt)_4$ (12.6 g, 55.4 mmol, 1.50 *eq*) dropwise at room temperature with the temperature maintained below 30 °C. The reaction mixture was warmed to 40 °C and stirred for 1 hour. LCMS showed that the reaction was completed. Water (80 mL) and EtOAc (80 mL) was added into the mixture and stirred at room temperature for 5 mins. The mixture was filtered and washed with EtOAc (50 mL). The filtrate was separated. The organic layer was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give crude product (*R*, *E*)-*N*-(5-bromo-2-fluoro-3-methylbenzylidene)-2-methylpropane-2-sulfinamide as a yellow solid (12.0 g, crude) which was used in the next step without further purification. Yield 100% (ESI 320.0 $[M+H]^+$).

Step 3: ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate



To a mixture of Zn (12.2 g, 187.5 mmol, 5.0 *eq*) in anhydrous THF (200 mL) under nitrogen atmosphere was added chlorotrimethylsilane (0.8 g, 7.5 mmol, 0.2 *eq*) dropwise at room temperature. The mixture was stirred at 60 °C for 1 hour under nitrogen atmosphere and cooled to 20-30°C. Ethyl 2-bromoacetate (1.57 g, 9.4 mmol, 0.25 *eq*) was added dropwise at 20-30 °C. When the reaction mixture started to be exothermic, the rest of ethyl 2-bromoacetate (14.4 g, 86.3 mmol, 2.3 *eq*) was added dropwise during which time the reaction mixture was kept at 50-60 °C. After the completion of the addition, the reaction mixture was stirred at 60°C for 1 hour under nitrogen atmosphere. The reaction mixture was cooled to 0 °C, (*R*, *E*)-*N*-(5-bromo-2-fluoro-3-methylbenzylidene)-2-methylpropane-2-sulfinamide (12.0 g, 37.5 mmol) in anhydrous THF (30 mL) was added dropwise and stirred at 25 °C for 1 hour. LCMS showed that the reaction was completed. MTBE (150 mL) and a solution of citric acid (3 g) in water (100 mL) were added into the mixture. The mixture was separated. The aqueous layer was extracted with MTBE (150 mL x 2). The combined organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 3:1) to provide ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (9.0 g). Yield 59% (ESI 408.0 $[M+H]^+$).

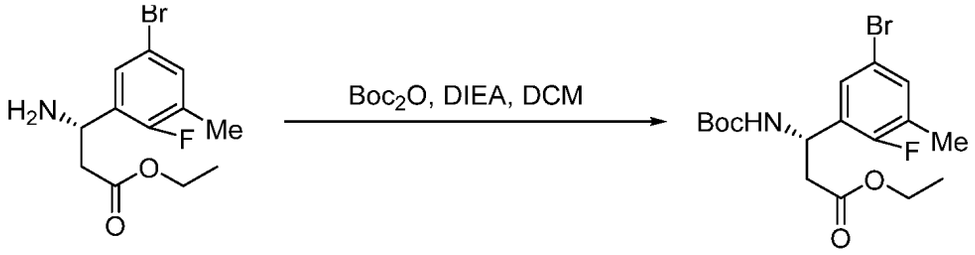
Step 4: ethyl (*S*)-3-amino-3-(5-bromo-2-fluoro-3-methylphenyl)propanoate



To a solution of ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (8.0 g, 19.6 mmol, 1.00 *eq*) in DCM (20 mL) was added HCl-dioxane (4 M, 20 mL, 80.0 mmol, 4.08 *eq*) and stirred at room temperature for 4 hours. LCMS showed that the reaction was completed. The mixture was filtered and

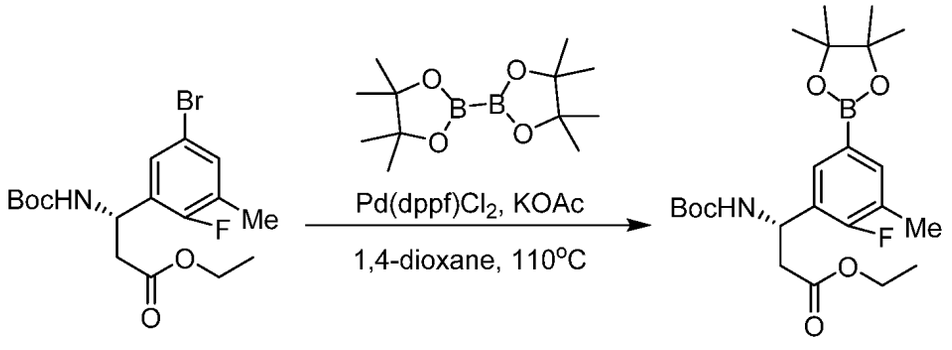
concentrated *in vacuo* to give crude product ethyl (*S*)-3-amino-3-(5-bromo-2-fluoro-3-methylphenyl)propanoate as a yellow oil (8.0 g) used in the next step without further purification. Yield 100% (ESI 304.2 $[M+H]^+$).

Step 5: ethyl (*S*)-ethyl 3-(5-bromo-2-fluoro-3-methylphenyl)-3-(*tert*-butoxycarbonylamino)propanoate



To a solution of ethyl (S)-3-amino-3-(5-bromo-2-fluoro-3-methylphenyl)propanoate (8.0 g, 19.6 mmol, 1.00 *eq*) in DCM (100 mL) was added DIEA (7.6 g, 59.0 mmol, 3.00 *eq*) and Boc_2O (8.6 g, 39.2 mmol, 2.00 *eq*). The reaction mixture was stirred at room temperature for 16 hours. LCMS showed that the reaction was completed. The reaction mixture was diluted with DCM (200 mL) and washed with 0.5 N HCl (50 mL x 3), saturated $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 3:1) to provide ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate as a brown oil (6.0 g). Yield 75% (ESI 404.1 $(M+H)^+$).

Preparation of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate

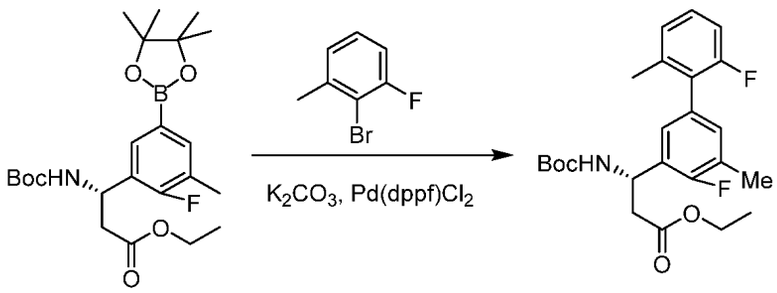


A mixture of ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-((*tert*-butoxycarbonyl)amino)propanoate (1.0 g, 2.48 mmol, 1.0 *eq*), bis(pinacolato)diboron (756.28

mg, 2.98 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (90.65 mg, 0.13 mmol, 0.05 *eq*) and KOAc (729.12 mg, 7.44 mmol, 3.0 *eq*) in 1,4-dioxane (20 mL) was stirred at 110 °C for 3 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 2:1) to give (*S*)-ethyl 3-(*tert*-butoxycarbonylamino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate as a colorless oil (1.0 g). Yield 89% (ESI 452.2 $(M+H)^+$).

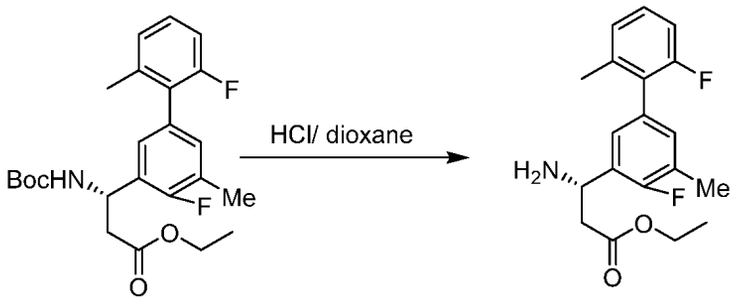
Preparation of ethyl (*S*)-3-amino-3-(2',4-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',4-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (300 mg, 0.66 mmol, 1.0 *eq*) in dioxane (5 mL) was added 2-bromo-1-fluoro-3-methylbenzene (150 mg, 0.79 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (48 mg, 0.066 mmol, 0.1 *eq*), K_2CO_3 (182 mg, 1.32 mmol, 2.0 *eq*) and water (1 mL). The reaction mixture was stirred at 110 °C for 3 hours under nitrogen atmosphere. Water (10 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 8:1) to provide ethyl (*S*)-3-((*ter*t-butoxycarbonyl)amino)-3-(2',4-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (210 mg). Yield 73% (ESI 334.1 $[M+H-100]^+$).

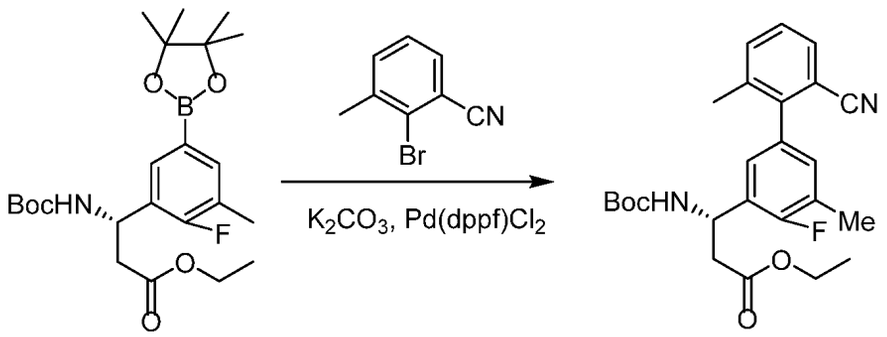
Step 2: ethyl (*S*)-3-amino-3-(2',4-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a stirred solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',4-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (210 mg, 0.48 mmol, 1.0 *eq*) in DCM (2 mL) was added HCl-dioxane (4 M, 3.0 mL, 6.0 mmol, 12.5 *eq*). The mixture was stirred at room temperature for 2 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(2',4-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (160 mg). Yield 99% (ESI 334.1 $[M+H]^+$).

Preparation of ethyl (S)-3-amino-3-(2'-cyano-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

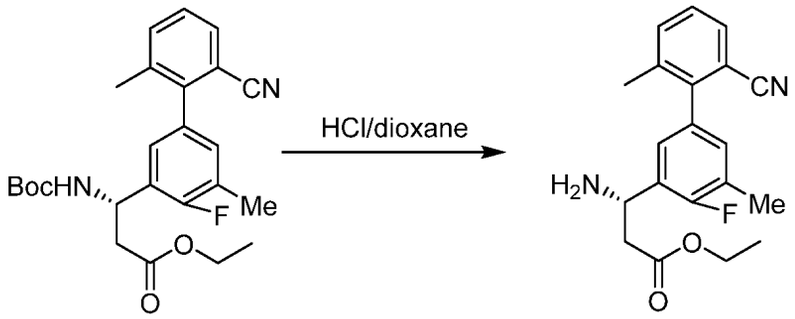
Step 1: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-cyano-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (350 mg, 0.77 mmol, 1.0 *eq*) in dioxane (10 mL) was added 2-bromo-3-methylbenzonitrile (226 mg, 1.16 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (56 mg, 0.077 mmol), K_2CO_3 (193 mg, 1.4 mmol, 1.8 *eq*) and water (2 mL). The reaction mixture was stirred at 110 °C for 3 hours under nitrogen atmosphere. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether:

EtOAc 4:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-cyano-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (260 mg). Yield 76% (ESI 341.1 $[M+H-100]^+$).

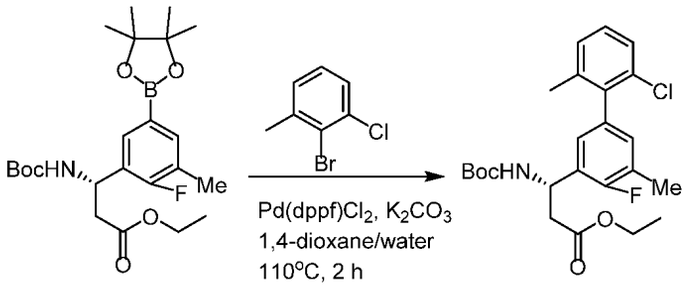
Step 2: ethyl (S)-3-amino-3-(2'-cyano-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride



To a stirred solution of ethyl (S)-3-((tert-butoxycarbonyl)amino)-3-(2'-cyano-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (230 mg, 0.52 mmol, 1.0 *eq*) in DCM (2 mL) was added HCl-dioxane (4 M, 2.0 mL, 4.0 mmol, 7.7 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(2'-cyano-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride as a yellow oil (180 mg). Yield 91% (ESI 341.1 $[M+H]^+$).

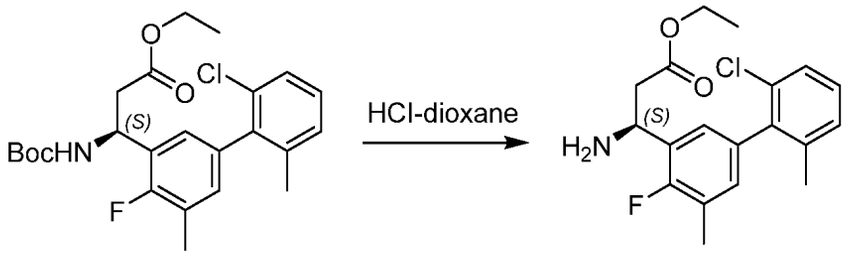
Preparation of ethyl (*S*)-3-amino-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (1.0 g, 2.22 mmol, 1.00 *eq*), 2-bromo-1-chloro-3-methylbenzene (543 mg, 2.66 mmol, 1.20 *eq*), K_2CO_3 (613 mg, 4.44 mmol, 2.0 *eq*) and $Pd(dppf)Cl_2$ (81 mg, 0.11 mmol, 0.05 *eq*) in dioxane (10 mL) and H_2O (2 mL) was stirred at 110 °C for 2 hours under nitrogen atmosphere. Water (30 mL) was added and the solution was extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 2:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (800 mg). Yield 80% (ESI 450.18 $[M+H]^+$).

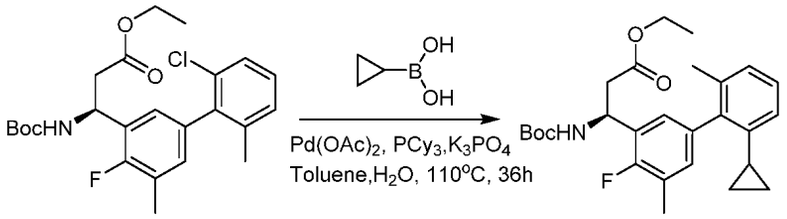
Step 2: ethyl (*S*)-3-amino-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (300 mg, 0.67 mmol, 1.00 *eq*) in DCM (9 mL) was added HCl-dioxane (4 M, 9.0 mL, 36.0 mmol, 53.73 *eq*) and stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (200 mg) used directly in the next reaction without further purification. Yield 86% (ESI 350.1$[M+H]^+$).

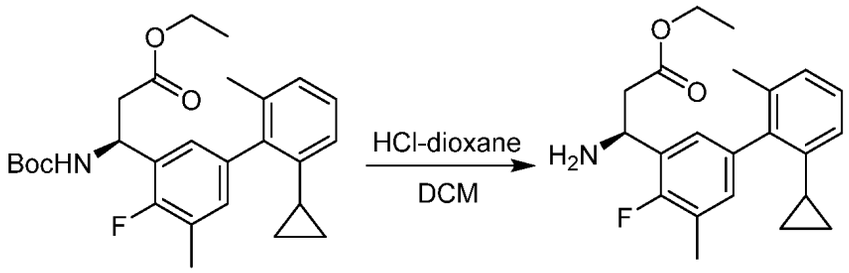
Preparation of ethyl (*S*)-3-amino-3-(2'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (S)-3-((tert-butoxycarbonyl)amino)-3-(2'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (500 mg, 1.12 mmol, 1.00 *eq*), cyclopropylboronic acid (116 mg, 1.35 mmol, 1.20 *eq*), K_3PO_4 (475 mg, 2.24 mmol, 2.00 *eq*), PCy_3 (31 mg, 0.11 mmol, 0.10 *eq*) and $Pd(OAc)_2$ (11 mg, 0.11 mmol, 0.10 *eq*) in dioxane (10 mL) and H_2O (2 mL) was stirred at 110 °C for 36 hours under nitrogen atmosphere. Water (30 mL) was added and the solution was extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 2:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (400 mg). Yield 79% (ESI 456.2 $[M+H]^+$).

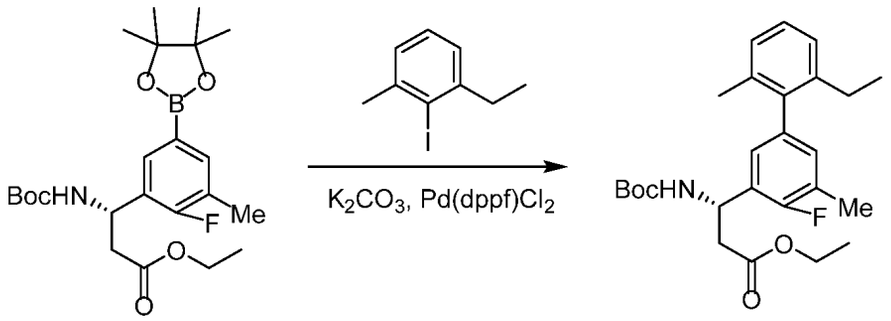
Step 2: ethyl (*S*)-3-amino-3-(2'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (400 mg, 0.88 mmol, 1.0 *eq*) in DCM (9 mL) was added HCl-dioxane (4 M, 9.0 mL, 36.0 mmol, 40.9 *eq*) and stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(2'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (300 mg) used directly in the next reaction without further purification. Yield 96% (ESI 356.2 $[M+H]^+$).

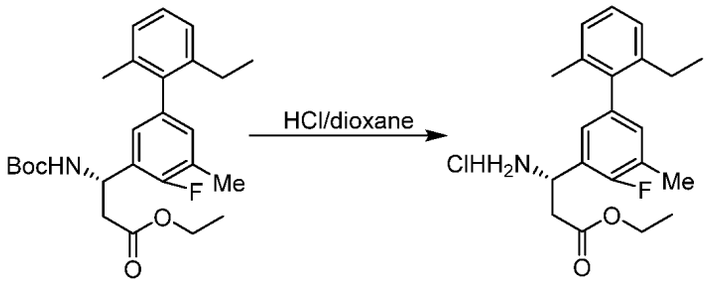
Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

Step 1: ethyl (*S*)-3-amino-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride



To a solution of ethyl (S)-3-((tert-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (350 mg, 0.77 mmol, 1.0 *eq*) in dioxane (10 mL) was added 1-ethyl-2-iodo-3-methylbenzene (286 mg, 1.16 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (56 mg, 0.077 mmol, 0.1 *eq*), K_2CO_3 (193 mg, 1.4 mmol, 1.8 *eq*) and water (2 mL). The reaction mixture was stirred at 110 °C for 3 hours under nitrogen atmosphere. Water (10 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 4:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (240 mg). Yield 70% (ESI 344.2 $[M+H-100]^+$).

Step 2: ethyl (*S*)-3-amino-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

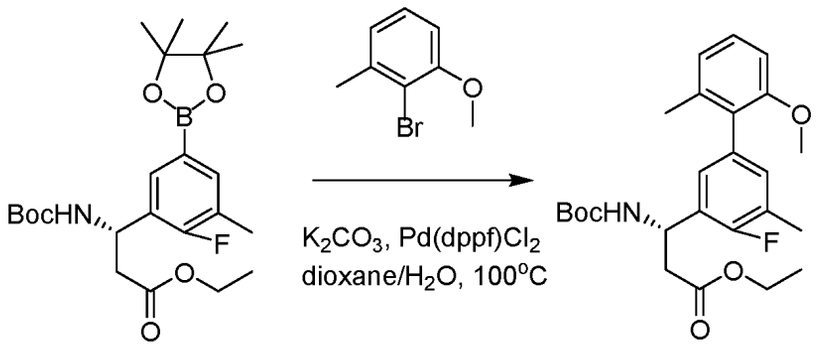


To a stirred solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (210 mg, 0.47 mmol, 1.0 *eq*) in DCM (2 mL) was

added HCl-dioxane (4 M, 3.0 mL, 6.0 mmol, 12.8 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (S)-3-amino-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride as a colorless oil (170 mg). Yield 94% (ESI 344.1 $[M+H]^+$).

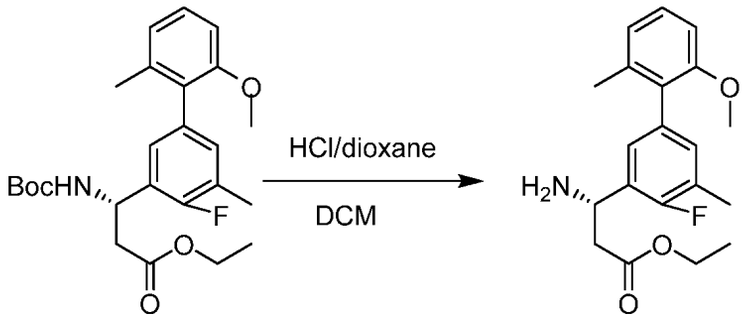
Preparation of (S)-ethyl 3-amino-3-(4-fluoro-2'-methoxy-5,6'-dimethylbiphenyl-3-yl)propanoate

Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (1 g, 2.22 mmol, 1.0 *eq*), 2-bromo-1-methoxy-3-methylbenzene (666 mg, 3.33 mmol, 1.5 *eq*), K_2CO_3 (919 mg, 6.66 mmol, 3.0 *eq*) and Pd(dppf)Cl_2 (162 mg, 0.222 mmol, 0.1 *eq*) in dioxane (15 mL) and H_2O (1.5 mL) was stirred at 100°C under nitrogen atmosphere for 3 hours. LCMS showed the reaction was completed. The reaction mixture was cooled to room temperature. Water (50 mL) was added and the mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-2'-methoxy-5,6'-dimethylbiphenyl-3-yl)propanoate as a yellow oil (0.96 g). Yield 97% (ESI 346.1 $[M+H]^+$).

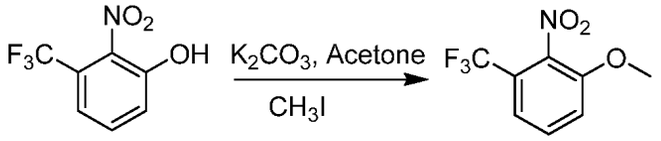
Step 2: (S)-ethyl 3-amino-3-(4-fluoro-2'-methoxy-5,6'-dimethylbiphenyl-3-yl)propanoate



To a stirred solution of (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-2'-methoxy-5,6'-dimethylbiphenyl-3-yl)propanoate (0.96 g, 2.15 mmol, 1.0 *eq*) in DCM (7 mL) was added HCl-dioxane (4 M, 2.15 mL, 4 *eq*) and stirred at 25 °C for 2 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (S)-ethyl 3-amino-3-(4-fluoro-2'-methoxy-5,6'-dimethylbiphenyl-3-yl)propanoate as a yellow oil (0.6 g). Yield 81% (ESI 346.1 $[M+H]^+$).

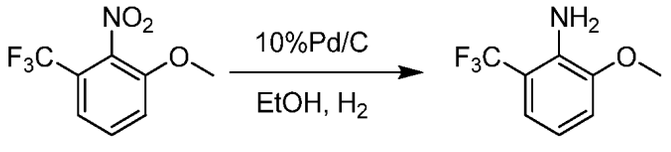
Preparation of (S)-ethyl 3-amino-3-(4-fluoro-2'-methoxy-5-methyl-6'-(trifluoromethyl)biphenyl-3-yl)propanoate

Step 1: 1-methoxy-2-nitro-3-(trifluoromethyl)benzene



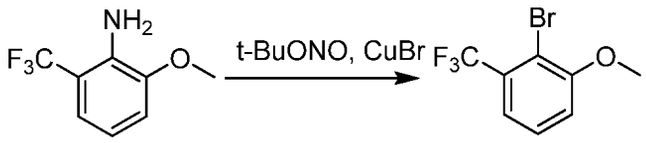
To a mixture of 2-nitro-3-(trifluoromethyl)phenol (1.5 g, 7.25 mmol, 1.0 *eq*) in acetone (20 mL) was added K_2CO_3 (3 g, 21.75 mmol, 3 *eq*) and CH_3I (5.15 g, 36.25 mmol, 5 *eq*) and stirred at room temperature for 16 hours. LCMS showed that the reaction was completed. The reaction mixture was filtered, washed with EtOAc (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide 1-methoxy-2-nitro-3-(trifluoromethyl)benzene as a white solid (1.3 g). Yield 81% .

Step 2: 2-methoxy-6-(trifluoromethyl)aniline



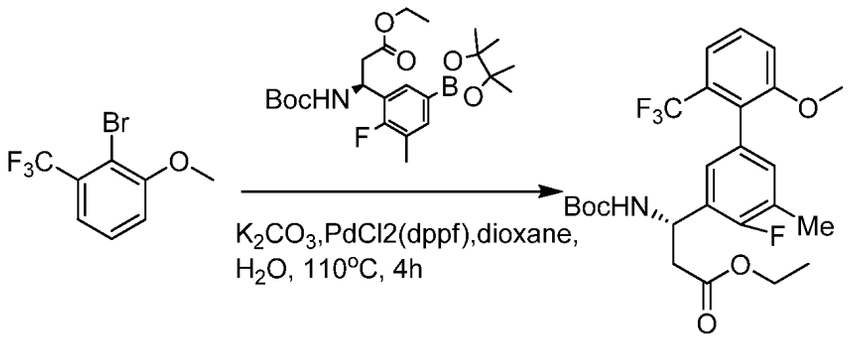
To a mixture of 1-methoxy-2-nitro-3-(trifluoromethyl)benzene (1.3 g, 5.88 mmol, 1.0 *eq*) in EtOH (20 mL) was added 10%Pd/C (700 mg) and stirred at room temperature for 16 hours under H_2 atmosphere(2L, 1 atm). LCMS showed that the reaction was completed. The reaction mixture was filtered and the filtrated concentrated *in vacuo* to provide 2-methoxy-6-(trifluoromethyl)aniline as a white solid (0.75 g). Yield 67% (ESI 192.1 $[M+H]^+$).

Step 3: 2-bromo-1-methoxy-3-(trifluoromethyl)benzene



To a mixture of 2-methoxy-6-(trifluoromethyl)aniline (700 mg, 3.66 mmol, 1.0 *eq*) in MeCN (15 mL) was added t-BuONO (565 mg, 5.49 mmol, 1.5 *eq*) and CuBr (628 mg, 4.39 mmol, 1.2 *eq*). The mixture was stirred at 60°C for 2 hours. LCMS showed that the reaction was completed. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide 2-bromo-1-methoxy-3-(trifluoromethyl)benzene as a colorless oil (400 mg). Yield 43%.

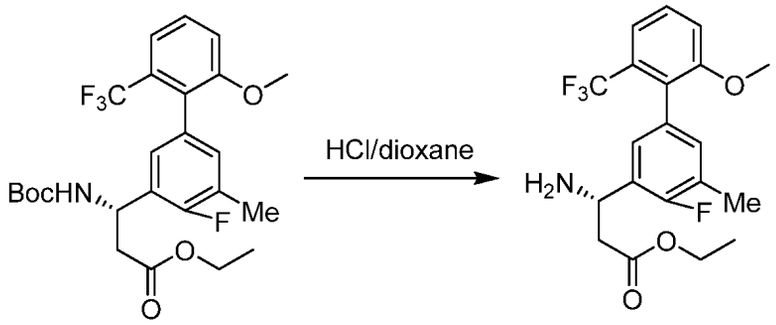
Step 4: (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-2'-methoxy-5-methyl-6'-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-bromo-1-methoxy-3-(trifluoromethyl)benzene (400 mg, 1.57 mmol, 1.00 *eq*), (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (708 mg, 1.57 mmol, 1.0 *eq*), K_2CO_3(650 mg, 4.71 mmol, 3.0 *eq*) and Pd(dppf)Cl_2 (115 mg, 0.157 mmol, 0.1 *eq*) in dioxane (8 mL) and H_2O (0.8 mL) was stirred at 110°C for 4 hours under nitrogen atmosphere. LCMS showed that the reaction was completed. The mixture was cooled to room temperature. Water (30 mL) was added and the mixture was extracted with EtOAc (30 mL x 3). The combined organic phases was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in*

vacuo. The residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-2'-methoxy-5-methyl-6'-(trifluoromethyl)biphenyl-3-yl)propanoate (400 mg) as a colorless oil. Yield 51% (ESI 400.1 $[M\text{-}Boc]^+$).

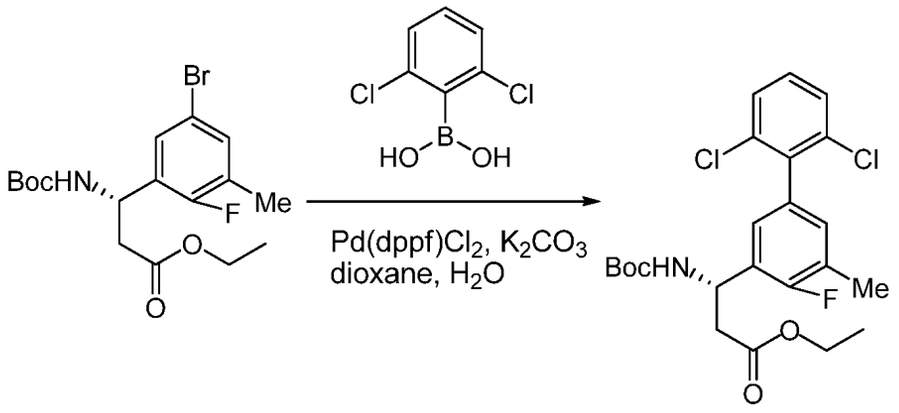
Step 5: (S)-ethyl 3-amino-3-(4-fluoro-2'-methoxy-5-methyl-6'-(trifluoromethyl)biphenyl-3-yl)propanoate



To a stirred solution of (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-2'-methoxy-5-methyl-6'-(trifluoromethyl)biphenyl-3-yl)propanoate (400 mg, 0.8 mmol, 1.00 *eq*) in DCM (6 mL) was added HCl-dioxane (4 M, 0.8 mL, 3.2 mmol, 4 *eq*) and stirred at room temperature for 2 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (S)-ethyl 3-amino-3-(4-fluoro-2'-methoxy-5-methyl-6'-(trifluoromethyl)biphenyl-3-yl)propanoate (280 mg) as a colorless oil. Yield 87% (ESI 400.1 $[M+H]^+$).

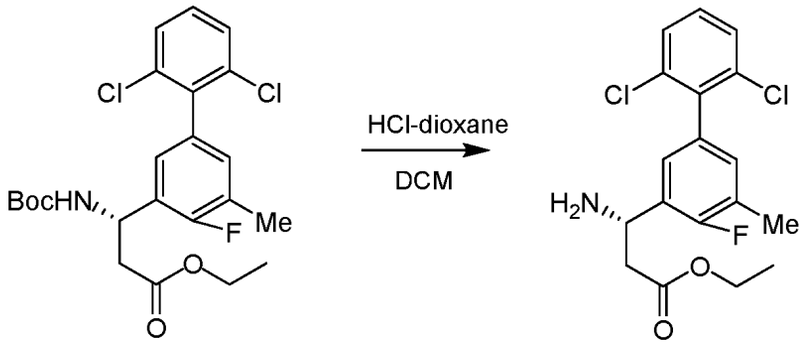
Preparation of (S)-ethyl 3-amino-3-(2',6'-dichloro-4-fluoro-5-methylbiphenyl-3-yl)propanoate

Step 1: (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2',6'-dichloro-4-fluoro-5-methylbiphenyl-3-yl)propanoate



To a mixture of methyl (S)-ethyl 3-(5-bromo-2-fluoro-3-methylphenyl)-3-(tert-butoxycarbonylamino)propanoate (0.5 g, 1.29 mmol, 1 *eq*) and 2,6-dichlorophenylboronic acid (0.26 g, 1.36 mmol, 1.1 *eq*) in dioxane (10 mL) was added a solution of K_2CO_3 (0.34 g, 2.48 mmol, 2 *eq*) in H_2O (2 mL) and $Pd(dppf)Cl_2$ (90 mg, 0.124 mmol, 0.1 *eq*). The mixture was heated to 110 °C for 2 hours under nitrogen atmosphere. The mixture was cooled to room temperature. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2',6'-dichloro-4-fluoro-5-methylbiphenyl-3-yl)propanoate a colorless oil (0.550 g). Yield 94% (ESI 470.4 $[M+H]^+$).

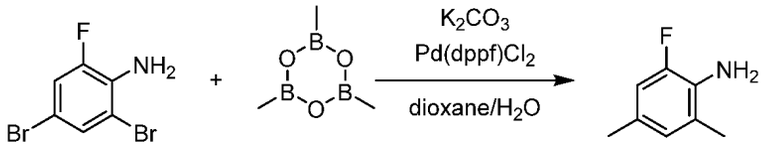
Step 2: (S)-methyl 3-amino-3-(2',6'-dichloro-4-fluoro-5-methylbiphenyl-3-yl)propanoate



To a mixture of methyl (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2',6'-dichloro-4-fluoro-5-methylbiphenyl-3-yl)propanoate (0.55 g, 1.21 mmol, 1 *eq*) in DCM (6 mL) was added HCl-dioxane (4 M, 3 mL, 12 mmol, 10 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to give crude product (S)-ethyl 3-amino-3-(2',6'-dichloro-4-fluoro-5-methylbiphenyl-3-yl)propanoate as a white solid (0.42 g) used directly in the next reaction without further purification. Yield 98% (ESI 370.3$[M+H]^+$).

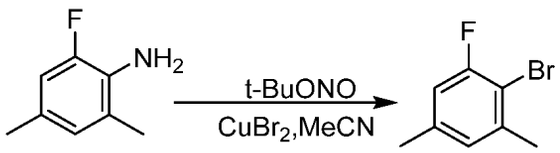
Preparation of ethyl (*S*)-3-amino-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: 2-fluoro-4,6-dimethylaniline



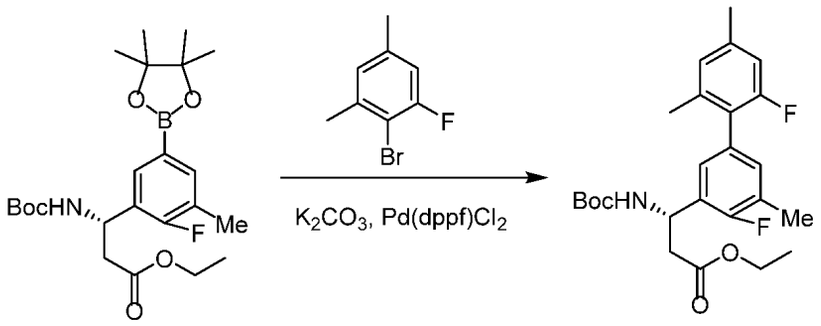
A mixture of 2,4-dibromo-6-fluoroaniline (5.0 g, 18.59 mmol, 1.0 *eq*), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M in THF, 21.2 mL, 74.36 mmol, 4.0 *eq*), $Pd(dppf)Cl_2$ (680 mg, 0.93 mmol, 0.05 *eq*) and K_2CO_3 (7.71 g, 55.78 mmol, 3.0 *eq*) in dioxane (60 mL) and H_2O (8 mL) was stirred at 110 °C for 12 hours under nitrogen atmosphere. The mixture was cooled to room temperature. Water (30 mL) was added and the solution was extracted with EtOAc (35 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 20:1) to provide 2-fluoro-4,6-dimethylaniline as a yellow oil (2.16 g). Yield 83.5% (ESI 140.2 $[M+H]^+$).

Step 2: 2-bromo-1-fluoro-3,5-dimethylbenzene



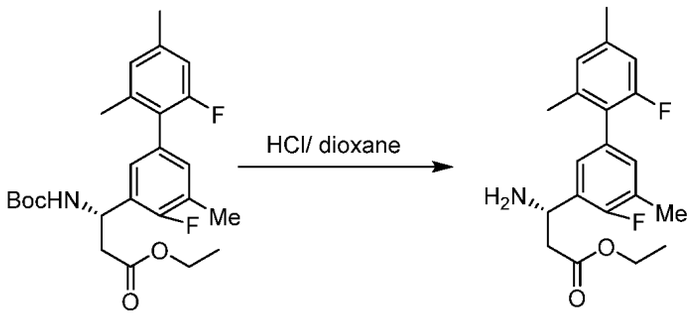
To a stirred solution of 2-fluoro-4,6-dimethylaniline (1.0 g, 7.2 mmol, 1.0 *eq*) and $CuBr_2$ (4.8 g, 21.6 mmol, 3.0 *eq*) in MeCN (7 mL) was added tert-Butyl nitrite (1.68 g, 14.4 mmol, 2.0 *eq*) and stirred at 60 °C for 1 hour under nitrogen atmosphere. LCMS showed that the reaction was completed. The mixture was filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether) to provide 2-bromo-1-fluoro-3,5-dimethylbenzene as a yellow oil (560 mg). Yield 38%.

Step 3: ethyl (*S*)-3-((tert-butoxycarbonyl)amino)-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (556 mg, 1.23 mmol, 1.0 *eq*), 2-bromo-1-fluoro-3,5-dimethylbenzene (250 mg, 1.23 mmol, 1.0 *eq*), $Pd(dppf)Cl_2$ (45 mg, 0.062 mmol, 0.05 *eq*) and K_2CO_3 (510 mg, 3.69 mmol, 3.0 *eq*) in dioxane (6 mL) and water (2 mL) was stirred at 110 °C for 2 hours under nitrogen atmosphere. Water (35 mL) was added and the solution was extracted with EtOAc (25 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 7:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (365 mg). Yield 66% (ESI 348.1 $[M+H-100]^+$).

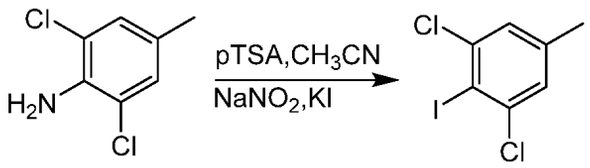
Step 4: ethyl (*S*)-3-amino-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a stirred solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (720 mg, 1.29 mmol, 1.0 *eq*) in DCM (2 mL) was added HCl-dioxane (4 M, 2.0 mL, 4.0 mmol, 3.1 *eq*) and stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (450 mg). Yield 93% (ESI 348.1 $[M+H]^+$).

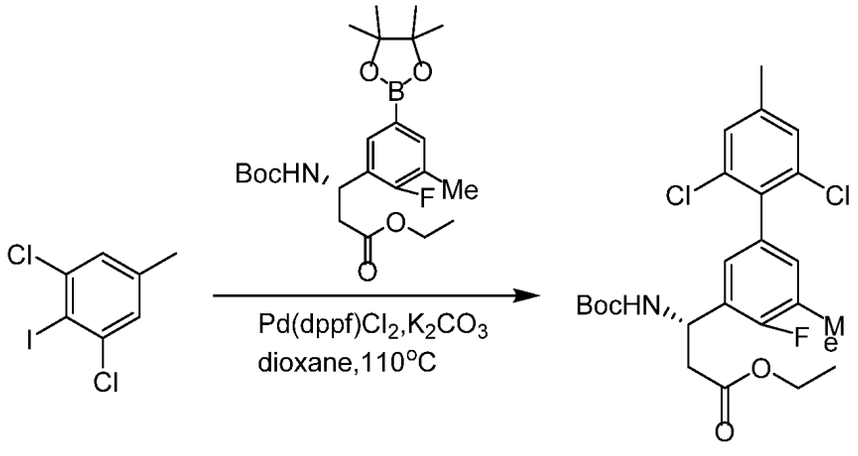
Preparation of (S)-ethyl 3-amino-3-(2',6'-dichloro-4-fluoro-4',5-dimethylbiphenyl-3-yl)propanoate

Step 1: 1,3-dichloro-2-iodo-5-methylbenzene



To a mixture of 2,6-dichloro-4-methylaniline (2.5 g, 14.3 mmol, 1.0 *eq*) in acetonitrile (10 mL) and water (1 mL) was added 4-methylbenzenesulfonic acid (9.8 g, 57.1 mmol, 4 *eq*) and stirred at 0 °C for 10 mins. A solution of $NaNO_2$ (2.0 g, 28.6 mmol, 2 *eq*) in H_2O (2 mL) was added dropwise and the mixture was stirred at 0 °C for 30 mins. Then a solution of potassium iodide (3.0 g, 17.9 mmol, 1.5 *eq*) in H_2O (2 mL) was added and heated to 50 °C for 2 hours under nitrogen atmosphere. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:1) to give 1,3-dichloro-2-iodo-5-methylbenzene as a colorless oil (1.8 g). Yield 44.2% (ESI 286.9[M+H]+).

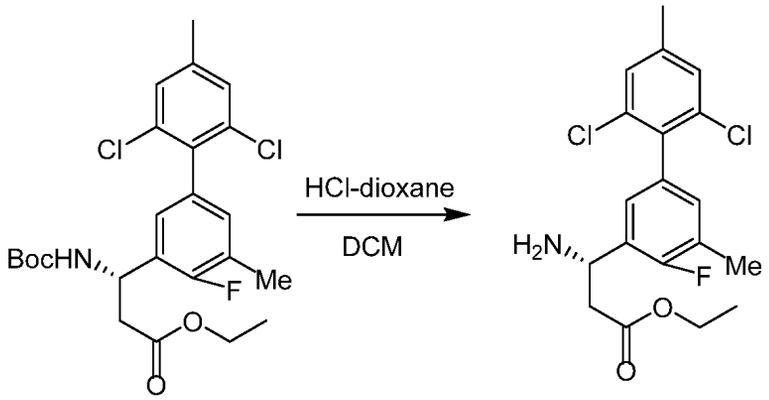
Step 2: (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2',6'-dichloro-4-fluoro-4',5-dimethylbiphenyl-3-yl)propanoate



To a mixture of methyl (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (1.5 g, 3.43 mmol, 1 *eq*) and 1,3-dichloro-2-iodo-5-methylbenzene (2.0 g, 6.86 mmol, 2 *eq*) in dioxane (10 mL) was added a solution of K_2CO_3 (1.9 g, 13.72 mmol, 4 *eq*) in H_2O (2 mL) and $Pd(dppf)Cl_2$ (250 mg, 0.343 mmol, 0.1 *eq*). The mixture was heated to 110 °C for 2 hours under nitrogen

atmosphere. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:1) to give methyl (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2',6'-dichloro-4-fluoro-4',5-dimethylbiphenyl-3-yl)propanoate as a colorless oil (1.3 g). Yield 78.3% (ESI 484.4 $[M+H]^+$).

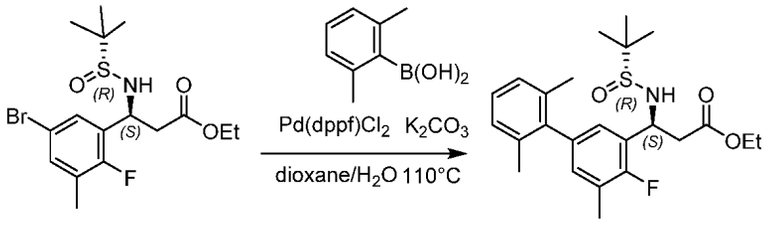
Step 3: (S)-ethyl 3-amino-3-(2',6'-dichloro-4-fluoro-4',5-dimethylbiphenyl-3-yl)propanoate



To a mixture of methyl (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2',6'-dichloro-4-fluoro-4',5-dimethylbiphenyl-3-yl)propanoate (1.3 g, 2.76 mmol, 4 *eq*) in DCM (6 mL) was added HCl-dioxane (4 M, 3 mL, 12 mmol, 4.3 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to give crude (S)-ethyl 3-amino-3-(2',6'-dichloro-4-fluoro-4',5-dimethylbiphenyl-3-yl)propanoate as a white solid (1.0 g) used directly in the next reaction without further purification. Yield 91% (ESI 384.3 $[M+H]^+$).

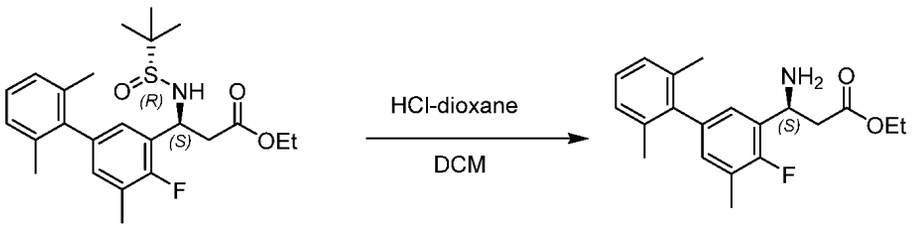
Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (4.0 g, 9.8 mmol, 1.00 *eq*), (2,6-dimethylphenyl)boronic acid (2.9 g, 19.6 mmol, 2.00 *eq*), K_2CO_3 (4.1 g, 29.4 mmol, 3.0 *eq*), $Pd(dppf)Cl_2$ (717 mg, 0.98 mmol, 0.05 *eq*) in dioxane (24 mL) and H_2O (9 mL) was stirred at 110°C for 2 hours under nitrogen atmosphere. LCMS showed that the reaction was completed. The mixture was cooled to room temperature. Water (30 mL) was added and the solution was extracted with EtOAc (30 mL x 3). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (4.0 g) as a yellow oil. Yield 94% (ESI 434.1 $[M+H]^+$).

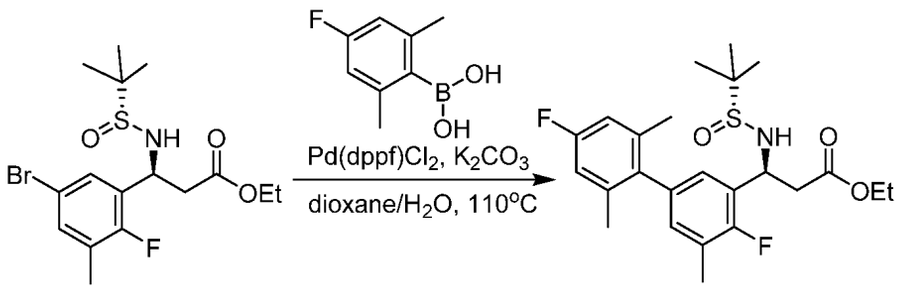
Step 2: ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a stirred solution of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (4.0 g, 9.2 mmol, 1.00 *eq*) in DCM (6 mL) was added HCl-dioxane (4 M, 4 mL, 16.0 mmol, 1.7 *eq*). The mixture was stirred at room temperature for 30 mins. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (2.0 g) as a colorless oil. Yield 61% (ESI 330.1 $[M+H]^+$).

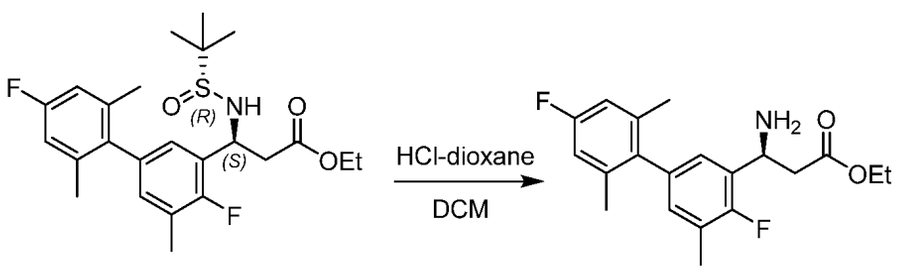
Preparation of ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (6.0 g, 14.7 mmol, 1.00 *eq*), (4-fluoro-2,6-dimethylphenyl)boronic acid (3.7g, 22.1 mmol, 1.5 *eq*), K_2CO_3 (6.1 g, 44.1 mmol, 3.0 *eq*) and $Pd(dppf)Cl_2$ (1.1 g, 1.47 mmol, 0.01 *eq*) in dioxane (50 mL) and H_2O (5 mL) was stirred at 110°C under nitrogen atmosphere for 1 hour. LCMS showed that the reaction was completed. The mixture was cooled to room temperature. Water (50 mL) was added and the solution was extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (5.5 g). Yield 83% (ESI 452.0 $(M+H)^+$)

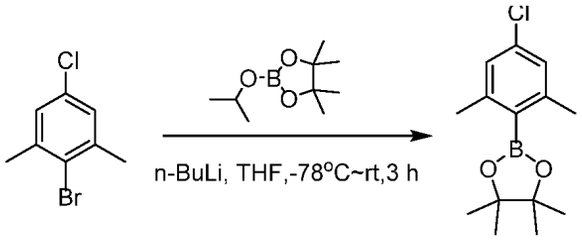
Step 2: ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To the solution of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (5.5 g, 12.2 mmol, 1.00 *eq*) in DCM (6 mL) was added HCl-dioxane (4M, 6 mL, 24.0 mmol, 1.97 *eq*) and stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 120 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (4.0 g). Yield 95% (ESI 348.1 $(M+H)^+$).

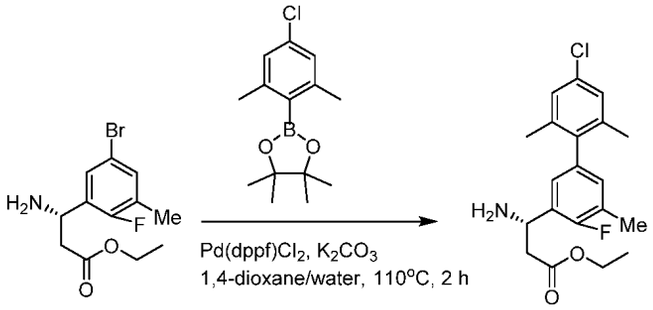
Preparation of ethyl (*S*)-3-amino-3-(4'-chloro-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: 2-(4-chloro-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane



To a solution of 2-bromo-5-chloro-1,3-dimethylbenzene (4.0 g, 18.2 mmol, 1.0 *eq*) in anhydrous THF (40 mL) under nitrogen atmosphere was added *n*-BuLi (2 N, 11.0 mL, 22.0 mmol, 1.2 *eq*) at -78 °C. The reaction mixture was stirred at -78 °C for 40 mins and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.1 g, 27.5 mmol, 1.5 *eq*) in anhydrous THF (40 mL) was added and stirred at -78 °C for 3 hours. After completion, a saturated NH_4Cl solution (aq) (100 mL) was added. The mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue obtained was purified by silica gel (petroleum ether: EtOAc 2:1) to give the desired 2-(4-chloro-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane as a white solid (4.4 g). Yield 90%.

Step 2: ethyl (*S*)-3-amino-3-(4'-chloro-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

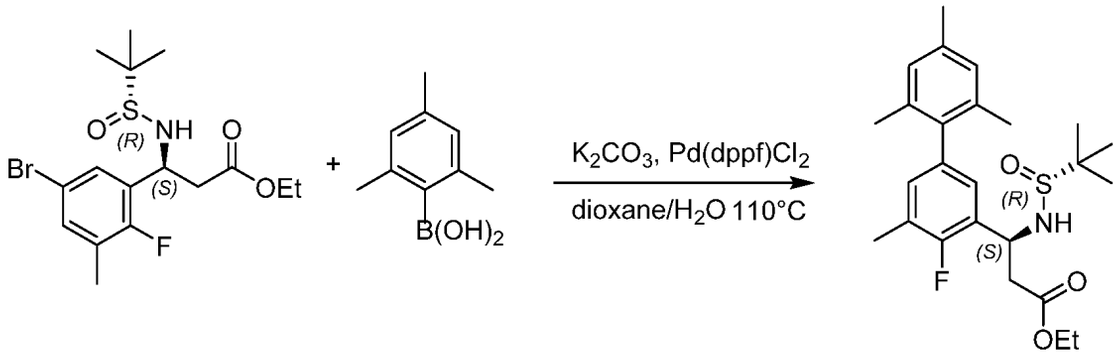


A mixture of ethyl (*S*)-3-amino-3-(5-bromo-2-fluoro-3-methylphenyl)propanoate (500 mg, 1.7 mmol, 1.0 *eq*), 2-(4-chloro-2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (544 mg, 2.04 mmol, 1.2 *eq*), $Pd(dppf)Cl_2$ (62 mg, 0.085 mmol, 0.05 *eq*) and K_2CO_3 (704 mg, 5.1 mmol, 3.0 *eq*) in 1,4-dioxane (10 mL) and water (2 mL) was stirred at 110 °C for 2 hours under nitrogen atmosphere. Water (20 mL) was added and the solution was extracted

with EtOAc (30 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 1:2) to provide ethyl (*S*)-3-amino-3-(4'-chloro-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (250 mg). Yield 41% (ESI 364.2 $[M+H]^+$).

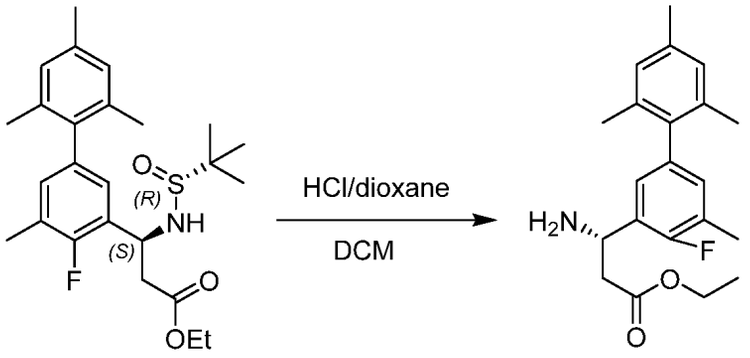
Preparation of ethyl (S)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-2-fluoro-3-methylphenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (3.8 g, 9.3 mmol, 1.0 *eq*), mesitylboronic acid (3.05 g, 18.6 mmol, 2.0 *eq*), K_2CO_3 (3.85 g, 27.9 mmol, 3.0 *eq*) and $Pd(dppf)Cl_2$ (340 mg, 0.465 mmol, 0.05 *eq*) in Dioxane (30 mL) and H_2O (5 mL) was stirred at 110°C under nitrogen atmosphere for 2 hours. LCMS showed the reaction was complete. The reaction mixture was cooled to room temperature. Water (80 mL) was added and the mixture was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (3.1 g). Yield 75% (ESI 448.2 $[M+H]^+$).

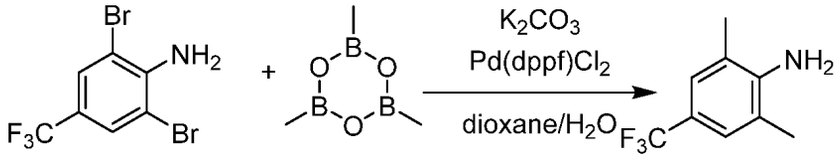
Step 2: ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



To a stirred solution of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (3.1 g, 6.94 mmol, 1.0 *eq*) in DCM (7 mL) was added HCl-dioxane (4 M, 6.8 mL, 3.9 *eq*) and stirred at 25 °C for 2 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (S)-ethyl 3-amino-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate as a yellow oil (1.6 g). Yield 67% (ESI 344.2 $[M+H]^+$).

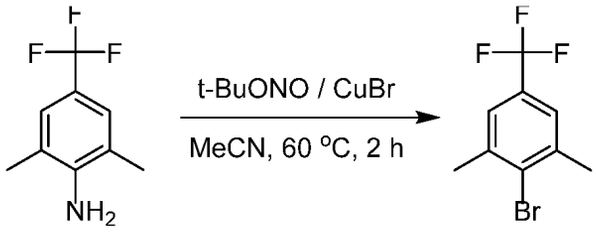
Example: Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

Step 1: 2,6-dimethyl-4-(trifluoromethyl)aniline



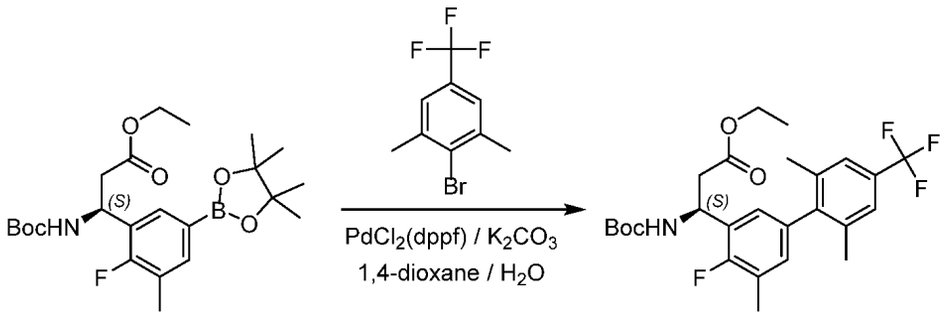
A mixture of 2,6-dibromo-4-(trifluoromethyl)aniline (638 mg, 2.00 mmol, 1.0 *eq*), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M in THF, 3.43 mL, 12.00 mmol, 6.0 *eq*), K_2CO_3 (1.10 g, 7.96 mmol, 3.98 *eq*) and $Pd(dppf)Cl_2$ (245 mg, 0.30 mmol, 0.15 *eq*) in dioxane (6 mL) and water (1 mL) was stirred at 90 °C for 8 hours under nitrogen atmosphere. The mixture was filtered through a pad of Celite, washed with ethyl acetate (100 mL) and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 20:1) to provide 2,6-dimethyl-4-(trifluoromethyl)aniline as a colorless oil (1.63 g). Yield 48% (ESI 190.1 $(M+H)^+$).

Step 2: 2-bromo-1,3-dimethyl-5-(trifluoromethyl)benzene



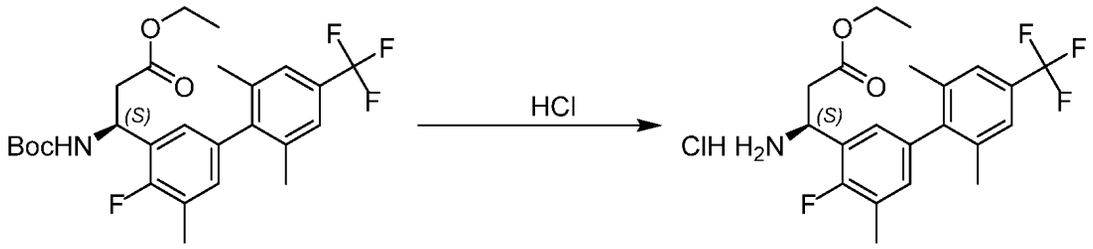
A mixture of 2,6-dimethyl-4-(trifluoromethyl)aniline (793 mg, 4.19 mmol, 1.0 *eq*), tert-butyl nitrite (0.94 mL, 7.84 mmol, 1.9 *eq*) and copper(I) bromide (794 mg, 5.53 mmol, 1.3 *eq*) in anhydrous acetonitrile (16 mL) was stirred at 60 °C for 2 hours under nitrogen atmosphere. LCMS showed that the reaction was completed. The mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 6:1) to provide 2-bromo-1,3-dimethyl-5-(trifluoromethyl)benzene as a colorless oil (975 mg). Yield 46%. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ: 7.55 (s, 2H), 2.42 (s, 6H).

Step 3: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



To a solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (519 mg, 1.15 mmol, 1.0 *eq*) in dioxane (36 mL) was added 2-bromo-1,3-dimethyl-5-(trifluoromethyl)benzene (306 mg, 1.21 mmol, 1.1 *eq*), Pd(dppf)Cl$_2$ (188 mg, 0.23 mmol, 0.2 *eq*), K$_2$CO$_3$ (477 mg, 3.45 mmol, 3.0 *eq*) and water (3.6 mL). The reaction mixture was stirred at 110 °C for 18 hours under nitrogen atmosphere. The mixture was filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 6:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a light brown oil (308 mg). Yield 54%. (ESI 398.1 [M+H-100]$^+$).

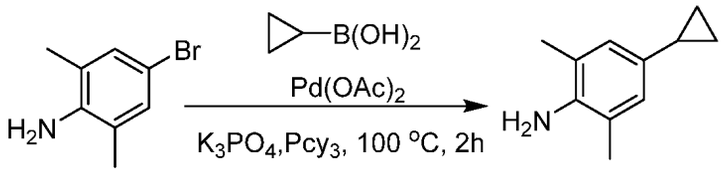
Step 5: ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride



To a stirred solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (308 mg, 0.62 mmol, 1.0 *eq*) in DCM (4 mL) was added HCl-dioxane (4 M, 4.0 mL, 16.0 mmol, 25.8 *eq*). The mixture was stirred at room temperature for 2 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride as a yellow oil (260 mg). Yield 97% (ESI 398.1 $[M+H]^+$).

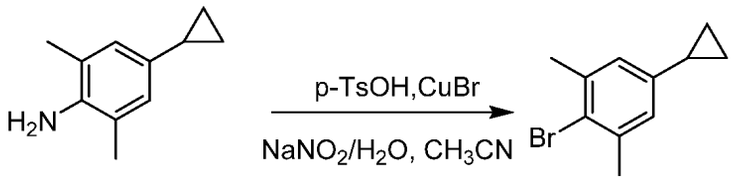
Preparation of ethyl (*S*)-3-amino-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: 4-cyclopropyl-2,6-dimethylaniline



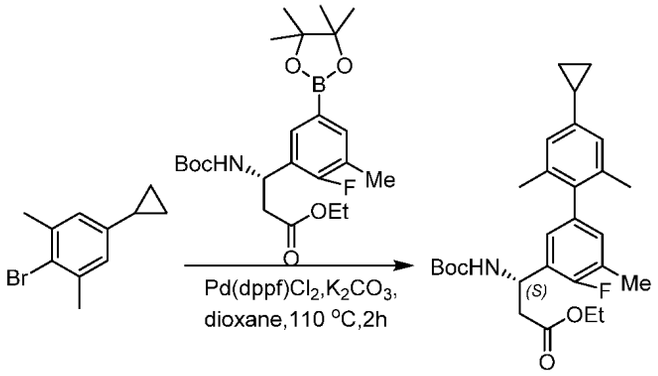
To a mixture of 4-bromo-2,6-dimethylaniline (2.0 g, 10.0 mmol, 1.0 *eq*), cyclopropylboronic acid (1.03 g, 12.0 mmol, 1.2 *eq*) in toluene (15 mL) under nitrogen atmosphere was added a solution of K_3PO_4 (4.2 g, 20.0 mmol, 2.0 *eq*) in H_2O (3 mL), PCy_3 (280.0 mg, 1.0 mmol, 0.1 *eq*) and $Pd(OAc)_2$ (224.0 mg, 1.0 mmol, 0.1 *eq*). The mixture was stirred at 100 °C for 4 hours under nitrogen atmosphere. Water (30 mL) was added and the solution was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 2:1) to provide 4-cyclopropyl-2,6-dimethylaniline (0.8 g) used in the next step without further purification. Yield 93% (ESI 162.2 $[M+H]^+$).

Step 2: 2-bromo-5-cyclopropyl-1,3-dimethylbenzene



To a mixture of 4-cyclopropyl-2,6-dimethylaniline (800.0 mg, 4.9 mmol, 1.0 *eq*) in ACN (10 mL) and H_2O (1 mL) was added p-toluenesulphonic acid (3.4 g, 19.8 mmo, 4.0 *eq*). The mixture was stirred at 0 °C for 10 mins under under nitrogen atmosphere. A solution of $NaNO_2$ (685.0 mg, 9.93 mmol, 2.0 *eq*) in H_2O (2 mL) was added dropwise and the mixture was stirred 0 °C for 30 mins. CuBr (4.4 g, 19.8 mmol, 4.0 *eq*) was added to the reaction mixture and stirred at room temperature for 4 hours. Water (50 mL) was added and the solution was extracted with DCM (50 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (petroleum ether: EtOAc 19:1) to provide 2-bromo-5-cyclopropyl-1,3-dimethylbenzene as a yellow oil (800.0 mg) used in the next step without further purification. Yield 49% (ESI 225.1 $(M+H)^+$, 227.1 $(M+H)^+$).

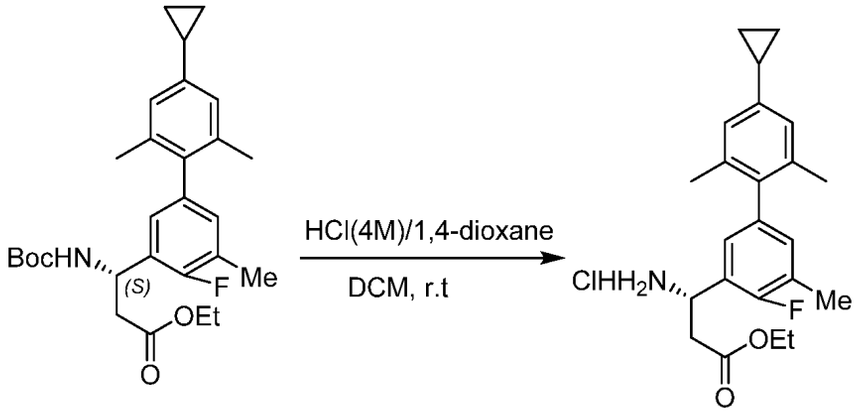
Step 3: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of 2-bromo-5-cyclopropyl-1,3-dimethylbenzene (800 mg, 3.6 mmol, 1.0 *eq*) and ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (1.6 g, 3.6 mmol, 1.0 *eq*) in 1,4-dioxane (10 mL) under nitrogen atmosphere was added a solution of K_2CO_3 (1.0 g, 7.2 mmol, 2.0 *eq*) in H_2O (1 mL) and $Pd(dppf)Cl_2$ (260 mg, 0.36 mmol, 0.1 *eq*). The mixture was stirred at 110 °C for 2 hours under nitrogen atmosphere. Water (30 mL) was added and the solution was extracted with EtOAc (50 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica

gel column (petroleum ether: EtOAc 19:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoateas a brown oil (500 mg). Yield 30% (ESI 370.1 $[M-100+H]^+$).

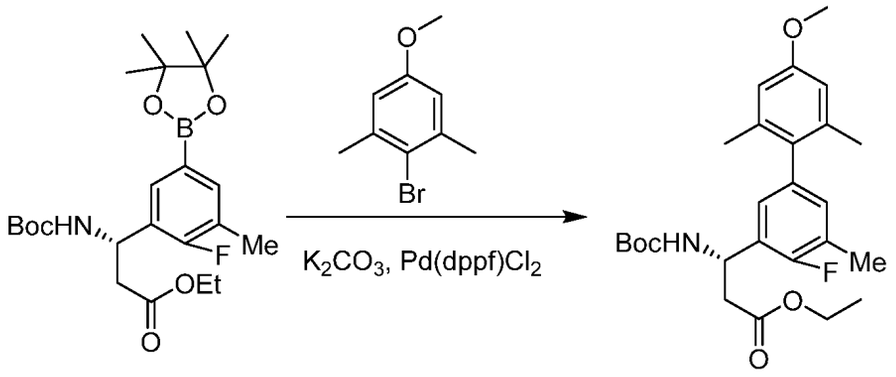
Step 4: ethyl (*S*)-3-amino-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride



To a stirred solution of ethyl (*S*)-3-((tert-butoxycarbonyl)amino)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (900 mg, 1.91 mmol, 1.0 *eq*) in DCM (5 mL) was added HCl-dioxane (4 M, 5.0 mL, 20.0 mmol, 10.47 *eq*) and stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride as a green-yellow foam (710 mg). Yield 91% (ESI 370.2 $[M+H]^+$).

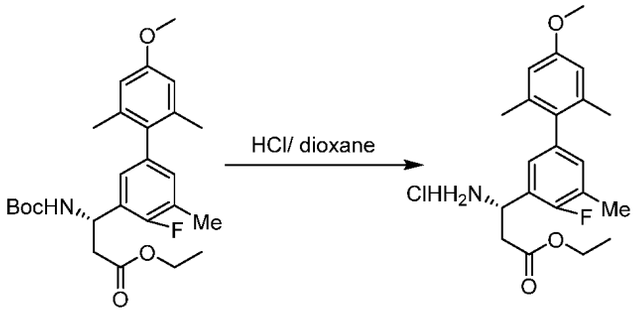
Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

Step 1: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (350 mg, 0.77 mmol, 1.0 *eq*) in dioxane (10 mL) was added 2-bromo-5-methoxy-1,3-dimethylbenzene (166 mg, 0.77 mmol, 1.0 *eq*), $Pd(dppf)Cl_2$ (56 mg, 0.077 mmol, 0.1 *eq*), K_2CO_3 (213 mg, 1.54 mmol, 2.0 *eq*) and water (2 mL). The reaction mixture was stirred at 110 °C for 3 hours under nitrogen atmosphere. Water (10 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 7:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (230 mg). Yield 65% (ESI 360.2 $[M+H-100]^+$).

Step 2: ethyl (*S*)-3-amino-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride

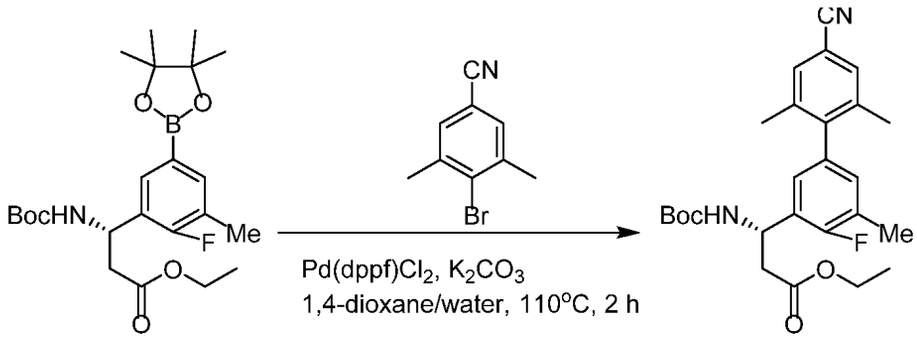


To a stirred solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.43 mmol, 1.0 *eq*) in DCM (7 mL) was added HCl-dioxane (4 M, 2.0 mL, 4.0 mmol, 9.3 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(4-fluoro-4'-methoxy-2',5,6'-

trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride as a yellow oil (160 mg). Yield 93% (ESI 360.2 $[M+H]^+$).

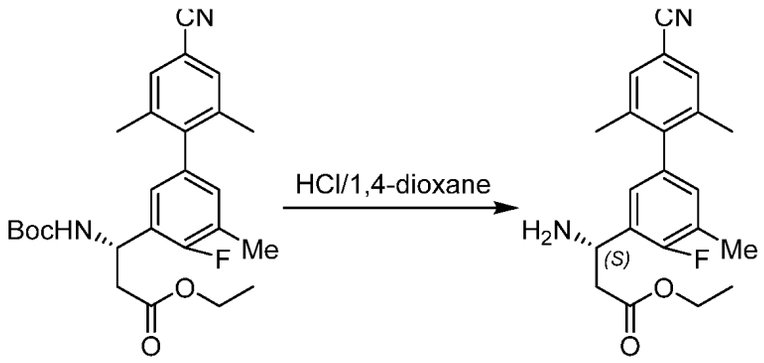
Preparation of ethyl (*S*)-3-amino-3-(4'-cyano-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyano-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (450 mg, 1 mmol, 1.0 *eq*), 4-bromo-3,5-dimethylbenzonitrile (316 mg, 1.5 mmol, 1.5 *eq*), $Pd(dppf)Cl_2$ (37 mg, 0.05 mmol, 0.05 *eq*) and K_2CO_3 (414 mg, 3 mmol, 3.0 *eq*) in 1,4-dioxane (8 mL) and water (2 mL) was stirred at 110 °C for 2 hours under nitrogen atmosphere. Water (10 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 1:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-cyano-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (320 mg). Yield 70% (ESI 455.2 $[M+H]^+$).

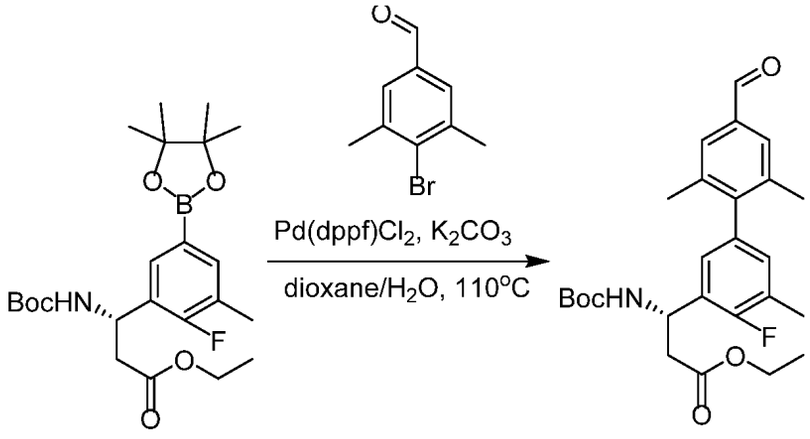
Step 2: ethyl (*S*)-3-amino-3-(4'-cyano-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a stirred solution of ethyl (S)-3-((tert-butoxycarbonyl)amino)-3-(4'-cyano-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (320 mg, 0.7 mmol, 1.0 *eq*) in DCM (2 mL) was added HCl-dioxane (4 M, 2.0 mL, 4.0 mmol, 5.7 *eq*). The mixture was stirred at room temperature for 2 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (S)-3-amino-3-(4'-cyano-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (250 mg). Yield 100% (ESI 355.1 $[M+H]^+$).

Preparation of ethyl (*S*)-3-amino-3-(4'-((dimethylamino)methyl)-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

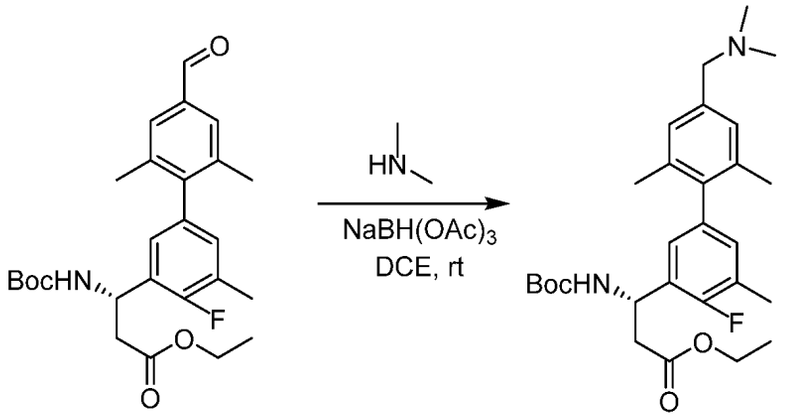
Step 1: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-4'-formyl-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (465 mg, 1.03 mmol, 1.1 *eq*), 4-bromo-3,5-dimethylbenzaldehyde (200 mg, 0.93 mmol, 1.0 *eq*), K_2CO_3 (259 mg, 1.87 mmol, 2.0 *eq*) and 1,1'-Bis(diphenylphosphino) ferrocene-palladium(II)dichloride dichloromethane complex (68 mg, 0.09 mmol, 0.1 *eq*) in dioxane (10 mL) and H_2O (1 mL) was stirred at 80 °C

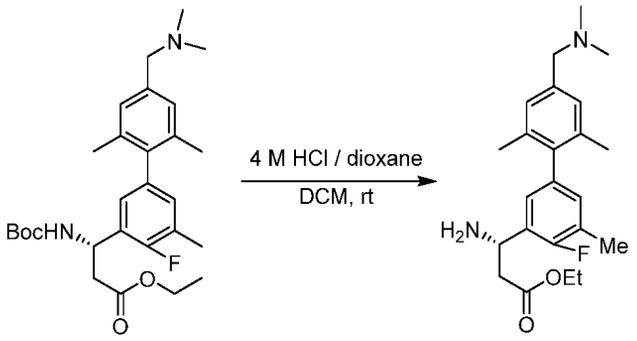
for 3 hours under nitrogen atmosphere. LCMS showed that the reaction was completed. The mixture was cooled to room temperature. Water (50 mL) was added and the solution was extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 1:3) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-4'-formyl-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (300 mg). Yield 64% (ESI 358.1 $[M+H-100]^+$)

Step 2: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-((dimethylamino)methyl)-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-4'-formyl-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.3 g, 2.8 mmol, 1.0 *eq*) and dimethylamine hydrochloride (233 mg, 2.9 mmol, 1.05 *eq*) in DCE (10 mL) was stirred at room temperature for 30 mins. Sodium triacetoxyborohydride (1.2 g, 5.6 mmol, 2.0 *eq*) was added and stirred at room temperature for 16 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 9:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-((dimethylamino)methyl)-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (800 mg). Yield 58.7% (ESI 487.2 $(M+H)^+$).

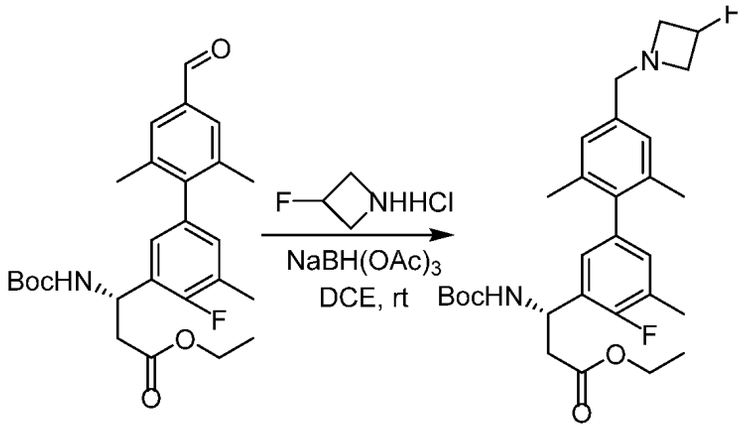
Step 3: ethyl (*S*)-3-amino-3-(4'-((dimethylamino)methyl)-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a stirred solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4'-((dimethylamino)methyl)-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (800 mg, 1.64 mmol, 1.0 *eq*) in DCM (10 mL) was added HCl-dioxane (4 M, 3mL, 12.0 mmol) and stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provideethyl (S)-3-amino-3-(4'-((dimethylamino)methyl)-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (600 mg). Yield 94% (ESI 387.2 $(M+H)^+$).

Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-4'-((3-fluoroazetidin-1-yl)methyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

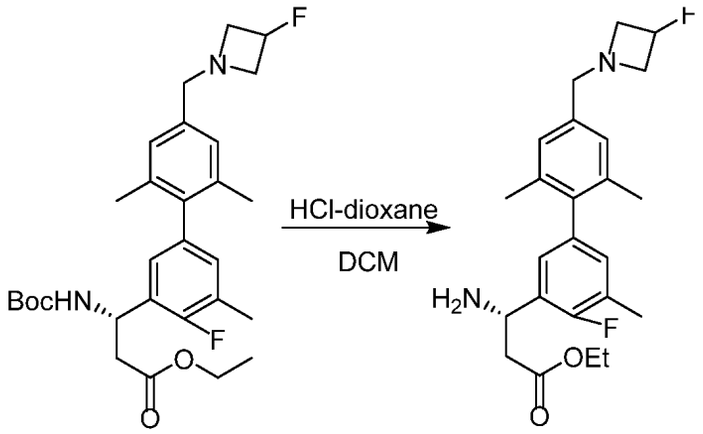
Step 1: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(4-fluoro-4'-((3-fluoroazetidin-1-yl)methyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (S)-3-((tert-butoxycarbonyl)amino)-3-(4-fluoro-4'-formyl-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.3 g, 2.8 mmol, 1.0 *eq*) and 3-fluoroazetidine hydrochloride (233 mg, 2.9 mmol, 1.05 *eq*) in DCM (10 mL) was stirred at room temperature for 30 mins. Sodium triacetoxyborohydride (1.2 g, 5.6 mmol, 2.0 *eq*) was added and stirred at

room temperature for 16 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 9:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4-fluoro-4'-((3-fluorocyclobutyl)methyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as yellow oil (800 mg). Yield 54.7% (ESI 517.2 $[M+H]^+$).

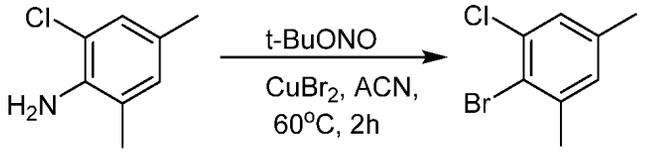
Step 2: ethyl (*S*)-3-amino-3-(4-fluoro-4'-((3-fluoroazetidin-1-yl)methyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a solution of ethyl (*S*)-3-((*t*ert-butoxycarbonyl)amino)-3-(4-fluoro-4'-((3-fluoroazetidin-1-yl)methyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (800 mg, 1.5 mmol, 1.0 *eq*) in DCM (10 mL) was added HCl-dioxane (4M, 10.0 mL, 40.0 mmol, 26.7 *eq*) and stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 120 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(4-fluoro-4'-((3-fluoroazetidin-1-yl)methyl)-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (500 mg). Yield 78% (ESI 417.1 $[M+H]^+$).

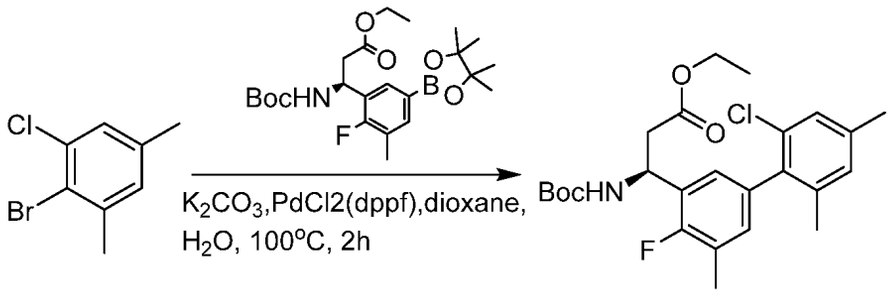
Preparation of ethyl (*S*)-3-amino-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: 2-bromo-1-chloro-3,5-dimethylbenzene



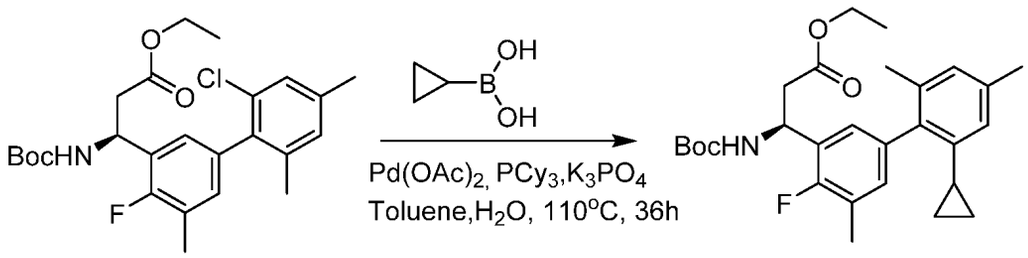
To a mixture of 2-chloro-4,6-dimethylaniline (3.0 g, 19.3 mmol, 1.00 *eq*) and $CuBr_2$ (21.5 g, 96.5 mmol, 5.00 *eq*) in ACN (50 mL) was added t-BuONO (5.96 g, 58.9 mmol, 3.00 *eq*) and stirred at 60 °C for 2 hours under nitrogen atmosphere. The mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether 100%) to give compound 2-bromo-1-chloro-3,5-dimethylbenzene as colorless oil (2.8 g). Yield: 67% (ESI 220 [M+H]+).

Step 2: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



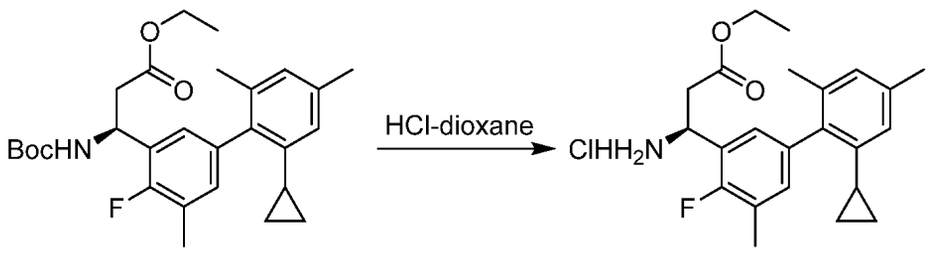
To a mixture of 2-bromo-1-chloro-3,5-dimethylbenzene (483 mg, 2.2 mmol, 1.10 *eq*), ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (902 mg, 2.0 mmol, 1.00 *eq*) in dioxane (10 mL) under nitrogen atmosphere was added a solution of K_2CO_3 (552 mg, 4.0 mmol, 2.00 *eq*) in H_2O (5 mL) and $Pd(dppf)Cl_2$ (146 mg, 0.2 mmol, 0.10 *eq*). The mixture was stirred at 100 °C for 2 hours under nitrogen atmosphere. Water (30 mL) was added and the solution was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (70 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as colorless oil (880 mg). Yield 95% (ESI 364 $[M-100+H]^+$).

Step 3: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-chloro-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (880 mg, 1.9 mmol, 1.00 *eq*), cyclopropylboronic acid (327 mg, 3.8 mmol, 2.00 *eq*) in toluene (10 mL) under nitrogen atmosphere was added a solution of K_3PO_4 (807 mg, 3.8 mmol, 2.00 *eq*) in H_2O (2 mL), $Pd(OAc)_2$ (43 mg, 0.19 mmol, 0.10 *eq*) and PCy_3 (107 mg, 0.38 mmol, 0.20 *eq*). The mixture was stirred at 110 °C for 36 hours under nitrogen atmosphere. Water (30 mL) was added and the solution was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (70 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether EtOAc 2:1) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a gray solid (625 mg). Yield 70% (ESI 370 $[M-100+H]^+$).

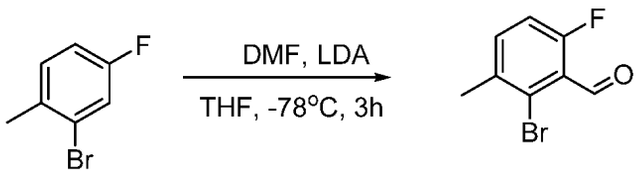
Step 4: ethyl (*S*)-3-amino-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride



To a solution of ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (250 mg, 0.53 mmol, 1.00 *eq*) in 1,4-dioxane (6 mL) was added HCl-dioxane (4M4.0 mL, 16.0 mmol, 30.2 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride as a white solid (215 mg), used directly in the next reaction without further purification. Yield 100% (ESI 370 $[M+H]^+$).

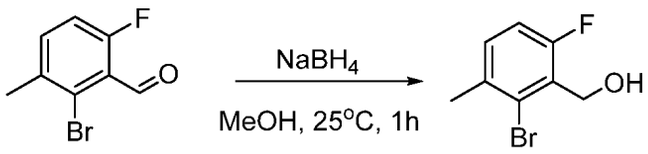
Preparation of ethyl (*S*)-3-amino-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: 2-bromo-6-fluoro-3-methylbenzaldehyde



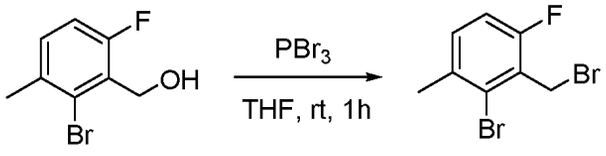
To a mixture of 2-bromo-4-fluoro-1-methylbenzene (5.0 g, 26.5 mmol, 1.00 *eq*) in anhydrous THF (50 mL) under nitrogen atmosphere was added lithium diisopropylamide (2.0 M, 14.6 mL, 29.2 mmol, 1.10 *eq*) at -78°C and stirred at -78°C for 1 hour. DMF (3.87 g, 53 mmol, 2.00 *eq*) was added to the reaction mixture at -78°C and stirred at -78°C for 0.5 hour, then slowly warmed to room temperature and stirred for 2 hours. The reaction was quenched with water (20 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product 2-bromo-6-fluoro-3-methylbenzaldehyde as a brown liquid (4.2 g). Yield 73%. ^{1}H NMR (400 MHz, MeOD) δ 10.02 (s, 1H), 7.45-7.17 (m, 1H), 7.05-7.00 (m, 1H), 2.26 (s, 3H).

Step 2: (2-bromo-6-fluoro-3-methylphenyl)methanol



To a mixture of 2-bromo-6-fluoro-3-methylbenzaldehyde (3.0 g, 13.8 mmol, 1.00 *eq*) in MeOH (30 mL) under nitrogen atmosphere was added $NaBH_4$ (1.5 g, 41.4 mmol, 3.00 *eq*) at 0°C and stirred at room temperature for 2 hours. The mixture was quenched with water (50 mL), extracted with EtOAc (50 mL x 3). The combined organic phase was washed with brine (80 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide (2-bromo-6-fluoro-3-methylphenyl)methanol as a white solid (2.7 g). Yield 90%

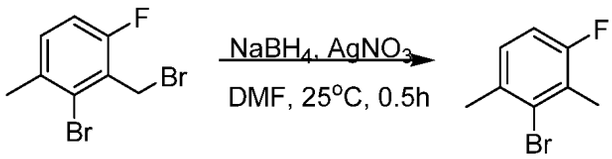
Step 3: (2-bromo-3-(bromomethyl)-4-fluoro-1-methylbenzene



To a mixture of (2-bromo-6-fluoro-3-methylphenyl)methanol (3.2 g, 14.6 mmol, 1.00 *eq*) in THF (50 mL) under nitrogen atmosphere was added PBr_3 (3 mL, 29.2 mmol, 2.00 *eq*) at

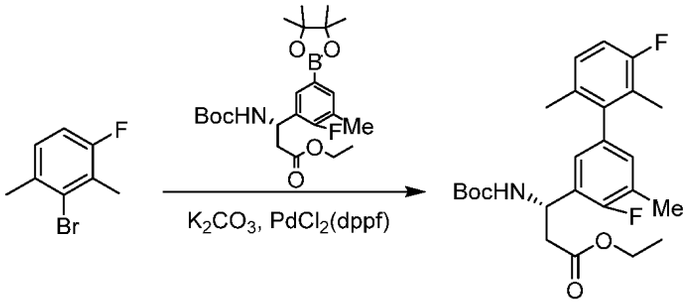
room temperature and stirred for 1 hour. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 99:1) to provide 2-bromo-3-(bromomethyl)-4-fluoro-1-methylbenzene as a white solid (3.58 g). Yield 90% ^{1}H NMR (400 MHz, MeOD) δ 7.33-7.30 (m, 1H), 7.09-7.04 (m, 1H), 4.72 (d, *J*=2.0 Hz, 2H), 2.40 (s, 3H).

Step 4: 2-bromo-4-fluoro-1,3-dimethylbenzene



To a mixture of 2-bromo-3-(bromomethyl)-4-fluoro-1-methylbenzene (2.0 g, 7.09 mmol, 1.00 *eq*) in DMF (20 mL) was added $NaBH_4$ (0.536 g, 14.18 mmol, 2.00 *eq*) and $AgNO_3$ (2.4 g, 14.18 mmol, 2.00 *eq*) at room temperature. The reaction was stirred at room temperature for 0.5 hour. The mixture was quenched with water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (DCM 100%) to provide 2-bromo-4-fluoro-1,3-dimethylbenzene as colorless oil (1.00 g). Yield 69% ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 – 7.01 (m, 1H), 6.90 (t, *J* = 8.7 Hz, 1H), 2.37 (s, 3H), 2.34 (d, *J* = 2.4 Hz, 3H).

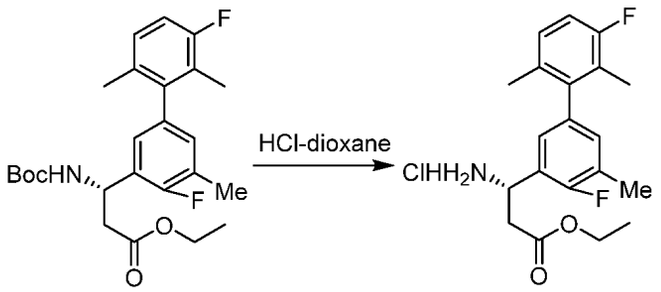
Step 5: ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of 2-bromo-4-fluoro-1,3-dimethylbenzene (800 mg, 3.93 mmol, 1.00 *eq*), ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (1.77 g, 3.93 mmol, 1.00 *eq*) in dioxane (12 mL) under nitrogen atmosphere was added a solution of K_2CO_3 (1.08 g, 7.86 mmol, 2.00 *eq*) in H_2O (2 mL) and $Pd(dppf)Cl_2$ (658 mg, 0.39 mmol, 0.10 *eq*). The mixture was stirred at 100 °C for 2 hours under nitrogen atmosphere. Water (30 mL) was added and the solution was extracted

with EtOAc (30 mL x 3). The combined organic layers were washed with brine (70 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as colorless oil (1.2 g). Yield 68% (ESI 348.1 $[M-100+H]^+$).

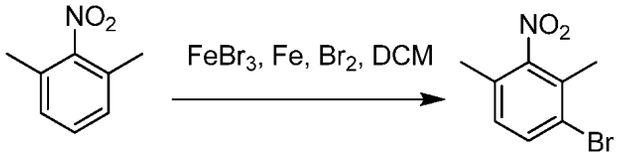
Step 6: ethyl (*S*)-3-amino-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride



To a mixture of product ethyl (*S*)-3-((*tert*-butoxycarbonyl)amino)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.2 g, 2.68 mmol, 1.00 *eq*) in 1,4-dioxane (6 mL) was added HCl-dioxane (4M 4.0 mL, 16.0 mmol, 5.97 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide ethyl (*S*)-3-amino-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (1.0 g crude) used directly in the next reaction without further purification. (ESI 348.2 $[M+H]^+$).

Preparation of (S)-ethyl 3-amino-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate

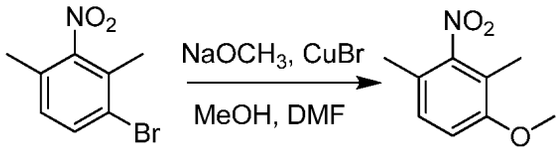
Step 1: 1-bromo-2,4-dimethyl-3-nitrobenzene



To a mixture of 1,3-dimethyl-2-nitrobenzene (10 g, 66 mmol, 1.0 *eq*) in DCM (100 mL) was added $FeBr_3$ (390 mg, 211.32 mmol, 0.02 *eq*) and Fe (1.12 g, 20 mmol, 0.3 *eq*). Br_2 (11.6 g,

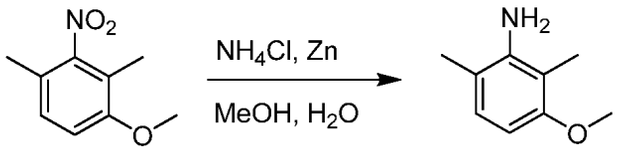
72.6 mmol, 1.1 eq) was added dropwise and stirred at 60°C for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether) to provide 1-bromo-2,4-dimethyl-3-nitrobenzene as a white solid (10 g). Yield 66%.

Step 2: 1-methoxy-2,4-dimethyl-3-nitrobenzene



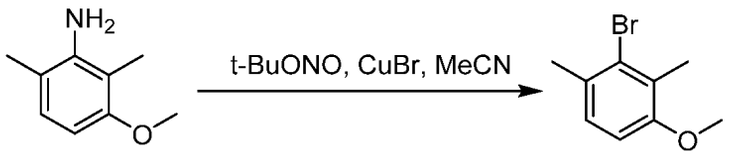
To a mixture of 1-bromo-2,4-dimethyl-3-nitrobenzene (8 g, 35 mmol, 1.0 *eq*) in MeOH (80 mL) and DMF (80 mL) was added $NaOCH_3$ (5.67 g, 105 mmol, 3 *eq*) and CuBr (1 g, 7 mmol, 0.2 *eq*) at room temperature. The mixture was stirred at 110°C for 16 hours. The reaction mixture was filtered. The filtrate was diluted with water (100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (100% pet ether) to provide 1-methoxy-2,4-dimethyl-3-nitrobenzene as a colorless oil (5.8 g). Yield 91% (ESI 182.2 $[M+H]^+$).

Step 3: 3-methoxy-2,6-dimethylaniline



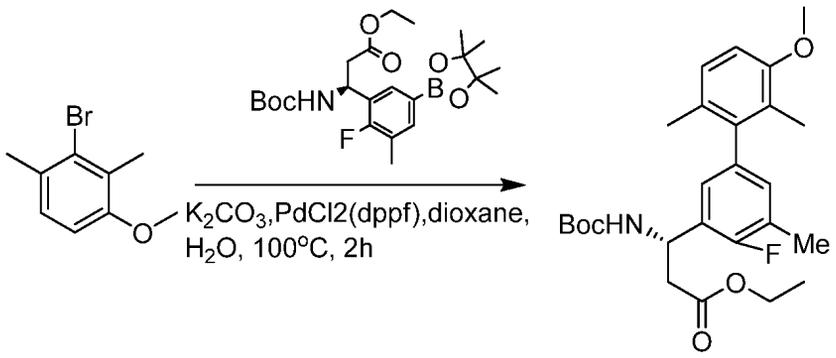
To a mixture of 1-methoxy-2,4-dimethyl-3-nitrobenzene (5.8 g, 32 mmol, 1.0 *eq*) in MeOH (60 mL) and H_2O (6 mL) at 0°C was added NH_4Cl (5.18 g, 96 mmol, 3.0 *eq*) and Zn (20.8 g, 320 mmol, 10 *eq*). The mixture was stirred at room temperature for 4 hours. LCMS showed that the reaction was completed. The reaction mixture was filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide 3-methoxy-2,6-dimethylaniline as yellow oil (2.8 g). Yield 58% (ESI 152.2$[M+H]^+$).

Step 4: 2-bromo-4-methoxy-1,3-dimethylbenzene



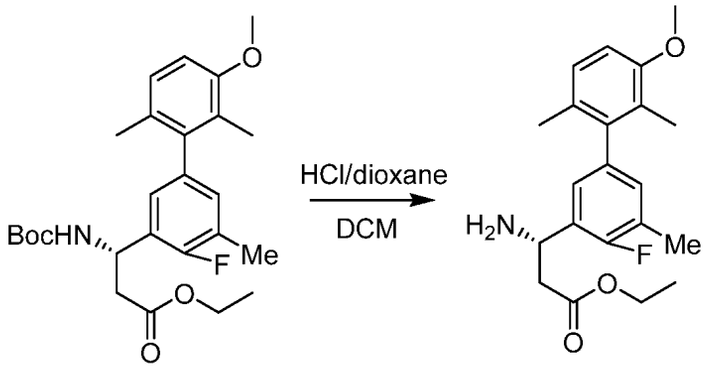
To a mixture of 3-methoxy-2,6-dimethylaniline (2 g, 13.24 mmol, 1.0 *eq*) in MeCN (30 mL) was added t-BuONO (2.06 g, 20 mmol, 1.5 *eq*) at 0°C, then CuBr(2.27 g, 15.89 mmol, 1.2 *eq*) was added. The mixture was stirred at 60°C for 2 hours. LCMS showed that the reaction was completed. The reaction mixture was concentrated *in vacuo* and purified by silica gel column (pet ether) to provide 2-bromo-4-methoxy-1,3-dimethylbenzene as a colorless oil (800 mg). Yield 28% .

Step 5: (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate



A mixture of 2-bromo-4-methoxy-1,3-dimethylbenzene (700 mg, 3.27 mmol, 1.00 *eq*), (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (1.47 g, 3.27 mmol, 1.0 *eq*), K_2CO_3 (1.35 g, 9.81 mmol, 3 *eq*) and $Pd(dppf)Cl_2$ (239 mg, 0.327 mmol, 0.1 *eq*) in dioxane (10 mL) and H_2O (1 mL) was stirred at 110°C for 4 hours under nitrogen atmosphere. LCMS showed that the reaction was completed. The mixture was cooled to room temperature. Water (30 mL) was added and the solution was extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 5:1) to provide (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate (1 g) as a colorless oil. Yield 67% (ESI 360.1 $[M\text{-}Boc+1]^+$).

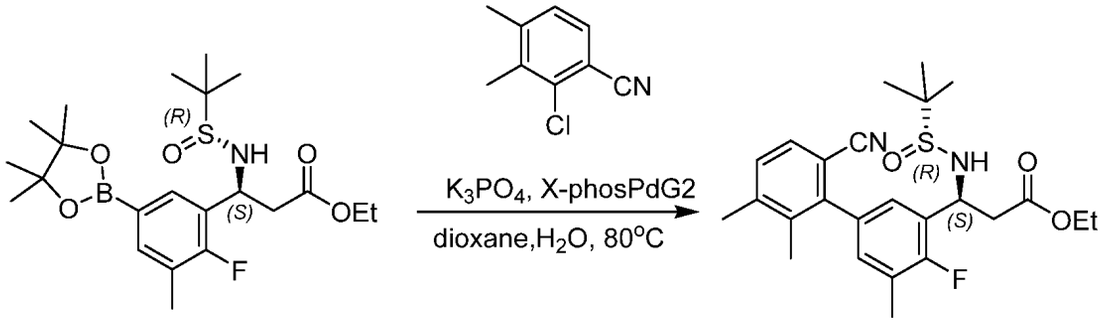
Step 6: (S)-ethyl 3-amino-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate



To a stirred solution of (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate (1 g, 2.18 mmol, 1.00 *eq*) in DCM (8 mL) was added HCl-dioxane (4 M, 2.18 mL, 8.72 mmol, 4 *eq*). The mixture was stirred at room temperature for 2 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/80g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (S)-ethyl 3-amino-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate (600 mg) as a colorless oil. Yield 77% (ESI 360.1 $[M+H]^+$).

Preparation of ethyl (*S*)-3-amino-3-(6'-cyano-4-fluoro-2',3',5-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

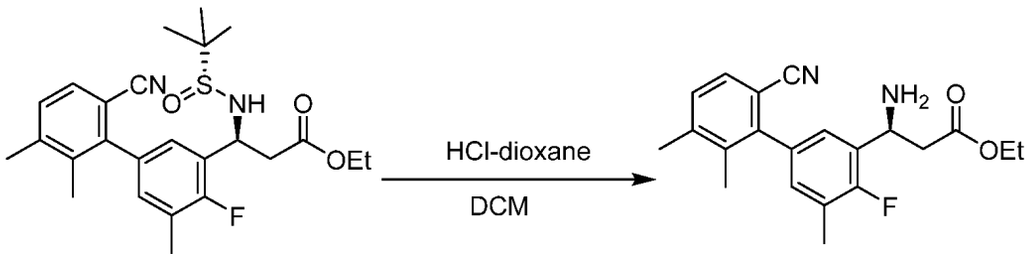
Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(6'-cyano-4-fluoro-2',3',5-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (1.7 g, 3.6 mmol,, 2.0 *eq*), 2-chloro-3,4-dimethylbenzonitrile (300 mg, 1.8 mmol, 1.0 *eq*), K_3PO_4 (1.2 g, 5.4 mmol, 3.0 *eq*) and XPhosPdG2 (140 mg, 0.18 mmol, 0.1 *eq*) in dioxane (30 mL) and H_2O (3 mL) was stirred at 80 °C for 2 hours under nitrogen atmosphere. LCMS showed that the reaction was completed. The mixture was cooled to room temperature. Water (20 mL) was added and the

solution was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(6'-cyano-4-fluoro-2',3',5-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (500 mg) as a yellow oil. Yield 60% (ESI 459.3 $[M+H]^+$).

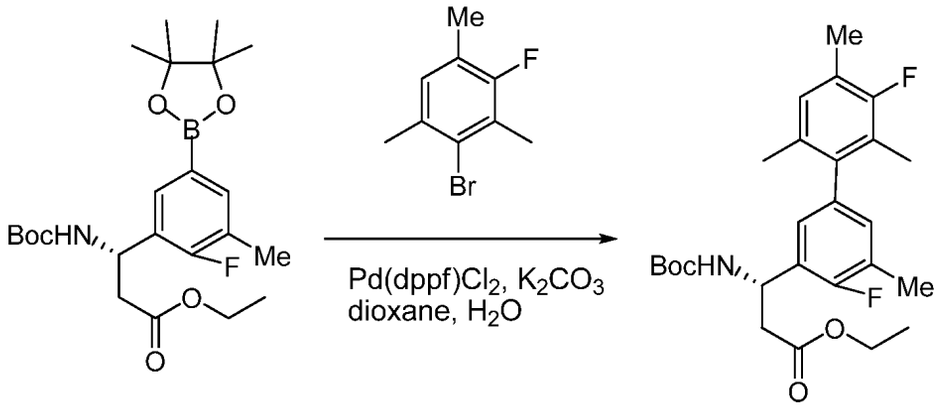
Step 2: ethyl (*S*)-3-amino-3-(6'-cyano-4-fluoro-2',3',5-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a stirred solution of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(6'-cyano-4-fluoro-2',3',5-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (500 mg, 1.1 mmol, 1.0 *eq*) in DCM (10 mL) was added HCl-dioxane (4 M, 10 mL, 40.0 mmol, 36.4 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(6'-cyano-4-fluoro-2',3',5-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (200 mg) as a colorless oil. Yield 51.8% (ESI 355.2 $[M+H]^+$).

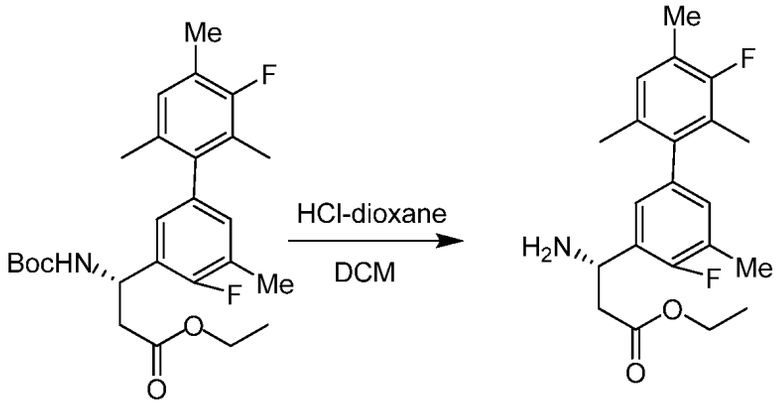
Preparation of (S)-ethyl 3-amino-3-(3',4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate

Step 1: (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(3',4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate



To a mixture of (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (500 mg, 1.14 mmol, 1 *eq*) and 2-bromo-4-fluoro-1,3,5-trimethylbenzene (309 mg, 1.43 mmol, 1.2 *eq*) in dioxane (10 mL) was added a solution of K_2CO_3 (314.6 mg, 2.28 mmol, 2 *eq*) in H_2O (2 mL) and $Pd(dppf)Cl_2$ (80 mg, 0.11 mmol, 0.1 *eq*). The mixture was heated to 110 °C for 2 hours under nitrogen atmosphere. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic layers were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:1) to give methyl (S)-ethyl 3-(tert-butoxycarbonylamino)-3-(3',4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate as a colorless oil (500 mg). Yield 97.8% (ESI 461.5 $[M+H]^+$).

Step 2: (S)-ethyl 3-amino-3-(3',4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate

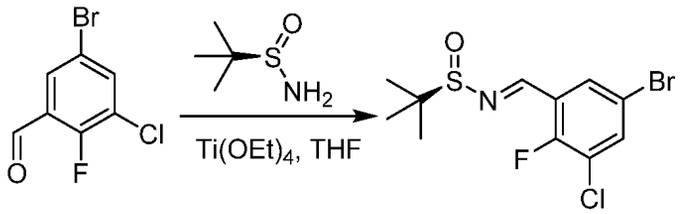


To a mixture of methyl (S)-methyl 3-(tert-butoxycarbonylamino)-3-(3',4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (500 mg, 1.12 mmol, 1 *eq*) in DCM (6 mL) was added HCl-dioxane (4 M, 3 mL, 12 mmol, 10 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to give crude product (S)-ethyl 3-amino-3-(3',4-difluoro-2',4',5,6'-

tetramethylbiphenyl-3-yl)propanoate as a white solid (300 mg) used directly in the next reaction without further purification. Yield 77% (ESI 361.4s $[M+H]^+$).

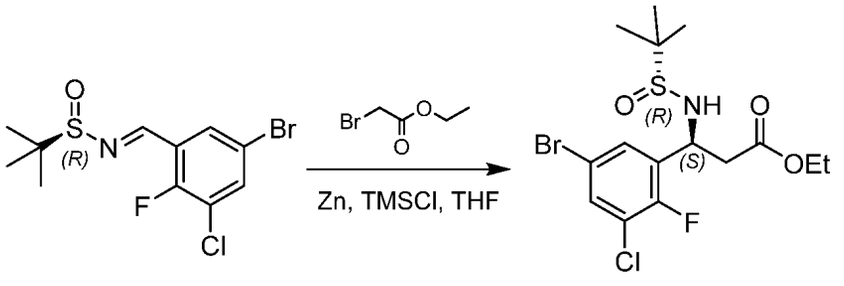
Preparation of ethyl (*S*)-3-(5-bromo-3-chloro-2-fluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

Step 1: (*R*, *E*)-*N*-(5-bromo-3-chloro-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide



To a mixture of 5-bromo-3-chloro-2-fluorobenzaldehyde (10.0 g, 42.2 mmol, 1.00 *eq*) and (*R*)-2-methylpropane-2-sulfinamide (5.6 g, 46.4 mmol, 1.1 *eq*) in anhydrous THF (100 mL) under nitrogen atmosphere was added $Ti(OEt)_4$ (14.4 g, 63.3 mmol, 1.50 *eq*) dropwise at room temperature and the temperature maintained below 30 °C. The reaction mixture was warmed to 35 °C and stirred for 1 hour. LCMS showed that the reaction was completed. Water (100 mL) and EtOAc (100 mL) were added into the mixture and stirred at room temperature for 5 mins. The mixture was filtered and washed with EtOAc (50 mL). The filtrate was separated. The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide *(R, E)*-*N*-(5-bromo-3-chloro-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide as a yellow oil (14.0 g). Yield 98% (ESI 341.9 $(M+H)^+$).

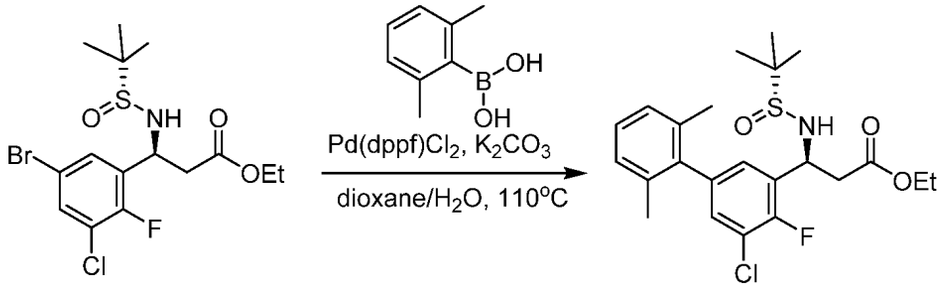
Step 2: ethyl (*S*)-3-(5-bromo-3-chloro-2-fluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate



To a mixture of Zn (13.0 g, 205.5 mmol, 5.00 *eq*) in anhydrous THF (200 mL) under nitrogen atmosphere was added chlorotrimethylsilane (888 mg, 8.22 mmol, 0.2 *eq*) dropwise at room temperature and stirred at 50 °C under nitrogen atmosphere for 1 hour. The mixture was cooled to 20-30°C. Ethyl 2-bromoacetate (17.1 g, 102.7 mmol, 2.50 *eq*) was added dropwise at room temperature under nitrogen atmosphere and stirred at 60 °C under for 1 hour. The reaction mixture was cooled to room temperature. A solution of *(R, E)-N*-(5-bromo-3-chloro-2-fluorobenzylidene)-2-methylpropane-2-sulfinamide (14.0 g, 41.1 mmol, 1.00 *eq*) in anhydrous THF (20 mL) was added dropwise into the mixture at room temperature under nitrogen atmosphere and stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. Water (100 mL) and EtOAc (100 mL) was added into the mixture and stirred at room temperature for 5 mins. The mixture was filtered. The filtrate was extracted with EtOAc (100 mL). The combined organic layers were washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl (*S*)-3-(5-bromo-3-chloro-2-fluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate as a yellow oil (12.0 g). Yield 73% (ESI 429.9 $(M+H)^+$).

Preparation of ethyl (*S*)-3-amino-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

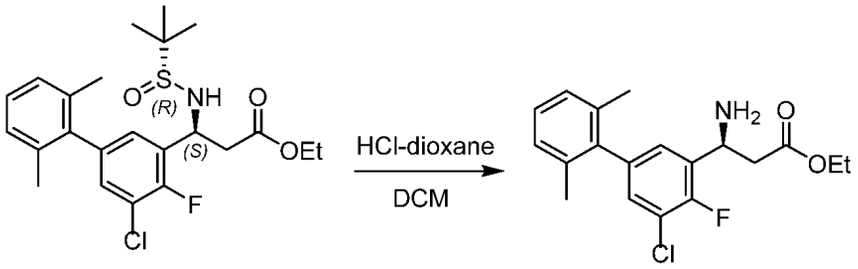
Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-3-chloro-2-fluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (4.0 g, 9.6 mmol, 1.00 *eq*), K_2CO_3 (8.0 g, 57.6 mmol, 2.0 *eq*) $Pd(dppf)Cl_2$ (1.4 g, 1.9 mmol, 0.1 *eq*) and (2,6-dimethylphenyl)boronic acid (2.8 g, 19.2 mmol, 2.00 *eq*) in dioxane (40 mL) and H_2O (4 mL) was stirred at 80 °C for 16 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature and poured into

50 mL of water and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (3.0 g). Yield 71% (ESI 454.1 $(M+H)^+$)

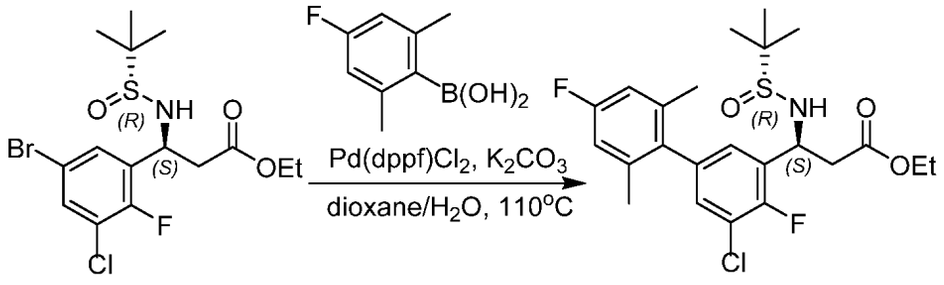
Step 2: ethyl (*S*)-3-amino-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (3.0 g, 43.66 mmol, 1.0 *eq*) in DCM (20 mL) was added HCl-dioxane (4 M, 20 mL, 80 mmol, 1.8 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (S)-3-amino-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (1.8 g). Yield 78% (ESI 350.0 $[M+H]^+$).

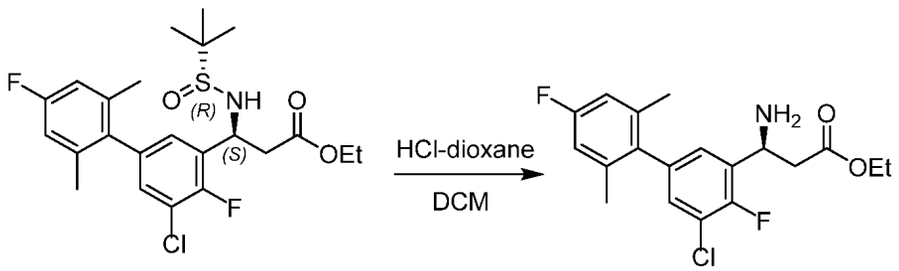
Preparation of ethyl (*S*)-3-amino-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-(5-bromo-3-chloro-2-fluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (2.0 g, 4.66 mmol, 1.0 *eq*) and (4-fluoro-2,6-dimethylphenyl)boronic acid (940 mg, 5.59 mmol, 1.2 *eq*) in dioxane (20 mL) was added a solution of K_2CO_3 (1.3 g, 9.32 mmol, 2.0 *eq*) in H_2O (2 mL) and $Pd(dppf)Cl_2$ (341 mg, 0.47 mmol, 0.1 *eq*). The mixture was heated to 110 °C for 2 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature and poured into water (50 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (1.2 g). Yield 54% (ESI 472.1 $[M+H]^+$).

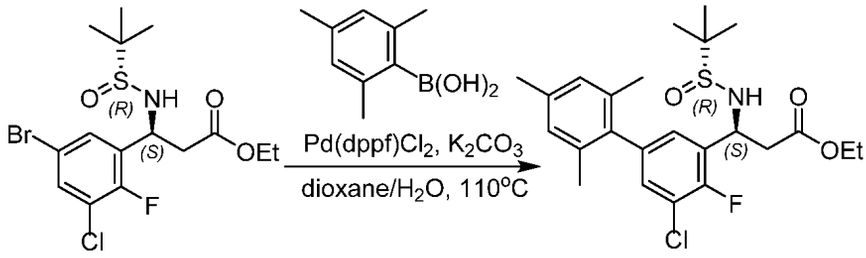
Step 2: ethyl (*S*)-3-amino-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.2 g, 2.54 mmol, 1.0 *eq*) in DCM (6 mL) was added HCl-dioxane (4 M, 3 mL, 12 mmol, 4.7 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/80g column (A: water 0.01% TFA, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (900 mg). Yield 96% (ESI 368.1 $[M+H]^+$).

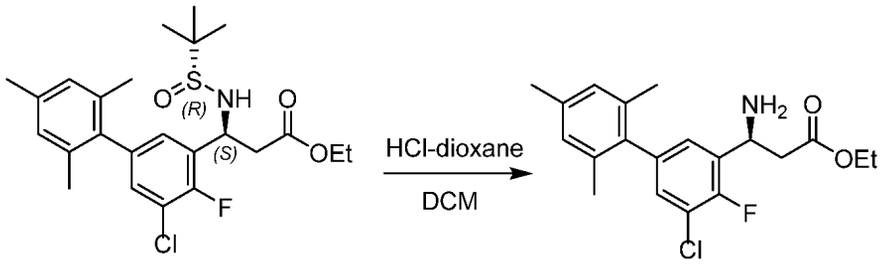
Preparation of ethyl (*S*)-3-amino-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-3-chloro-2-fluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (2.0 g, 4.66 mmol, 1.0 *eq*), mesitylboronic acid (1.5 g, 9.33 mmol, 2.0 *eq*), K_2CO_3 (1.29 g, 9.32 mmol, 2.0 *eq*) and $Pd(dppf)Cl_2$ (341 mg, 0.466 mmol, 0.1 *eq*) in dioxane (20 mL) and H_2O (2 mL) was stirred at 110 °C under nitrogen atmosphere overnight. After completion and cooling to room temperature, the reaction mixture was poured into water (50 mL), extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (1.9 g). Yield 87% (ESI 468 $(M+H)^+$).

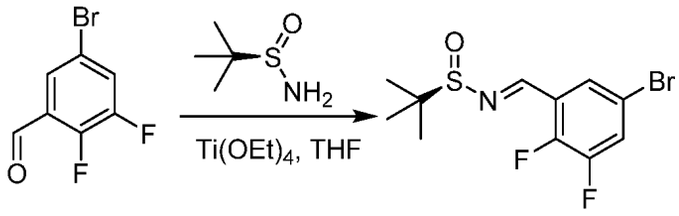
Step 2: ethyl (*S*)-3-amino-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.9 g, 4.06 mmol, 1.0 *eq*) in DCM (20 mL) was added HCl-dioxane (4 M, 3 mL, 12 mmol, 3.0 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (1.3 g). Yield 88% (ESI 364.1 $(M+H)^+$).

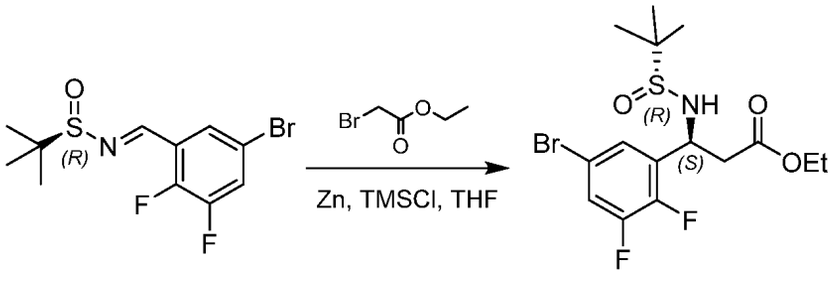
Preparation of ethyl (*S*)-3-(5-bromo-2,3-difluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

Step 1: (*R*, *E*)-*N*-(5-bromo-2,3-difluorobenzylidene)-2-methylpropane-2-sulfinamide



To a mixture of 5-bromo-2,3-difluorobenzaldehyde (4.5 g, 20.36 mmol, 1.0 *eq*) and (*R*)-2-methylpropane-2-sulfinamide (2.7 g, 22.40 mmol, 1.1 *eq*) in anhydrous THF (50 mL) under nitrogen atmosphere was added $Ti(OEt)_4$ (9.3 g, 40.72 mmol, 2.0 *eq*) dropwise at room temperature while maintaining the temperature below 30 °C. The reaction mixture was warmed to 35 °C and stirred for 1 hour. LCMS showed that the reaction was completed. Water (50 mL) and EtOAc (50 mL) was added into the mixture and stirred at room temperature for 10 mins. The mixture was filtered and washed with EtOAc (50 mL). The filtrate was separated. The organic layer was washed with water (70 mL) and brine (70 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide *(R, E)-N*-(5-bromo-2,3-difluorobenzylidene)-2-methylpropane-2-sulfinamide as a yellow oil (6.0 g). Yield 91% (ESI 325.9 $(M+H)^+$).

Step 2: ethyl (*S*)-3-(5-bromo-2,3-difluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

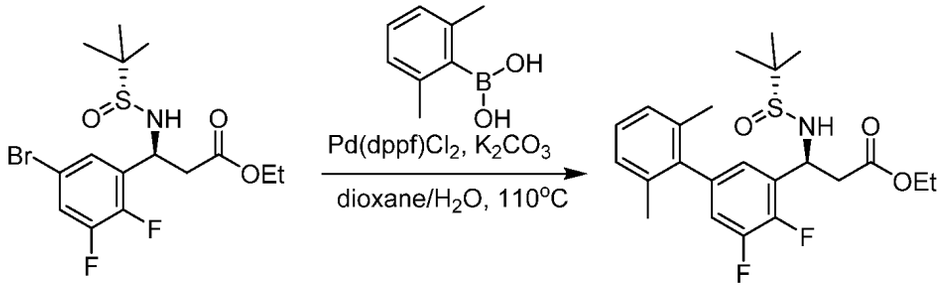


To a mixture of Zn (3.2 g, 49.2 mmol, 4.00 *eq*) in anhydrous THF (20 mL) under nitrogen atmosphere was added chlorotrimethylsilane (267 mg, 2.46 mmol, 0.2 *eq*) dropwise at room temperature. The mixture was stirred at 50 °C for 1 hour under nitrogen atmosphere and cooled to 20-30°C. Ethyl 2-bromoacetate (5.1 g, 30.75 mmol, 2.50 *eq*) was added dropwise at

room temperature under nitrogen atmosphere and then stirred at 60 °C for 1 hour under nitrogen atmosphere. The reaction mixture was cooled to room temperature. A solution of *(R,E)-N*-(5-bromo-2,3-difluorobenzylidene)-2-methylpropane-2-sulfinamide (4.0 g, 12.3 mmol, 1.00 *eq*) in anhydrous THF (5 mL) was added dropwise into the mixture at room temperature under nitrogen atmosphere and stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. Water (150 mL) and EtOAc (150 mL) were added into the mixture and stirred at room temperature for 10 mins. The mixture was filtered and washed with EtOAc (50 mL). The filtrate was separated. The organic layer was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 3:1) to provide ethyl (*S*)-3-(5-bromo-2,3-difluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate as a colorless oil (2.7 g). Yield 53% (ESI 412.0 $(M+H)^+$).

Preparation of ethyl (*S*)-3-amino-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

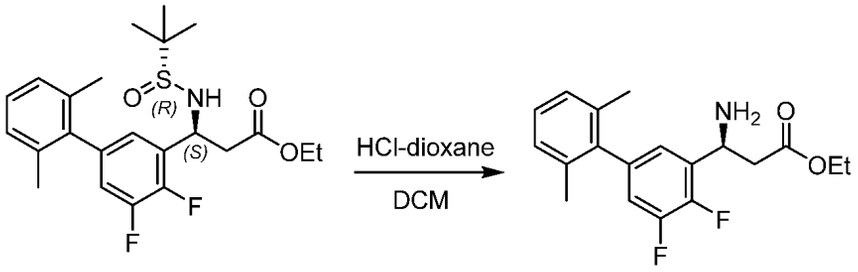
Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-2,3-difluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (1.0 g, 2.4 mmol, 1.00 *eq*), K_2CO_3 (664 mg, 4.8 mmol, 2.0 *eq*) $Pd(dppf)Cl_2$ (175 mg, 0.24 mmol, 0.1 *eq*) and (2,6-dimethylphenyl)boronic acid (720 mg, 4.8 mmol, 2.00 *eq*) in dioxane (12 mL) and H_2O (1.2 mL) was stirred at 110 °C under nitrogen atmosphere for 2 hours. LCMS showed that the reaction was completed. The reaction mixture was poured into 50 mL of water and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 2:1) to give desired product ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,5-

difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoateas a yellow oil (900 mg). Yield 85% (ESI 438.1 $(M+H)^+$).

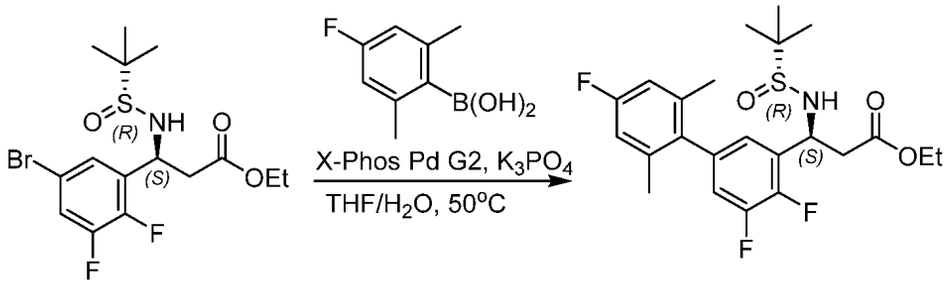
Step 2: ethyl (*S*)-3-amino-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (900 mg, 2.06 mmol, 1.0 *eq*) in DCM (4 mL) was added HCl-dioxane (4 M, 2 mL, 8.0 mmol, 3.88 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (800 mg). Yield 90% (ESI 334.1 $[M+H]^+$).

Preparation of ethyl (*S*)-3-amino-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

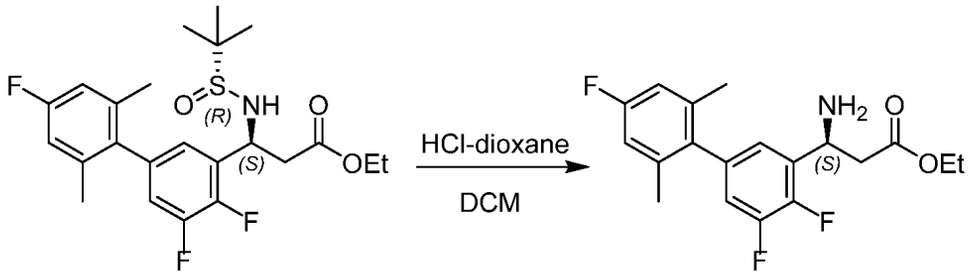
Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-2,3-difluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (1.1 g, 2.68 mmol, 1.00 *eq*), K_3PO_4 (1.7 g, 8.04 mmol, 3.00 *eq*), X-Phos Pd G2 (212 mg, 0.27 mmol, 0.10 *eq*) and (4-fluoro-2,6-dimethylphenyl)boronic

acid (900 mg, 5.36 mmol, 2.00 *eq*) in THF (10 mL) and H_2O (2 mL) was stirred at 50 °C under nitrogen atmosphere for 2 hours. LCMS showed that the reaction was completed. The reaction mixture was poured into 50 mL of water and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a brown oil (1 g). Yield 82% (ESI 456.1 $(M+H)^+$)

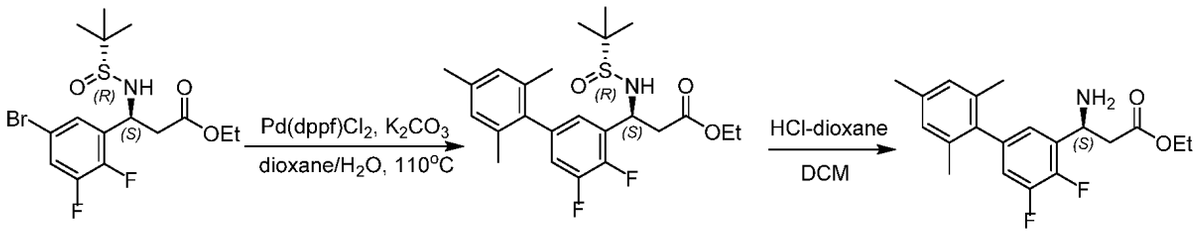
Step 2: ethyl (*S*)-3-amino-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



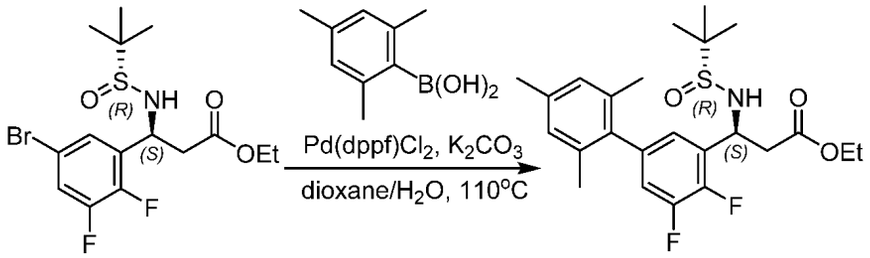
To a mixture of ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.0 g, 2.2 mmol, 1.0 *eq*) in DCM (4 mL) was added HCl-dioxane (4 M, 2 mL, 4.0 mmol, 1.8 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/80g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (750 mg). Yield 97% (ESI 352.1 $[M+H]^+$).

Preparation of ethyl (*S*)-3-amino-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Scheme:

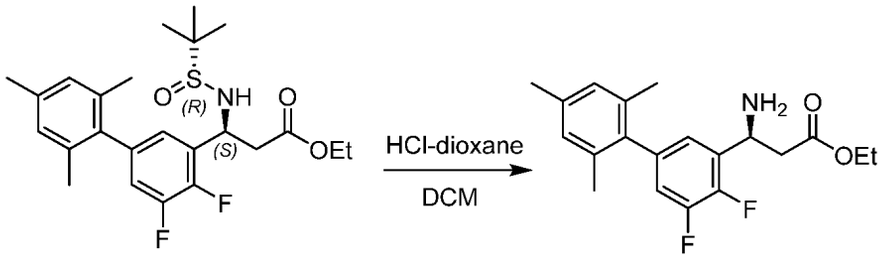


Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-2,3-difluorophenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (1.5 g, 3.65 mmol, 1.0 *eq*), mesitylboronic acid(1.2 g, 7.30 mmol, 2.0 *eq*), K_2CO_3 (1.5 g, 10.95 mmol, 3.0 *eq*) and $Pd(dppf)Cl_2$ (267 mg, 0.365 mmol, 0.1 *eq*) in dioxane (10 mL) and H_2O (1 mL) was stirred at 110 °C under nitrogen atmosphere for 1 hour. LCMS showed that the reaction was completed. The mixture was cooled to room temperature, poured into water (30 mL), extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (1.4 g). Yield 85% (ESI 452.2 $(M+H)^+$).

Step 2: ethyl (*S*)-3-amino-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

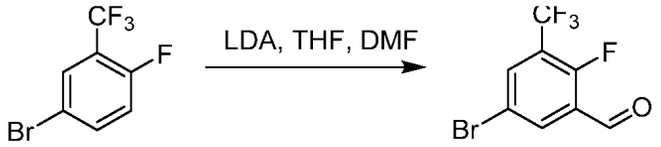


To a mixture of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.4 g, 3.1 mmol, 1.0 *eq*) in DCM (20 mL) was added HCl-

dioxane (4 M, 2 mL, 8.0 mmol, 2.58 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl (*S*)-3-amino-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (1.0 g). Yield 93% (ESI 348.1 $(M+H)^+$).

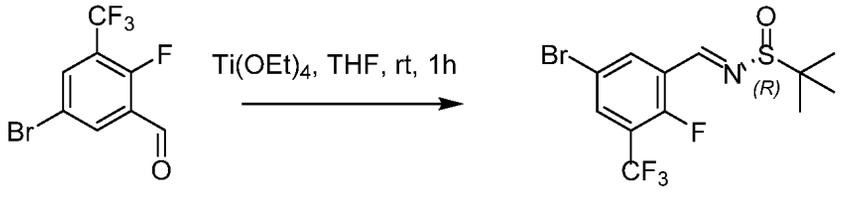
Preparation of ethyl (*S*)-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate

Step 1: 5-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde



To a solution of 4-bromo-1-fluoro-2-(trifluoromethyl)benzene (10.0 g, 41.15 mmol, 1.00 *eq*) in anhydrous THF (50 mL) under nitrogen atmosphere at -78 °C was added Lithium diisopropylamide (2.0 M, 30.9 mL, 61.73 mmol, 1.50 *eq*) dropwise and stirred at -78 °C for 1 hour under nitrogen atmosphere. *DMF* (15 mL) was added dropwise and the mixture was stirred at -78 °C for 1 hour. The mixture was quenched with 1M HCl aqueous solution (30 mL) and extracted with EtOAc (30 mL x 3). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue obtained was purified by silica gel column (pet ether: EtOAc 20:1) to provide 5-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde as a white solid (8.0 g). Yield 72%.^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.19 (dd, *J* = 5.4, 2.4 Hz, 1H), 7.98 (dd, *J* = 6.1, 2.5 Hz, 1H).

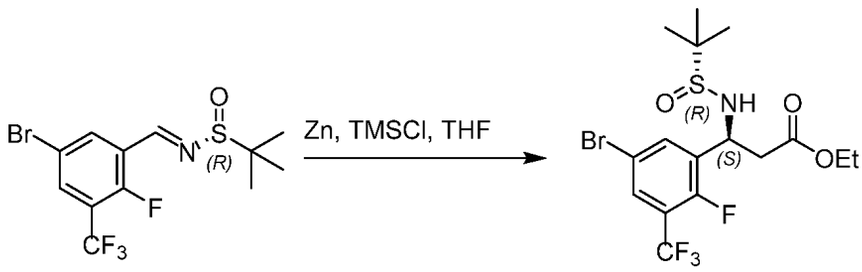
Step 2: (*R*, *E*)-*N*-(5-bromo-2-fluoro-3-(trifluoromethyl)benzylidene)-2-methylpropane-2-sulfinamide



To a mixture of 5-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde (8.0 g, 29.50 mmol, 1.00 *eq*) and (*R*)-2-methylpropane-2-sulfinamide (3.9 g, 32.45 mmol, 1.1 *eq*) in anhydrous THF (100 mL) under nitrogen atmosphere was added $Ti(OEt)_4$ (13.0 g, 59.00 mmol, 2.00

eq) dropwise at room temperature and maintained the temperature below 30 °C. The reaction mixture was stirred at room temperature for 1 hour under nitrogen atmosphere. LCMS showed that the reaction was completed. Water (100 mL) and EtOAc (100 mL) was added into the mixture and stirred at room temperature for 5 mins. The mixture was filtered and washed with EtOAc (50 mL). The filtrate was separated. The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 5:1) to provide (*R*, *E*)-*N*-(5-bromo-2-fluoro-3-(trifluoromethyl)benzylidene)-2-methylpropane-2-sulfinamide as a yellow oil (8.0 g). Yield 72% (ESI 373.9 $(M+H)^+$).

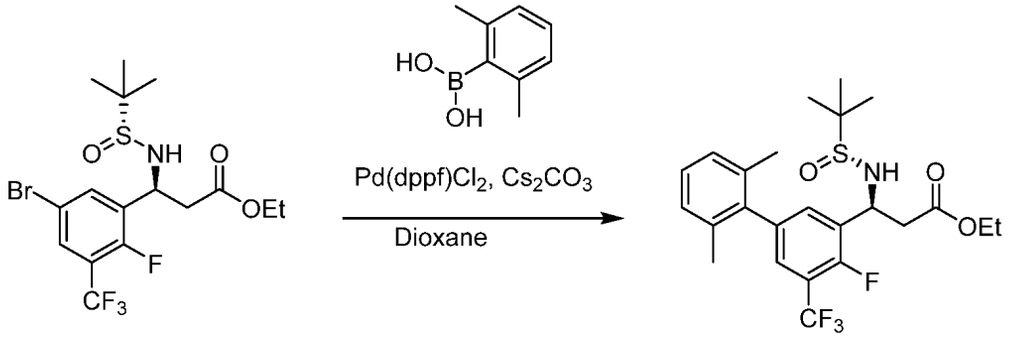
Step 3: ethyl (*S*)-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate



To a mixture of Zn (5.6 g, 85.6 mmol, 4.00 *eq*) in anhydrous THF (100 mL) under nitrogen atmosphere was added chlorotrimethylsilane (465 mg, 4.28 mmol, 0.2 *eq*) dropwise at room temperature. The mixture was stirred at 45 °C for 1 hour under nitrogen atmosphere and cooled to 20-30°C. Ethyl 2-bromoacetate (8.9 g, 53.5 mmol, 2.50 *eq*) was added dropwise at room temperature. The reaction mixture was stirred at 50 °C for 1 hour under nitrogen atmosphere and then cooled to room temperature. A solution of (*R*,*E*)-*N*-(5-bromo-2-fluoro-3-(trifluoromethyl)benzylidene)-2-methylpropane-2-sulfinamide (8.0 g, 21.4 mmol, 1.00 *eq*) in anhydrous THF (10 mL) was added dropwise into the mixture at room temperature under nitrogen atmosphere. The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. Water (100 mL) and EtOAc (100 mL) was added into the mixture and stirred at room temperature for 5 mins. The mixture was filtered and washed with EtOAc (100 mL). The filtrate was separated. The organic layer was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl (*S*)-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate as a colorless oil (6.3 g). Yield 64% (ESI 462.0 $(M+H)^+$).

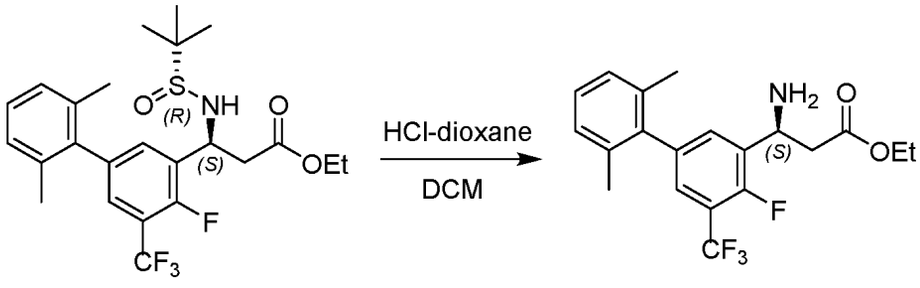
Preparation of ethyl (S)-ethyl 3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate

Step 1: ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



To a solution of ethyl (S)-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-(((R)-tert-butylsulfinyl)amino)propanoate (3 g, 6.49 mmol) and (2,6-dimethylphenyl)boronic acid (1.46 g, 9.73 mmol) in Dioxane (24 mL) was added a solution of Cs2CO3 (4.23 g, 12.98 mmol) in Water (8 mL). The reaction was purged with N2 for 5 min, followed by addition of PdCl2(dppf) (0.712 g, 0.973 mmol) and another N2 purge for 1 min. The reaction was stirred at 70C for 4 hours. The reaction mixture was diluted into 250 mL EtOAc, then washed with 1N HCl (250 mL), Sat. NaHCO3 (205 mL) and Brine (250 mL). The residue was concentrated and purified by silica gel chromatography to provide ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (2.71 g). Yield 86% (ESI 488 (M+H)+).

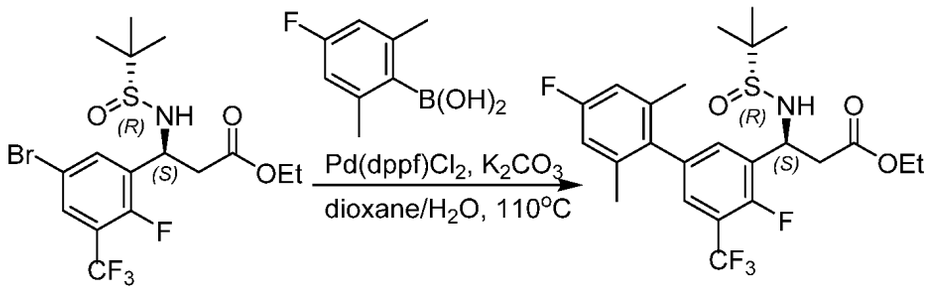
Step 2: (S)-ethyl 3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



To a solution of (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (0.93 g, 1.9 mmol, 1.00 *eq*) in DCM (8 mL) was added HCl-dioxane (4M, 1.9 mL, 7.6 mmol, 4 *eq*) and stirred at room temperature for 2 hours. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 120 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide (R)-ethyl 3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow solid (0.6 g). Yield 82% (ESI 384.1 $(M+H)^+$).

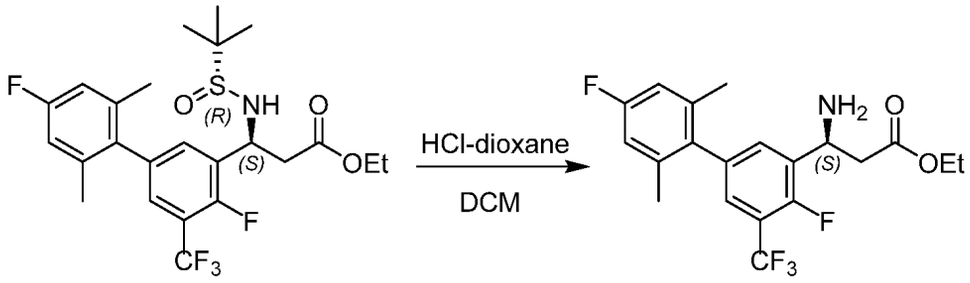
Preparation of ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-(((*R*)-*tert*-butylsulfinyl)amino)propanoate (2.0 g, 4.3 mmol, 1.00 *eq*), K_2CO_3 (1.8 g, 12.9 mmol, 3.00 *eq*), $Pd(dppf)Cl_2$ (315 mg, 0.43 mmol, 0.10 *eq*) and (4-fluoro-2,6-dimethylphenyl)boronic acid (1.1 g, 6.45 mmol, 1.50 *eq*) in dioxane (50 mL) and H_2O (5 mL) was stirred at 110 °C for 2 hours under nitrogen atmosphere. LCMS showed that the reaction was completed. The reaction mixture was poured into 50 mL of water, extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 3:1) to provideethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (1.4 g). Yield 64% (ESI 506.0 $(M+H)^+$)

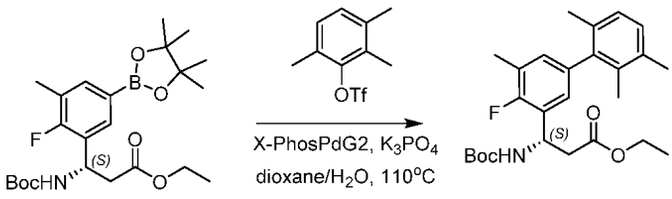
Step 2: ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (1.4 g, 2.77 mmol, 1.0 *eq*) in DCM (10 mL) was added HCl-dioxane (4 M, 6 mL, 24.0 mmol, 8.66 *eq*). The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl (S)-3-amino-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (880 mg). Yield 79% (ESI 402.1 $[M+H]^+$).

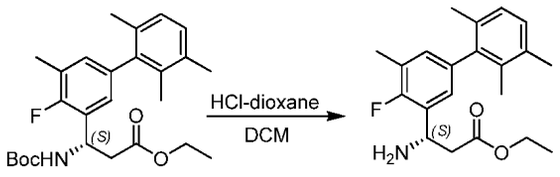
Preparation of (*S*)-ethyl 3-amino-3-(4-fluoro-2',3',5,6'-tetramethylbiphenyl-3-yl)propanoate

Step 1: (*S*)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-2',3',5,6'-tetramethylbiphenyl-3-yl)propanoate



To a mixture of (*S*)-ethyl 3-(tert-butoxycarbonylamino)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (3.0 g, 6.7 mmol), 2,3,6-trimethylphenyl trifluoromethanesulfonate (2.2 g, 8.0 mmol) and K_3PO_4 (4.3 g, 20.1 mmol) in dioxane (30 mL) and H_2O (3 mL) was added X-Phos Pd G2 (550 mg, 0.7 mmol). The mixture was heated to 110°C for 1 hr under nitrogen atmosphere. Water (50 mL) was added and the solution was extracted with EtOAc (60 mL x 3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide (*S*)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-2',3',5,6'-tetramethylbiphenyl-3-yl)propanoate as a dark solid (1.7 g). Yield 57 % (ESI 344.1 $[M+H-100]^+$).

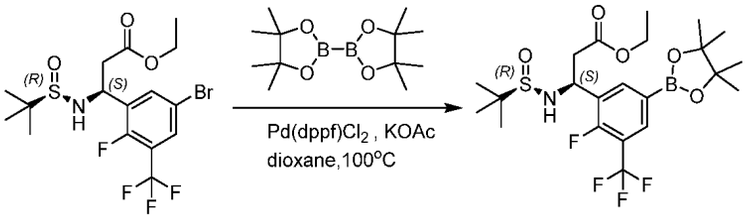
Step 2: (*S*)-ethyl 3-amino-3-(4-fluoro-2',3',5,6'-tetramethylbiphenyl-3-yl)propanoate



To a mixture of (*S*)-ethyl 3-(tert-butoxycarbonylamino)-3-(4-fluoro-2',3',5,6'-tetramethylbiphenyl-3-yl)propanoate (1.7 g, 3.8 mmol) in DCM (2 mL) was added HCl-dioxane (4M, 5 mL, 20.0 mmol) and the mixture was stirred at rt for 30 minutes. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120g column (A: water 10mM NH_4HCO_3, B: CH_3CN, 0~100%) to provide (*S*)-ethyl 3-amino-3-(4-fluoro-2',3',5,6'-tetramethylbiphenyl-3-yl)propanoate as a colorless oil (1.0 g). Yield 76 % (ESI 344.1 $[M+H]^+$).

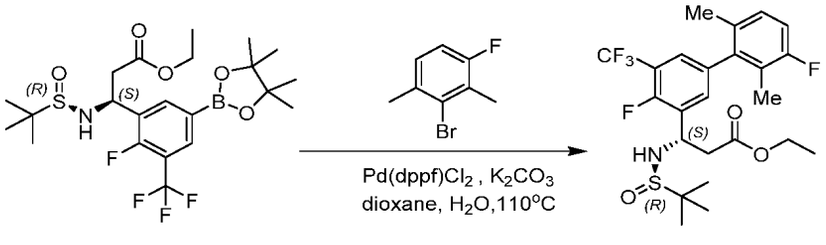
Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-3-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenyl)propanoate



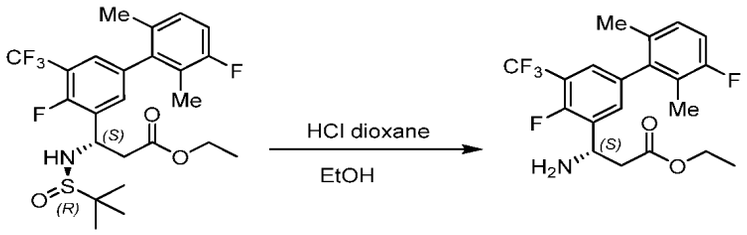
A mixture of ethyl (*S*)-3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-(((*R*)-tert-butylsulfinyl)amino)propanoate (2.8 g, 6.1 mmol), KOAc (1.8 g, 18.3mmol), $Pd(dppf)Cl_2$ (446 mg, 0.61 mmol) and (4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (2.3 g, 9.15 mmol) in dioxane (30 mL) was stirred at 100 °C for 2 hours under nitrogen. The reaction mixture was poured into 50 mL of water and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 3:1) to provideethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-3-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenyl)propanoate as a colorless oil (2.6 g). Yield 84 % (ESI 510.1 $(M+H)^+$)

Step 2: ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-3-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenyl)propanoate (600 mg, 1.2 mmol), K_2CO_3 (497mg, 3.6 mmol), $Pd(dppf)Cl_2$ (88 mg, 0.12 mmol) and 2-bromo-4-fluoro-1,3-dimethylbenzene (363.6 mg, 1.8 mmol) in dioxane (6 mL) and H_2O (0.6 mL) was stirred at 110 °C under nitrogen for 2 hours. The reaction mixture was poured into 20 mL of water and extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 3:1) to provideethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (460 mg). Yield 77 % (ESI 506.1 $(M+H)^+$)

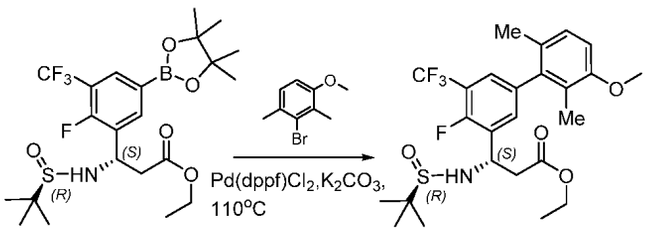
Step 3: ethyl (*S*)-3-amino-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (*S*)-3-(((*R*)-tert-butylsulfinyl)amino)-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (460 mg, 0.91 mmol) in EtOH (5 mL) was added HCl-dioxane (4 M, 2 mL, 8.0 mmol). The mixture was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water/0.05%TFA, B: MeOH, 0~100%) to provideethyl (*S*)-3-amino-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (230 mg). Yield 63% (ESI 402.1 $[M+H]^+$).

Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

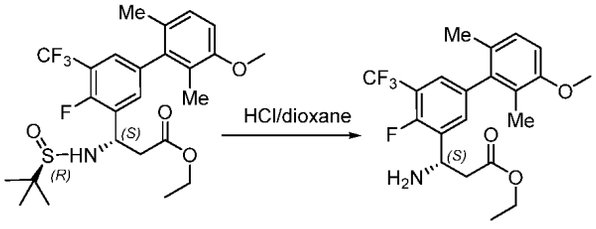
Step 1: ((S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenyl)propanoate (600 mg, 1.18 mmol), K_2CO_3 (488 mg, 3.54

mmol), $Pd(dppf)Cl_2$ (43 mg, 0.06 mmol) and 2-bromo-4-methoxy-1,3-dimethylbenzene (300 mg, 1.42 mmol) in dioxane (10 mL) and H_2O (1 mL) was stirred at 110 °C under nitrogen atmosphere for 1 hour. The reaction mixture was poured into 50 mL of water and extracted with EtOAc (50 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 3:2) to provide (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a colorless oil (400 mg). Yield 65 % (ESI 518.3 $(M+H)^+$)

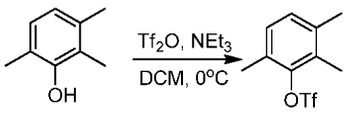
Step 2: (S)-ethyl 3-amino-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



To a mixture of (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (400 mg, 0.77 mmol) in DCM (2 mL) was added HCl-dioxane (4 M, 1 mL, 4.0 mmol). The mixture was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: CH_3CN, 0~100%) to provide (S)-ethyl 3-amino-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (200 mg). Yield 63% (ESI 414.1 $[M+H]^+$).

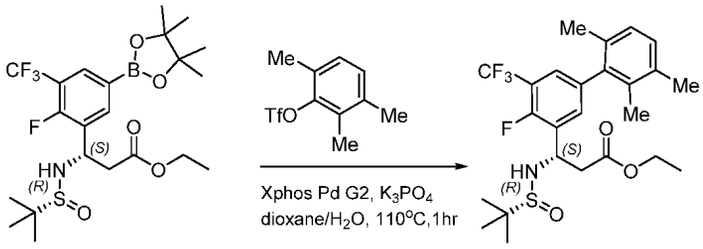
Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

Step 1: 2,3,6-trimethylphenyl trifluoromethanesulfonate



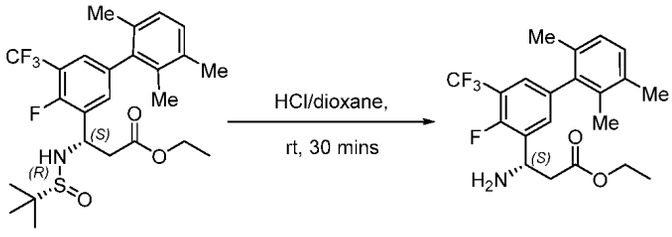
To a mixture of 2,3,6-trimethylphenol (5 g, 36.8 mmol), NEt_3 (9.3 g, 92.0 mmol) in DCM (100 mL) was added Tf_2O (15.6 g, 55.2 mmol) at 0 °C dropwise and stirred at room temperature for 3 hours. The reaction mixture was poured into 100 mL of water and extracted with DCM (100 x 3mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether) to provide 2,3,6-trimethylphenyl trifluoromethanesulfonate as a colorless oil (8 g). Yield 80 % (ESI 269.3 $(M+H)^+$).

Step 2: (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



To a mixture of (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)phenyl)propanoate (400 mg, 0.79 mmol), 2,3,6-trimethylphenyl trifluoromethanesulfonate (253 mg, 0.94 mmol) and K_3PO_4 (502 mg, 2.37 mmol) in dioxane (10 mL) and H_2O (1 mL) was added Xphos Pd G2 (63 mg, 0.08 mmol). The mixture was heated to 110°C for 30 mins under nitrogen atmosphere. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a dark solid (300 mg). Yield 76 % (ESI 502.1 $[M-100+H]^+$).

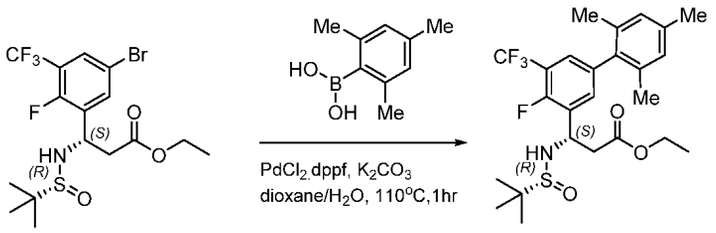
Step 3: (S)-ethyl 3-amino-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



To a mixture of (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (300 mg, 0.6 mmol) in DCM (1mL) was added HCl-dioxane (4N, 1 mL, 2.5 mmol) and the mixture was stirred at room temperature for 0.5 hr. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: CH_3CN, 0~100%) to provide (S)-ethyl 3-amino-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a colorless oil (170 mg). Yield 71% (ESI 398.1$(M+H)^+$).

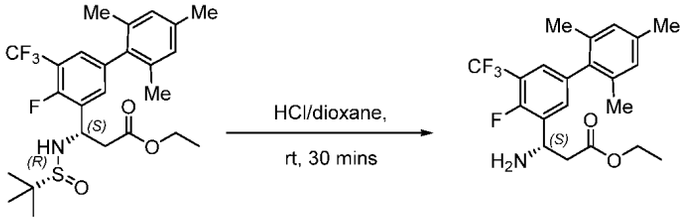
Preparation of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

Step 1: (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



To a mixture of (S)-ethyl 3-(5-bromo-2-fluoro-3-(trifluoromethyl)phenyl)-3-((R)-1,1-dimethylethylsulfinamido)propanoate (461 mg, 1.0 mmol), mesitylboronic acid (197 mg, 1.2 mmol) and K_2CO_3 (414 mg, 3.0 mmol) in dioxane (10 mL) and H_2O (1 mL) was added $Pd(dppf)Cl_2$ (73 mg, 0.1 mmol). The mixture was heated to 110°C for 2 hrs under nitrogen atmosphere. Water (20 mL) was added and the mixture was extracted with EtOAc (20 mL x 3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a dark solid (400 mg). Yield 80 % (ESI 502.1 $[M-100+H]^+$).

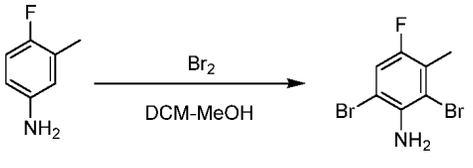
Step 2: (S)-ethyl 3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



To a mixture of (S)-ethyl 3-((R)-1,1-dimethylethylsulfinamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (400 mg, 0.8 mmol) in DCM (1mL) and EtOH (2mL) was added HCl-dioxane (4M, 2 mL, 8 mmol) and stirred at rt for 0.5 hr. The mixture was concentrated *in vacuo* to provide theproduct as a yellow oil (350 mg, crude).(ESI 398.1$[M+H]^+$).

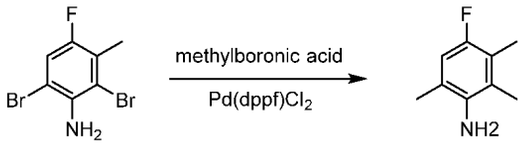
Preparation of ethyl (3S)-3-amino-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

Step 1: 2,6-dibromo-4-fluoro-3-methylaniline



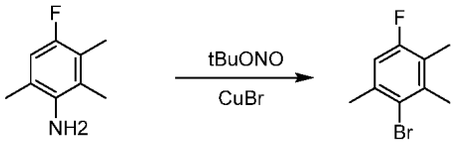
To a mixture of 4-fluoro-3-methylaniline (50.0 g, 400 mmol,) in MeOH (120 mL) and DCM (120 mL) was added bromine (52 mL, 1.0 mol) dropwise at room temperature over 1.5 hour and stirred at room temperature for 4 hours. 1N $Na_2S_2O_3$ aqueous solution (300 mL) and ethyl acetate (500 mL) was added and stirred for 10 mins, then carefully basified with 1N Na_2CO_3 aqueous solution (300 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with 1N $Na_2S_2O_3$ aqueous solution (300 mL) and brine (200 mL) dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide 2,6-dibromo-4-fluoro-3- methylaniline as a white solid (80 g). Yield 70.7 % (ESI 284.0$[M+H]^+$).

Step 2: 4-fluoro-2,3,6-trimethylaniline



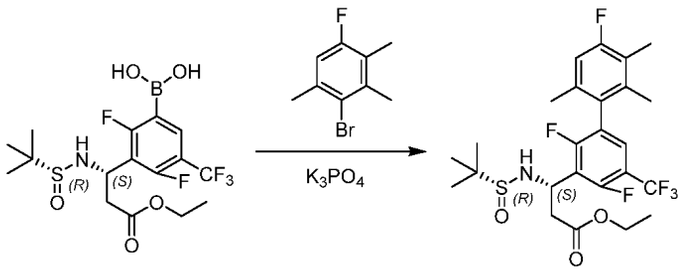
To a solution of ethyl 2,6-dibromo-4-fluoro-3-methylaniline (50.0 g, 273 mmol) in dioxane (500.0 mL) and water (50 mL) was added methylboronic acid (49.0 g, 819 mmol), K_2CO_3 (111.0 g, 819 mmol) and 1,1'-Bis(diphenylphosphino) ferrocene-palladium(II)dichloride dichloromethane complex (10.0 g, 13.65 mmol).The mixture was stirred at 110 °C overnight. The reaction was poured into water (500 mL) and extracted with Ethyl Acetate (500 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:5) to provide 4-fluoro-2,3,6-trimethylaniline as a colorless oil (20.0 g). Yield 47.6 % (ESI 154.3 $(M+H)^+$)

Step 3: 2-bromo-5-fluoro-1,3,4-trimethylbenzene



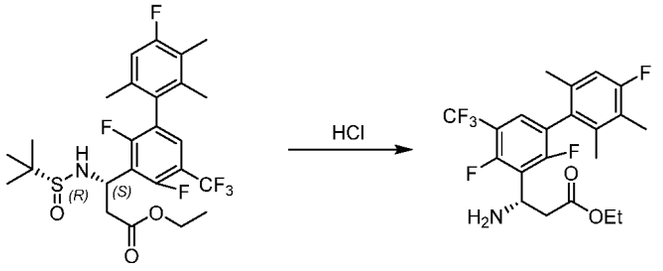
To a mixture of 4-fluoro-2,3,6-trimethylaniline (3.8 g, 24.8 mmol) in MeCN (30 mL) was added t-BuONO (3.8 g, 37.2 mmol) at 0°C, then CuBr(4.3 g, 29.7 mmol) was added. The mixture was stirred at 60°C for 2 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether) to provide 2-bromo-5-fluoro-1,3,4-trimethylbenzene as a colorless oil (1.3 g). Yield 33.9 % .

Step 4: ethyl (3S)-3-(((R)-tert-butylsulfinyl)amino)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of (3-((S)-1-(((R)-tert-butylsulfinyl)amino)-3-ethoxy-3-oxopropyl)-2,4-difluoro-5-(trifluoromethyl)phenyl)boronic acid (1.5 g, 3.3 mmol), 2-bromo-5-fluoro-1,3,4-trimethylbenzene (950 mg, 4.3 mmol), K_3PO_4 (2.1 g, 9.9 mmol), X-Phos Pd G2 (285 mg, 0.33 mmol) in dioxane (10 mL) and H_2O (2 mL) was stirred at 110°C for 2h under N2 atmosphere. The mixture was poured into water (100 mL) and extracted with EtOAc (100 mL X 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl (3S)-3-(((R)-tert-butylsulfinyl)amino)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (380 mg) as a yellow oil. Yield 21.3% (ESI 538.0$(M+H)^+$).

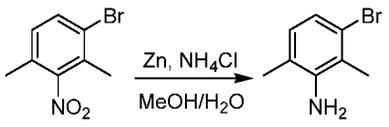
Step 5: ethyl (3S)-3-amino-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



To a solution of ethyl (3S)-3-(((R)-tert-butylsulfinyl)amino)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (380 mg, 0.70 mmol) in DCM (5 mL) was added HCl-dioxane (4 M, 5 mL) and stirred at at room temperature for 1 hour. The mixture was concentrated *in vacuo* to provide ethyl (3S)-3-amino-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoateas a yellow oil (340 mg) used directly in the next step without further purification. Yield 100% (ESI 434.2 $[M+H]^+$).

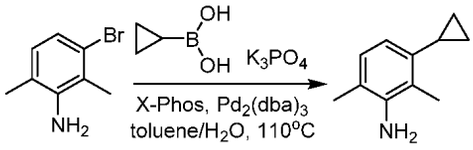
Preparation of ethyl (3S)-3-amino-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

Step 1: 3-bromo-2,6-dimethylaniline



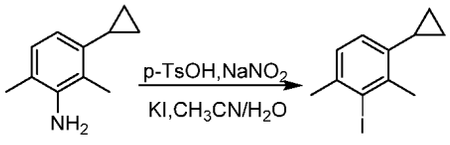
To a mixture of 1-bromo-2,4-dimethyl-3-nitrobenzene (3.0 g, 13.0 mmol) in MeOH (30 mL) and H_2O (3 mL) at 0°C was added NH_4Cl (2.1 g, 39.0 mmol) and Zn (8.5 g, 130.0 mmol). The mixture was stirred at room temperature for 20 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 3:2) to provide 3-bromo-2,6-dimethylaniline as a brown solid (2.0 g). Yield 77 % (ESI 200.1 $[M+H]^+$).

Step 2: 3-cyclopropyl-2,6-dimethylaniline



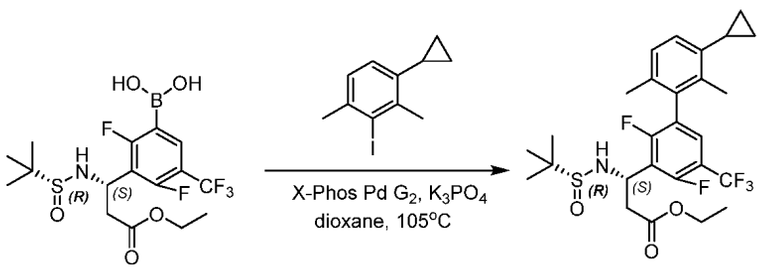
A mixture of 3-bromo-2,6-dimethylaniline (1.5 g, 7.5 mmol), cyclopropylboronic acid (3.2 g, 37.5 mmol), X-Phos (357.5 mg, 0.75 mmol), $Pd_2(dba)_3$ (343.4 mg, 0.38 mmol) and K_3PO_4 (4.8 g, 22.5 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was stirred at 110 °C for overnight under nitrogen atmosphere. The reaction mixture was cooled to room temperature, filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether: EtOAc 5:1) to provide 3-cyclopropyl-2,6-dimethylaniline as a colorless oil (1.1 g). Yield 91 % (ESI 162.2 $[M+H]^+$).

Step 3: 1-cyclopropyl-3-iodo-2,4-dimethylbenzene



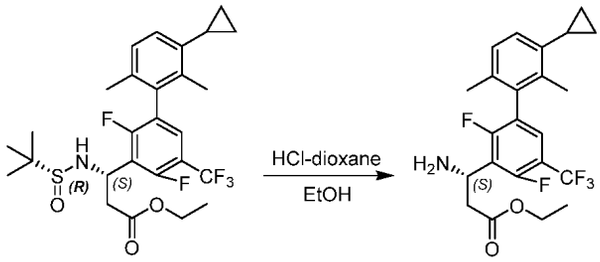
To a mixture of 3-cyclopropyl-2,6-dimethylaniline (1.1 g, 6.8 mmol) in CH_3CN (10 mL) and H_2O (1 mL) was added p-toluenesulphonic acid (5.9 g, 34.0 mmo). The mixture was stirred at 0 °C for 10 mins under under nitrogen atmosphere. A solution of $NaNO_2$ (703.8 mg, 10.2 mmol) in H_2O (2 mL) was added dropwise and the mixture was stirred 0 °C for 1 hour. Then KI (3.4 g, 20.4 mmol) was added to the reaction mixture and stirred at 0 °C for 2 hours. After completion, water (20 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (petroleum ether) to provide 1-cyclopropyl-3-iodo-2,4-dimethylbenzene as a colorless oil (240 mg) used without further purification. Yield 13%. ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 7.8 Hz, 1H), 6.93 (d, J = 7.8 Hz, 1H), 2.63 (s, 3H), 2.44 (s, 3H), 1.94 – 1.85 (m, 1H), 0.95 – 0.86 (m, 2H), 0.62 – 0.55 (m, 2H).

Step 4: ethyl (3*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of (3-((*S*)-1-(((*R*)-tert-butylsulfinyl)amino)-3-ethoxy-3-oxopropyl)-2,4-difluoro-5-(trifluoromethyl)phenyl)boronic acid (350 mg, 0.79 mmol), 1-cyclopropyl-3-iodo-2,4-dimethylbenzene (240 mg, 0.88 mmol), X-Phos Pd G2 (62.1 mg, 0.08 mmol) and K_3PO_4 (503.1 mg, 2.37 mmol) in 1,4-dioxane (10 mL) and water (1 mL) was stirred at 105 °C for 1 hour under nitrogen atmosphere. TheThe reaction mixture was cooled to room temperature, filtered through a pad of Celite and the filtrate was concentrated *in vacuo.* The residue was purified by silica gel column (petroleum ether: EtOAc 3:2) to provide ethyl (3*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a brown oil (270 mg). Yield 63% (ESI 546.2 $[M+H]^+$).

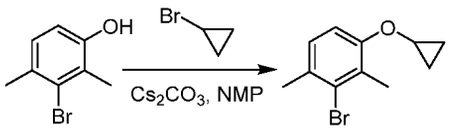
Step 5: ethyl (3*S*)-3-amino-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (3*S*)-3-(((*R*)-*tert*-butylsulfinyl)amino)-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (270.0 mg, 049 mmol) in EtOH (2 mL) was added HCl-dioxane (4 M, 2 mL, 8.0 mmol). The mixture was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* to provide ethyl (3*S*)-3-amino-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (210.0 mg), used without further purification. Yield 96% (ESI 442.2 $[M+H]^+$).

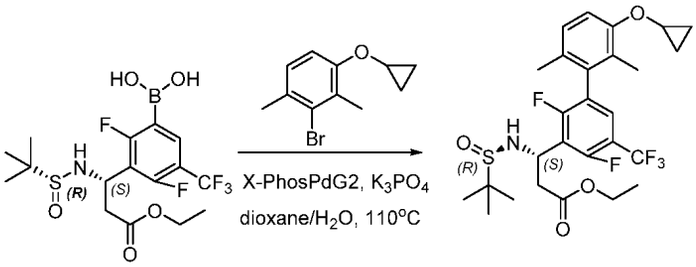
Preparation of (3*S*)-ethyl 3-amino-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate

Step 1: 2-bromo-4-cyclopropoxy-1,3-dimethylbenzene



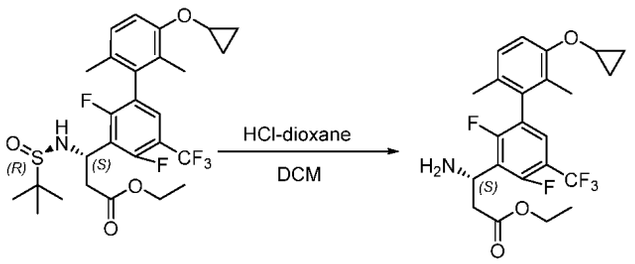
A mixture of 3-bromo-2,4-dimethylphenol (1.0 g, 4.98 mmol), bromocyclopropane (3.0 g, 24.8 mmol) and Cs_2CO_3(4.9 g, 14.9 mmol) in NMP (20 mL) was stirred at 140 °C for 20 hours. The mixture was cooled to room temperature and poured into NH_4Cl (aq.) (20 mL). The solution was extracted with EtOAc (200 mL x 3). The combined organic layer was washed with brine (20 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether) to provide 2-bromo-4-cyclopropoxy-1,3-dimethylbenzene as a colorless oil (1.0 g). Yield 83 % . ^1H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 3.75 – 3.65 (m, 1H), 2.35 (s, 3H), 2.27 (s, 3H), 0.79 – 0.73 (m, 4H).

Step 2: (3*S*)-ethyl 3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-((*R*)-1,1-dimethylethylsulfinamido)propanoate



To a mixture of 3-((*S*)-1-((*R*)-1,1-dimethylethylsulfinamido)-3-ethoxy-3-oxopropyl)-2,4-difluoro-5-(trifluoromethyl)phenylboronic acid (400 mg, 0.9 mmol), 2-bromo-4-cyclopropoxy-1,3-dimethylbenzene (260 mg, 1.1 mmol) and K_3PO_4 (636 mg, 3.0 mmol) in dioxane (5 mL) and H_2O (0.5 mL) was added X-Phos Pd G2 (79 mg, 0.1 mmol). The mixture was heated to 110°C for 1 hr under nitrogen atmosphere. Water (10 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide (3*S*)-ethyl 3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-((R)-1,1-dimethylethylsulfinamido)propanoate as a dark solid (300 mg). Yield 59 % (ESI 562.1 $[M+H]^+$).

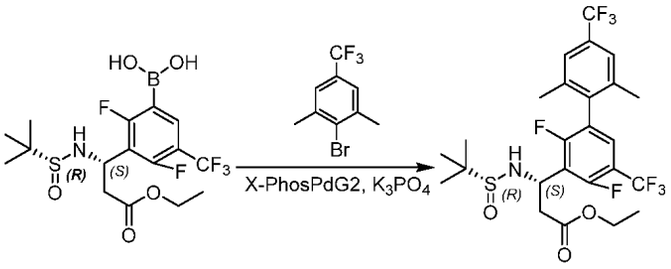
Step 3: (3*S*)-ethyl 3-amino-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



To a mixture of (3*S*)-ethyl 3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-((*R*)-1,1-dimethylethylsulfinamido)propanoate (300 mg, 0.53 mmol) in DCM (1 mL) was added 4M HCl-dioxane (0.5 mL, 2.0 mmol). The mixture was stirred at rt for 0.5 hr. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase on a C18/120g column (A: water 10mM NH_4HCO_3, B: CH_3CN, 0~100%) to provide (3*S*)-ethyl 3-amino-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a colorless oil (150 mg). Yield 62 % (ESI 458.1 $[M+H]^+$).

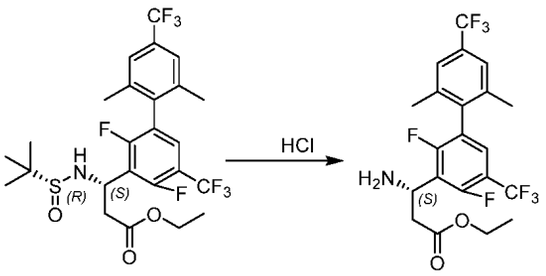
Preparation of ethyl (S)-3-amino-3-(2,4-difluoro-2',6'-dimethyl-4',5-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(2,4-difluoro-2',6'-dimethyl-4',5-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of (3-((S)-1-(((R)-tert-butylsulfinyl)amino)-3-ethoxy-3-oxopropyl)-2,4-difluoro-5-(trifluoromethyl)phenyl)boronic acid (900 mg, 2.0 mmol), K_3PO_4 (1.06 g, 5.0 mmol), X-Phos Pd G2 (157 mg, 0.2 mmol) and 2-bromo-1,3-dimethyl-5-(trifluoromethyl)benzene (607 mg, 2.4 mmol) in dioxane (20 mL) and H_2O (2 mL) was stirred at 100 °C under nitrogen atmosphere for 2 hours. The reaction mixture was poured into 50 mL of water and extracted with EtOAc (50 x 3mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 3:2) to provide ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(2,4-difluoro-2',6'-dimethyl-4',5-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (730 mg). Yield 63.6% (ESI 574.2 $(M+H)^+$)

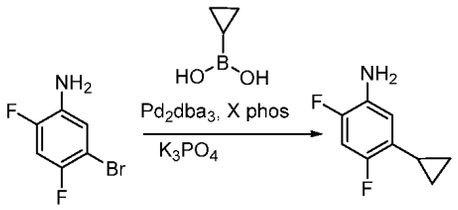
Step 2: ethyl (S)-3-amino-3-(2,4-difluoro-2',6'-dimethyl-4',5-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(2,4-difluoro-2',6'-dimethyl-4',5-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (730 mg, 1.27 mmol) in DCM (4 mL) was added HCl-dioxane (4 M, 1 mL, 4.0 mmol). The mixture was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10 mM NH_4HCO_3, B: CH_3CN, 0~100%) to provide ethyl (*S*)-3-amino-3-(2,4-difluoro-2',6'-dimethyl-4',5-bis(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (280 mg). Yield 47% (ESI 470.0 $[M+H]^+$).

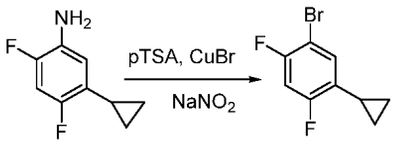
Preparation of ethyl (S)-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-(((R)-tert-butylsulfinyl)amino)propanoate

Step 1: 5-cyclopropyl-2,4-difluoroaniline



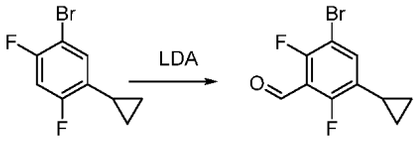
To a solution of 5-bromo-2,4-difluoroaniline (15.0 g, 72.1 mmol) in Toluene (50 mL) and H_2O (55 mL) under nitrogen atmosphere at room temperature was added X-phos (1.7 g, 3.6 mmol), Pd_2dba_3 (3.3 g, 3.6 mmol), cyclopropylboronic acid (12.4 g, 144.2 mmol) and K_3PO_4 (30.9 g, 144.2 mmol) and stirred at 100 °C for 16 hours under nitrogen atmosphere. The reaction was filtered and washed with EtOAc (50 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide 5-cyclopropyl-2,4-difluoroaniline as white solids (12.0 g). Yield 92 % (ESI 170.2 $(M+H)^+$).

Step 2: 1-bromo-5-cyclopropyl-2,4-difluorobenzene



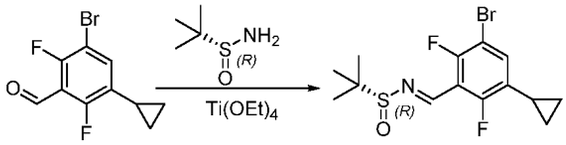
To a mixture of 5-cyclopropyl-2,4-difluoroaniline (12.0 g, 71.0 mmol) and CuBr (25.5 g, 177.5 mmol) in ACN (200 mL) and H_2O (40 mL) at 0 °C was added p-Toluenesulfonic acid (54.0 g, 284.0 mmol) and then stirred for 1 hour. To the mixture was added a solution of $NaNO_2$(7.3 g, 106.5 mmol) in H_2O (20 mL) dropwise. The mixture was extracted with EtOAc (80 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether) to provide 1-bromo-5-cyclopropyl-2,4-difluorobenzene (7.0 g, yield: 42%) as a colorless oil .

Step 3: 3-bromo-5-cyclopropyl-2,6-difluorobenzaldehyde



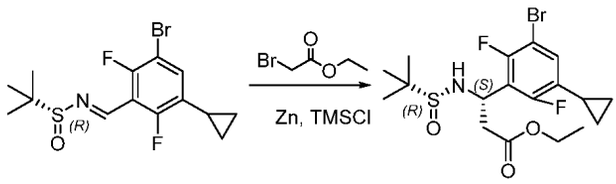
To a solution of 1-bromo-5-cyclopropyl-2,4-difluorobenzene(7.0 g, 30.0 mmol) in THF (50 mL) at -78 °C was added LDA(22.6 mL, 45.2 mmol) dropwise and stirred at -78 °C for 1h. Then DMF(5 mL) was added dropwise and stirred at -78 °C for another 1h. The reaction mixture was warmed to r.t. and quenched with saturated NH_4Cl (20 mL) aquous solution and stirred at room teperature for 30 mins. The the mixture was extracted with EtOAc(100 mL x 3). The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide 3-bromo-5-cyclopropyl-2,6-difluorobenzaldehyde as a yellow oil without further purification (6.5 g, yield:88%).

Step 4: (R,E)-N-(3-bromo-5-cyclopropyl-2,6-difluorobenzylidene)-2-methylpropane-2-sulfinamide



To a mixture of 3-bromo-5-cyclopropyl-2,6-difluorobenzaldehyde (7.3 g, 29.4 mmol) and (*R*)-2-methylpropane-2-sulfinamide (4.3 g, 35.3 mmol) in anhydrous THF (50 mL) under nitrogen atmosphere was added $Ti(OEt)_4$ (10.0 g, 44.1 mmol) dropwise at room temperature. During which the temperature was maintained below 30 °C. The reaction mixture was stirred at room temperature for 1 hour under nitrogen atmosphere. Water (100 mL) and EtOAc (100 mL) was added into the mixture and stirred at room temperature for 5 mins. The mixture was filtered and washed with EtOAc (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 5:1) to provide (R,E)-N-(3-bromo-5-cyclopropyl-2,6-difluorobenzylidene)-2-methylpropane-2-sulfinamide as a yellow oil (6.3 g). Yield 61% (ESI 364.0 $(M+H)^+$, 366.0 $(M+2+H)^+$).

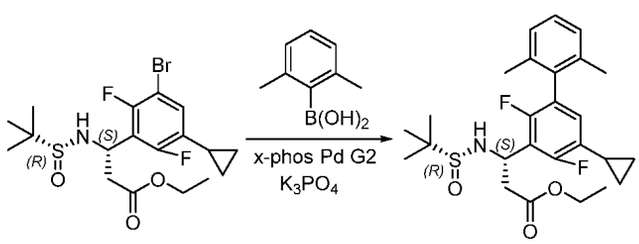
Step 5: ethyl (S)-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-(((R)-tert-butylsulfinyl)amino)propanoate



To a mixture of Zn (10.0 g, 149.3 mmol) in anhydrous THF (100 mL) under nitrogen atmosphere was added chlorotrimethylsilane (1.0 g, 9.8 mmol) dropwise at room temperature. The mixture was stirred at 50 °C for 1 hour under nitrogen atmosphere. This mixture was then cooled to 20-30°C. Ethyl 2-bromoacetate (12.4 g, 74.3 mmol) was added dropwise at room temperature and the mixture was stirred at 50 °C for 1 hour under nitrogen atmosphere. The reaction mixture was cooled to room temperature. A solution of (R,E)-N-(3-bromo-5-cyclopropyl-2,6-difluorobenzylidene)-2-methylpropane-2-sulfinamide (9.0 g, 24.7 mmol) in anhydrous THF (10 mL) was added dropwise into the mixture at room temperature and the mixture was stirred at room temperature for 1 hour. Water (100 mL) and EtOAc (100 mL) was added into the mixture and stirred at room temperature for 5 mins. The mixture was filtered and washed with EtOAc (100 mL x 2). The organic layer was washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide ethyl (S)-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-(((R)-tert-butylsulfinyl)amino)propanoate as a colorless oil (7.1 g). Yield 78 % (ESI 452.0 $(M+H)^+$,454.0$(M+2+H)^+$).

Preparation of ethyl (S)-3-amino-3-(5-cyclopropyl-2,4-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

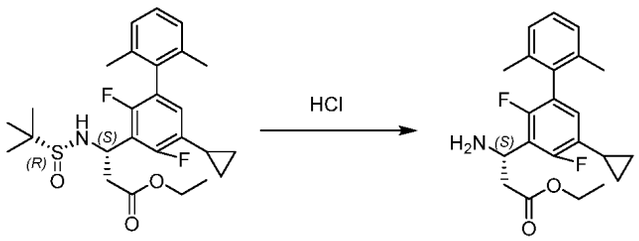
Step 1: ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,4-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (S)-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-(((R)-tert-butylsulfinyl)amino)propanoate (800.0 mg, 1.77 mmol), (2,6-dimethylphenyl)boronic acid (380.0 mg, 2.3 mmol), X-Phos Pd G2 (133.0 mg, 0.17 mmol) and K_3PO_4 (1.1 g, 5.31 mmol) in Toluene (7 mL) and H_2O (0.7 mL) was stirred at 100 °C for 4 hours under a nitrogen atmosphere. The reaction was concentrated in vacuo and the residue purified by silica gel column (pet ether:EtOAc = 3:1) to provide

ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,4-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (700.0 mg, Yield 83%) as a light yellow foam (ESI 478.2 $[M+H]^+$).

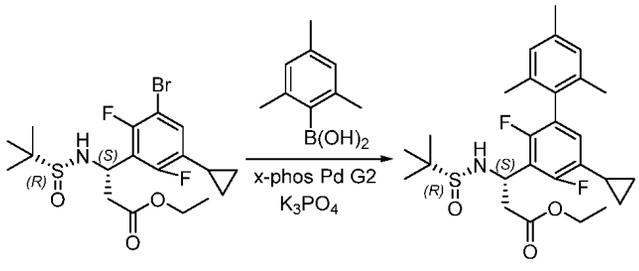
Step 2: ethyl (S)-3-amino-3-(5-cyclopropyl-2,4-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To the solution of ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,4-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (700.0 mg, 1.47 mmol) in DCM (8 mL) was added HCl-dioxane (4M, 1.9 mL, 7.6 mmol) and stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 120 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl (S)-3-amino-3-(5-cyclopropyl-2,4-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride as a yellow solid (500 mg). Yield 91% (ESI 374.2 $(M+H)^+$).

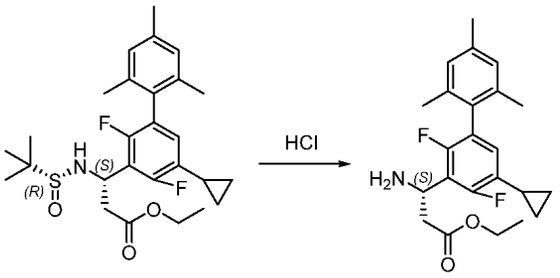
Preparation of ethyl (S)-3-amino-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: (*S*)-ethyl 3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-((*R*)-1,1-dimethylethylsulfinamido)propanoate



To a mixture of (*S*)-ethyl 3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-((*R*)-1,1-dimethylethylsulfinamido)propanoate (600 mg, 1.3 mmol), mesitylboronic acid (246 mg, 1.5 mmol) and K_3PO_4 (848 mg, 43.0 mmol) in dioxane (10 mL) and H_2O (1 mL) was added X-Phos Pd G2 (79 mg, 0.1 mmol). The mixture was heated to 110°C for 2 hrs under a nitrogen atmosphere. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL x 3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide (*S*)-ethyl 3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-((*R*)-1,1-dimethylethylsulfinamido)propanoate as a dark solid (400 mg). Yield 80 % (ESI 492.1 $[M-100+H]^+$).

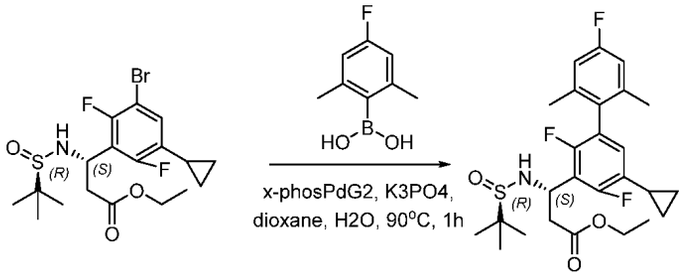
Step 2: ethyl (S)-3-amino-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of (*S*)-ethyl 3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-((*R*)-1,1-dimethylethylsulfinamido)propanoate (550 mg, 1.12 mmol) in DCM (1mL) and EtOH (2mL) was added 4M HCl-dioxane (2 mL, 5.0 mmol) and the mixture was stirred at rt for 0.5 hr. Then the mixture was concentrated *in vacuo* to provide ethyl (S)-3-amino-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (360 mg, crude) used directly in the next reaction. (ESI 388.1$(M+H)^+$).

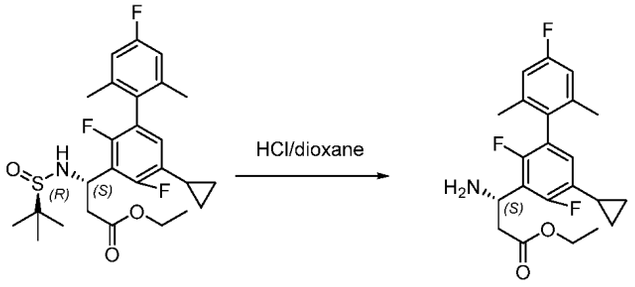
Preparation of ethyl (S)-3-amino-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



To a mixture of ethyl (S)-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-(((R)-tert-butylsulfinyl)amino)propanoate (700 mg, 1.55 mmol), 4-fluoro-2,6-dimethylphenylboronic acid (260 mg, 1.55 mmol), and K_3PO_4 (657 mg, 3.1 mmol) in 1,4-dioxane (5 mL) and water (0.5 mL) was added X-Phos Pd G2 (117 mg, 0.16 mmol). The mixture was stirred at 90°C for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (petroleum ether: EtOAc 5:1) to provide ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a pale yellow oil (420.0 mg). Yield 54.6% (ESI 496.2 $(M+H)^+$).

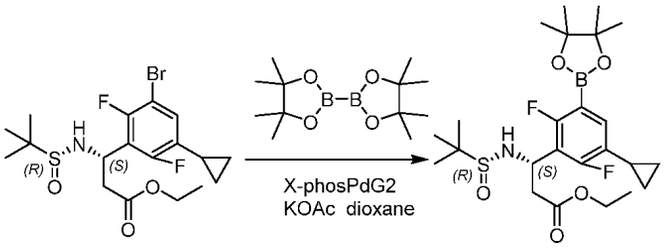
Step 2: ethyl (S)-3-amino-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (420 mg, 0.85 mmol) in HCl-dioxane (4 M, 3 mL, 12 mmol) was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* to provide ethyl (S)-ethyl 3-amino-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethylbiphenyl-3-yl)propanoate as a colorless oil (290 mg) used without further purification. Yield 87.4% (ESI 392.1 $[M+H]^+$).

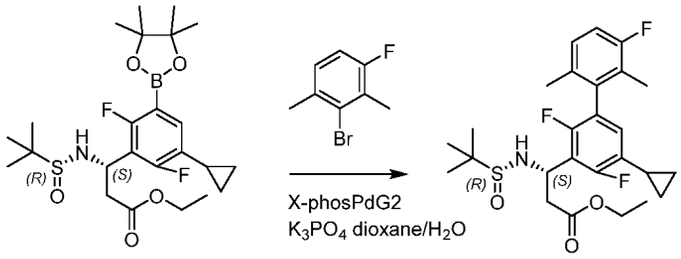
Preparation of ethyl (3*S*)-3-amino-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

Step 1: ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(3-cyclopropyl-2,6-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate



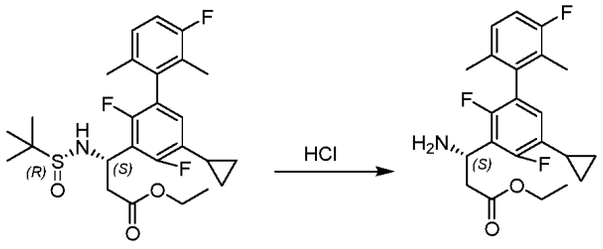
A mixture of ethyl (S)-3-(3-bromo-5-cyclopropyl-2,6-difluorophenyl)-3-(((R)-tert-butylsulfinyl)amino)propanoate (800 mg, 1.8 mmol), KOAc (529 mg, 5.4 mmol), Xphos-PdG_2 (142 mg, 0.18 mmol) and 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (686 mg, 2.7 mmol) in dioxane (10 mL) was stirred at 110 °C for 2 hours under a nitrogen atmosphere. The reaction mixture was poured into 15 mL of water and extracted with EtOAc (15 x 3mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo.* The residue was purified by silica gel column (pet ether: EtOAc 3:1) to provide ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(3-cyclopropyl-2,6-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate as a colorless oil (500 mg). Yield 56 % (ESI 500.2 $(M+H)^+$)

Step 2: ethyl (3S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (S)-3-(((R)-tert-butylsulfinyl)amino)-3-(3-cyclopropyl-2,6-difluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (500 mg, 1.0 mmol), K_3PO_4 (636 mg, 3.0 mmol), Xphos-PdG_2 (78.7 mg, 0.1 mmol) and 2-bromo-4-fluoro-1,3-dimethylbenzene (263 mg, 1.3 mmol) in dioxane (10 mL) and H_2O (1 mL) was stirred at 110 °C for 2 hours under a nitrogen atmosphere. The reaction mixture was poured into 15 mL of water and extracted with EtOAc (15 x 3mL x 3). The combined organic layers were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 3:1) to provide ethyl (3S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a colorless oil (200 mg). Yield 40 % (ESI 496.2 $(M+H)^+$)

Step 3: ethyl (3*S*)-3-amino-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate

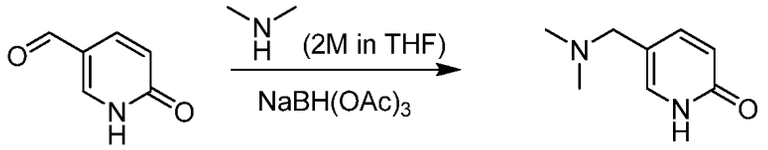


To a mixture of ethyl (3S)-3-(((R)-tert-butylsulfinyl)amino)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.4 mmol) in EtOH (2 mL) was added HCl-dioxane (4 M, 2 mL, 8.0 mmol). The mixture was stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-amino-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate oil (120 mg). Yield 76% (ESI 392.2 $[M+H]^+$).

Example 2B. Preparation of Intermediates

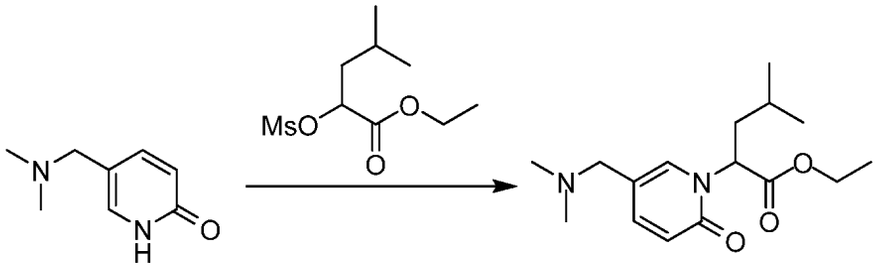
Preparation of 2-(5-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 5-((dimethylamino)methyl)pyridin-2(1H)-one



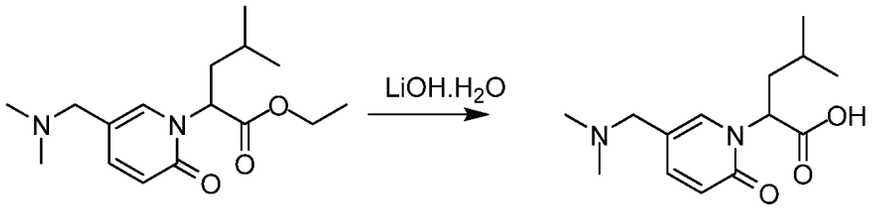
A mixture of 6-oxo-1,6-dihydropyridine-3-carbaldehyde (2 g, 16.2 mmol), dimethylamine (2M in THF, 4 mL) in DCM (10 mL) was stirred at room temperature for 30 mins. Then $NaBH(OAc)_3$ (5.2 g, 24.39 mmol) was added portion-wise and stirred at room temperature overnight. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC (Eluent A: water 10 mM NH_4HCO_3, Eluent B: MeOH, gradient A->B 0~100%) to provide 5-((dimethylamino)methyl)pyridin-2(1H)-one as a yellow oil (1 g). Yield 41% (ESI 153 $(M+H)^+$).

Step 2: ethyl 2-(5-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of 5-((dimethylamino)methyl)pyridin-2(1H)-one (500 mg, 3.28 mmol), K_2CO_3 (1.36 g, 9.86 mmol) and ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.17 g, 4.93 mmol) in CH_3CN (20 mL) was stirred at 70 ºC overnight. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:2) to provide ethyl 2-(5-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (300 mg). Yield 31% (ESI 295$(M+H)^+$).

Step 3: 2-(5-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

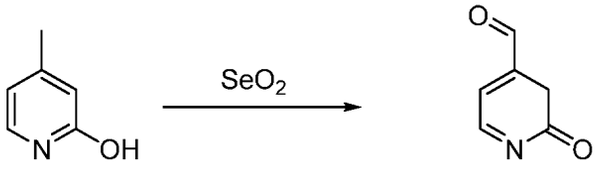


Ethyl 2-(5-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (300 mg, 1.02 mmol) was treated with $LiOH\text{-}H_2O$ (120 mg, 3.02 mmol) in methanol (2 mL) and water (1 mL) at room temperature for 2 hours. The reaction was acidified with 1N HCl to pH = 3.

The solvent was removed *in vacuo* and the residue was purified by preparatory-HPLC A conditions (30-80% MeCN) to provide 2-(5-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (100 mg). Yield 37% (ESI 267$(M+H)^+$).

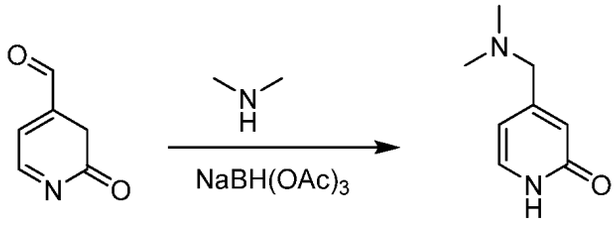
Preparation of 2-(4-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 2-oxo-2,3-dihydropyridine-4-carbaldehyde



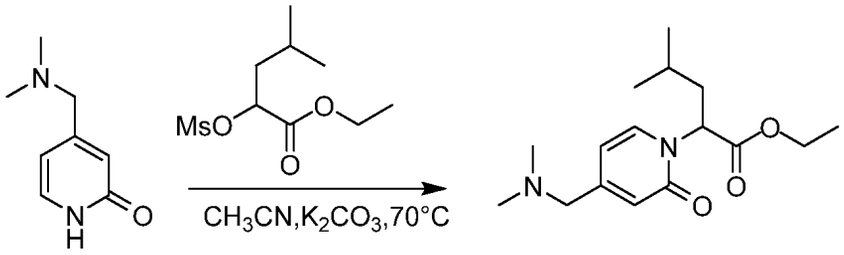
A mixture of 4-methylpyridin-2-ol (3 g, 27.5 mmol) and SeO_2 (4 g, 35.8 mmol) in dioxane (40 mL) was refluxed under N_2 atmosphere overnight and filtered. The filtrate was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH = 1: 10) to provide 2-oxo-2,3-dihydropyridine-4-carbaldehyde as a yellow oil (300 mg). Yield 9% (ESI 124 $(M+H)^+$)

Step 2: 4-((dimethylamino)methyl)pyridin-2(1H)-one



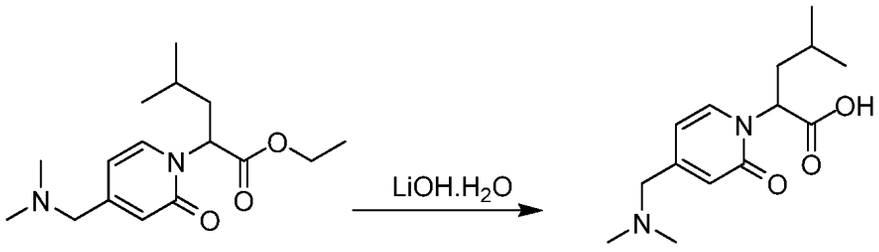
A mixture of 2-oxo-2,3-dihydropyridine-4-carbaldehyde (300 mg, 2.4 mmol), dimethylamine (2M in THF, 6 mL) in DCM (5 mL) was stirred at room temperature for 30 minutes. $NaBH(OAc)_3$ (775.6 mg, 3.65 mmol) was added portion-wise and stirred at room temperature overnight. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC (Eluent A: water 10 mM NH_4HCO_3, Eluent B: MeOH, gradient A->B 0~100%) to provide 4-((dimethylamino)methyl)pyridin-2(1H)-one as a yellow oil (150 mg). Yield 41% (ESI 153 $(M+H)^+$).

Step 3: ethyl 2-(4-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of 4-((dimethylamino)methyl)pyridin-2(1H)-one (150 mg, 0.98 mmol), K_2CO_3 (409 mg, 2.96 mmol) and ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (350 mg, 1.47 mmol) in CH_3CN (5 mL) was stirred at 70 ºC overnight. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:2) to provide ethyl 2-(4-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (100 mg). Yield 35% (ESI 295$(M+H)^+$).

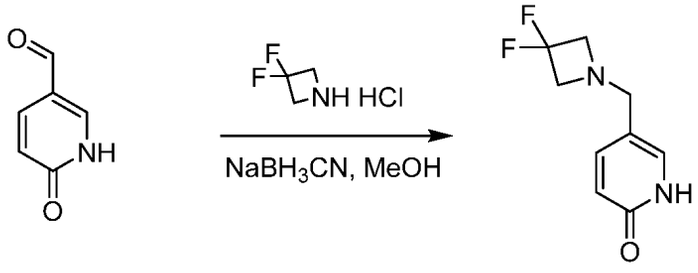
Step 4: 2-(4-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(4-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (100 mg, 0.33 mmol) was treated with LiOH-H_2O (40 mg, 1.01 mmol) in methanol (2 mL) and water (1 mL) at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was purified by preparatory-HPLC A (30-80% MeCN) to provide 2-(4-((dimethylamino)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (80 mg). Yield 90% (ESI 267$(M+H)^+$).

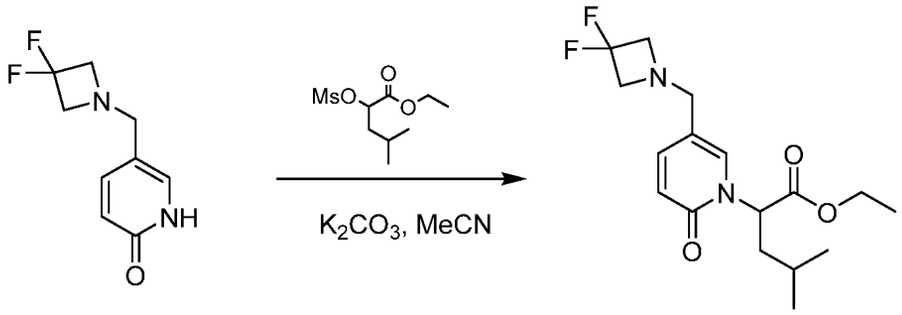
Preparation of Acid 3: 2-(5-((3, 3-difluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid

Step 1: 5-((3, 3-difluoroazetidin-1-yl)methyl)pyridin-2(1*H*)-one



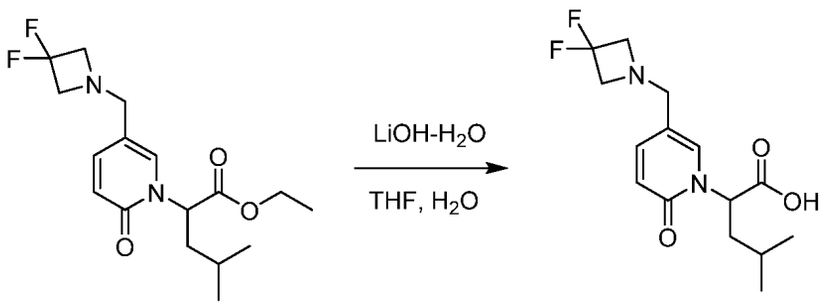
A mixture of 6-oxo-1,6-dihydropyridine-3-carbaldehyde (153 mg, 1.24 mmol) and 3,3-difluoroazetidine hydrochloride (193 mg, 1.49 mmol) in MeOH (3 mL) was stirred at room temperature for 30 mins. $NaBH_3CN$ (231 mg, 3.73 mmol) was added and stirred at room temperature for 1 hour. The solvent was removed *in vacuo* to provide the crude 5-((3, 3-difluoroazetidin-1-yl)methyl)pyridin-2(1*H*)-one as white solid (248 mg) used without further purification. (ESI 201.1 $(M+H)^+$).

Step 2: ethyl 2-(5-((3, 3-difluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



A mixture of 5-((3,3-difluoroazetidin-1-yl)methyl)pyridin-2(1H)-one (248 mg, 1.24 mmol), ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (443 mg, 1.86 mmol) and K_2CO_3 (514 mg, 3.72 mmol) in MeCN (5 mL) was stirred at 80 °C overnight. The mixture was filtered and washed with MeCN (5 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (petroleum ether: EtOAc 2:1) to provide ethyl 2-(5-((3, 3-difluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a colorless oil (150 mg). Yield 36% (ESI 343.1 $(M+H)^+$).

Step 3: 2-(5-((3, 3-difluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid

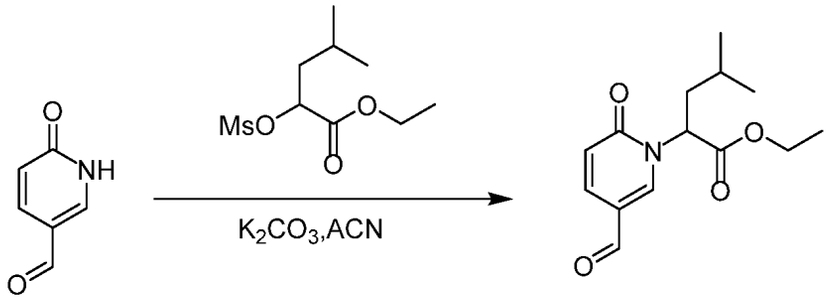


Ethyl 2-(5-((3,3-difluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (151 mg, 0.44 mmol) was treated with $LiOH-H_2O$ (28 mg, 0.66 mmol) in THF (3 mL) and

H_2O (0.5 mL) at room temperature for 30 mins. The mixture was acidified to pH 4~5 with 1N HCl. The mixture was concentrated *in vacuo* to provide 2-(5-((3, 3-difluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid as white solid (138 mg) used without further purification. Yield 100% (ESI 315.1 $(M+H)^+$).

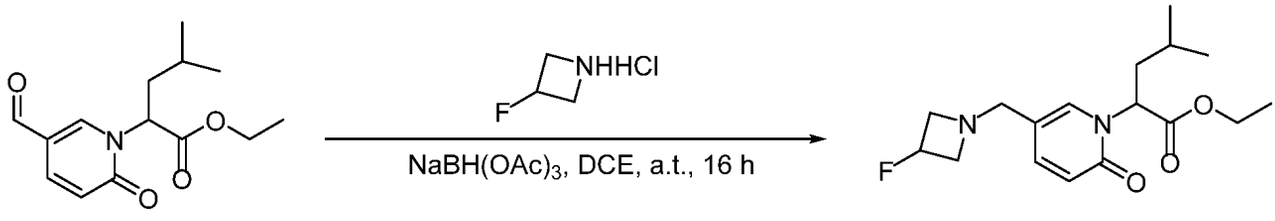
Preparation of 4-methyl-2-(5-(morpholinomethyl)-2-oxopyridin-1(2H)-yl)pentanoic acid

Step 1: ethyl 2-(5-formyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of 6-oxo-1,6-dihydropyridine-3-carbaldehyde (400 mg, 3.2 mmol), ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1 g, 4.2 mmol) and K_2CO_3 (1.1 g, 8 mmol) in MeCN (10 mL) was stirred at 80°C overnight. The mixture was filtered and washed with MeCN (5 mL). The filtrate was concentrated *in vacuo* and purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-formyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a colorless oil (650 mg). Yield 70% (ESI 266.3 $(M+H)^+$).

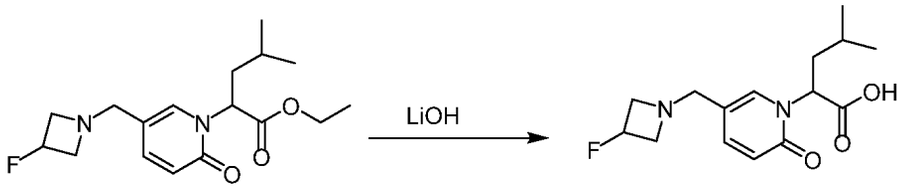
Step 2: ethyl 2-(5-((3-fluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



A mixture of ethyl 2-(5-formyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (300 mg, 1.13 mmol) and 3-fluoroazetidine hydrochloride (251 mg, 2.26 mmol) in DCE (4 mL) was stirred at room temperature for 30 mins. Sodium triacetoxyborohydride (959 mg, 4.52 mmol) was added and stirred at room temperature overnight. The mixture was concentrated *in vacuo* and purified by silica gel column (DCM: MeOH 10:1) to provide ethyl 2-(5-((3-fluoroazetidin-1-

yl)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a colorless oil (264 mg). Yield 72% (ESI 325.2 $(M+H)^+$).

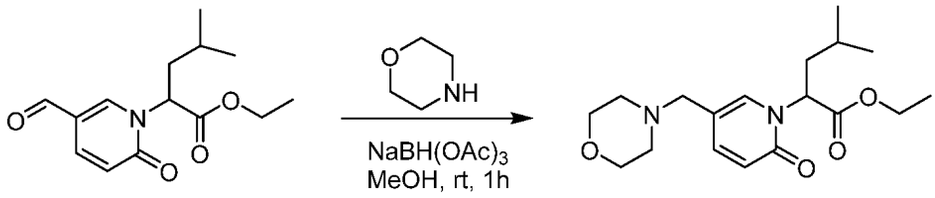
Step 3: 2-(5-((3-fluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid



Ethyl 2-(5-((3-fluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (264 mg, 0.81 mmol) was treated with LiOH-H_2O (171 mg, 4 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl. The mixture was concentrated *in vacuo* and purified by silica gel column (DCM: MeOH 10:1) to provide 2-(5-((3-fluoroazetidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid as a white solid (217 mg). Yield 90% (ESI 297.1 $(M+H)^+$).

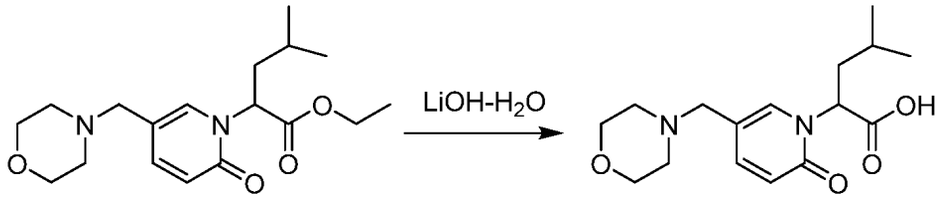
Preparation of 4-methyl-2-(5-(morpholinomethyl)-2-oxopyridin-1(2H)-yl)pentanoic acid

Step 1: ethyl 4-methyl-2-(5-(morpholinomethyl)-2-oxopyridin-1(2H)-yl)pentanoate



A mixture of ethyl 2-(5-formyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (300 mg, 1.13 mmol) and morpholine (147 mg, 1.70 mmol) in DCE (5 mL) was stirred at room temperature for 30 mins. $NaBH(OAc)_3$ (715 mg, 3.39 mmol) was added and stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 2:1) to provide ethyl 4-methyl-2-(5-(morpholinomethyl)-2-oxopyridin-1(2H)-yl)pentanoate as yellow oil (150 mg). Yield 39% (ESI 337.2 $(M+H)^+$).

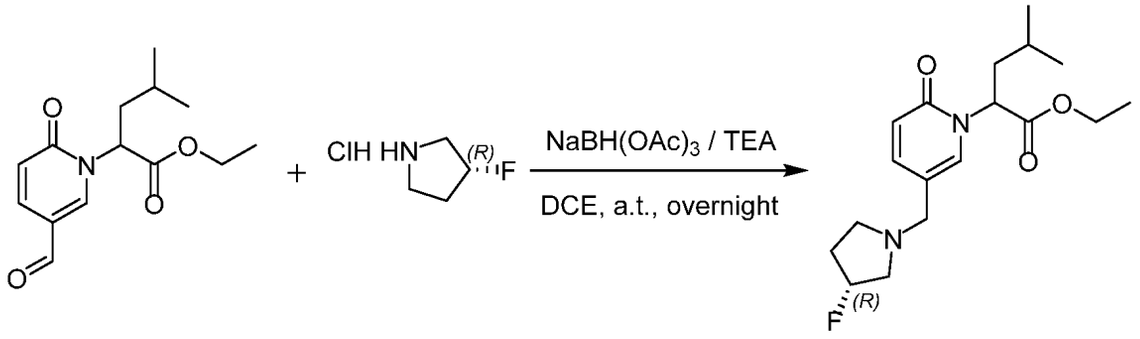
Step 2: 4-methyl-2-(5-(morpholinomethyl)-2-oxopyridin-1(2H)-yl)pentanoic acid



Ethyl 4-methyl-2-(5-(morpholinomethyl)-2-oxopyridin-1(2H)-yl)pentanoate (150 mg, 0.45 mmol) was treated with LiOH-H_2O (56 mg, 1.34 mmol) in THF (3 mL) and H_2O (0.5 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 4-methyl-2-(5-(morpholinomethyl)-2-oxopyridin-1(2H)-yl)pentanoic acid as white solid (110 mg). Yield 80% (ESI 309.3 $(M+H)^+$).

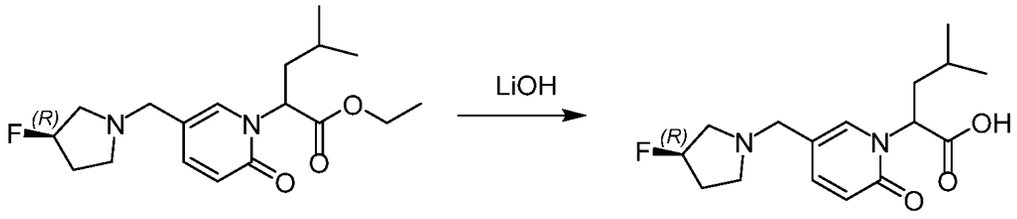
Preparation of 2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-(((R)-3-fluoropyrrolidin-1-yl)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of ethyl 2-(5-formyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (300 mg, 1.13 mmol), (R)-3-fluoropyrrolidine hydrochloride (284 mg, 2.26 mmol) and triethylamine (0.31 mL, 2.26 mmol) in DCE (10 mL) was stirred at room temperature for 30 mins. Sodium triacetoxyborohydride (959 mg, 4.52 mmol) was added and stirred at room temperature overnight. The mixture was concentrated *in vacuo* and purified by silica gel column (DCM: MeOH 10:1) to provide ethyl 2-(5-(((R)-3-fluoropyrrolidin-1-yl)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a colorless oil (237 mg). Yield 62% (ESI 339.2 $(M+H)^+$).

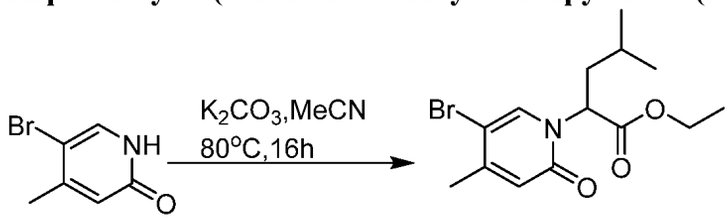
Step 2: 2-(5-(((R)-3-fluoropyrrolidin-1-yl)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(((R)-3-fluoropyrrolidin-1-yl)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (426 mg, 1.13 mmol) was treated with LiOH-H_2O (237 mg, 5.65 mmol) in EtOH (6 mL) and H_2O (0.6 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl. The mixture was concentrated *in vacuo* and the residue purified by silica gel column (DCM: MeOH 10:1) to provide 2-(5-(((R)-3-fluoropyrrolidin-1-yl)methyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (348 mg). Yield 99% (ESI 311.1 $(M+H)^+$).

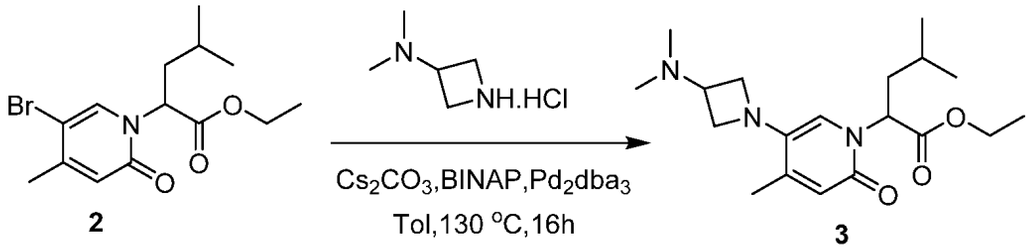
Preparation of 2-(5-(3-(dimethylamino)azetidin-1-yl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-bromo-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



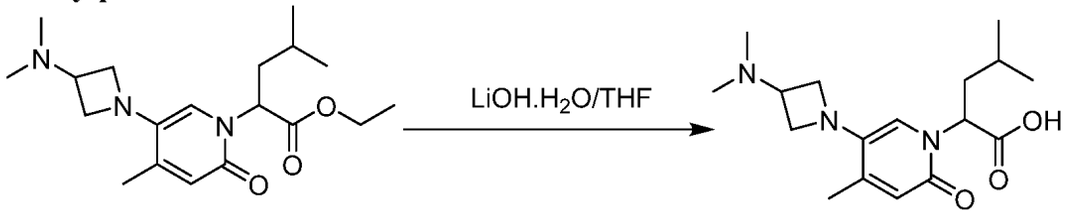
A mixture of 5-bromo-4-methylpyridin-2(1H)-one (3.0 g, 16 mmol, 1.0 *eq*), K_2CO_3 (4.4 g, 32 mmol, 2.0 *eq*) and ethyl 4-methyl-2-((methylsulfonyl)oxy)pentanoate (5.7 g, 24 mmol, 1.5 *eq*) in CH_3CN (50 mL) was stirred at 80°C for 16 h. LCMS showed the reaction was completed. The mixture was filtered and washed with CH_3CN (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 3:1) to provide ethyl 2-(5-bromo-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (4.5 g). Yield 85% (ESI 330 $(M+H)^+$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 6.49 (d, J = 0.6 Hz, 1H), 5.67 (dd, J = 10.6, 5.3 Hz, 1H), 4.20 (qd, J = 7.1, 0.8 Hz, 2H), 2.24 (d, J = 0.8 Hz, 3H), 1.97 – 1.93 (m, 1H), 1.87 – 1.80 (m, 1H), 1.51 – 1.43 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 6.3 Hz, 6H).

Step 2: ethyl 2-(5-(3-(dimethylamino)azetidin-1-yl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



To a solution of ethyl 2-(5-bromo-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (2.0 g, 6.06 mmol, 1.0 *eq*), N,N-dimethylazetidin-3-amine dihydrochloride (1.57 g, 9.07 mmol, 1.5 *eq*), and $CsCO_3$ (8.0 g, 24.5 mmol, 4.0 *eq*) in toluene (50 mL) was added BINAP (376 mg, 0.606 mmol, 0.1 *eq*) and Pd_2dba_3 (250 mg, 0.27 mmol, 0.05 *eq*) under N_2 and then heated to 120 °C for 3h. LCMS showed the reaction was completed. The mixture was filtered and washed with both EtOAc (20 mL) and EtOH (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl 2-(5-(3-(dimethylamino)azetidin-1-yl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1.4 g). Yield 66% (ESI 350 $(M+H)^+$).

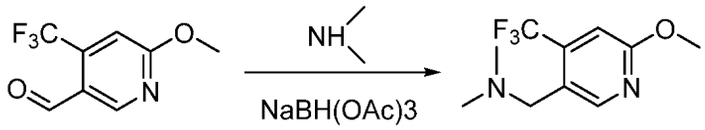
Step 3: 2-(5-(3-(dimethylamino)azetidin-1-yl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(3-(dimethylamino)azetidin-1-yl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate(1.4 g, 4.0 mmol, 1.0 eq) was treated with LiOH-H_2O (840 mg, 20.0 mmol, 5.0 *eq*) in THF (20 mL) and water (6 mL) at room temperature for 2 hours. The MeOH was removed and the aqueous material acidified with 1N HCl to pH 4. The mixture was purified by reverse phase HPLC in neutral condition (A: water, B: MeOH, 60%B) to provide 2-(5-(3-(dimethylamino)azetidin-1-yl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (800 mg). Yield 62% (ESI 322 $(M+H)^+$). 1H- NMR (400 MHz, MeOD) δ 6.75 (s, 1H), 6.31 (s, 1H), 5.45-5.38(m, 1H), 3.87-3.28(m, 2H), 3.24(s, 3H), 3.17-2.42(m, 6H), 2.19-2.06(m, 3H), 1.24-1.19(m, 1H), 0.85-0.74(m, 6H).

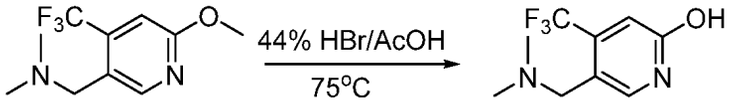
Preparation of 2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid

Step 1: 1-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)-*N*,*N*-dimethylmethanamine



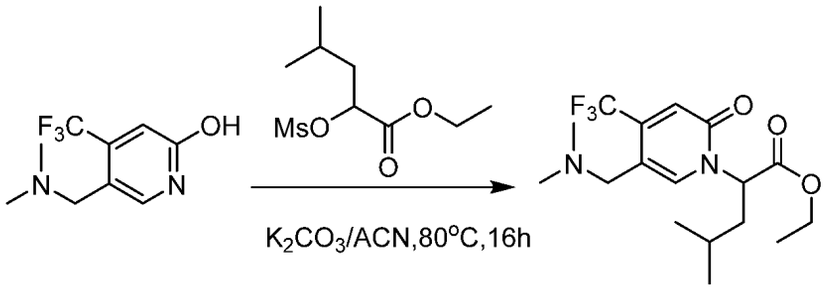
A mixture of 6-methoxy-4-(trifluoromethyl)nicotinaldehyde (0.5 g, 2.44 mmol), dimethylamine (2.0 M in THF, 1.5 mL, 2.92 mmol) in DCE (10 mL) was stirred at room temperature for 15 mins. $NaBH(OAc)_3$ (1.03 g, 4.88 mmol) was added and stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 10:1) to provide 1-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)-N,N-dimethylmethanamine as yellow oil (220 mg). Yield 38% (ESI 235.1$(M+H)^+$).

Step 2: 5-((dimethylamino)methyl)-4-(trifluoromethyl)pyridin-2-ol



A mixture of 1-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)-N,N-dimethylmethanamine (220 mg, 0.94 mmol) in 33% HBr/AcOH (10 mL) was heated at 75°C for 16 hours. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 5-((dimethylamino)methyl)-4-(trifluoromethyl)pyridin-2-ol as a red solid (180 mg). Yield 87% (ESI 221.1 $(M+H)^+$).

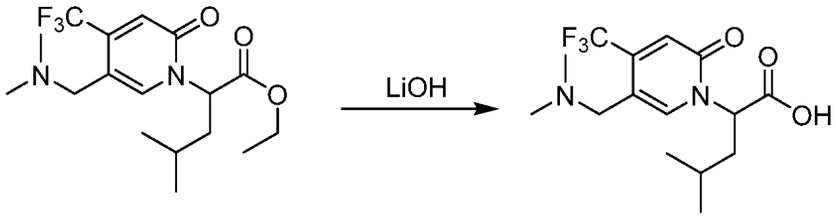
Step 3: ethyl 2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate



A mixture of 5-((dimethylamino)methyl)-4-(trifluoromethyl)pyridin-2-ol (150 mg, 0.68 mmol), ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (194 mg, 0.816 mmol) and K_2CO_3 (281.5 mg, 2.04 mmol) in MeCN (10 mL) was stirred at 80°C overnight. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate (170 mg). Yield 68% (ESI 363.1 $(M+H)^+$).

Step 4: 2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-

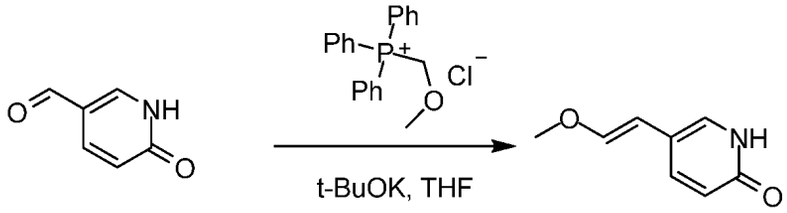
methylpentanoic acid



Ethyl 2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (170 mg, 0.47 mmol) was treated with LiOH-H_2O (98.7 mg, 2.35 mmol) in MeOH (10 mL) and H_2O (2 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl and purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid as white solid (120 mg). Yield 76% (ESI 335.2 $(M+H)^+$).

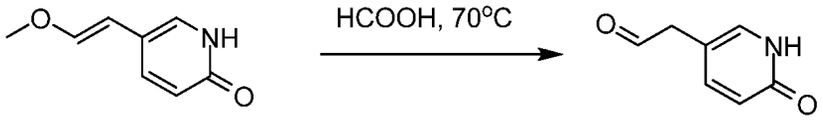
Preparation of 2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 5-(2-methoxyvinyl)pyridin-2(1H)-one



A mixture of (methoxymethyl)triphenylphosphonium chloride (12.5 g, 36.6 mmol), t-BuOK (6.83 g, 61 mmol) in dioxane (60 mL) was stirred at room temperature for 15 minutes. Then 6-oxo-1,6-dihydropyridine-3-carbaldehyde (3 g, 24.4 mmol) in 20 mL THF was added. The mixture was stirred for 16 h at room temperature. To the reaction mixture was added 80 mL water. The mixture was extracted with EtOAc (80 mL x 2) and the aqueous phase concentrated *in vacuo*. The residue was purified by reverse phase HPLC (Eluent A: water 10 mM NH_4HCO_3, Eluent B: MeOH, gradient A->B 0~100%) to provide 5-(2-methoxyvinyl)pyridin-2(1H)-one as a red oil (1.3 g). Yield 35% (ESI 152.2 $(M+H)^+$).

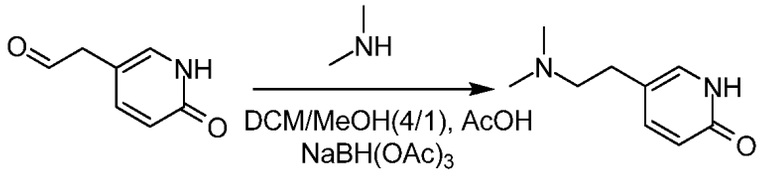
Step 2: 2-(6-oxo-1,6-dihydropyridin-3-yl)acetaldehyde



5-(2-methoxyvinyl)pyridin-2(1H)-one (1.2 g, 7.95 mmol) was treated with HCOOH (20 mL) at 70°C for 2 hours. The solvent was removed *in vacuo* to provide the crude product 2-(6-

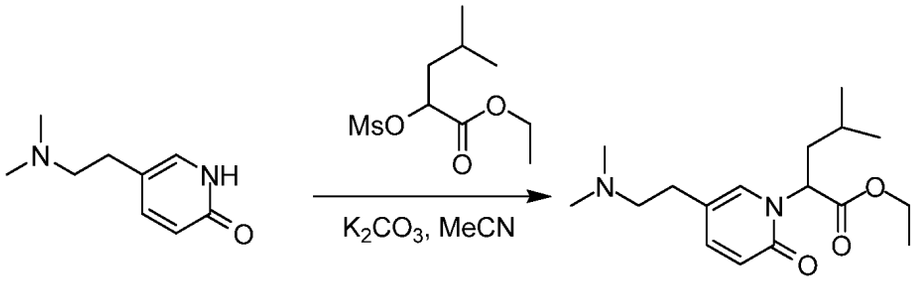
oxo-1,6-dihydropyridin-3-yl)acetaldehyde as a red oil (0.8 g, crude). (ESI 138.3 $(M+H)^+$).

Step 3: 5-(2-(dimethylamino)ethyl)pyridin-2(1H)-one



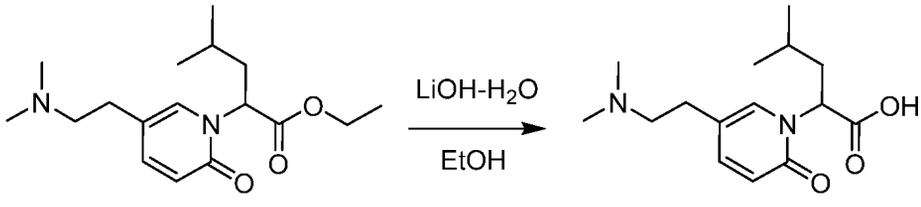
A mixture of methyl 2-(6-oxo-1,6-dihydropyridin-3-yl)acetaldehyde (750 mg, 5.47 mmol), AcOH (394 mg, 6.56 mmol) and dimethylamine (40% in water) (1.23 g, 10.94 mmol) in DCM (10 mL) and MeOH (2.5 mL) was stirred at room temperature for 30 minutes then $NaBH(OAc)_3$ (2.32 g, 10.94 mmol) was added. The mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 2:1) to provide 5-(2-(dimethylamino)ethyl)pyridin-2(1H)-one as yellow oil (500 mg). Yield 55% (ESI 167.2 $(M+H)^+$).

Step 4: ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of methyl 5-(2-(dimethylamino)ethyl)pyridin-2(1H)-one (500 mg, 3 mmol), ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.07 g, 4.5 mmol) and K_2CO_3 (828 mg, 6 mmol) in MeCN (15 mL) was stirred at 70°C overnight. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 1:2) to provide methyl ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a white solid (100 mg). Yield 11% (ESI 309.2$(M+H)^+$).

Step 5: 2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

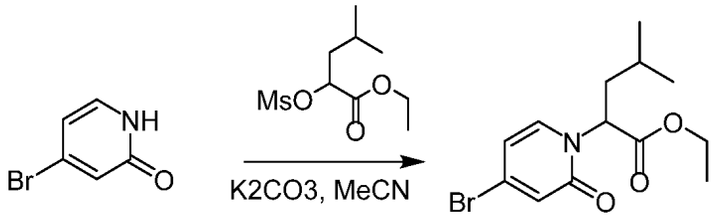


Ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (100 mg, 0.32 mmol) was treated with $LiOH-H_2O$ (54 mg, 1.28 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1 N HCl. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC

(Eluent A: water 10 mM NH_4HCO_3, Eluent B: MeOH, gradient A->B 0~100%) to provide 2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as white solids (70 mg). Yield 78% (ESI 281.2$(M+H)^+$).

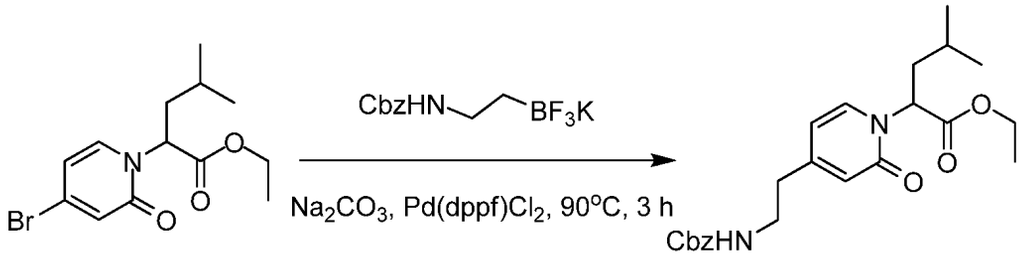
Preparation of 2-(4-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(4-bromo-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



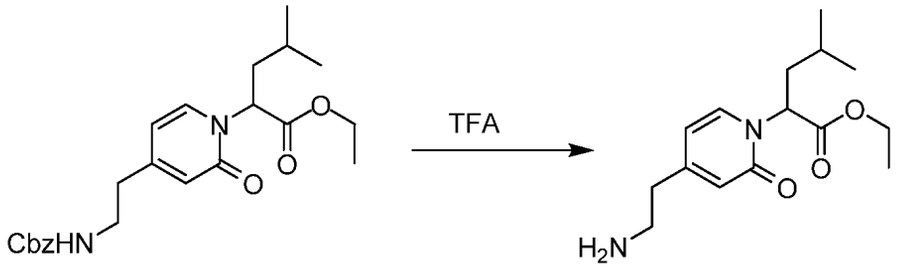
A mixture of 4-bromopyridin-2(1H)-one (1.2 g, 6.94 mmol), K_2CO_3 (1.92 g, 13.88 mmol) and ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.98 g, 8.33 mmol) in CH_3CN (20 mL) was stirred at 80°C overnight. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:1) to give ethyl 2-(4-bromo-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (1.6 g). Yield 73% (ESI 316.1$(M+H)^+$).

Step 2: ethyl 2-(4-(2-(benzyloxycarbonylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



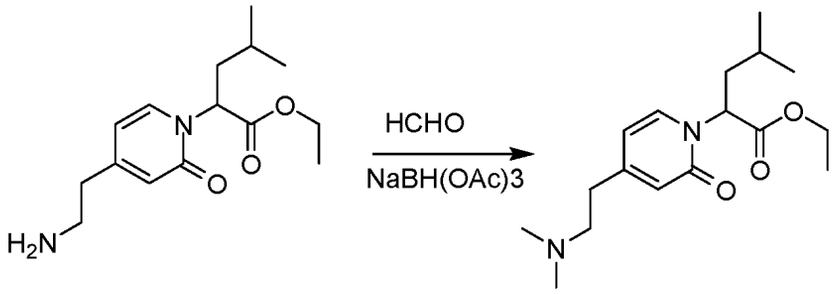
A mixture of ethyl 2-(4-bromo-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1.6 g, 5.0 mmol), potassium benzyl N-[2-(trifluoroboraly)ethyl]carbamate (1.71 g, 6 mmol), $Pd(dppf)Cl_2$ (366 mg, 0.5 mmol) and Na_2CO_3 (1.06 g, 10 mmol) in 1,4-dioxane (20 mL) and H_2O (10 mL) was stirred at 90°C under N_2 atmosphere for 4 hours. The reaction was concentrated and purified by reverse phase HPLC on a C18/40 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl 2-(4-(2-(benzyloxycarbonylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (700 mg). Yield 35% (ESI 415.1 $(M+H)^+$).

Step 3: ethyl 2-(4-(2-aminoethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



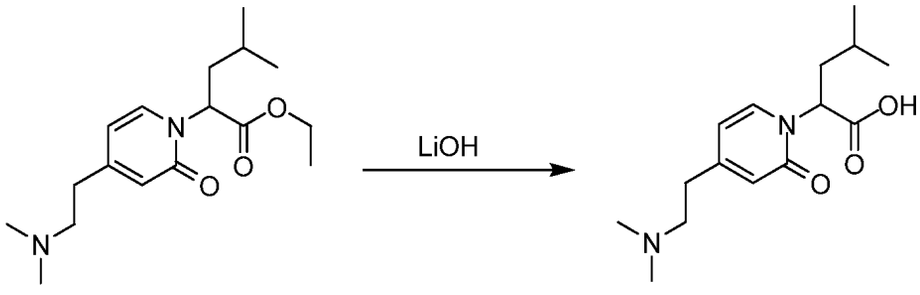
Ethyl 2-(4-(2-(benzyloxycarbonylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (0.7 g, 1.7 mmol) was treated with TFA (10 mL) at 50°C for 4 hours. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(4-(2-aminoethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a red oil (0.4 g). Yield 84%. (ESI 281.2 $(M+H)^+$).

Step 4: ethyl 2-(4-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



To a mixture of ethyl 2-(4-(2-aminoethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (400 mg, 1.43 mmol) in MeOH (10 mL) was added HCHO (37% in H_2O, 1 mL) and stirred at room temperature for 5 mins. $NaBH(OAc)_3$ (1.21 g, 5.72 mmol) was added and stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(4-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as yellow oil (400 mg). Yield 91% (ESI 309.2$(M+H)^+$).

Step 5: 2-(4-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

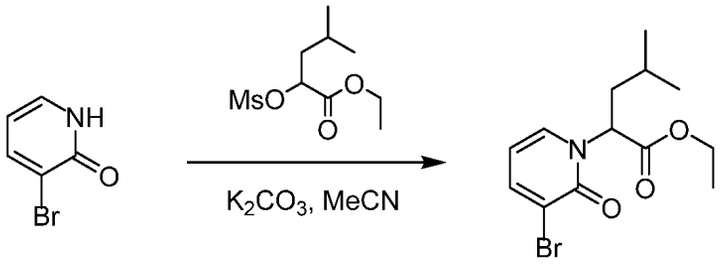


Ethyl 2-(4-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (400 mg, 1.3 mmol) was treated with LiOH-H_2O (218 mg, 5.2 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 1 hour. The mixture was acidified to pH 4~5 with 1N HCl. The

mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to give 2-(4-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as white solid (310 mg). Yield 85% (ESI 281.2$(M+H)^+$).

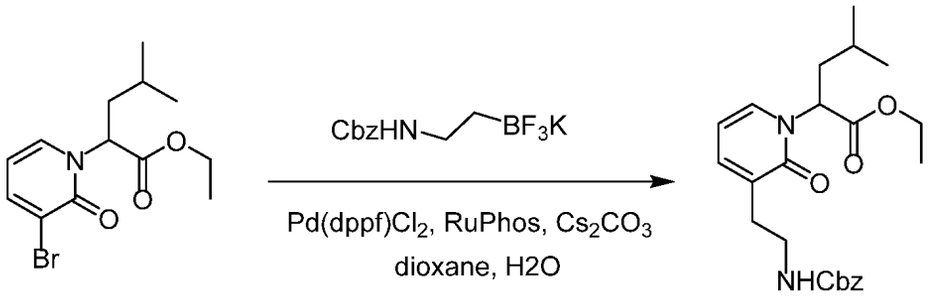
Preparation of 2-(3-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(3-bromo-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



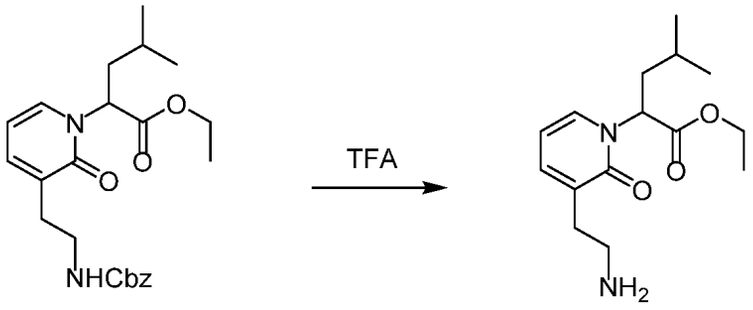
A mixture of 3-bromopyridin-2(1*H*)-one (1 g, 5.78 mmol), K_2CO_3 (1.6 g, 11.56 mmol) and ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.65 g, 6.94 mmol) in CH_3CN (20 mL) was stirred at 80°C overnight. The solvent was concentrated *in vacuo* and purified by silica gel column (petroleum ether: EtOAc 1:1) to provide ethyl 2-(3-bromo-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a white solid (1.6 g). Yield 88% (ESI 316.1$(M+H)^+$).

Step 2: ethyl 2-(3-(2-(benzyloxycarbonylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



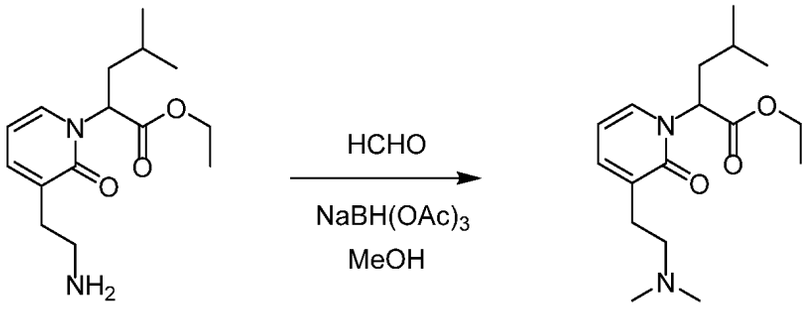
A mixture of ethyl 2-(3-bromo-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1 g, 3.17 mmol), potassium benzyl *N*-[2-(trifluoroboryl)ethyl]carbamate (1.08 g, 3.8 mmol), $Pd(dppf)Cl_2$ (36 mg, 0.16 mmol), Cs_2CO_3 (2 g, 6.34 mmol) and RuPhos (144 mg , 0.32 mmol) in 1,4-dioxane (20 mL) and H_2O (10 mL) was stirred at 110 °C for 2 hours. The reaction was concentrated and purified by reverse phase HPLC on a C18/40 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to give ethyl 2-(3-(2-(benzyloxycarbonylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow oil (1.1 g). Yield 84% (ESI 415.2 $(M+H)^+$).

Step 3: ethyl 2-(3-(2-aminoethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



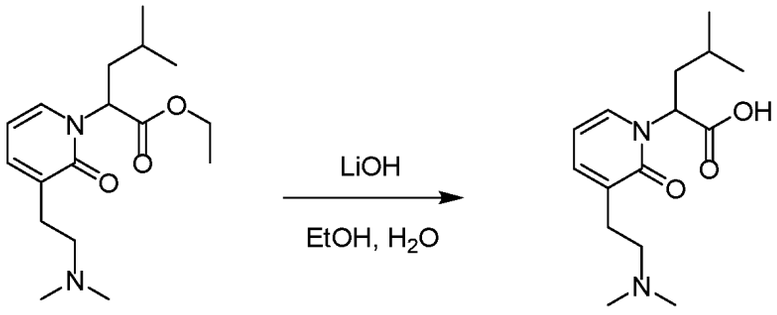
Ethyl 2-(3-(2-(benzyloxycarbonylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1.07 g, 2.58 mmol) was treated with TFA (20 mL) at 50 °C for 4 hours. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM $NH4HCO_3$, B: MeOH, 0~100%) to provide ethyl 2-(3-(2-aminoethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow oil (0.6 g). Yield 83%. (ESI 281.2 $(M+H)^+$).

Step 4: ethyl 2-(3-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



To a mixture of ethyl 2-(3-(2-aminoethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (600 mg, 2.14 mmol) in MeOH (10 mL) was added HCHO (37% in H_2O, 1 mL). The mixture was stirred at room temperature for 5 mins. $NaBH(OAc)_3$ (1.81 g, 8.56 mmol) was added and stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM $NH4HCO_3$, B: MeOH, 0~100%) to provide ethyl 2-(3-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as yellow oil (600 mg). Yield 91% (ESI 309.2$(M+H)^+$).

Step 5: 2-(3-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid

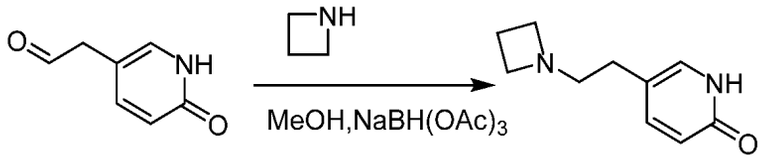


Ethyl 2-(3-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (600 mg,

1.95 mmol) was treated with LiOH monohydrate (328 mg, 7.8 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 1 hour. The mixture was acidified to pH 4~5 with 1N HCl aqueous solution. The mixture was concentrated *in vacuo* and the residue purified by reverse phase HPLC on a C18/40 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to give 2-(3-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid as white solid (500 mg). Yield 92% (ESI 281.2$(M+H)^+$).

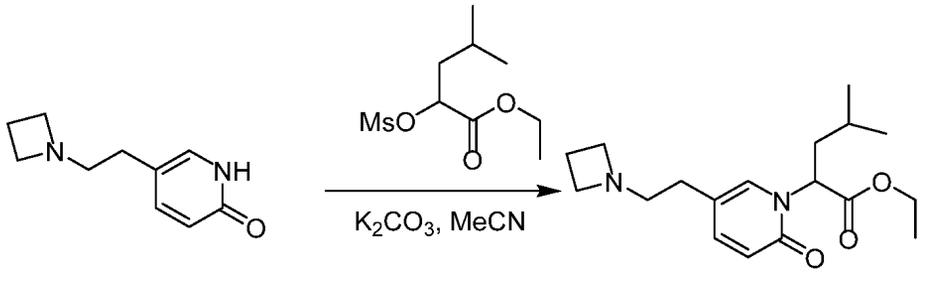
Preparation of Acid 9: 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 5-(2-(azetidin-1-yl)ethyl)pyridin-2(1H)-one



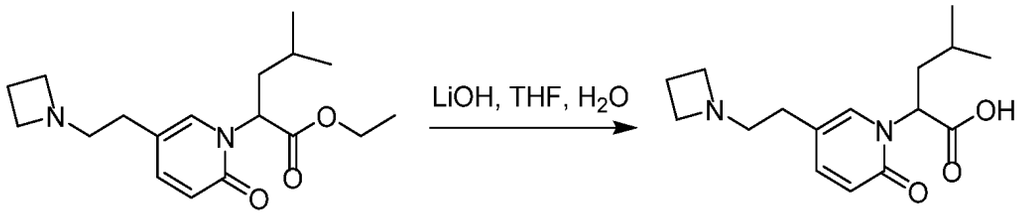
A mixture of methyl 2-(6-oxo-1,6-dihydropyridin-3-yl)acetaldehyde (1.0 g, 7.29 mmol) and azetidine (416 mg, 7.30 mmol) in MeOH (10 mL) was stirred at room temperature for 30 mins. $NaBH(OAc)_3$ (4.6 g, 21.9 mmol) was added and stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 2:1) to provide 5-(2-(azetidin-1-yl)ethyl)pyridin-2(1H)-one as yellow oil (800 mg). Yield 62% (ESI 179.1 $(M+H)^+$).

Step 2: ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of 5-(2-(azetidin-1-yl)ethyl)pyridin-2(1H)-one (800 mg, 4.49 mmol), ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (2.2 g, 6.74 mmol) and K_2CO_3 (1.8 g, 13.47 mmol) in MeCN (40 mL) was stirred at 80°C overnight. The mixture was filtered and washed with MeCN (5 mL). The filtrate was concentrated *in vacuo* and the residue purified by reverse phase HPLC on a C18/80 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a colorless oil (600 mg). Yield 42% (ESI 321.2 $(M+H)^+$).

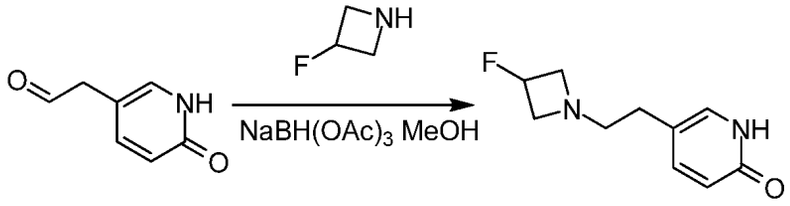
Step 3: 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (600 mg, 1.88 mmol) was treated with LiOH-H_2O (394 mg, 9.40 mmol) in THF (10 mL) and H_2O (2 mL) at room temperature for 1 hour. The mixture was acidified to pH 4~5 with 1N HCl. The mixture was concentrated *in vacuo* and the residue purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as red solid (150 mg). Yield 27% (ESI 293.2 $(M+H)^+$).

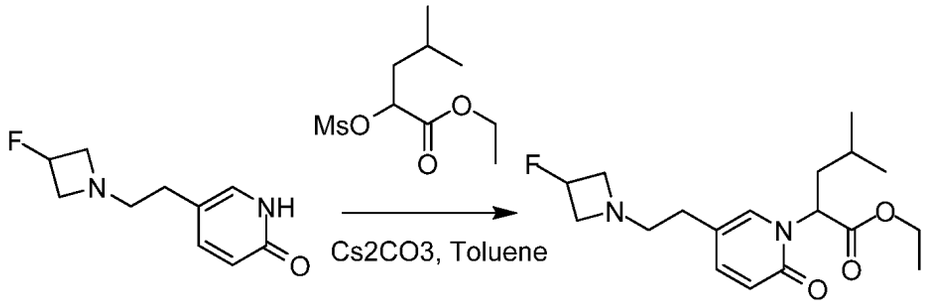
Preparation of 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 5-(2-(3-fluoroazetidin-1-yl)ethyl)pyridin-2(1H)-one



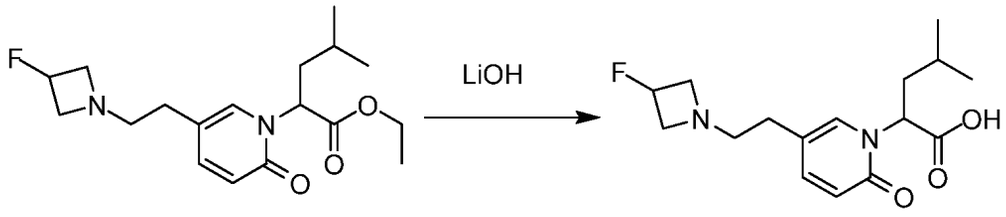
A mixture of 2-(6-oxo-1,6-dihydropyridin-3-yl)acetaldehyde (1.5 g, 11 mmol), AcOH (0.8 g, 13.2 mmol) and 3-fluoroazetidine hydrochloride (1.47 g, 13.2 mmol) in MeOH (30 mL) was stirred at room temperature for 30 mins. $NaBH(OAc)_3$ (4.66 g, 22 mmol) was added and stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 5-(2-(3-fluoroazetidin-1-yl)ethyl)pyridin-2(1H)-one asa yellow oil (2 g, crude). (ESI 197.2 $(M+H)^+$).

Step 2: ethyl 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of 5-(2-(3-fluoroazetidin-1-yl)ethyl)pyridin-2(1H)-one (1.9 g, 9.7 mmol), ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (3.45 g, 14.5 mmol) and Cs_2CO_3 (9.5 g, 29.1 mmol) in toluene (40 mL) was stirred 110°C overnight. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (650 mg). Yield 20% (ESI 339.1$(M+H)^+$).

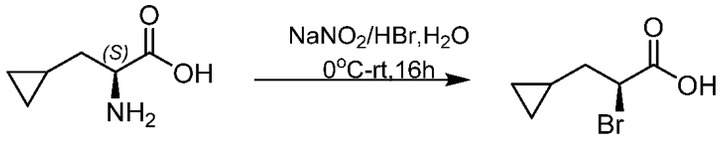
Step 3: 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (650 mg, 1.92 mmol) was treated with LiOH-H_2O (322 mg, 7.68 mmol) in MeOH (10 mL) and H_2O (2.5 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl, purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (350 mg). Yield 59% (ESI 311.2$(M+H)^+$).

Preparation of 3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)propanoic acid

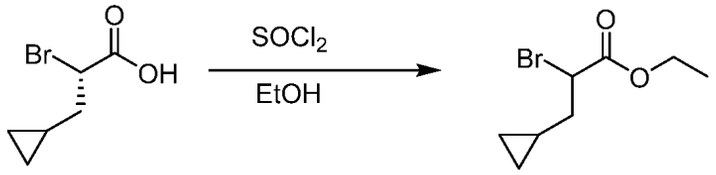
Step 1: (*S*)-2-bromo-3-cyclopropylpropanoic acid



To a solution of (*S*)-2-amino-3-cyclopropylpropanoic acid (5.0 g, 38.7 mmol) in H_2O (50 mL) was added 40% HBr (60 mL). The reaction mixture was stirred at 0 °C for 10 min. A solution of sodium nitrite (4.5 g, 24 mmol) in H_2O (10 mL) was added. The reaction mixture was

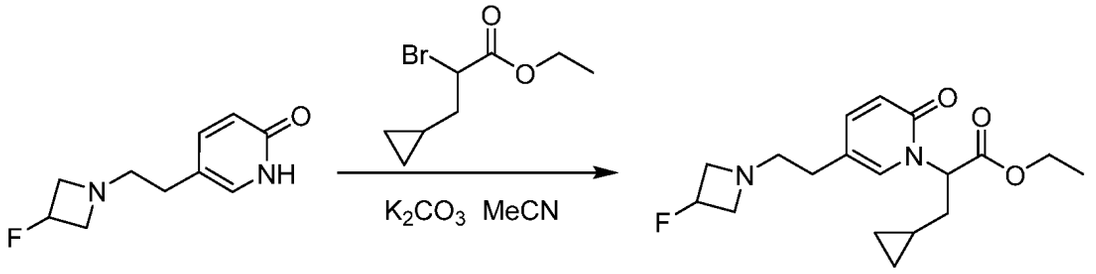
stirred at 0 °C for 30 min and warmed to room temperature overnight. The reaction mixture was extracted with EtOAc (100 mL X 3). The organic layer was washed with brine (100 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide (*S*)-2-bromo-3-cyclopropylpropanoic acid as a colorless oil used directly in the next reaction without further purification (5.0 g). Yield 74% (ESI 194 $(M+H)^+$).

Step 2: ethyl (*S*)-2-bromo-3-cyclopropylpropanoate



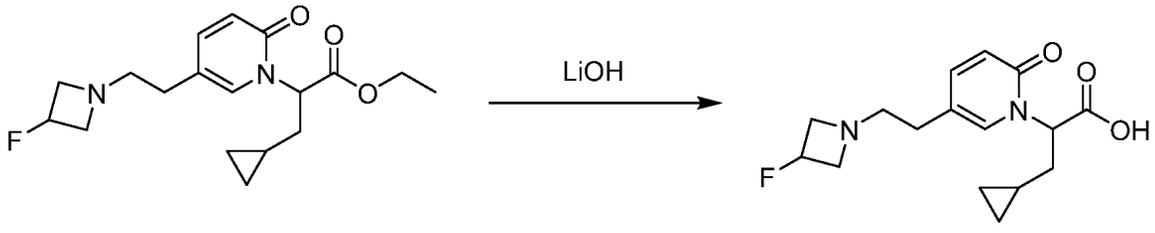
To a solution of (*S*)-2-bromo-3-cyclopropylpropanoic acid (1 g, 5.2 mmol) in EtOH (20 mL) was added $SOCl_2$ (1.8 g, 15.6 mmol) and stirred at ambient temperature for 2 hours. The solvent was removed in vacuo to provide ethyl 2-bromo-3-cyclopropylpropanoate as a white solid (1.2 g, crude) used directly in the next reaction. (ESI 221.0 $(M+H)^+$).

Step 3: ethyl 3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)propanoate



A mixture of ethyl 2-bromo-3-cyclopropylpropanoate (800 mg, 3.64 mmol), 5-(2-(3-fluoroazetidin-1-yl)ethyl)pyridin-2(1H)-one (1.07 g, 5.46 mmol) and K_2CO_3 (1.5 g, 10.92 mmol) in MeCN (10 mL) was stirred at 80 °C overnight. The mixture was filtered and washed with MeCN (10 mL). The filtrate was concentrated in vacuo and the residue was purified by silica gel column (petroleum ether: EtOAc 2:1) to provide ethyl 3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)propanoate as a colorless oil (400 mg). Yield 32% (ESI 337.2 $(M+H)^+$).

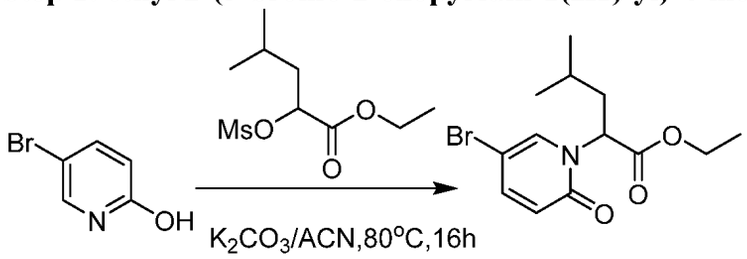
Step 4: 3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)propanoic acid



Ethyl 3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)propanoate (400 mg, 1.20 mmol) was treated with LiOH-H_2O (201 mg, 4.80 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to provide 3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)propanoic acid as a white solid (310 mg). Yield 85% (ESI 309.15 $(M+H)^+$).

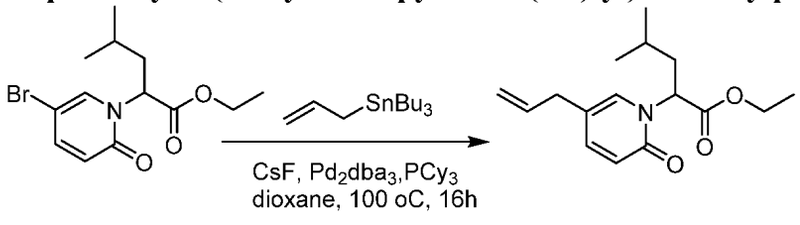
Preparation of 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-bromo-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



A mixture of 5-bromopyridin-2-ol (12.0 g, 69.0 mmol), K_2CO_3 (19.1 g, 138.0 mmol) and ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (18.5 g,77.7 mmol) in CH_3CN (230 mL) was stirred at 80°C overnight. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:2) to provide ethyl 2-(5-bromo-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow oil (13.0 g). Yield 60% (ESI 316.0$(M+H)^+$).

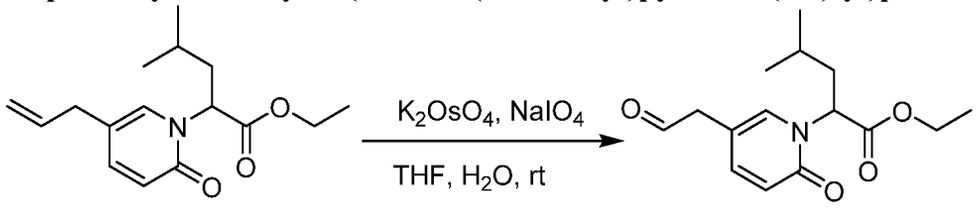
Step 2: ethyl 2-(5-allyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



A mixture of ethyl 2-(5-bromo-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (13.0 g, 41.1 mmol), allyltributylstannane (14.9 g, 45.1 mmol), Pd_2dba_3 (1.8 g, 2.06 mmol), PCy_3 (1.1 g, 4.11 mmol) and CsF (12.5 g, 82.2 mmol) in anhydrous dioxane (50 mL) was stirred under N_2 at 100°C for 16 h. The mixture was cooled to room temperature and quenched with saturated NH_4Cl solution (100 mL) and extracted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (200 mL x 2). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was

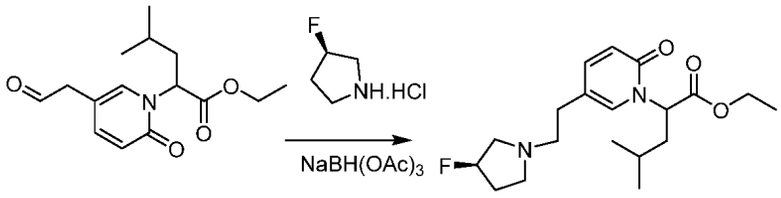
purified by silica gel column (pet ether: EtOAc 19:1) to provide ethyl 2-(5-allyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow solid (7.1 g). Yield 62% (ESI 278.1 $(M+H)^+$).

Step 3: ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)pentanoate



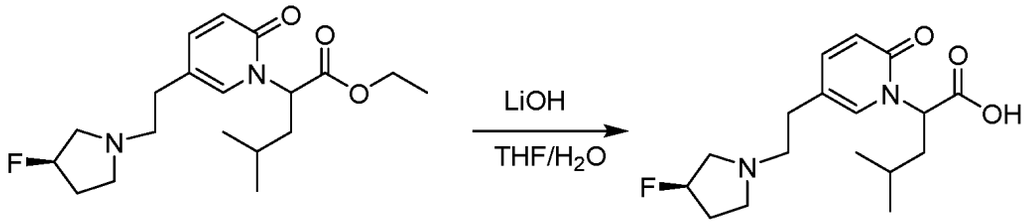
To a solution of ethyl 2-(5-allyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (7.1 g, 25.6 mmol) in THF/H_2O (80 mL/30 mL) was added a solution of K_2OsO_4-$2H_2O$ (94.0 mg, 0.26 mmol) in H_2O (4 mL) and stirred at room temperature for 1 h. A solution of $NaIO_4$ (10.8 g, 51.2 mmol) in H_2O (20 mL) was added and stirred at room temperature for 2 h. LCMS showed the reaction was completed. The reaction mixture was diluted with 100 mL of water and extracted with EtOAc (120 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)pentanoate as a yellow oil (7.0 g, crude) used directly in the next reaction without further purification. (ESI 280.3 $(M+H)^+$).

Step 4: ethyl 2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



To a mixture of ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)pentanoate (7.0 g, 25.0 mmol) in DCE (70 mL) at 25 °C was added (*R*)-3-fluoropyrrolidine hydrochloride (2.7 g, 25.0 mmol) and stirred at 25 °C for 30 mins. Then $NaBH(OAc)_3$ (10.6 g, 50.0 mmol) was added at 5 °C and stirred at 25 °C for 16 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 19:1) to give compound ethyl 2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (1.3 g) as a yellow oil. Yield: 15% (ESI 353.2 $(M+H)^+$).

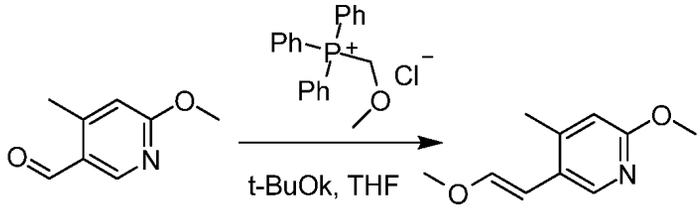
Step 5: 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1.3 g, 3.69 mmol) was treated with LiOH-H_2O (775.0 mg, 18.4 mmol) in MeOH (12 mL) and water (5 mL) at room temperature for 2 hours. The MeOH was removed *in vacuo*, acidified with 1N HCl to pH = 5. The residue was purified by reverse phase HPLC on a C18/120 g column (A: water, B: MeOH, 0~100%) to provide 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (1.03 g). Yield 86% (ESI 325.1 $(M+H)^+$).

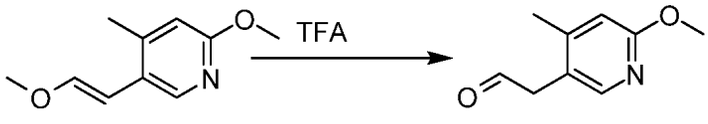
Preparation of 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: (E)-2-methoxy-5-(2-methoxyvinyl)-4-methylpyridine



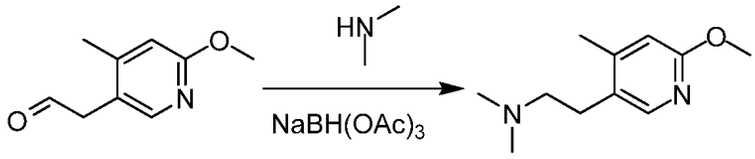
A mixture of (methoxymethyl)triphenyl phosphonium chloride (8.5 g, 24.8 mmol) and t-BuOK (4.6 g, 41.3 mmol) in THF (40 mL) was stirred at room temperature for 20 mins. 6-methoxy-4-methylnicotinaldehyde (2.5 g, 16.5 mmol) in 10 mL of THF was added and the mixture stirred at room temperature for 2 hours. The reaction mixture was poured into 40 mL of water and extracted with EtOAc (50 mL x 2). The organic phase was concentrated *in vacuo* and the residue purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (E)-2-methoxy-5-(2-methoxyvinyl)-4-methylpyridine as a colorless oil (1.8 g). Yield 61% (ESI 180.1$(M+H)^+$).

Step 2: 2-(6-methoxy-4-methylpyridin-3-yl)acetaldehyde



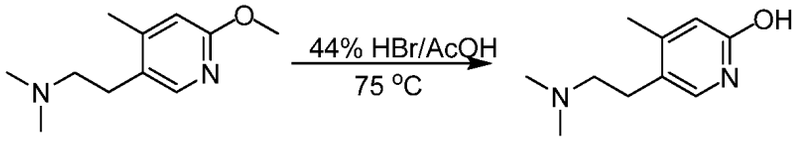
(E)-2-methoxy-5-(2-methoxyvinyl)-4-methylpyridine (1.8 g, 10 mmol) was treated with TFA (20 mL) at room temperature for 4 hours. The solvent was removed *in vacuo* to provide 2-(6-methoxy-4-methylpyridin-3-yl)acetaldehyde as a red oil (1.5 g, crude) used without further purification. (ESI 166.1 $(M+H)^+$).

Step 3: 2-(6-methoxy-4-methylpyridin-3-yl)-N,N-dimethylethanamine



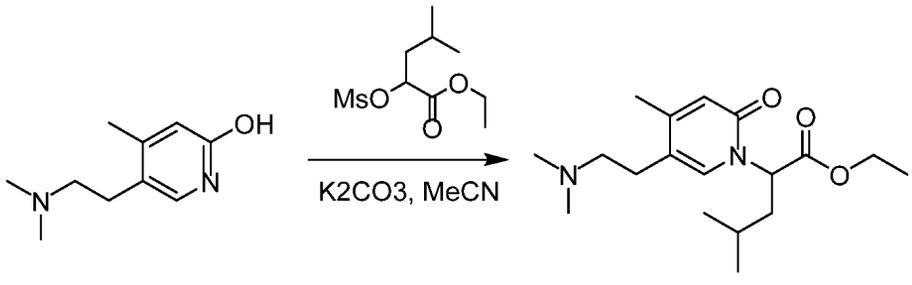
A mixture of 2-(6-methoxy-4-methylpyridin-3-yl)acetaldehyde (1.45 g, 8.78 mmol), dimethylamine (2M in THF, 17.5 mL, 35.72 mmol) and AcOH (0.8 g, 13.2 mmol) in DCE (30 mL) was stirred at room temperature for 15 mins. $NaBH(OAc)_3$ (3.71 g, 17.5 mmol) was added and stirred at room temperature for 3 hours. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 10:1) to provide 2-(6-methoxy-4-methylpyridin-3-yl)-N,N-dimethylethanamine as a yellow oil (850 mg). Yield 50% (ESI 195.1$(M+H)^+$).

Step 4: 5-(2-(dimethylamino)ethyl)-4-methylpyridin-2-ol



A mixture of 2-(6-methoxy-4-methylpyridin-3-yl)-N,N-dimethylethylamine (850 mg, 4.38 mmol) in HBr/AcOH (20 mL) was heated at 75°C for 16 h. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 5-(2-(dimethylamino)ethyl)-4-methylpyridin-2-ol as a red solid (650 mg). Yield 82% (ESI 181.1 $(M+H)^+$).

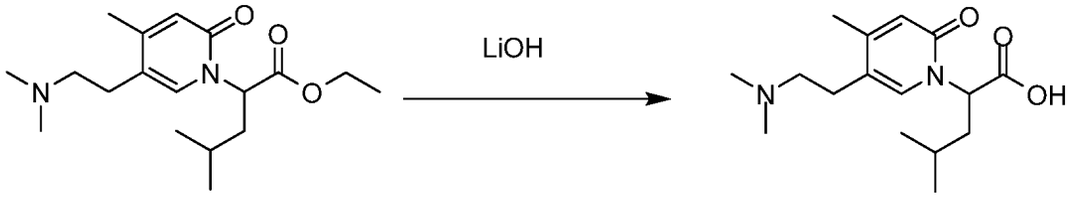
Step 5: ethyl 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of 5-(2-(dimethylamino)ethyl)-4-methylpyridin-2-ol (650 g, 3.6 mmol), ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.71 g, 7.2 mmol) and K_2CO_3 (1.49 g, 10.8 mmol) in MeCN (20 mL) was stirred at 80°C overnight. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-

1(2H)-yl)-4-methylpentanoate (500 mg). Yield 43% (ESI 323.2(M+H)$^+$).

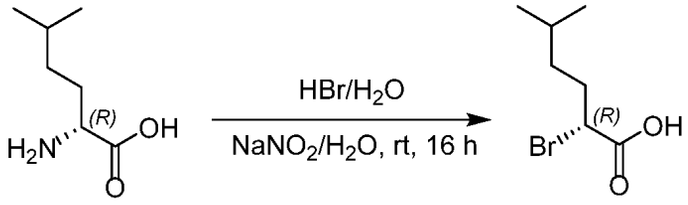
Step 6: 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (500 mg, 1.55 mmol) was treated with LiOH-H_2O (260 mg, 6.2 mmol) in MeOH (10 mL) and H_2O (2 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl and purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (420 mg). Yield 92% (ESI 295.2(M+H)$^+$).

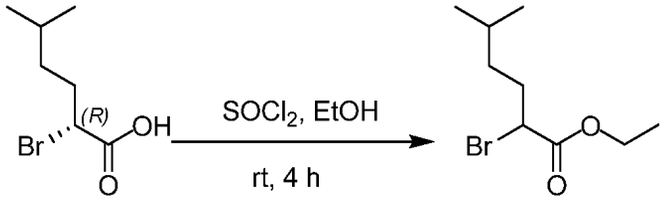
Preparation of 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoic acid

Step 1: (R)-2-bromo-5-methylhexanoic acid



To a mixture of (R)-2-amino-5-methylhexanoic acid (30 g, 207 mmol) in 40% HBr (200 mL) and H_2O (200 mL) at 0°C was added a solution of $NaNO_2$ (17 g, 248 mmol) in H_2O(15 mL) dropwise. The mixture was stirred at room temperature overnight. The mixture was extracted with DCM (200 mL). The organic phase was washed with brine (200 mL), dried over Na_2SO_4, concentrated *in vacuo* to provide (R)-2-bromo-5-methylhexanoic acid as a yellow oil (30 g). Yield 70% (ESI 211.1(M+H)$^+$).

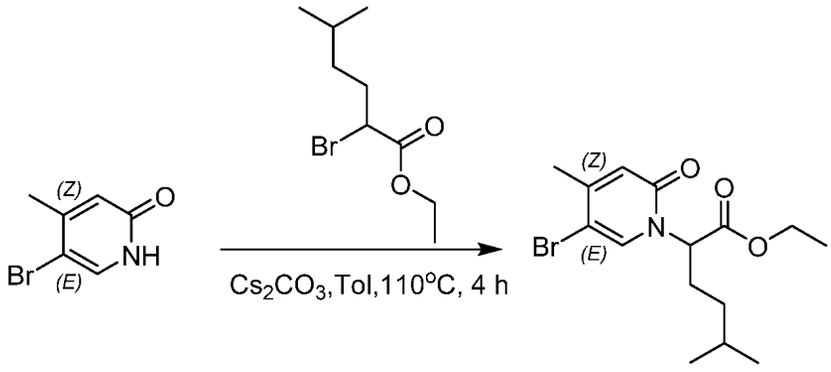
Step 2: ethyl 2-bromo-5-methylhexanoate



To a mixture of (R)-2-bromo-5-methylhexanoic acid (30 g, 144 mmol) in EtOH (200 mL) at 0°C was added $SOCl_2$ (86 g, 720 mmol). The mixture was stirred for 4 h at room temperature.

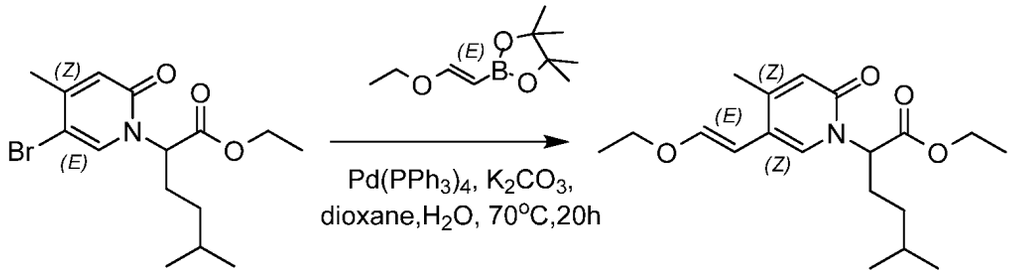
The solvent was removed *in vacuo* to provide ethyl 2-bromo-5-methylhexanoate as a colorless oil (35 g, crude). (ESI 239.1 $(M+H)^+$).

Step 3: ethyl 2-(5-bromo-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoate



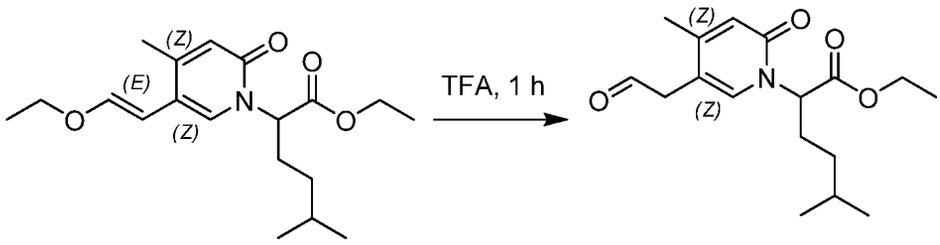
A mixture of 5-bromo-4-methylpyridin-2(1H)-one (8 g, 42.78 mmol), Cs_2CO_3 (27.9 g, 85.56 mmol) and ethyl 2-bromo-5-methylhexanoate (15 g, 64.17 mmol) in toluene (160 mL) was stirred at 110 °C for 4hours. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-bromo-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoateas a colorless oil (6.5 g). Yield 44% (ESI 346.1$(M+H)^+$).

Step 4: (E)-ethyl 2-(5-(2-ethoxyvinyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoate



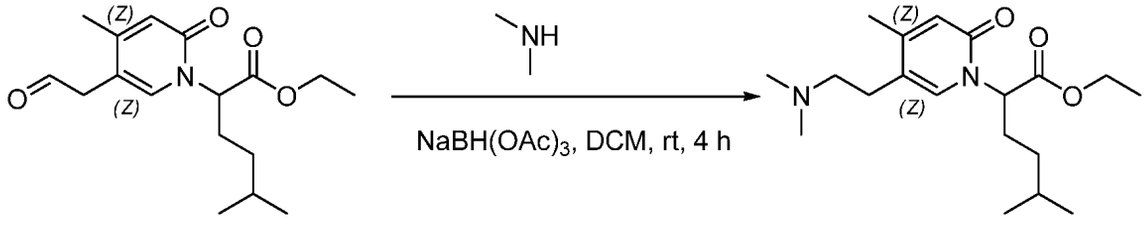
A mixture of ethyl 2-(5-bromo-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoate (5.4 g, 15.7 mmol), (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.22 g, 31.4 mmol), $Pd(PPh_3)_4$ (912 mg, 0.79 mmol) and K_2CO_3 (4.33 g, 31.4 mmol) in 1,4-dioxane (70 mL) and water (7 mL) was stirred at 70°C under N_2 for 20 h. The reaction mixture was diluted with 100 mL of water, extracted with EtOAc (100 mL x 2). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide (E)-ethyl 2-(5-(2-ethoxyvinyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoate (3.8 g) as a yellow oil. Yield 72% (ESI 336.2 $(M+H)^+$).

Step 5: ethyl 5-methyl-2-(4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)hexanoate



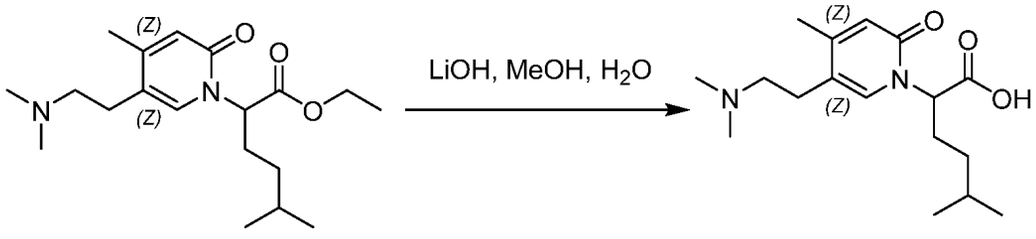
(E)-ethyl 2-(5-(2-ethoxyvinyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoate (3.8 g, 11.34 mmol) was treated with TFA (40 mL) at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (EtOAc) to provide ethyl 5-methyl-2-(4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)hexanoate as a colorless oil (2 g). Yield 57% (ESI 308.2 $(M+H)^+$).

Step 6: ethyl 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoate



To a mixture of ethyl 5-methyl-2-(4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)hexanoate (2 g, 6.51 mmol) in DCM (30 mL) was added dimethylamine (2 M) (6.5 mL, 13.02 mmol) and stirred at room temperature for 20 minutes. Then $NaBH(OAc)_3$ (2.76 g, 13.02 mmol) was added and stirred at room temperature for 4 h. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoate as a colorless oil (1.4 g). Yield 64% (ESI 337.3 $(M+H)^+$).

Step 7: 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoic acid

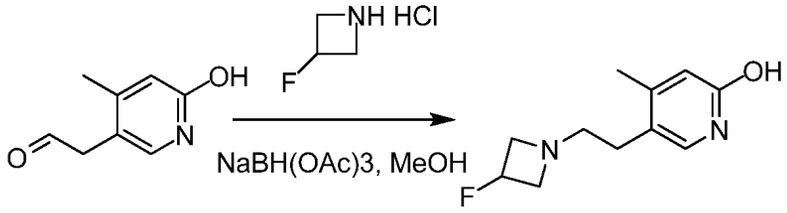


Ethyl 2 - (5- (2- (dimethylamino)ethyl) - 4-methyl – 2 – oxopyridin - 1(2H) - yl) – 5 -

methylhexanoate (1.4 g, 4.17 mmol) was treated with LiOH-H_2O (700 mg, 16.68 mmol) in MeOH (20 mL) and H_2O (4 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1 N HCl. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-5-methylhexanoic acid (900 mg) as a white solid. Yield 70% (ESI 309.2$(M+H)^+$).

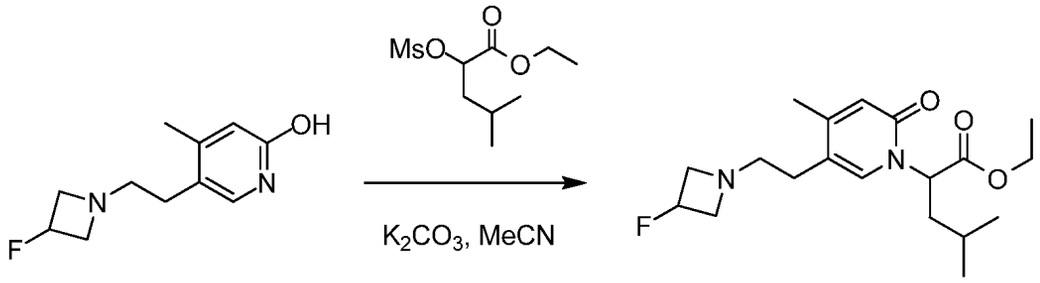
Preparation of 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methylpyridin-2-ol



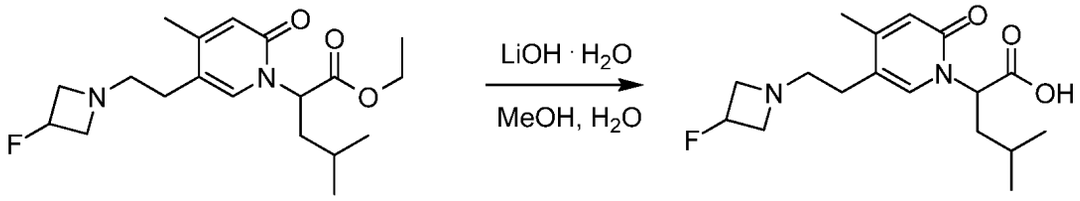
A mixture of 2-(6-hydroxy-4-methylpyridin-3-yl)acetaldehyde (2 g, 13.2 mmol), 3-fluoroazetidine hydrochloride (2.2 g, 19.8 mmol) in MeOH (20 mL) was stirred at room temperature for 30 mins. $NaBH(OAc)_3$ (5.6 g, 26.4 mmol) was added and stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 2:1) to provide 5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methylpyridin-2-ol as a yellow oil (1 g). Yield 36% (ESI 211.1$(M+H)^+$).

Step 2: ethyl 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of methyl 5-(2-(dimethylamino)ethyl)pyridin-2(1H)-one (1 g, 4.76 mmol), ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.36 g, 5.71 mmol) and K_2CO_3 (1.97 g, 14.28 mmol) in MeCN (20 mL) was stirred at 85°C overnight. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 1:2) to provide ethyl 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a white solid (500 mg). Yield 30% (ESI 353.2$(M+H)^+$).

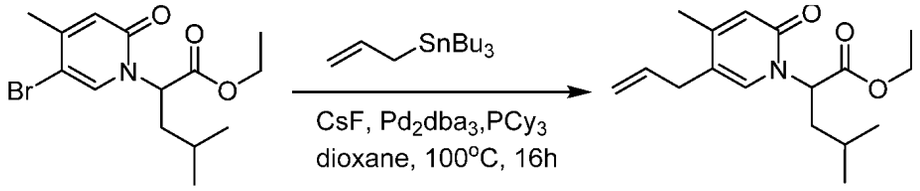
Step 3: 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (500 mg, 1.42 mmol) was treated with LiOH-H_2O (298 mg, 7.1 mmol) in MeOH (10 mL) and H_2O (2.5 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl, purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to give 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (360 mg). Yield 78% (ESI 325.1$(M+H)^+$).

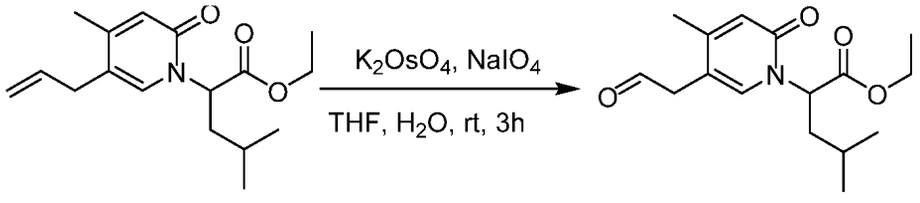
Preparation of 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-allyl-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



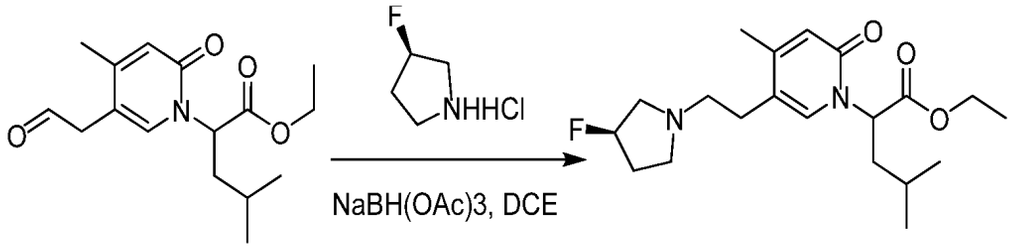
A mixture of ethyl 2-(5-bromo-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (2.9 g, 8.78 mmol) , allyltributylstannane (3.5 g, 10.54 mmol), Pd_2dba_3 (402 mg, 0.44 mmol), PCy_3 (247 mg, 0.88 mmol) and CsF (2.7 g, 17.56 mmol) in anhydrous dioxane (100 mL) was stirred at 100°C for 16 h. The mixture was cooled to room temperature. The mixture was filtered and washed with dioxane (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 3:1) to provide ethyl 2-(5-allyl-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (1.6 g). Yield 60% (ESI 292 $(M+H)^+$).

Step 2: ethyl 4-methyl-2-(4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)pentanoate



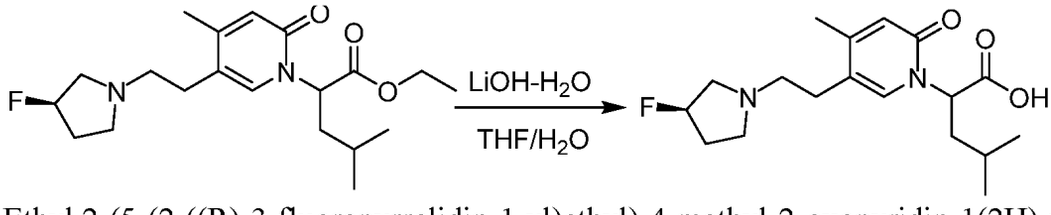
To a solution of ethyl 2-(5-allyl-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1.6 g, 5.49 mmol) in THF/H_2O (20 mL/10 mL) was added a solution of K_2OsO_4-$2H_2O$ (20 mg, 0.055 mmol) in H_2O (1 mL) dropwise and stirred at room temperature for 1 h. A solution of $NaIO_4$ (2.3 g, 10.98 mmol) in H_2O (5 mL) was added dropwise and stirred at room temperature for 3 h. LCMS showed the reaction was completed. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (50 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide ethyl 4-methyl-2-(4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)pentanoate as a brown oil which was used in next step without further purification. (ESI 294 $(M+H)^+$).

Step 3: ethyl 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of ethyl 4-methyl-2-(4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)pentanoate (950 mg, 3.24 mmol) and (R)-3-fluoropyrrolidine hydrochloride (814 mg, 6.48 mmol) in DCE (20 mL) was stirred at room temperature for 1 h. Then $NaBH(OAc)_3$ (2.1 g, 9.72 mmol) was added and stirred at room temperature for 2 h. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water/10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (550 mg). Yield 46% (ESI 367 $(M+H)^+$).

Step 4: 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

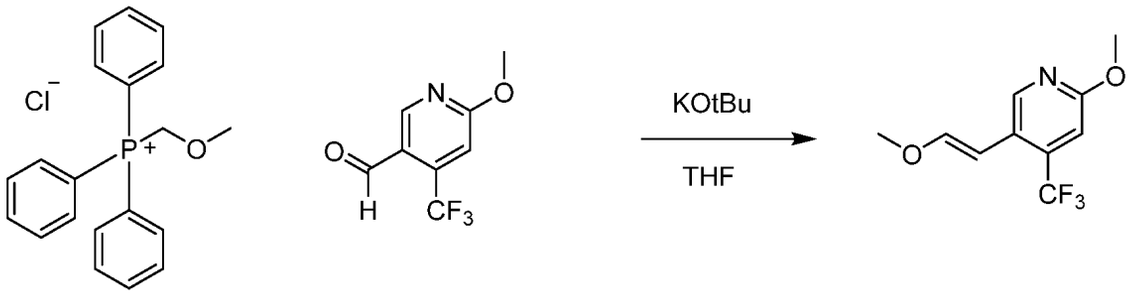


Ethyl 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (550 mg, 1.50 mmol) was treated with LiOH-H_2O (120 mg, 4.50 mmol) in THF (6 mL) and water (2 mL) at room temperature for 2 hours. The reaction was acidified with 1N HCl to pH = 8. The solvent was removed *in vacuo* and the residue was purified by

reverse phase HPLC on a C18/40 g column (A: water/10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (270 mg). Yield 53% (ESI 339 $(M+H)^+$).

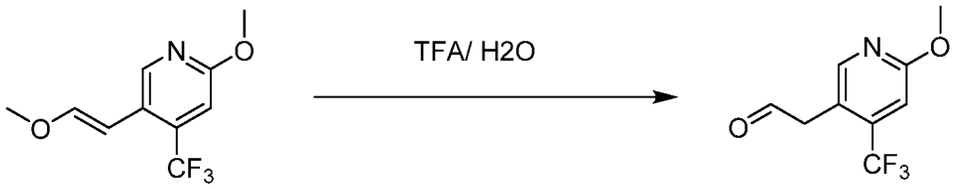
Preparation of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: (E)-2-methoxy-5-(2-methoxyvinyl)-4-(trifluoromethyl)pyridine



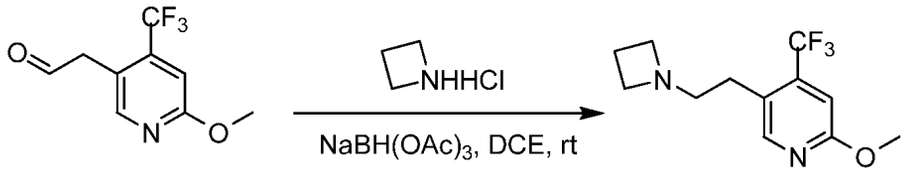
To a solution of (methoxymethyl)triphenylphosphonium chloride (1.0 g, 2.95 mmol) in THF (13.406 mL) at 0°C was added potassium tert-butoxide (376 mg, 3.35 mmol). After stirring for 1 hour at 0°C, a solution of 6-methoxy-4-(trifluoromethyl)nicotinaldehyde (550 mg, 2.68 mmol) in THF (6.5 mL) was added. The reaction was allowed to stir overnight at room temperature and quenched with a NH_4Cl solution. The mixture was extracted (EtOAc x 3), concentrated and purified by silica gel chromatography (0-100 Ethyl acetate: Hexanes) to provide (E)-2-methoxy-5-(2-methoxyvinyl)-4-(trifluoromethyl)pyridine (450 mgs). Yield 72% (ESI 234.2 $(M+H)^+$).

Step 2: 2-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)acetaldehyde



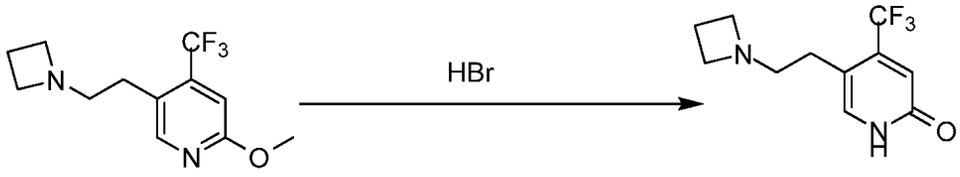
To a solution of (E)-2-methoxy-5-(2-methoxyvinyl)-4-(trifluoromethyl)pyridine (450 mg, 1.930 mmol) in DCM (29.689 mL) was added TFA (0.595 mL, 7.72 mmol) and water (0.591 mL, 32.8 mmol). The reaction was stirred for 18 hrs at 45 °C. The reaction was diluted with DCM and quenched with $NaHCO_3$. The mixture was washed with water, dried with Na_2SO_4, filtered and concentrated to provide 2-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)acetaldehyde (343 mgs) used without further purification. Yield 81% (ESI 220.18 $(M+H)^+$).

Step 3: 5-(2-(azetidin-1-yl)ethyl)-2-methoxy-4-(trifluoromethyl)pyridine



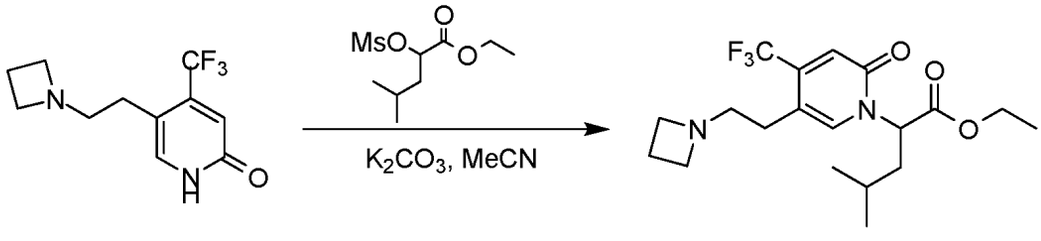
To a solution of 2-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)acetaldehyde (4 g, 18.1 mmol) in DCE (50 mL) was added azetidine hydrochloride (3.4 g, 36.2 mmol). The reaction mixture was stirred at room temperature for 20 mins. $NaBH(OAc)_3$ (7.7 g, 36.2 mmol) was added and stirred at room temperature for 16 hours. The reaction mixture was quenched by addition of MeOH (20 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/80 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 5-(2-(azetidin-1-yl)ethyl)-2-methoxy-4-(trifluoromethyl)pyridine as a yellow oil (3 g). Yield 63% (ESI 261.2$(M+H)^+$).

Step 4: 5-(2-(azetidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-2(1H)-one



A mixture of 5-(2-(azetidin-1-yl)ethyl)-2-methoxy-4-(trifluoromethyl)pyridine (2.95 g, 11.3 mmol) in HBr/AcOH (20 mL) was stirred at 50°C for 5 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/80 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 5-(2-(azetidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-2(1H)-one as a yellow oil (710 mg). Yield 25% (ESI 247.1$(M+H)^+$).

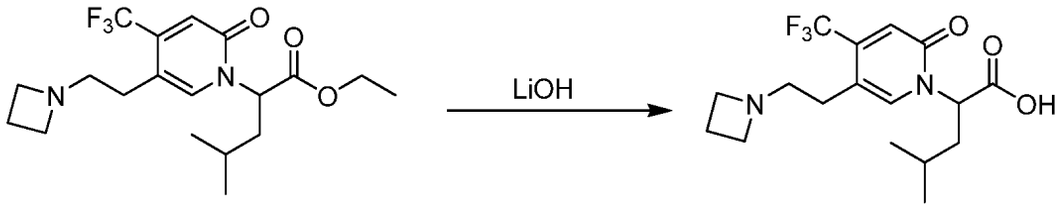
Step 5: ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a solution of 5-(2-(azetidin-1-yl)ethyl)-4-(trifluoromethyl)pyridin-2(1H)-one (710 mg, 2.9 mmol) in MeCN (10 mL) was added ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.1 g, 4.4 mmol) and K_2CO_3 (1.2 g, 8.7 mmol). The reaction mixture was stirred at 80°C for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH,

0~100%) to provide ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (500 mg). Yield 44% (ESI 389.2(M+H)$^+$).

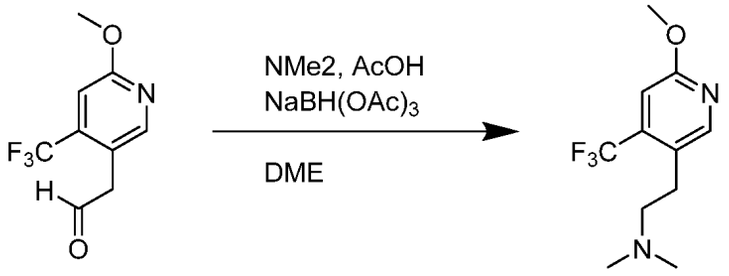
Step 6: 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (500 mg, 1.3 mmol) was treated with LiOH-H_2O (270 mg, 6.5 mmol) in EtOH (5 mL) and water (1 mL) at room temperature for 2 hours. The reaction mixture was neutralized with 2 N HCl and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid as a yellow oil (410 mg). Yield 88% (ESI 361.2(M+H)$^+$).

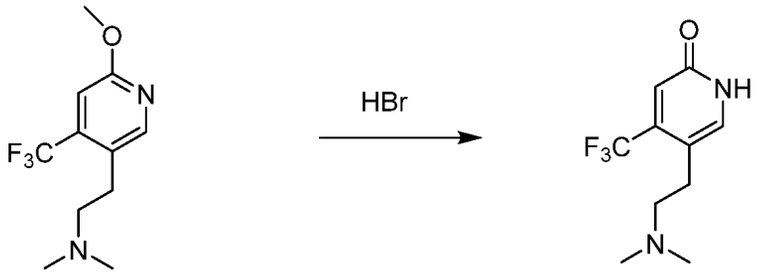
Preparation of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 2-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)-N,N-dimethylethan-1-amine



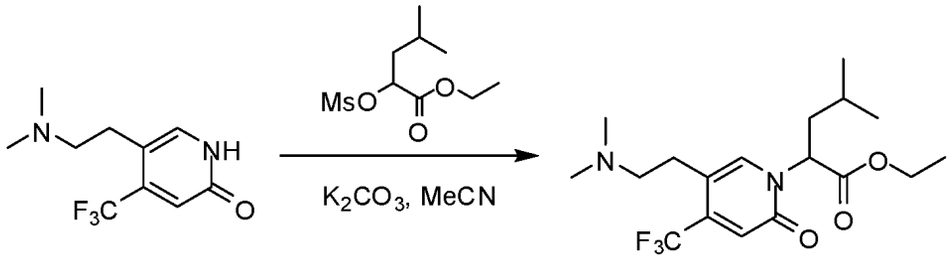
To a solution of 2-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)acetaldehyde (0.34 g, 1.6 mmol) in DCE (7.8 mL) was added dimethylamine (3.9 mL, 7.8 mmol) and acetic acid (0.05 mL, 0.78 mmol) and stirred for 1 hour. To the solution was added sodium triacetoxyborohydride (0.6 g, 3.1 mmol). The reaction was allowed to stir for 12 hours then concentrated and purified by silica gel chromatography (0-35% DCM (1% TEA):MeOH 0-30%) to provide 2-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)-N,N-dimethylethan-1-amine (305 mg). Yield 79% (ESI 249.27 (M+H)$^+$).

Step 2: 5-(2-(dimethylamino)ethyl)-4-(trifluoromethyl)pyridin-2(1H)-one



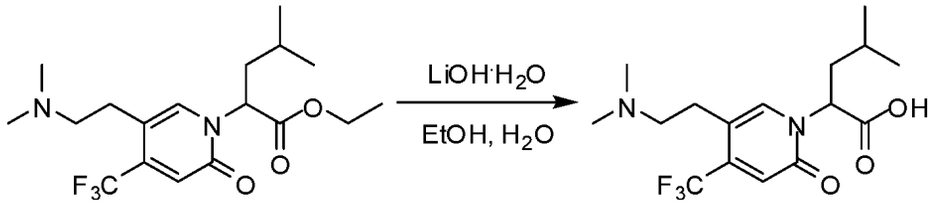
HBr (33% in Acetic Acid) (4.04 mL, 24.57 mmol) was added to 2-(6-methoxy-4-(trifluoromethyl)pyridin-3-yl)-N,N-dimethylethan-1-amine (0.305 g, 1.229 mmol) and heated to 75 °C in a pressure vessel. After 4 hours, the solvent was removed and the residue purify by silica gel chromatography (0-25% DCM:MeOH with 1% TEA as a modifier) to provide 5-(2-(dimethylamino)ethyl)-4-(trifluoromethyl)pyridin-2(1H)-one (219 mg). Yield 76% (ESI 235.15 $(M+H)^+$). ^{1}H NMR (400 MHz, MeOD) δ 7.56 (s, 1H), 6.85 (s, 1H), 2.76 (m, 2H), 2.61 (m, 1H), 2.37 (m, 6H)

Step 3: ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



A mixture of 5-(2-(dimethylamino)ethyl)-4-(trifluoromethyl)pyridin-2(1H)-one (685 mg, 2.92 mmol), K_2CO_3 (1.60 g, 11.55 mmol) and ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.60 g, 6.70 mmol) in CH_3CN (60 mL) was stirred at 85°C overnight. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 2:1) to give ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate as brown oil (390 mg). Yield 35% (ESI 377.2 $(M+H)^+$). ^{1}H NMR (500 MHz, MeOD) δ 7.84 (s, 1H), 6.68 (s, 1H), 5.51 (dd, J = 11.0, 5.0 Hz, 1H), 4.23 (q, J = 7.0 Hz, 2H), 2.77 (t, J = 8.0 Hz, 2H), 2.53 (t, J = 8.0 Hz, 2H), 2.33 (s, 6H), 2.18 – 2.12 (m, 1H), 2.08 – 2.02 (m, 1H), 1.46 – 1.38 (m, 1H), 1.27 (t, J = 7.0 Hz, 3H), 0.97 (t, J = 7.0 Hz, 6H).

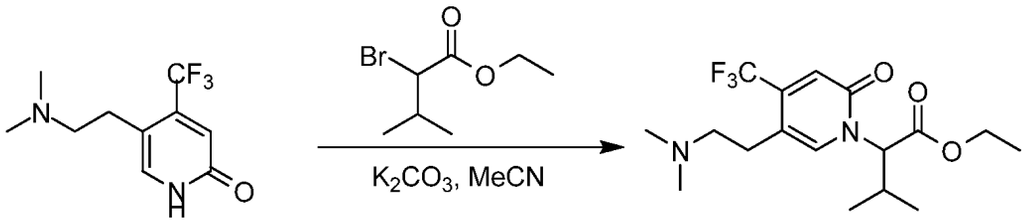
Step 4: 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (390 mg, 1.0 mmol) was treated with LiOH monohydrate (435 mg, 10.36 mmol) in EtOH (10 mL) and H_2O (1 mL) at room temperature for 1 hour. The mixture was acidified to pH 4~5 with 1N HCl aqueous solution. The mixture was concentrated *in vacuo* and purified by silica gel column (MeOH: EtOAc 1:2) to give 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid as an oil (358 mg). Yield 99% (ESI 349.1 $(M+H)^+$).

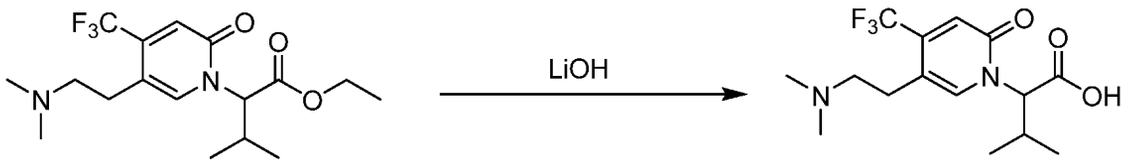
Preparation of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylbutanoic acid

Step 1: ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylbutanoate



To a solution of 5-(2-(dimethylamino)ethyl)-4-(trifluoromethyl)pyridin-2(1H)-one (2.4 g, 10.2 mmol) in MeCN (40 mL) was added ethyl 2-bromo-3-methylbutanoate (4.3 g, 20.4 mmol) and K_2CO_3 (2.8 g, 20.4 mmol). The reaction mixture was stirred at 80°C for 16 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylbutanoate as a yellow oil (2.6 g). Yield 69% (ESI 363.2$(M+H)^+$).

Step 2: 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylbutanoic acid

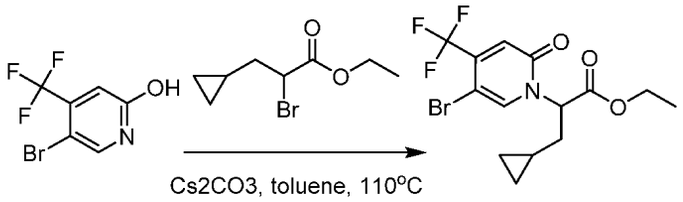


Ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylbutanoate (2.6 g, 7.1 mmol) was treated with LiOH-H_2O (1.47 g, 35 mmol) in EtOH (15 mL) and water (3 mL) at room temperature for 2 h. The reaction mixture was neutralized with 2 N HCl, concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-

(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylbutanoic acid as a yellow oil (1.8 g). Yield 75% (ESI 335.2(M+H)$^+$).

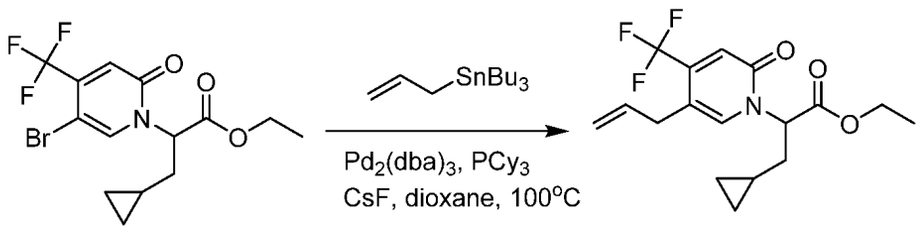
Preparation of 3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoic acid

Step 1: ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-cyclopropylpropanoate



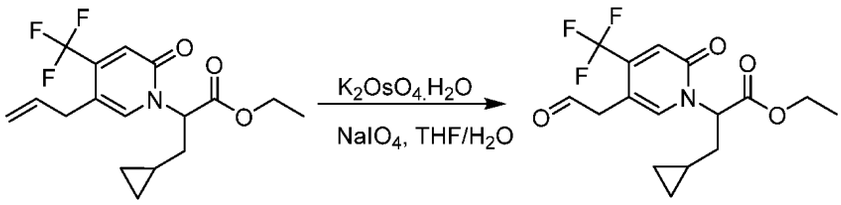
A mixture of 5-bromo-4-(trifluoromethyl)pyridin-2-ol (2.5 g, 10.33 mmol), Cs_2CO_3 (6.7 g, 20.66 mmol) and ethyl 2-bromo-3-cyclopropylpropanoate (3.4 g, 15.50 mmol) in toluene (100 mL) was stirred at 110 °C for 16 h. LCMS showed the reaction was completed. The mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-cyclopropylpropanoate as a colorless oil (1.5 g). Yield 38% (ESI 384.0 (M+H)$^+$).

Step 2: ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-cyclopropylpropanoate



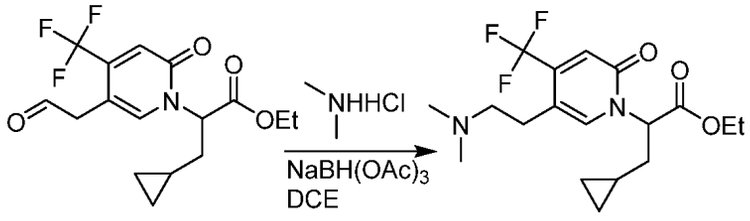
To a solution of ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-cyclopropylpropanoate (2.3 g, 6.02 mmol) and allyltributylstannane (2.4 g, 7.22 mmol) under nitrogen atmosphere in dioxane (50 mL) was added Pd_2dba_3 (348 mg, 0.30 mmol), PCy_3 (168 mg, 0.60 mmol), CsF (1.8 g, 12.04 mmol) and stirred at 100°C for 16 h. The mixture was cooled to room temperature. A saturation NH_4Cl solution (100 mL) and EtOAc (100 mL) was added to the mixture and the the aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-cyclopropylpropanoate as a colorless oil (1.5 g). Yield 72% (ESI 344.0 (M+H)$^+$).

Step 3: ethyl 3-cyclopropyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoate



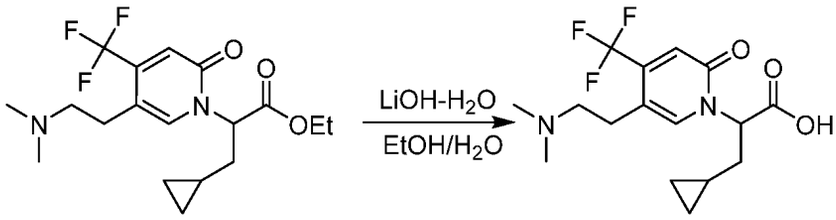
To a solution of ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-cyclopropylpropanoate (1.5 g, 4.37 mmol) in THF/H_2O (20 mL/20 mL) was added a solution of K_2OsO_4-$2H_2O$ (16.0 mg, 0.0437 mmol) in H_2O (3 mL) and stirred at room temperature for 1 hour. A solution of $NaIO_4$ (1.8 g, 8.74 mmol) in H_2O (10 mL) was added dropwise and the mixture was stirred at room temperature for another hour. LCMS showed the reaction was completed. The reaction mixture was diluted with water (40 mL) and extracted with EtOAc (50 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide ethyl 3-cyclopropyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoate as a brown oil used directly in the next reaction without further purification (1.5 g, crude). (ESI 346.1 $(M+H)^+$).

Step 4: ethyl 3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoate



To a mixture of ethyl 3-cyclopropyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoate (1.5 g, 4.34 mmol) in DCE (20 mL) at 25 °C was added dimethylamine hydrochloride (708 mg, 8.68 mmol) and stirred for 1 hour. $NaBH(OAc)_3$ (2.8 g, 13.02 mmol) was added at 5 °C and stirred at 25 °C for 16 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to provideethyl 3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoate as a colorless oil (400 mg) Yield 25% (ESI 375.1 $[M+H]^+$).

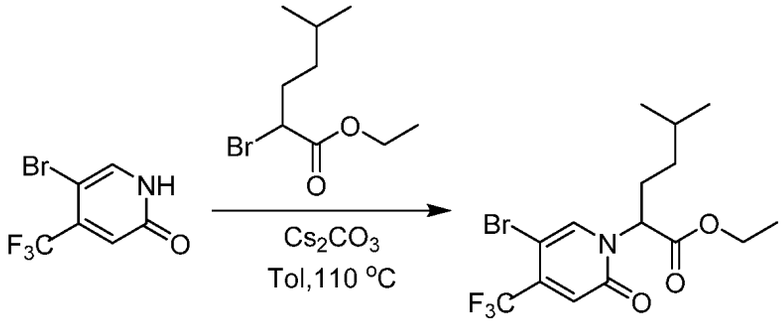
Step 5: 3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoic acid



Ethyl 3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoate (400 mg, 1.07 mmol) was treated with LiOH-H_2O (224 mg, 5.35 mmol) in EtOH (5 mL) and water (2 mL) and the mixture was stirred at room temperature for 30 minutes. The mixture was acidified with 1N HCl to pH 5~6 and purified by reverse phase HPLC on a C18/120 g column (A: water/10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoic acid as a white solid (150 mg). Yield 41% (ESI 347.0 $(M+H)^+$).

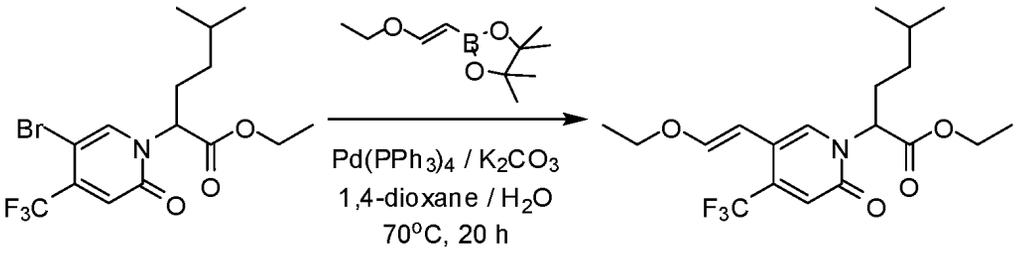
Preparation of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoic acid

Step 1: ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate



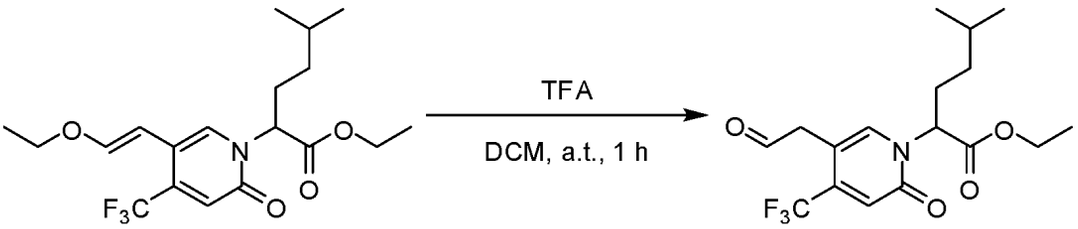
A mixture of 5-bromo-2-hydroxy-4-(trifluoromethyl)pyridine (6.00 g, 24.79 mmol), ethyl 2-bromo-5-methylhexanoate (8.82 g, 37.19 mmol) and Cs_2CO_3 (24.24 g, 74.38 mmol) in anhydrous toluene (120 mL) was heated at 110 °C under nitrogen atmosphere for 3 h. The solvent was removed *in vacuo* and the residue was purified by silica gel column (petroleum ether: EtOAc 23:1) to provide ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate as brown oil (5.9 g). Yield 59%. (ESI 400.0 $(M+H)^+$, ESI 422.0 $(M+Na)^+$).

Step 2: (E)-ethyl 2-(5-(2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate



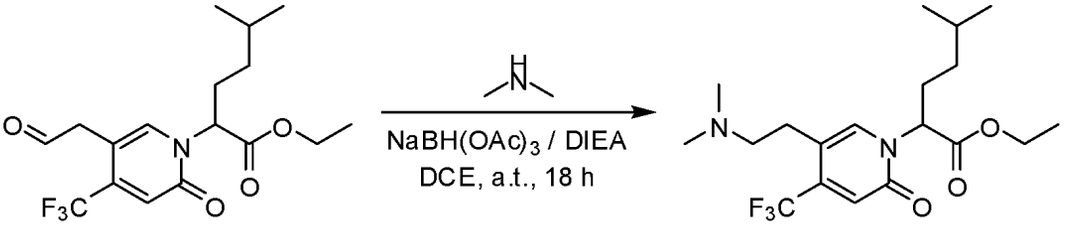
A mixture of ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate (5.56 g, 13.97 mmol), (E)-1-ethoxyethene-2-boronic acid pinacol ester (4.15 g, 20.95 mmol), tetrakis(triphenylphosphine)palladium(0) (2.42 g, 2.10 mmol) and K_2CO_3 (5.79 g, 41.91 mmol) in co-solvent of anhydrous 1,4-dioxane (140 mL) and water (14 mL) was heated at 70 °C under nitrogen atmosphere for 20 h. The solvent was removed *in vacuo* and the residue was purified by silica gel column (petroleum ether: EtOAc 10:1) to provide (E)-ethyl 2-(5-(2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate as brown oil (3.4 g). Yield 63%. (ESI 390.1 $(M+H)^+$).

Step 3: ethyl 5-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)hexanoate



Trifluoroacetic acid (32 mL, 430.80 mmol) was added to a stirring solution of (E)-ethyl 2-(5-(2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate (5.2 g, 13.35 mmol) in DCM (64 mL) and the reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* to provide ethyl 5-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)hexanoate as brown oil (5.2 g, crude). (ESI 362.1 $(M+H)^+$).

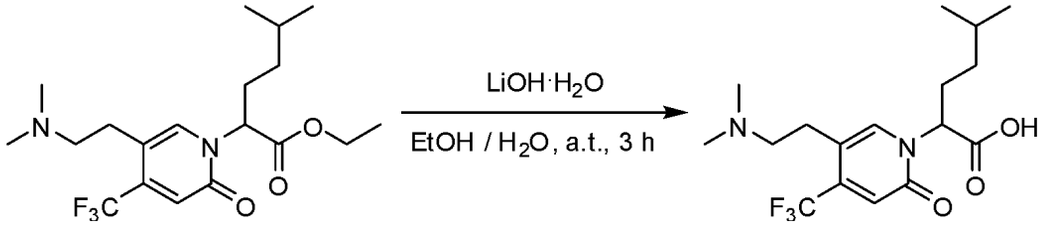
Step 4: ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate



The mixture of ethyl 5-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)hexanoate (1.6 g, 4.45 mmol) and dimethylamine (60 mL, 2M in THF, 120 mmol) in 1,2-dichloroethane (43 mL) was stirred at ambient temperature for 1 h. Sodium triacetoxyborohydride (14.91 g, 70.34 mmol) was added in one portion and stirred at ambient

temperature for 18 h. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 3:1) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate as brown oil (1.2 g). Yield 72%. (ESI 391.1 $(M+H)^+$).

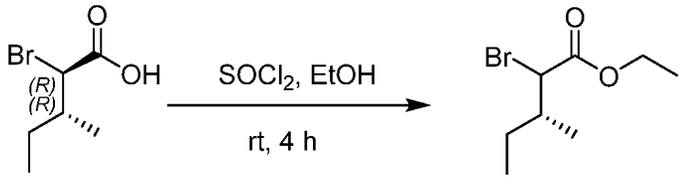
Step 5: 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoic acid



Ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoate (925 mg, 2.37 mmol) was treated with LiOH monohydrate (298 mg, 7.11 mmol) in EtOH (10 mL) and H_2O (0.7 mL) at room temperature for 3 h. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~80%) to provide 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanoic acid as a yellow solid (617 mg). Yield 72% (ESI 363.1 $(M+H)^+$).

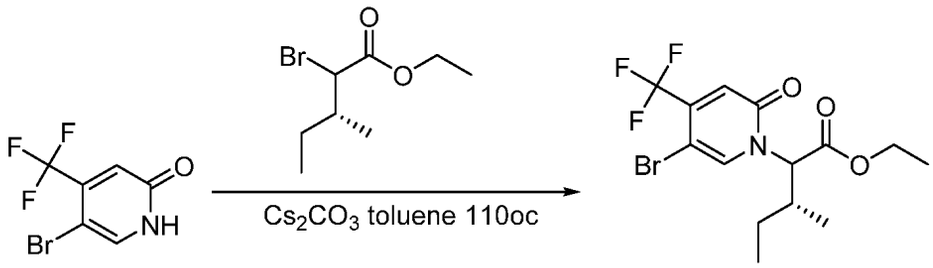
Preparation of (3R)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoic acid

Step 1: ethyl (3R)-2-bromo-3-methylpentanoate



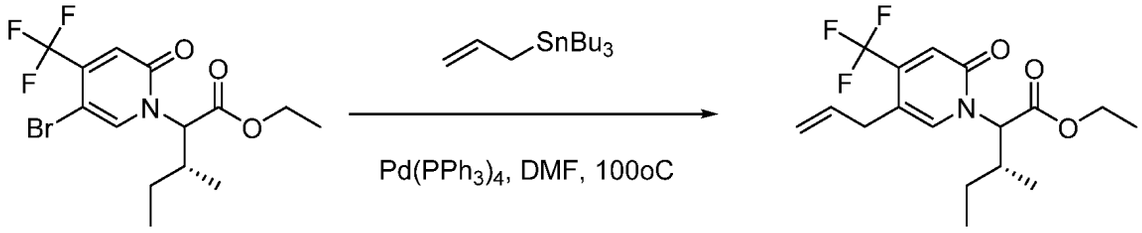
To a mixture of (2R,3R)-2-bromo-3-methylpentanoic acid (5 g, 25.6 mmol) in EtOH (50 mL) at 0°C was added $SOCl_2$ (6.1 g, 51.2 mmol). The mixture was stirred for 4 h at room temperature. The solvent was removed *in vacuo* to provide ethyl (3R)-2-bromo-3-methylpentanoate as a yellow oil (5.3, crude). (ESI 223 $(M+H)^+$).

Step 2: ethyl (3R)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoate



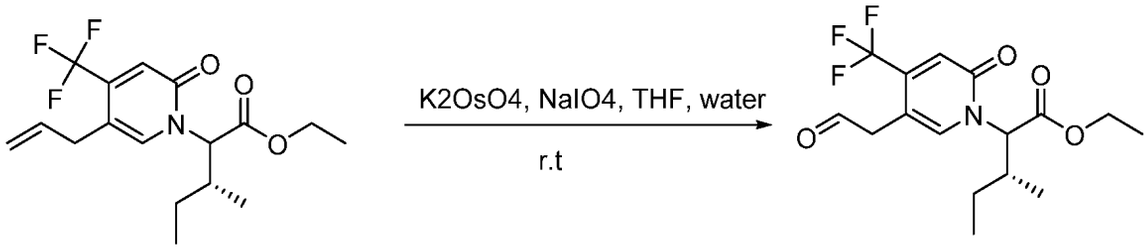
To a stirred solution of 5-bromo-4-(trifluoromethyl)pyridin-2(1H)-one (3.50 g, 14.52 mmol) and ethyl (3R)-2-bromo-3-methylpentanoate (3.54 g, 15.97 mmol) in toluene (50 mL) was added Cs_2CO_3 (5.38 g, 16.58 mmol) and stirred at 110°C for 2 hours. The reaction was cooled to room temperature, filtered and washed with 20 mL of EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 20:1) to provide ethyl (3R)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoate as a white solid (2.2 g). Yield 40% (ESI 384.0$(M+H)^+$).

Step 3: ethyl (3R)-2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoate



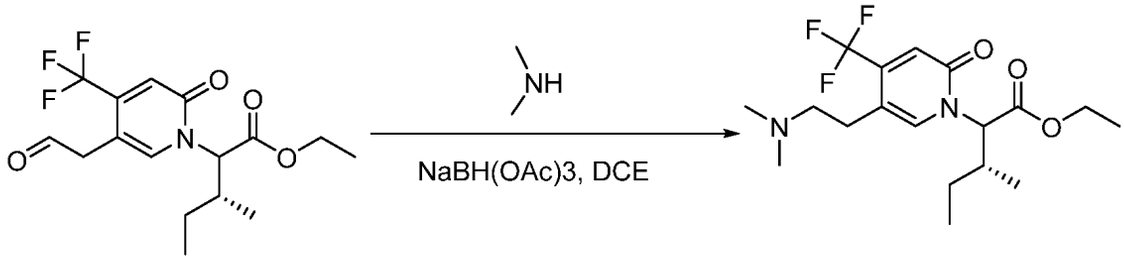
To a solution of ethyl (3R)-2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoate (2.2 g, 5.74 mmol) and allyltributylstannane (2.28 g, 6.89 mmol) under N_2 atmosphere in DMF (15 mL) was added $Pd(PPh_3)_4$ (0.67 g, 0.58 mmol) and stirred at 100°C for 16 hours. The reaction mixture was concentrated *in vacuo*. The residue was diluted with 50 mL of EtOAc, poured into 20% aq. KF (100 mL), stirred at 20°C for 1 hour and then filtered and washed with 100 mL of EtOAc. The filtrate was extracted with EA (100 mL x 3). The combined organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 20:1) to provide ethyl (3R)-2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoate as a colorless oil (1.51 g). Yield 76% (ESI 346$(M+H)^+$).

Step 4: ethyl (3R)-3-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate



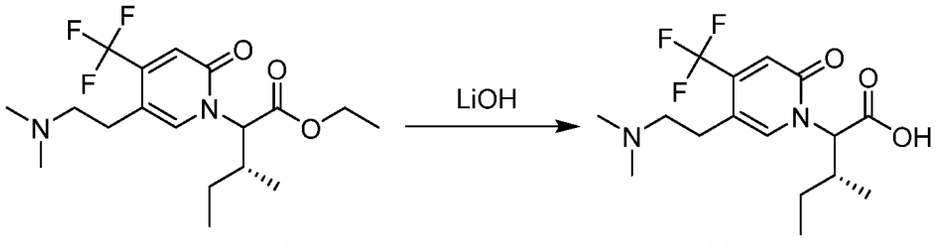
To a mixture of ethyl (3R)-2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoate (1.51 g, 4.36 mmol) in THF (15 mL) and H_2O (10 mL) at 0 °C was added K_2OsO_4-$2H_2O$ (130 mg, 0.345 mmol) and stirred at 0 °C for 5 mins. Then a solution of $NaIO_4$ (2.80 g, 13.08 mmol) in H_2O (5 mL) was added dropwise and stirred at 0 °C for 2 hours and then at 25 °C for 2 hours. The mixture was quenched with a saturated $Na_2S_2O_3$ solution (50 mL) and the mixture was extracted with EA (60 mL x 3). The combined organics were washed with brine (30 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to providecrude product ethyl (3R)-3-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (1.5 g, crude) as yellow oil. (ESI 348$(M+H)^+$).

Step 5: ethyl (3R)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoate



To a mixture of ethyl (3R)-3-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (1 g, 2.87 mmol) in DCE (10 mL) at 25 °C was added dimethylamine hydrochloride (700 mg, 8.62 mmol) and stirred at 25 °C for 10 min. Then $NaBH(OAc)_3$ (1.22 g, 5.74 mmol) was added and stirred at 25 °C for 2 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to provide ethyl (3R)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoate as a yellow oil (550 mg). Yield 51% (ESI 377 $(M+H)^+$).

Step 6: (3R)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoic acid

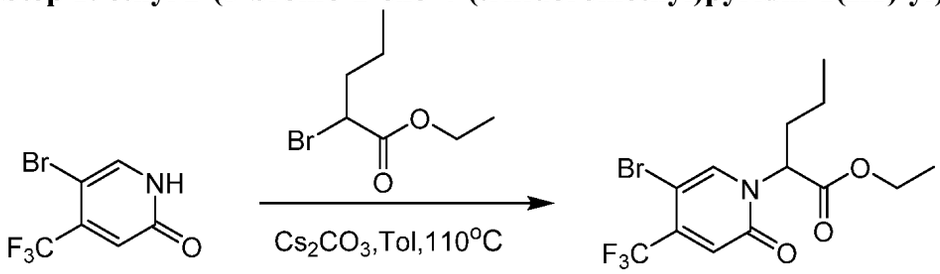


Ethyl (3R)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-

methylpentanoate (550 mg, 1.46 mmol) was treated with LiOH-H_2O (240 mg, 5.84 mmol) in MeOH (5 mL) and water (1 mL) at room temperature for 1 hour. The MeOH was removed and the aqueous material acidified with 1N HCl to pH 4. The mixture was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (3R)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-3-methylpentanoic acid as a yellow oil (400 mg). Yield 78.5% (ESI 349 $(M+H)^+$).

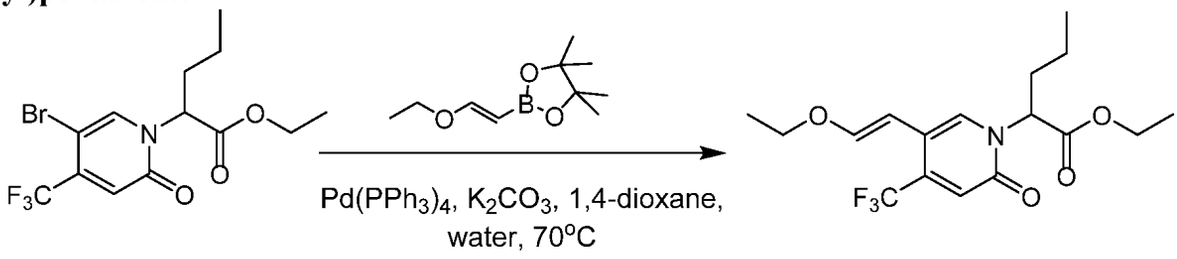
Preparation of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoic acid

Step 1: ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate



To a stirred solution of 5-bromo-4-(trifluoromethyl)pyridin-2(1*H*)-one (2 g, 8.29 mmol) and methyl 2-bromo-4-methylpentanoate (2.24 g, 10.78 mmol) in toluene (40 mL) was added Cs_2CO_3 (5.38 g, 16.58 mmol) portionwise and stirred at 110°C for 2 hours. The reaction mixture was diluted with 50 mL of EtOAc, filtered and washed with 20 mL of EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 20:1) to provide ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate as a white solid (2.3 g). Yield 65% (ESI 372.0$(M+H)^+$).

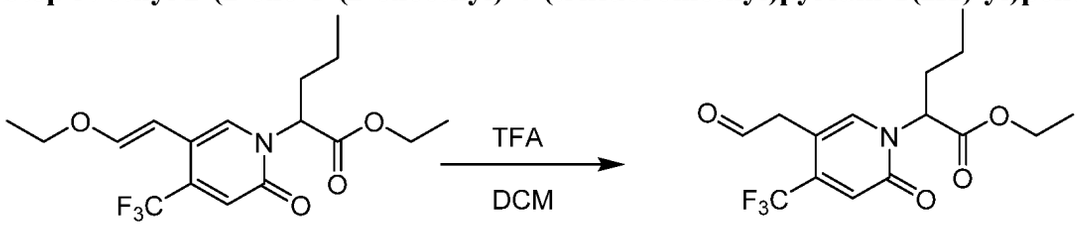
Step 2: ethyl (E)-2-(5-(2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate



A mixture of ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate (2.2 g, 5.96 mmol), (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.35 g, 6.85 mmol), $Pd(PPh_3)_4$ (206 mg, 0.17 mmol) and K_2CO_3 (1.64 g, 11.92 mmol) in 1,4-dioxane (30 mL) and water (3 mL) was stirred at 70°C under N_2 for 20 h. The reaction mixture was poured into 100 mL of water, extracted with EA (50 mL x 3). The combined organic phase was washed with brine (150 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*, purified by silica gel column (pet ether: EtOAc 10:1) to provide ethyl (*E*)-2-(5-(2-

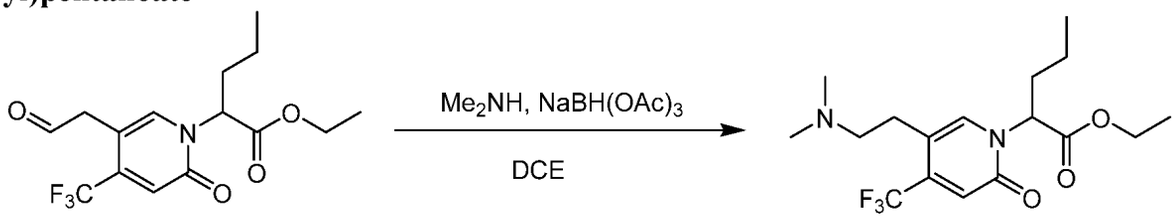
ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate as a white solid (1 g). Yield 46% (ESI 362.1 $(M+H)^+$).

Step 3: ethyl 2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate



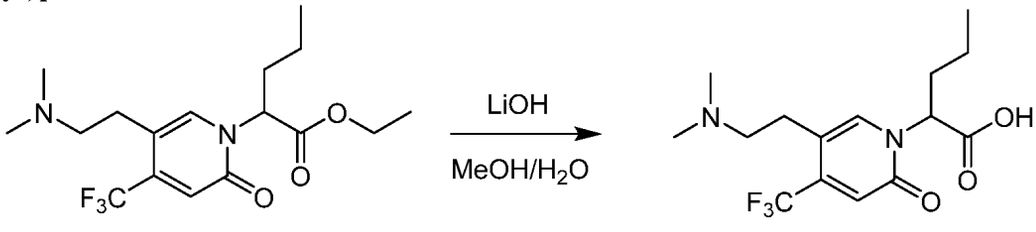
To a mixture of (*E*)-2-(5-(2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate (920 mg, 2.55 mmol) in DCM (20 mL) was added TFA (10 mL). The mixture was stirred at room temperature for 4 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to give crude product ethyl 2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate as a yellow oil (800 mg) used directly in the next reaction without further purification. Yield 94% (ESI 334.1 $[M+H]^+$).

Step 4: ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate



To a mixture of ethyl 2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoate (750 mg, 2.25 mmol) in DCE (10 mL) at 25 °C was added dimethylamine (2M in THF, 1.7 mL, 3.4 mmol) and stirred at 25 °C for 10 min. $NaBH(OAc)_3$ (950 mg, 4.5 mmol) was added and stirred at 25 °C for 2 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate as a yellow oil (630 mg). Yield 77% (ESI 363.1 $(M+H)^+$).

Step 5: 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoic acid

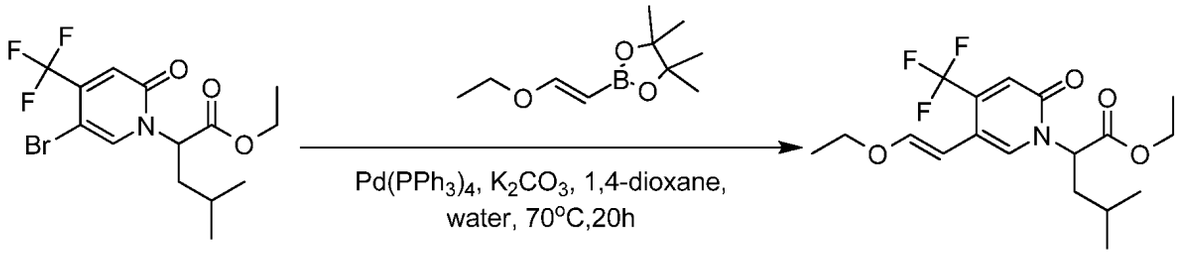


Ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (630 g, 1.74 mmol) was treated with $LiOH\text{-}H_2O$ (142 mg, 3.48 mmol) in MeOH (6 mL) and water (3 mL) at 20 °C for 1 hour. The MeOH was removed and the remaining aqueous

acidified with 1N HCl to pH = 4. The mixture was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoic acid as a yellow oil (430 mg). Yield 73% (ESI 335.1 $(M+H)^+$).

Preparation of 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 2 (E)-ethyl 2-(5-(2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



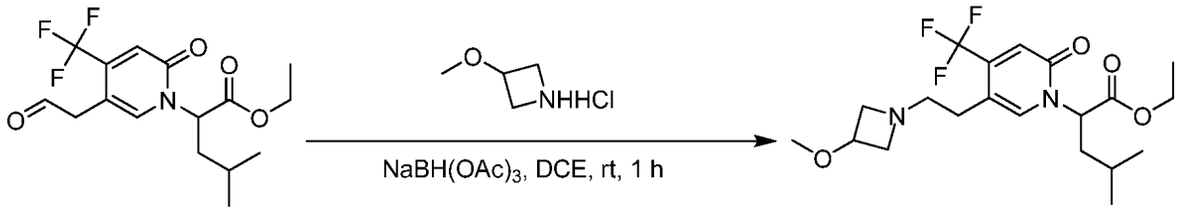
To a solution of ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (12 g, 31 mmol) in 1,4-dioxane (150 mL) and water (15 mL) was added (E)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9.3 g, 45.5 mmol), K_2CO_3 (12.8 g, 93 mmol) and $Pd(PPh_3)_4$ (1.8 g, 1.55 mmol). The reaction mixture was stirred at 70°C for 20 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (300 mL) and washed with brine, dried over Na_2SO_4, concentrated *in vacuo*. The residue was purified by silica gel column (pet. Ether: EtOAc 1:2) to provide (E)-ethyl 2-(5-(2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (9 g). Yield 76% (ESI 376.1$(M+H)^+$).

Step 2: ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate



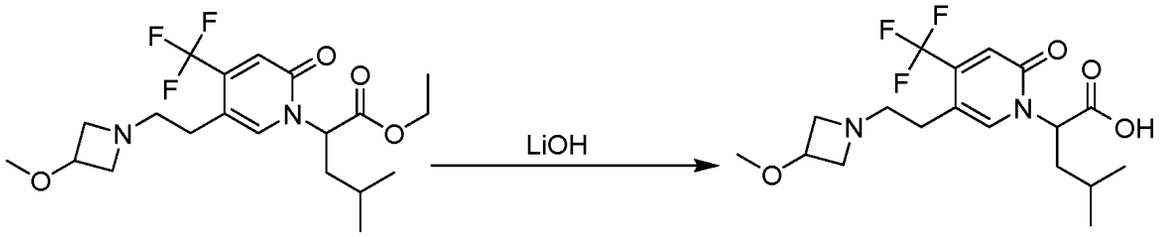
A mixture of (E)-ethyl 2-(5-(2-ethoxyvinyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (9 g, 24 mmol) in TFA (25 mL) and DCM (25 mL) was stirred at room temperature for 16 h. The reaction mixture was concentrated *in vacuo* to give crude ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate as a yellow oil (9 g). Yield 100% (crude) (ESI 348.1$(M+H)^+$).

Step 3: ethyl 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a solution of ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (10 g crude, 24 mmol) in DCE (100 mL) was added 3-methoxyazetidine hydrochloride (5.9 g, 48 mmol) and stirred at room temperature for 20 min. $NaBH(OAc)_3$ (10.1 g, 48 mmol) was added and stirred at room temperature for 1 h. The reaction was quenched with MeOH (30 mL) and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (8 g). Yield 79% (ESI 419.2$(M+H)^+$).

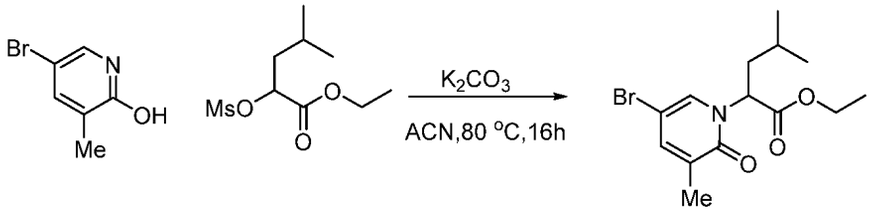
Step 4: 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (8 g, 19 mmol) was treated with $LiOH-H_2O$ (2.4 g, 57 mmol) in EtOH (60 mL) and water (12 mL) at room temperature for 2 h. The reaction mixture was neutralized by 2 N HCl and concentrated *in vacuo*. The residue was purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid as a yellow solid (6 g). Yield 80% (ESI 391.1$(M+H)^+$).

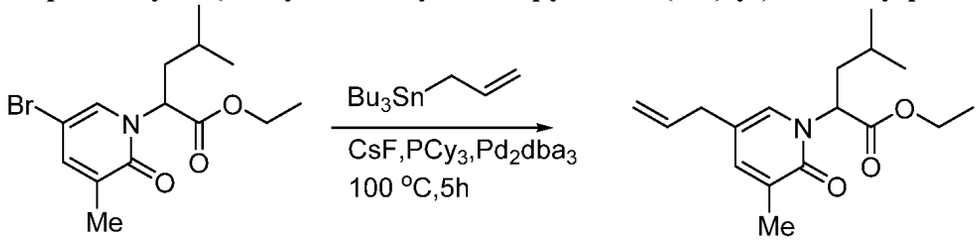
Preparation of 2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-bromo-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



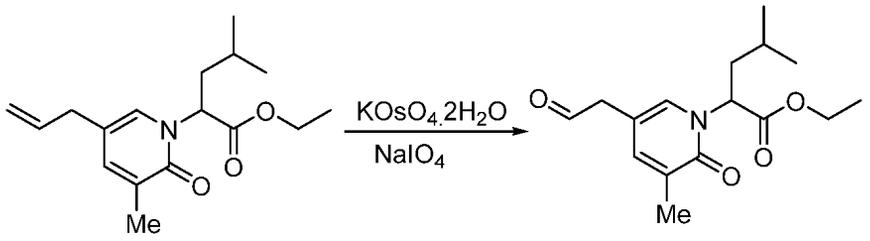
A mixture of 5-((dimethylamino)methyl)pyridin-2(1H)-one (500 mg, 3.28 mmol), K_2CO_3 (1.36 g, 9.86 mmol) and ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (1.17 g, 4.93 mmol) in CH_3CN (20 mL) was stirred at 80 °C overnight. The solvent was removed *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:2) to provide ethyl 2-(5-((dimethylamino)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow oil (300 mg). Yield 31% (ESI 330 $(M+H)^+$).

Step 2: ethyl 2-(5-allyl-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



To a solution of ethyl 2-(5-bromo-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (2.5 g, 7.57 mmol) and allyltributylstannane (2.5 g, 7.57 mmol) under N_2 atmosphere in dioxane (25 mL) was added $Pd_2(dba)_3$ (0.3 g, 0.38 mmol) and CsF (2.3 g,15.1 mmol) and PCy_3 (212.0 mg, 0.76 mmol) and stirred at 100 °C for 5 hours. The mixture was cooled to room temperature, filtered and washed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 20:1) to provide ethyl 2-(5-allyl-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a colorless oil (1.61 g). Yield 73% (ESI 292 $(M+H)^+$).

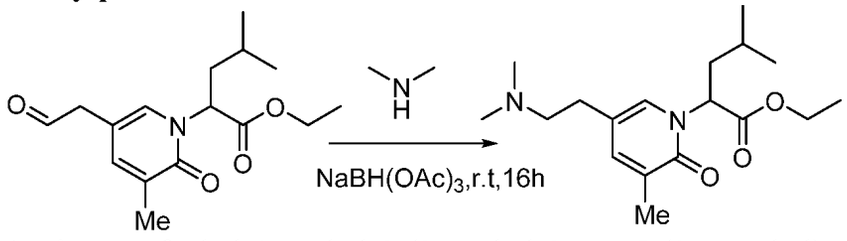
Step 3: ethyl 4-methyl-2-(3-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)pentanoate



To a solution of ethyl 2-(5-allyl-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (1.61 g, 5.53 mmol) in THF/H_2O (24 mL/12 mL) was added a solution of K_2OsO_4-$2H_2O$ (21 mg, 0.058 mmol) in H_2O (4 mL) and stirred at room temperature for 1 h. A solution of $NaIO_4$ (2.37 g, 11.1 mmol) in H_2O (20 mL) was added and stirred at room temperature for 2 h. LCMS showed the reaction was completed. The reaction mixture was diluted with 100 mL of

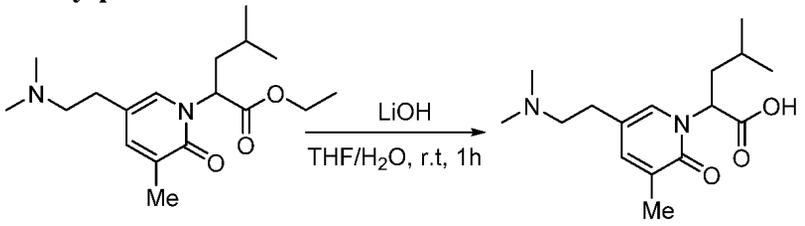
water and extracted with EtOAc (100 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product ethyl 4-methyl-2-(3-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)pentanoate as a yellow oil (1.6 g, crude) used directly in the next reaction. (ESI 294.1 $(M+H)^+$).

Step 4: ethyl 2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



A mixture of ethyl 4-methyl-2-(3-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)pentanoate (2 g, 16.2 mmol), dimethylamine (2M in THF) (41 mL) in DCE (10 mL) was stirred at room temperature for 30 mins. Then $NaBH(OAc)_3$ (5.2 g, 24.39 mmol) was added and stirred at room temperature overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow oil (1 g). Yield 46% (ESI 323.2 $(M+H)^+$).

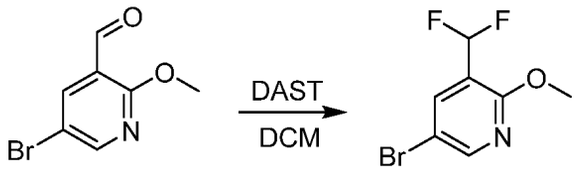
Step 5: 2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid



Ethyl 2-(5-((dimethylamino)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (606 mg, 1.88 mmol) was treated with $LiOH\text{-}H_2O$ (395 mg, 9.4 mmol) in THF (8 mL) and water (3 mL) at room temperature for 2 hours. The reaction was acidified with 1N HCl to pH = 3~4. The solvent was removed *in vacuo* and the residue was purified by preparatory-HPLC A (30-80% MeCN) to provide 2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid as a white solid (480 mg). Yield 87% (ESI 295$(M+H)^+$).

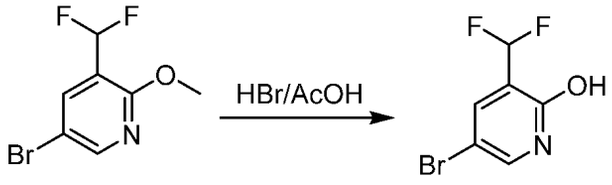
Preparation of 2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 5-bromo-3-(difluoromethyl)-2-methoxypyridine



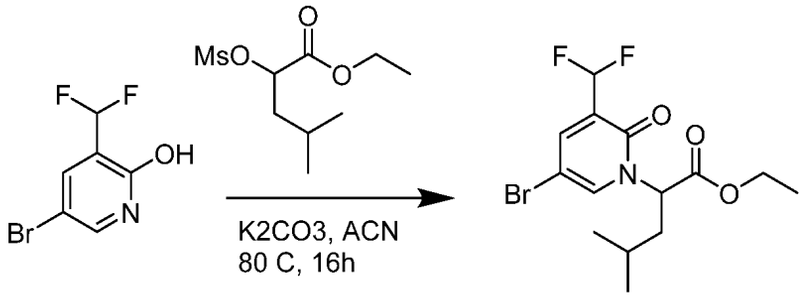
To a mixture of 5-bromo-2-methoxynicotinaldehyde (10.0 g, 46.3 mmol) in dry DCM (100 mL) under N_2 at 0°C was added DAST (29.8 g, 185.2 mmol) and stirred at 0°C for 2 days. The reaction was quenched with 100 mL of a saturated NaHCO3 solution. The aqueous layer was extracted with DCM (100 mL x 3). The combined organic layers were washed with $NaHCO_3$ (sat, 100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give 5-bromo-3-(difluoromethyl)-2-methoxypyridine as a yellow oil (11.0 g). Yield 100% (ESI 238.1$(M+H)^+$).

Step 2: 5-bromo-3-(difluoromethyl)pyridin-2-ol



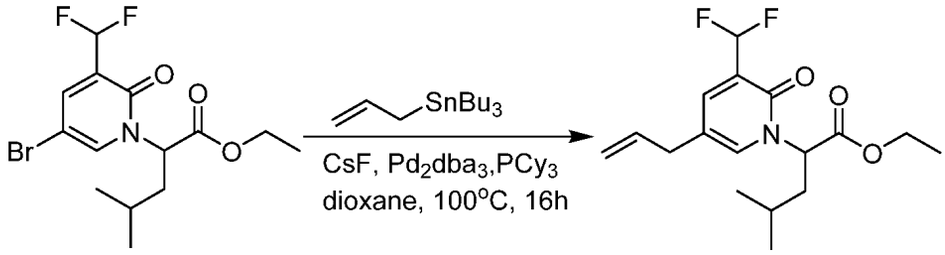
A mixture of 5-bromo-3-(difluoromethyl)-2-methoxypyridine (11.0 g, 46.2 mmol) in HBr (33% in acetic acid, 100 mL) was stirred at room temperature for 5 hours and then at 40°C for 75 mins. The mixture was concentrated and poured into 100 mL of saturated $NaHCO_3$ solution and extracted with DCM. The combined organic layers dried over Na_2SO_4 and concentrated *in vacuo* to give 5-bromo-3-(difluoromethyl)pyridin-2-ol as a white solid (8.5 g) used without further purification. Yield 73.2% (ESI 226.0$(M+H)^+$).

Step 3: ethyl 2-(5-bromo-3-(difluoromethyl)-2-oxopyridin-1(2H)-yl)-4



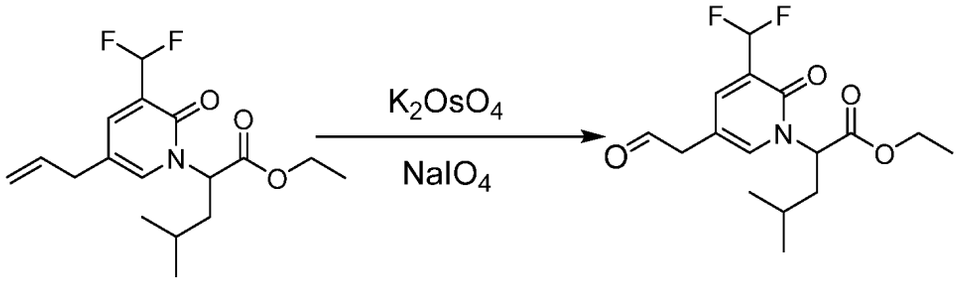
A mixture of 5-bromo-3-(difluoromethyl)pyridin-2-ol (7.0 g, 31.2 mmol), ethyl 4-methyl-2-((methylsulfonyl)oxy)pentanoate (14.0 g, 37.4 mmol) and K_2CO_3 (14.0 g, 62.5 mmol) in ACN (100 mL) was stirred at 80°C overnight. The mixture was filtered and washed with ACN (20 mL). The filtrate was concentrated *in vacuo* and the residue purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-bromo-3-(difluoromethyl)-2-oxopyridin-1(2H)-yl)-4 as a white solid (10.0 g). Yield 80.3% (ESI 366.0$(M+H)^+$).

Step 4: ethyl 2-(5-allyl-3-(difluoromethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



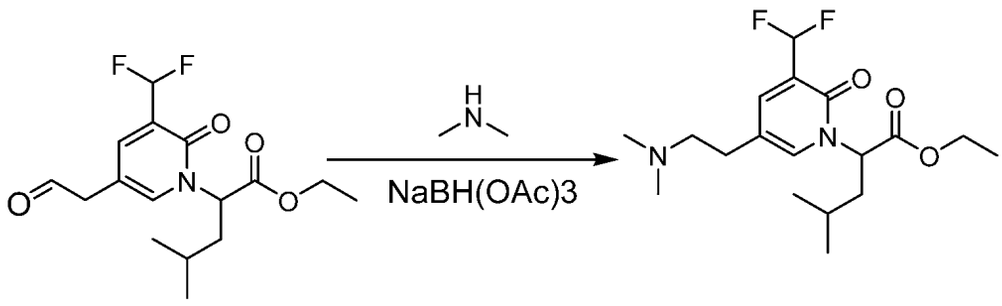
A mixture of ethyl 2-(5-bromo-3-(difluoromethyl)-2-oxopyridin-1(2H)-yl)-4 (6.0 g, 16.2 mmol), allyltributylstannane (7.0 g, 19.2 mmol), CsF (5.0 g, 32.4 mmol), $Pd(dba)_3$ (720 mg, 1.62 mmol) and PCy_3 (450 mg, 0.135 mmol) in dioxane (100 mL) was stirred at 100°C overnight. The mixture was poured into water (200 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 4:1) to give ethyl 2-(5-allyl-3-(difluoromethyl)-2-oxopyridin-1(2H)-yl)-4 as a white solid (3.0 g). Yield 71.6% (ESI 328.1(M+H)+).

Step 5: ethyl 2-(3-(difluoromethyl)-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate



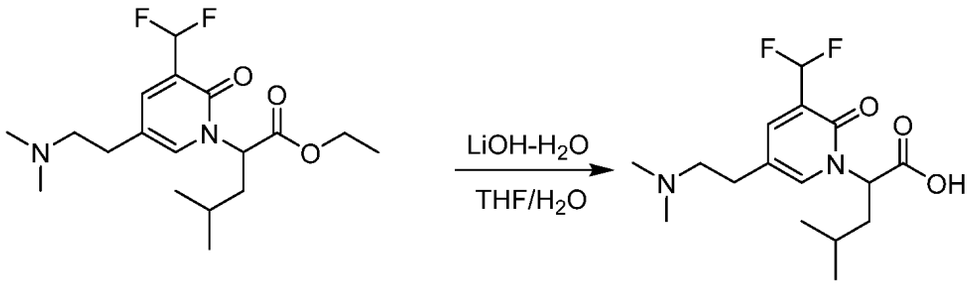
To a mixture of ethyl 2-(5-allyl-3-(difluoromethyl)-2-oxopyridin-1(2H)-yl)-4 (3.0 g, 9.1 mmol) in THF/H_2O (2/1, 100 mL) was added K_2OsO_4 (33.7 mg, 0.09 mmol) and stirred at room temperature for 1 hour. $NaIO_4$ (3.9, 18.3 mmol) was added and the mixture was stirred for 2 hours. The mixture was poured into water (200 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed brine (200 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo* to give ethyl 2-(3-(difluoromethyl)-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (3.0 g, crude) used without further purification. (ESI 330.1(M+H)+).

Step 6: ethyl 2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of ethyl 2-(3-(difluoromethyl)-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate (3.0 g, 9.1 mmol), dimethylamine (2M in THF, 14 mL, 28 mmol) in DCE (50 mL) was stirred at room temperature for 30 mins. $NaBH(OAc)_3$ (3.8 g, 18.2 mmol) was added portion-wise and the reaction was stirred at room temperature overnight. The solvent was concentrated *in vacuo* and the residue purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to give ethyl 2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (2.0 g). Yield 33.6% (ESI 359.2 $(M+H)^+$).

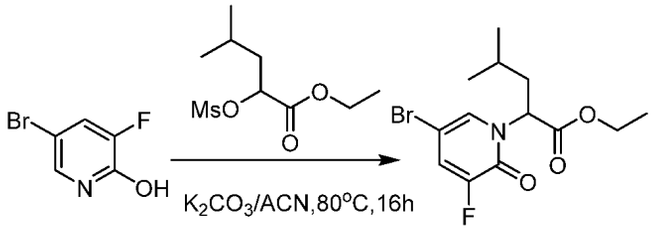
Step 7: 2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



A mixture of ethyl 2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (2.0 g, 5.5 mmol) was treated with $LiOH-H_2O$ (40 mg, 1.01 mmol) in THF (20 mL) and water (10 mL) at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to give 2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (1.2 g). Yield 85.6% (ESI 331.1$(M+H)^+$).

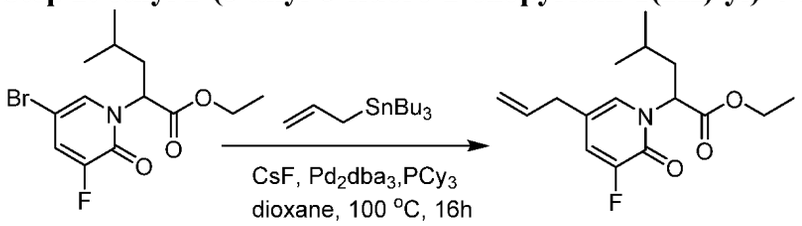
Preparation of 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



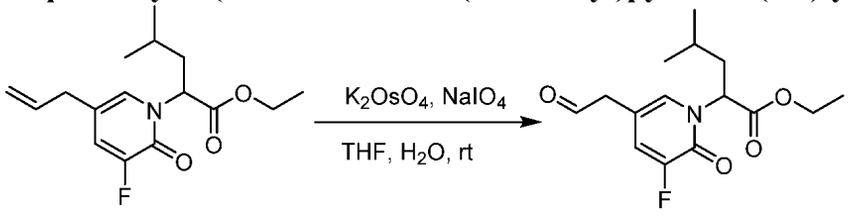
A mixture of 5-bromo-3-fluoropyridin-2-ol (5.0 g, 15.6 mmol), K_2CO_3 (7.36 g, 53.3 mmol) and ethyl 4-methyl-2-(methylsulfonyloxy)pentanoate (9.9 g, 23.4 mmol) in CH_3CN (180 mL) was stirred at 80°C overnight. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:2) to give ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow oil (6.5 g). Yield 81% (ESI 334.0$(M+H)^+$).

Step 2: ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (5.0 g, 7.6 mmol), allyltributylstannane (6.0 g, 9.1 mmol), Pd_2dba_3 (240.0 mg, 0.76 mmol), PCy_3 (450 mg, 0.76 mmo), CsF (4.6 g, 15.1 mmol) in anhydrous dioxane (100 mL) was stirred under N_2 at 100°C for 16 h. The mixture was cooled to room temperature and diluted with a saturated NH_4Cl solution (100 mL) and EtOAc (100 mL). Separated the mixture and the aqueous layer was extracted with EtOAc (100 mL x 2). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-allyl-3-fluoro-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow solid (3.0 g). Yield 69% (ESI 296.2 $(M+H)^+$).

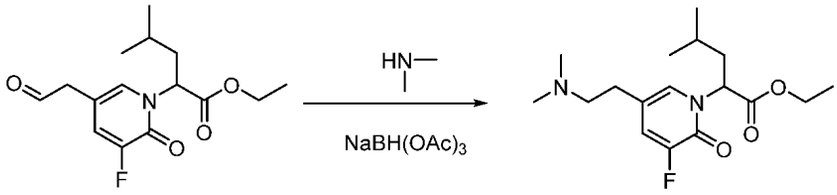
Step 3: ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate



To a solution of ethyl 2-(5-allyl-3-fluoro-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (5.5 g, 18.6 mmol) in THF/H_2O (60 mL/20 mL) was added a solution of K_2OsO_4-$2H_2O$ (60.0 mg, 0.16 mmol) in H_2O (4 mL) and stirred at room temperature for 1 h.

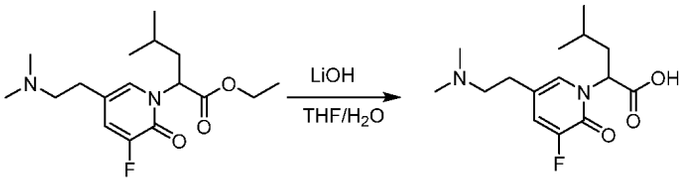
A solution of $NaIO_4$ (7.8 g, 37.2 mmol) in H_2O (20 mL) was added and stirred at room temperature for 2 h. LCMS showed the reaction was completed. The reaction mixture was diluted with 100 mL of water and extracted with EtOAc (120 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give the crude product ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow oil (5.0 g, crude) used directly in the next reaction without further purification. (ESI 298.1 $(M+H)^+$).

Step 4: ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



To a mixture of ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate (1.2 g, 4.0 mmol) in DCE (50 mL) at 25 °C was added dimethylamine (2.0 M in THF, 8.0 mL, 16.0 mmol) and stirred at 25 °C for 30 mins. $NaBH(OAc)_3$ (1.7 g, 8.0 mmol) was added at 5 °C and stirred at 25 °C for 16 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (800 mg) as a colorless oil. Yield 60% (ESI 327.1 $(M+H)^+$).

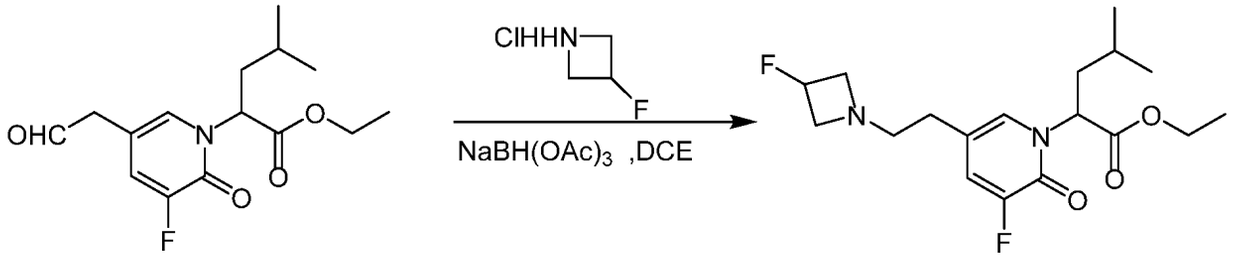
Step 5: 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (800 mg, 2.45 mmol) was treated with LiOH-H_2O (310.0 mg, 7.35 mmol) in THF (4 mL) and water (1 mL) at room temperature for 2 hours. The THF was removed and the aqueous acidified with 1N HCl to pH 5~6. The residue was purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid as a white solid (700 mg). Yield 88% (ESI 299.2 $(M+H)^+$).

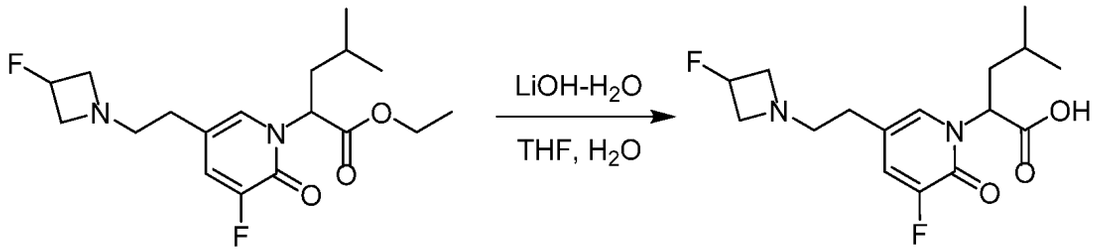
Preparation of 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



To a mixture of ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate (5 g, 15 mmol) in DCE (70 mL) at 25 °C was added 3-fluoroazetidine hydrochloride (1.8 g, 22.5 mmol) and stirred at 25 °C for 10 min. $NaBH(OAc)_3$ (6.4 g, 30 mmol) was added at 5 °C and stirred at 25 °C for 2 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to provide ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (3.8 g) as yellow oil. Yield: 63% (ESI 357.2 $(M+H)^+$).

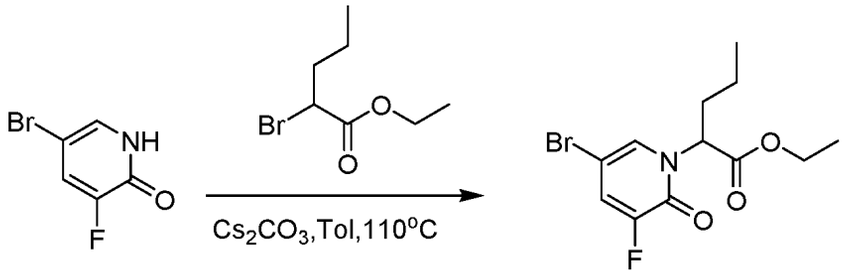
Step 2: 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Methyl ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (86 mg, 0.24 mmol) was treated with LiOH monohydrate (50 mg, 1.2 mmol) in THF (3 mL) and H_2O (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The residue was purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (55 mg). Yield 70% (ESI 329.1 $(M+H)^+$).

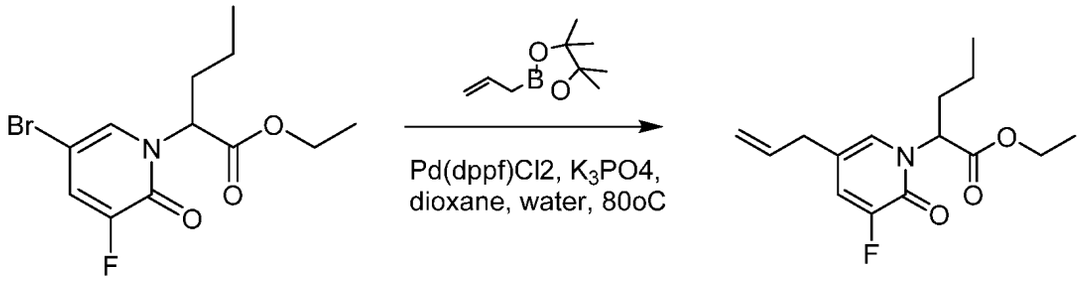
Preparation of 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)pentanoic acid

Step 1: ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2H)-yl)pentanoate



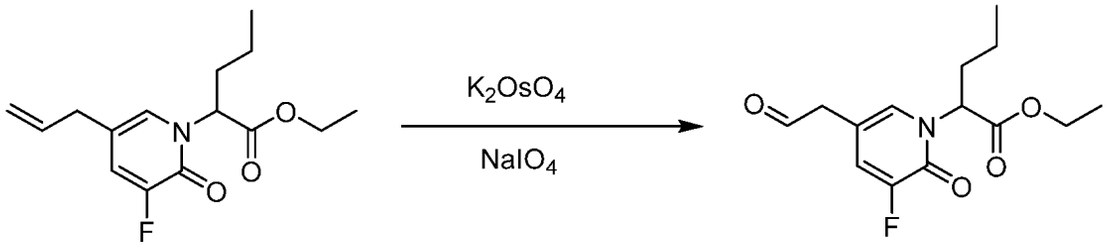
A mixture of 5-bromo-3-fluoropyridin-2(1H)-one (2.1 g, 11.0 mmol), ethyl 2-bromopentanoate (3.43 g, 16.5 mmol) and Cs_2CO_3 (7.17 g, 22.0 mmol) in Toluene (50 mL) was stirred at 110°C overnight. The reaction mixture was filtered, washed with EtOAc, concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2H)-yl)pentanoate as a white oil (2.9 g). Yield 82% (ESI 320.02$(M+H)^+$).

Step 2: ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2H)-yl)pentanoate



A mixture of ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2H)-yl)pentanoate (2.9 g, 13.2 mmol), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2.66 g, 15.8 mmol), $Pd(dppf)Cl_2$ (482.5 mg, 0.66 mmol), and K_3PO_4 (5.60 g, 26.4 mmol) in 1,4-dioxane (30 mL) and H_2O (5 mL) was stirred at 80°C for 2 hours. The reaction mixture was diluted with 50 mL of water, extracted with EA (60 mL x 2). The combined organic phase was washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue purified by silica gel column (pet ether: EtOAc 1:2) to provide ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2H)-yl)pentanoate as a white oil (1.9 g). Yield 75% (ESI 282.24$(M+H)^+$).

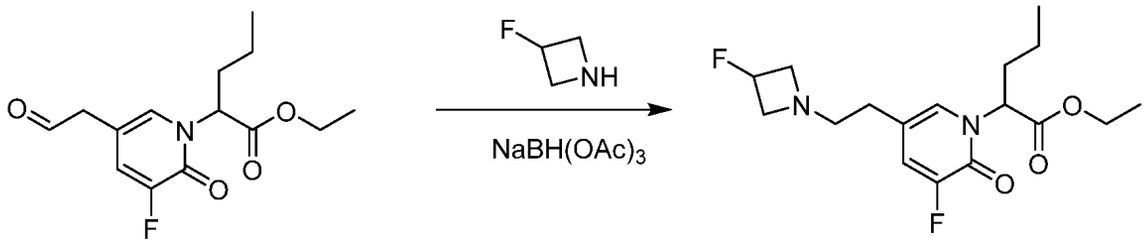
Step 3: ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)pentanoate



To a mixture of ethyl ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2H)-yl)pentanoate (1.9 g, 6.7 mmol) in THF (20 mL) and H_2O (30 mL) was added K_2OsO_4 (25.8 mg, 0.07 mmol) and

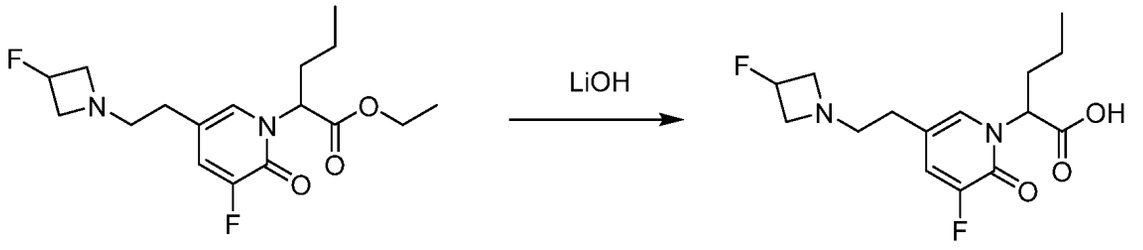
stirred at room temperature for 1 hour. $NaIO_4$ (3.9, 13.4 mmol) was added and the mixture was stirred at room temperature for 2 hours. The mixture was poured into water (100 mL) and extracted with EtOAc (50 mL x 3). The combined organic layers were washed brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)pentanoate as a yellow oil (1.7 g, crude) used directly in the next reaction. (ESI 284.12(M+H)+).

Step 4: ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)pentanoate



A mixture of ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)pentanoate (1.7 g, 6 mmol), AcOH (0.44 g, 7.2 mmol) and 3-fluoroazetidine hydrochloride (1.0 g, 9.0 mmol) in MeOH (30 mL) was stirred at room temperature for 30 mins. $NaBH(OAc)_3$ (2.54 g, 12 mmol) was added and stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)pentanoate as a yellow oil (700 mg). Yield 40% (ESI 343.18$(M+H)^+$).

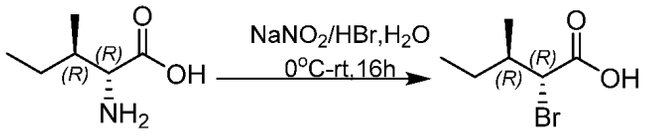
Step 5: 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)pentanoic acid



Ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)pentanoate (700 mg, 2.05 mmol) was treated with LiOH-H_2O (344 mg, 8.2 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The mixture was acidified to pH 4~5 with 1N HCl. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 20%) to provide 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)pentanoic acid as a yellow solid (500 mg). Yield 78% (ESI 315.14 $(M+H)^+$).

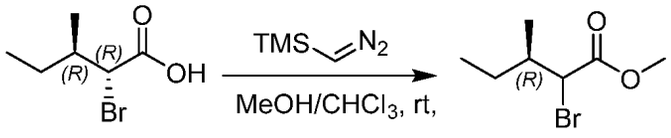
Preparation of (3*R*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoic acid

Step 1: (2*R*, 3*R*)-2-bromo-3-methylpentanoic acid



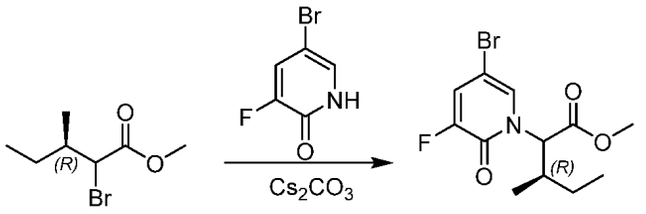
To a solution of D-isoleucine (10.0 g, 76.23 mmol) in H_2O (50 mL) was added 40% HBr in water (100 mL). The reaction mixture was cooled to 0 °C. A solution of sodium nitrite (7.9 g, 114.35 mmol) in H_2O (10 mL) was added dropwise. Then the reaction mixture was stirred at room temperature for 3 hours. The reaction mixture was extracted with EtOAc (100 mL X 3). The organic layer was washed with brine (50 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide (2*R*, 3*R*)-2-bromo-3-methylpentanoic acid as a brown oil used directly in the next reaction without further purification (14.0 g). Yield 95% (ESI 195.1 $(M+H)^+$).

Step 2: methyl (3*R*)-2-bromo-3-methylpentanoate



A mixture of (2*R*, 3*R*)-2-bromo-3-methylpentanoic acid (12.6 g, 64.60 mmol) in MeOH/$CHCl_3$ (30 mL/90 mL) was cooled to 0°C. (Diazomethyl)trimethylsilane (2.0 M in hexane; 64.6 m L, 129.20 mmol) was added dropwise. The mixture was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo* to provide methyl (3*R*)-2-bromo-3-methylpentanoate as a yellow oil used directly in the next reaction without further purification (12.0 g). Yield 89% (ESI 209.1 $(M+H)^+$).

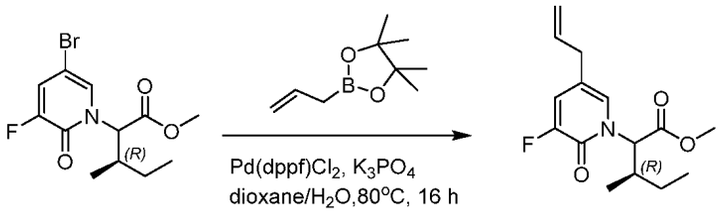
Step 3: methyl (3*R*)-2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoate



A mixture of 5-bromo-3-fluoropyridin-2(1*H*)-one (3.1 g, 16.15 mmol), Cs_2CO_3 (10.5 g, 32.3 mmol) and methyl (3*R*)-2-bromo-3-methylpentanoate (5.06 g, 24.23 mmol) in dioxane (100

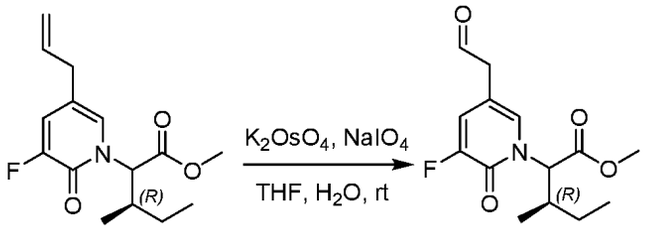
mL) was stirred at 110°C for 16 h. LCMS showed the reaction was completed. The mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide methyl (3R)-2-(5-bromo-3-fluoro-2-oxopyridin-1(2H)-yl)-3-methylpentanoate as a colorless oil (2.2 g). Yield 43% (ESI 322.0 $(M+H)^+$).

Step 4: methyl (3*R*)-2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoate



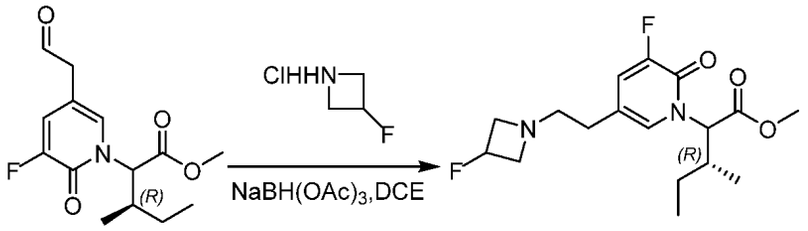
A mixture of methyl (3*R*)-2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoate (2.2 g, 6.87 mmol), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.5 g, 20.61 mmol), $Pd(dppf)Cl_2$ (251 mg, 0.34 mmol) and K_3PO_4 (2.9 g, 13.74 mmol, 2.0 *eq*) in dioxane (100 mL) and H_2O(10 mL) was stirred under nitrogen atmosphere at 80°C for 16 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide methyl (3*R*)-2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoate as a yellow oil (1.2 g). Yield 55% (ESI 282.1 $(M+H)^+$).

Step 5: methyl (3*R*)-2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-3-methylpentanoate



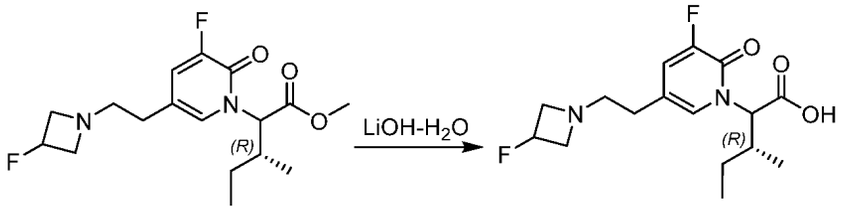
To a solution of methyl (3*R*)-2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoate (1.2 g, 4.27 mmol) in THF/H_2O (20 mL/20 mL) was added a solution of K_2OsO_4-$2H_2O$ (15.7 mg, 0.043 mmol) in H_2O (3 mL) and stirred at room temperature for 1 hour. Then a solution of $NaIO_4$ (1.8 g, 8.54 mmol) in H_2O (10 mL) was added dropwise and the mixture was stirred at room temperature for 2 hours. LCMS showed the reaction was completed. The reaction mixture was diluted with H_2O (50 mL), extracted with EtOAc (50 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide methyl (3*R*)-2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-3-methylpentanoate as a colorless oil used directly in the next reaction without further purification (1.3 g, crude). (ESI 284.1 $(M+H)^+$).

Step 6: methyl (3*R*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoate



To a mixture of methyl (3*R*)-2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-3-methylpentanoate (1.3 g, 4.59 mmol) in DCE (20 mL) at 25 °C was added 3-fluoroazetidine hydrochloride (768 mg, 6.89 mmol) and stirred at 25 °C for 1 hour. $NaBH(OAc)_3$ (2.9 g, 13.77 mmol) was added at 5 °C and stirred at 25 °C for 16 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 20:1) to provide methyl (3*R*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoate as a brown oil (800 mg). Yield 51% (ESI 343.1 $[M+H]^+$).

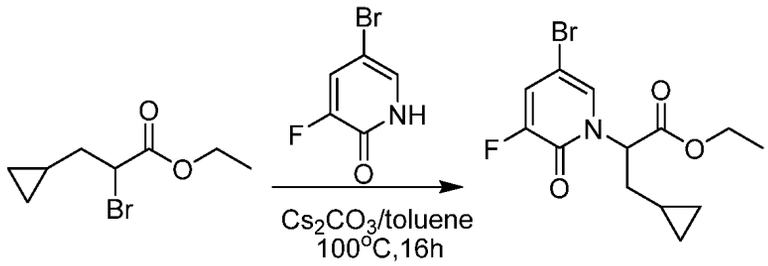
Step 7: (3*R*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoic acid



Methyl (3*R*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoate (800 mg, 2.34 mmol) was treated with $LiOH-H_2O$ (491 mg, 11.7 mmol) in EtOH (5 mL) and water (2 mL) and the mixture was stirred at room temperature for 30 minutes. The mixture was acidified with 1N HCl to pH 5~6, concentrated and purified by reverse phase HPLC on a C18/40 g column (A: water/0.01%TFA, B: MeOH, 0~100%) to provide (3*R*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylpentanoic acid as a white solid (600 mg). Yield 78% (ESI 329.2 $(M+H)^+$).

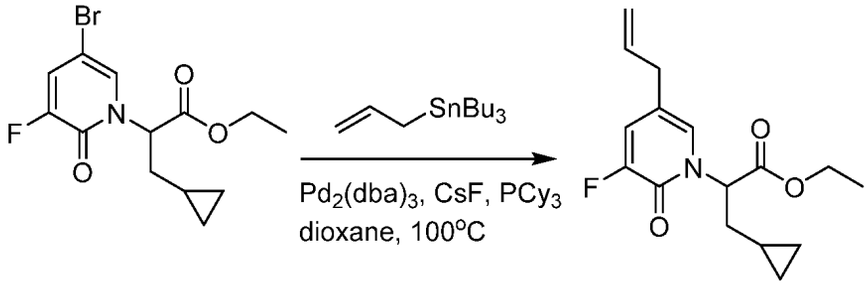
Preparation of 3-cyclopropyl-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanoic acid

Step 1: ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-cyclopropylpropanoate



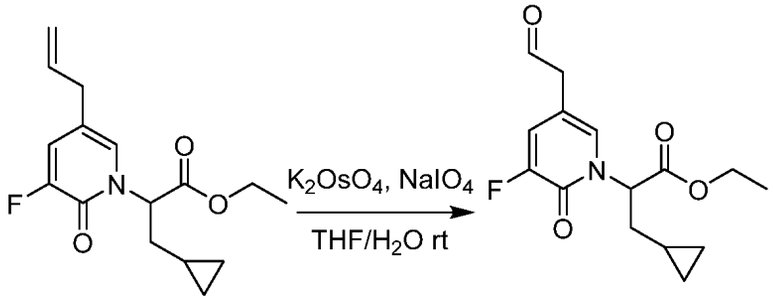
A mixture of 5-bromo-3-fluoropyridin-2(1*H*)-one (2.0 g, 10.4 mmol), Cs_2CO_3 (6.5 g, 20.8 mmol) and ethyl 2-bromo-3-cyclopropylpropanoate (2.7 g, 12.4 mmol) in toluene (50 mL) was stirred at 110 °C for 16 hours. LCMS showed the reaction was completed. The mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-cyclopropylpropanoate as a yellow oil (2.0 g). Yield 58% (ESI 333 $(M+H)^+$).

Step 2: ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-cyclopropylpropanoate



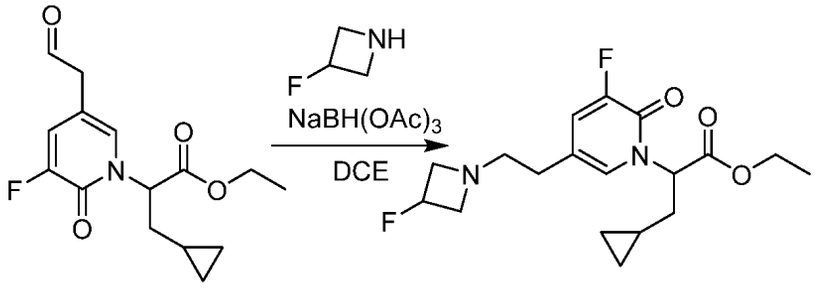
A mixture of ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-cyclopropylpropanoate (1.5 g, 4.5 mmol), allyltributylstannane (1.5 g, 5.4 mmol), CsF (1.4 g, 9 mmol), $Pd(dba)_3$ (126 mg, 0.45 mmol) and PCy_3 (206 mg, 0.225 mmol) in dioxane (100 mL) was stirred at 100 °C overnight. The mixture was poured into water (200 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-cyclopropylpropanoate as a yellow oil (1.0 g). Yield 83% (ESI 294(M+H)+).

Step 3: ethyl 3-cyclopropyl-2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)propanoate



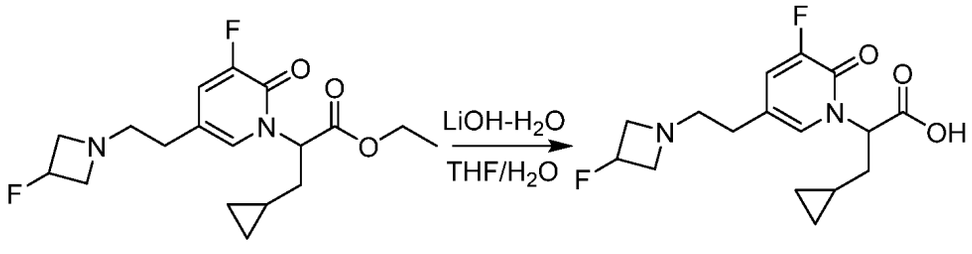
To a solution of ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-cyclopropylpropanoate (800 mg, 2.7 mmol) in THF/H_2O (60 mL/20 mL) was added a solution of K_2OsO_4-$2H_2O$ (10 mg, 0.027 mmol) in H_2O (4 mL) and stirred at room temperature for 1 h. Then a solution of $NaIO_4$ (1.1 g, 5.4 mmol) in H_2O (20 mL) was added and stirred at room temperature for 2 h. LCMS showed the reaction was completed. The reaction mixture was diluted with 100 mL of water and extracted with EtOAc (100 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide ethyl 3-cyclopropyl-2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)propanoate as a yellow oil used directly in the next reaction without further purification (820 mg, crude). (ESI 296 $(M+H)^+$).

Step 4: ethyl 3-cyclopropyl-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanoate



A mixture of ethyl 3-cyclopropyl-2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)propanoate (500 mg, 1.7 mmol) and 3-fluoroazetidine hydrochloride (188 mg, 1.7 mmol) in DCE (20 mL) was stirred at room temperature for 10 minutes. $NaBH(OAc)_3$ (530 g, 1.5 mmol) was added and stirred at room temperature for 2 h. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 3-cyclopropyl-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanoate as a yellow oil (300 mg). Yield 31% (ESI 355 $(M+H)^+$).

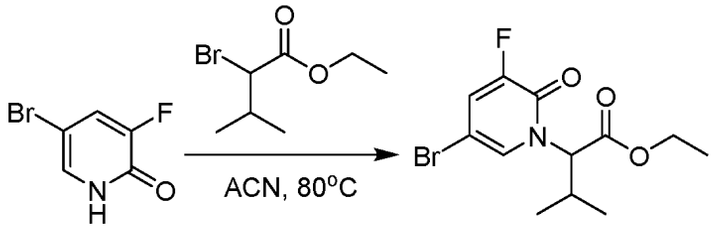
Step 5: 3-cyclopropyl-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanoic acid



Ethyl 3-cyclopropyl-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanoate (300 mg, 0.84 mmol) was treated with LiOH-H_2O (178 mg, 4.20 mmol) in THF (10 mL) and water (5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5 with 1N HCl and concentrated. The mixture was purified by reverse phase HPLC on a C18 / 40 g column (A: water, B: MeOH, 0~100%) to provide 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid as a white solid (200 mg). Yield 86% (ESI 327 $(M+H)^+$).

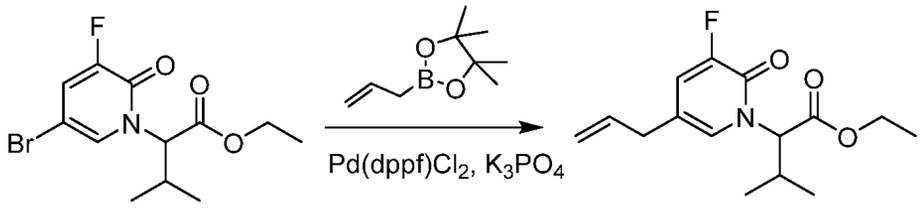
Preparation of 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoic acid

Step 1: ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate



A mixture of 5-bromo-3-fluoropyridin-2(1*H*)-one (5.0 g, 26.2 mmol, 1.0 *eq*), K_2CO_3 (7.2 g, 52.4 mmol, 2.0 *eq*) and ethyl 2-bromo-3-methylbutanoate (6.5 g, 31.4 mmol, 1.2 *eq*) in ACN (100 mL) was stirred at 80 °C for 16 hours. LCMS showed the reaction was completed. The mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate as a yellow oil (3.0 g). Yield 36% (ESI 320.1 $(M+H)^+$).

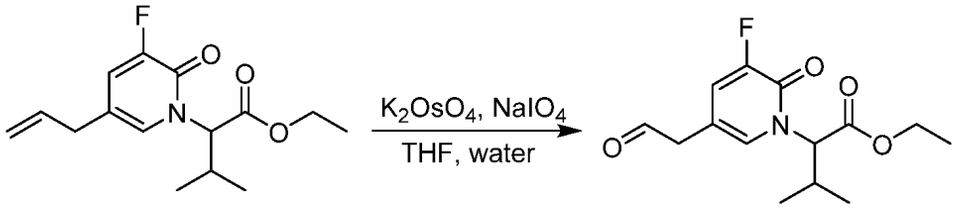
Step 2: ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate



A mixture of ethyl 2-(5-bromo-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate (3.0 g, 9.4 mmol, 1 *eq*), 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.9 g, 11.3 mmol, 1.2*eq*), $Pd(dppf)Cl_2$ (343.6 mg, 0.47 mmol, 0.05 *eq*) and K_3PO_4 (4.0 g, 18.8 mmol, 2.0 *eq*) in dioxane (100 mL) and H_2O (10 mL) was stirred at 100 °C overnight. Water (200 mL) was added and the solution was extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in*

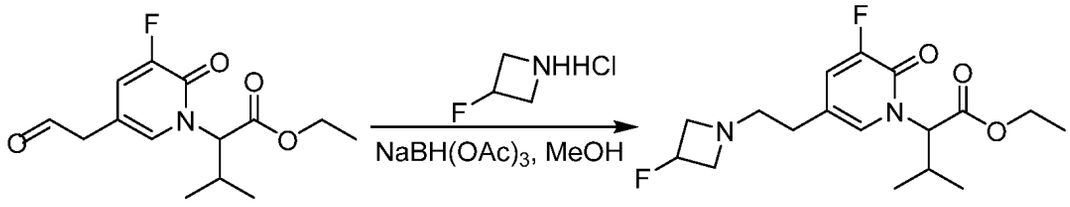
vacuo. The residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate as a yellow oil (2.4 g). Yield 92% (ESI 282.0 (M+H)+).

Step 3: ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-3-methylbutanoate



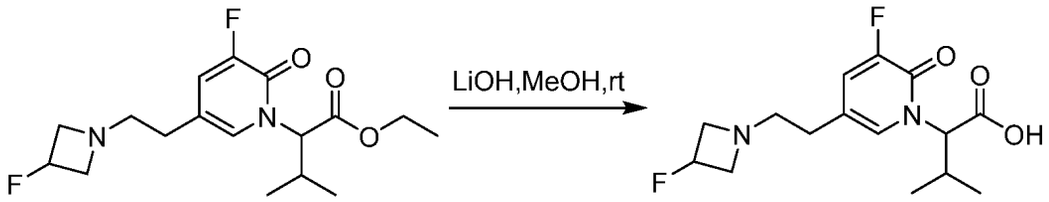
To a solution of ethyl 2-(5-allyl-3-fluoro-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate (2.4 g, 8.6 mmol, 1.0 *eq*) in THF (100 mL) and H_2O (30 mL) was added a solution of K_2OsO_4-$2H_2O$ (32 mg, 0.086 mmol, 0.01 *eq*) in H_2O (4 mL). The mixture was stirred at room temperature for 1 hour. Then a solution of $NaIO_4$ (3.7 g, 17.2 mmol, 2.0 *eq*) in H_2O (20 mL) was added and stirred at room temperature for 2 hours. LCMS showed the reaction was completed. Water (100 mL) was added and the solution was extracted with EtOAc (100 mL x 3). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-3-methylbutanoate as a yellow oil used directly in the next reaction without further purification (1.6 g, crude). (ESI 284.1 $(M+H)^+$).

Step 4: ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate



A mixture of ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-3-methylbutanoate (1.6 g, 5.7 mmol, 1.0 *eq*) and 3-fluoroazetidine hydrochloride (427.5 mg, 5.7 mmol, 1.0 *eq*) in MeOH (20 mL) was stirred at room temperature for 10 minutes. $NaBH(OAc)_3$ (1.8 g, 8.6 mmol， 1.5 *eq*) was added and stirred at room temperature for 2 hours. LCMS showed the reaction was completed. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 1:1) to provide ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate as a yellow oil (700 mg).Yield 24% for two steps (ESI 343.1 $(M+H)^+$).

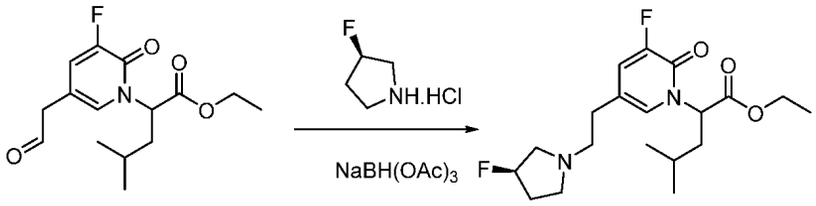
Step 5: 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoic acid



Ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoate (700 mg, 2.0 mmol, 1.0 *eq*) was treated with LiOH-H_2O (336 mg, 8.0 mmol, 4.0 *eq*) in MeOH (10 mL) and water (5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5 with 1N HCl and concentrated. The mixture was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylbutanoic acid as a white solid (500 mg). Yield 78% (ESI 315.1 $(M+H)^+$).

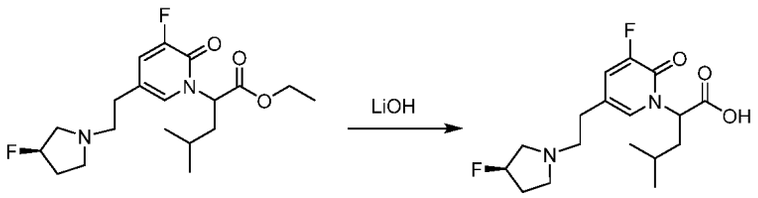
Preparation of 2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(*2H*)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



To a mixture of ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate (3.3 g, 11.2 mmol) in DCE (70 mL) at 25 °C was added (R)-3-fluoropyrrolidine hydrochloride (1.4 g, 11.2 mmol) and stirred at 25 °C for 30 mins. $NaBH(OAc)_3$ (4.6 g, 22.4 mmol) was added at 5 °C and stirred at 25 °C for 16 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to give compound ethyl 2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (1.7 g) as a yellow oil. Yield 41% (ESI 371.2 $(M+H)^+$).

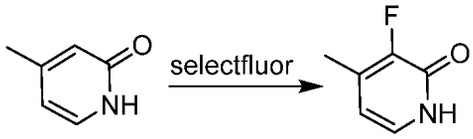
Step 2: 2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(*2H*)-yl)-4-methylpentanoic acid



Ethyl 2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate (1.7 g, 4.59 mmol) was treated with LiOH-H_2O (960.0 mg, 23.0 mmol, 5.0 *eq*) in MeOH (12 mL) and water (5 mL) at room temperature for 2 hours. The MeOH was removed and the aqueous acidified with 1N HCl to pH = 5. The residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid as a white solid (1.1 g). Yield 70% (ESI 343.1 $(M+H)^+$).

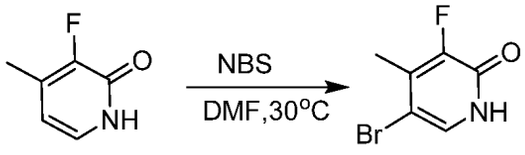
Preparation of 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: 3-fluoro-4-methylpyridin-2(1H)-one



A mixture of 4-methylpyridin-2(1H)-one (10 g, 92 mmol, 1.0 *eq*) and selectfluor (16 g, 46 mmol, 0.5 *eq*) in $CHCl_3$ (100 mL) and water (100 mL) was stirred at 35°C for 16 h. The reaction mixture was diluted with a saturated NaCl solution (100 mL) and extracted with DCM (100 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (EtOAc: DCM: MeOH 100: 10: 6) to provide 3-fluoro-4-methylpyridin-2(1H)-one as a whitle solid (2.4 g). Yield 21% (ESI 128 $(M+H)^+$). ^1H NMR (400 MHz, $CDCl_3$) δ 13.53 (s, 1H), 7.20 (dd, J = 6.6, 0.6 Hz, 1H), 6.14 (t, J = 6.1 Hz, 1H), 2.24 (d, J = 2.5 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -140.20.

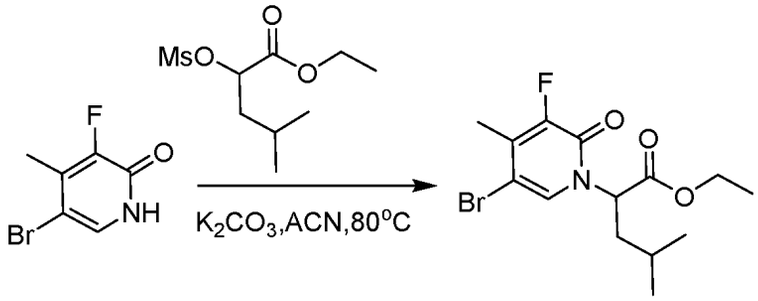
Step 2: 5-bromo-3-fluoro-4-methylpyridin-2(1H)-one



To a solution of 3-fluoro-4-methylpyridin-2(1H)-one (2.4 g, 18.9 mmol, 1.0 *eq*) in DMF (20 mL) was added NBS (3.7 g, 20.8 mmol, 1.1 *eq*) and stirred at 30°C for 1 h. The reaction mixture was purified by reverse phase HPLC (A: water(0.01%TFA); B ACN, 45% of B) to provide 5-bromo-3-fluoro-4-methylpyridin-2(1H)-one as a whitle solid (3 g). Yield 77% (ESI

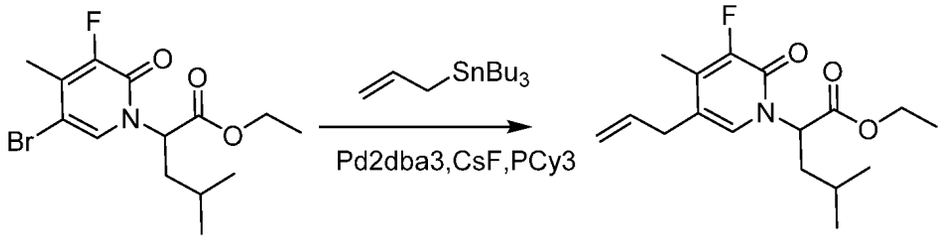
206 $(M+H)^+$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 1.3 Hz, 1H), 2.31 (d, J = 3.0 Hz, 3H).

Step 3: ethyl 2-(5-bromo-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of 5-bromo-3-fluoro-4-methylpyridin-2(1H)-one (3.0 g, 14.6 mmol, 1.0 *eq*), K_2CO_3 (4 g, 29.3 mmol, 2.0 *eq*) and ethyl 4-methyl-2-((methylsulfonyl)oxy)pentanoate (7 g, 29.3 mmol, 2 *eq*) in CH_3CN (50 mL) was stirred at 80°C for 16 h. LCMS showed the reaction was completed. The mixture was filtered and washed with CH_3CN (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-bromo-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (4.5 g). Yield 89% (ESI 348 $(M+H)^+$).

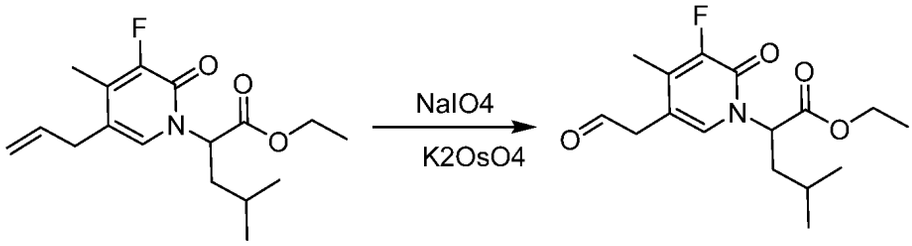
Step 4: ethyl 2-(5-allyl-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of ethyl 2-(5-bromo-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (4.5 g, 13 mmol, 1.0 *eq*), allyltributylstannane (35.6 g, 16.9 mmol, 1.3 *eq*), Pd_2dba_3 (595 mg, 0.65 mmol, 0.05 *eq*), PCy_3 (364 mg, 1.3 mmol, 0.1 *eq*) and CsF (4 g, 26 mmol, 2.0 *eq*) in anhydrous dioxane (100 mL) was stirred under N_2 at 100°C for 16 hours. The mixture was cooled to room temperature. A saturated NH4Cl solution (100 mL) was added and the solution was extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 4:1) to provide ethyl 2-(5-allyl-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow solid (2 g). Yield 50% (ESI 310 $(M+H)^+$). ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.93 – 5.84 (m, 1H), 5.77 – 5.73 (m, 1H), 5.18 – 5.03 (m, 2H), 4.20 (q, J = 8 Hz, 2H), 3.18 – 3.14 (m, 2H),

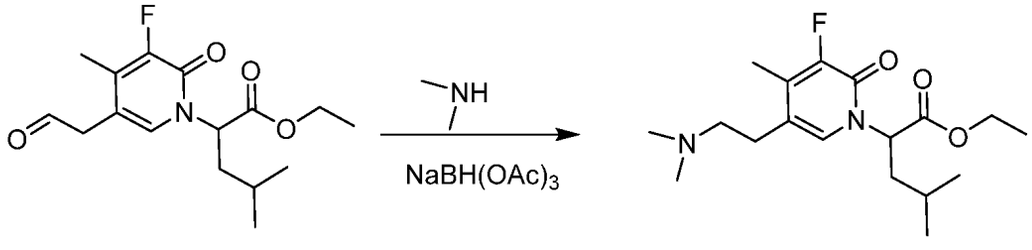
2.13 (d, J = 2.8 Hz, 3H), 2.01 – 1.94 (m, 1H), 1.90 – 1.84 (m, 1H), 1.45 – 1.37 (m, 1H), 1.26 (t, J = 8 Hz, 2H), 0.98 – 0.91 (m, 6H).

Step 5: ethyl 2-(3-fluoro-4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a solution of ethyl 2-(5-allyl-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1.8 g, 5.8 mmol, 1.0 *eq*) in THF/H_2O (60 mL/20 mL) was added a solution of K_2OsO_4-$2H_2O$ (21 mg, 0.058 mmol, 0.01 *eq*) in H_2O (4 mL) and stirred at room temperature for 1 h. Then a solution of $NaIO_4$ (1.25 g, 11.7 mmol, 2.0 *eq*) in H_2O (20 mL) was added and stirred at room temperature for 2 h. LCMS showed the reaction was completed. The reaction mixture was diluted with 100 mL of water and extracted with EtOAc (100 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to provide ethyl 2-(3-fluoro-4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil used directly in the next reaction without further purification (2 g, crude). (ESI 312 $(M+H)^+$).

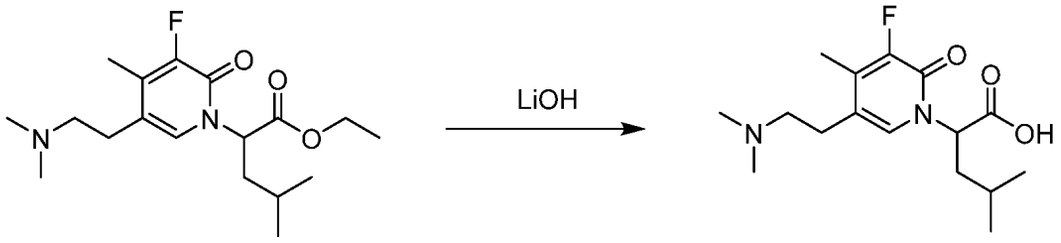
Step 6: ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of ethyl 2-(3-fluoro-4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate (2.0 g, 6.42 mmol) and dimethylamine (9.64 mL, 19.27 mmol) (2.0 M) in THF was added in DCE (32.1 mL) and stirred at room temperature for 10 mins. $NaBH(OAc)_3$ (4.08 g, 19.3 mmol, 3.0 *eq*) was added to the reaction mixture and stirred at room temperature for 2 h. . The mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC in NH_4HCO_3 condition (A: water

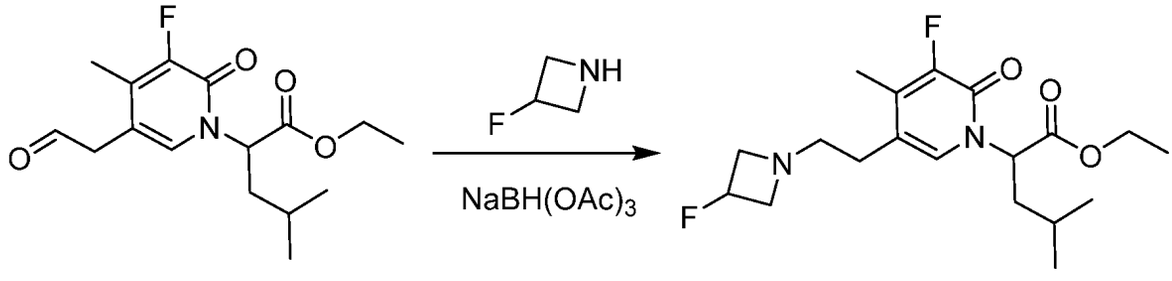
10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1.41g, 4.14 mmol, 64.5% yield) as yellow oil. (ESI 341 $(M+H)^+$).

Step 7: 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1.41 g, 4.14 mmol) was treated with lithium hydroxide (0.496 g, 20.71 mmol) in MeOH (10 mL) and water (5 mL) at room temperature for 2 hours. The MeOH was removed and the aqueous acidified with 1N HCl to pH = 5. The residue was purified by reverse phase HPLC in neutral condition (A: water, B: MeOH, 0~100%) to provide 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid (1.21 g, 3.87 mmol, 94% yield) (ESI 313 $(M+H)^+$).

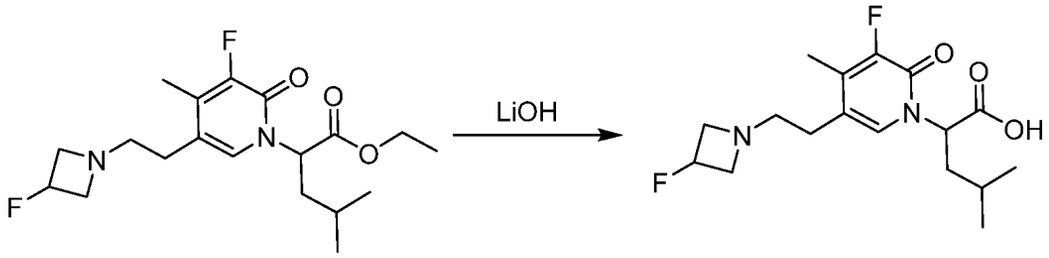
Preparation of 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid Step 1: ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate



A mixture of ethyl 2-(3-fluoro-4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2H)-yl)-4-methylpentanoate (2 g, 6.4 mmol) and 3-fluoroazetidine hydrochloride (2.1 g, 19.3 mmol, 3.0 *eq*) in DCE (20 mL) was stirred at room temperature for 10 minutes. $NaBH(OAc)_3$ (4.2 g, 19.3 mmol, 3.0 *eq*) was added to the reaction mixture and stirred at room temperature for 2 h. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in*

vacuo and the residue was purified by reverse phase HPLC (A: water 10 mM NH_4HCO_3, B: MeOH, 70%B) to provide ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate as a yellow oil (1 g). Yield 42% (ESI 371 $(M+H)^+$).

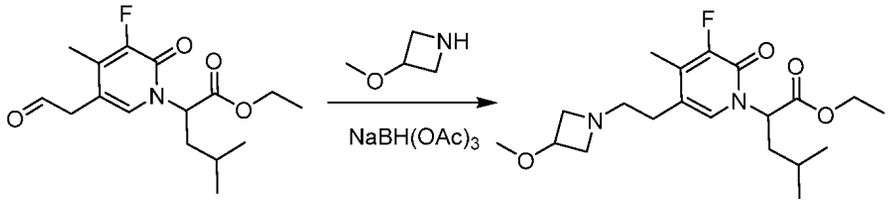
Step 2: 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid



Ethyl 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (1 g, 2.7 mmol, 1.0 *eq*) was treated with LiOH-H_2O (567 mg, 13.5 mmol, 5.0 *eq*) in MeOH (10 mL) and water (5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5 with 1N HCl and concentrated. The mixture was purified by reverse phase HPLC in neutral condition (A: water, B: MeOH, 60%B) to provide 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (800 mg). Yield 86% (ESI 343 $(M+H)^+$).

Preparation of 2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid

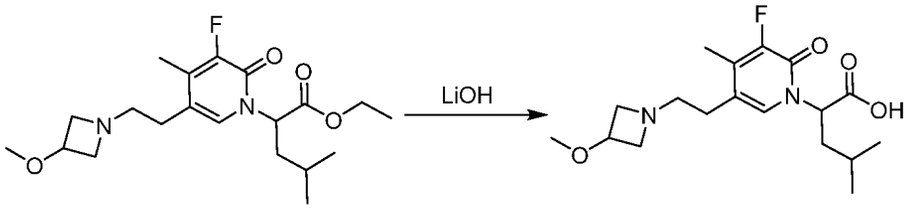
Step 1: ethyl 2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate



A mixture of ethyl 2-(3-fluoro-4-methyl-2-oxo-5-(2-oxoethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate (4.5 g, 14.4 mmol) and 3-methoxyazetidine hydrochloride (2.7 g, 21.7 mmol) in DCE (20 mL) was stirred at room temperature for 1h. $NaBH(OAc)_3$ (6.2 g, 29.2 mmol) was added and stirred at room temperature for 2 h. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL x 3). The combined organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120 g column (A: water 10 mM NH_4HCO_3, B: MeOH,

0~100%) to provide ethyl 2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoate as a yellow oil (2.7 g). Yield 49% (ESI 383.1 $(M+H)^+$).

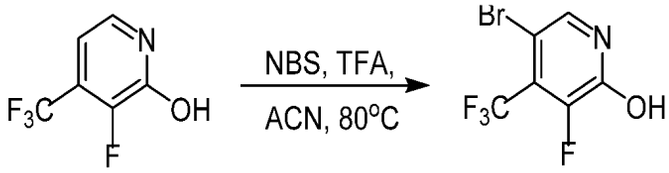
Step 2: 2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid



Ethyl 2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoate (3.0 g, 7.9 mmol) was treated with LiOH-H_2O (1.6 g, 39.3 mmol) in EtOH (20 mL) and water (5 mL) at room temperature for 2 hours. The EtOH was removed and the aqueouse acidified with 1N HCl to pH 5 and concentrated. The mixture was purified by reverse phase HPLC on a C18/120 g column (A: water, B: MeOH, 0~100%) to provide 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid as a white solid (2.4 g). Yield 86% (ESI 355.3 $(M+H)^+$).

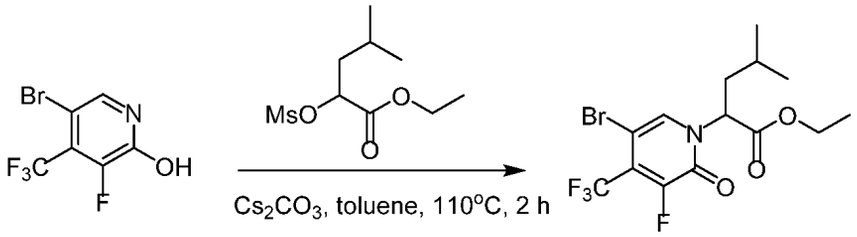
Preparation of 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid

Step 1: 5-bromo-3-fluoro-4-(trifluoromethyl)pyridin-2-ol



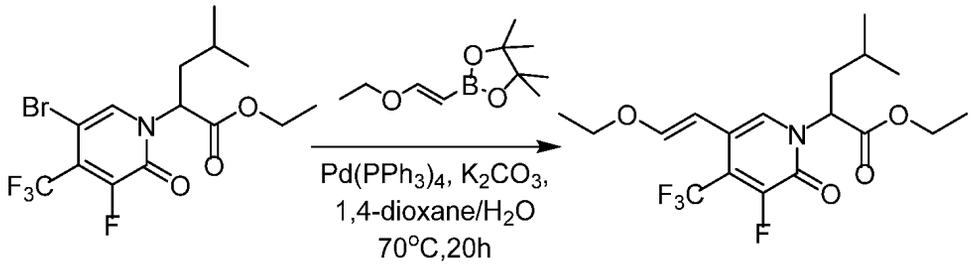
A mixture of 3-fluoro-4-(trifluoromethyl)pyridin-2-ol (16.0 g, 88.35 mmol) and NBS (23.5 g, 132.53 mmol) in TFA (32 mL) and MeCN (320 mL) was stirred at 80°C for 24 hours. LCMS showed the reaction was completed. The reaction was concentrated *in vacuo* and the residue was purified by silica gel column (petroleum ether: EtOAc 1: 1) to provide 5-bromo-3-fluoro-4-(trifluoromethyl)pyridin-2-ol as a white solid (19.7 g). Yield 86% (ESI 259.9 $(M+H)^+$).

Step 2: ethyl 2-(5-bromo-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate



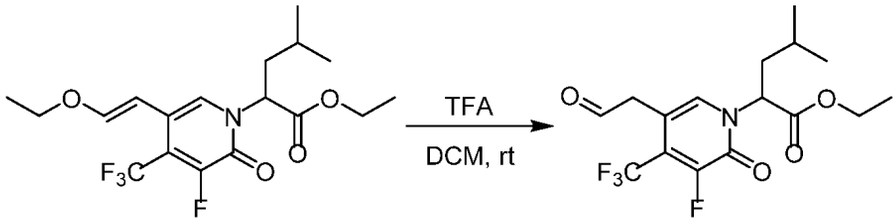
A mixture of 5-bromo-3-fluoro-4-(trifluoromethyl)pyridin-2-ol (19.7 g, 75.77 mmol), Cs_2CO_3 (49.3 g, 151.54 mmol) and ethyl 4-methyl-2-((methylsulfonyl)oxy)pentanoate (23.5 g, 98.5 mmol) in toluene (100 mL) was stirred at 110°C for 2 h. LCMS showed the reaction was completed. The mixture was filtered and washed with EtOAc (20 mL). The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide ethyl 2-(5-bromo-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate as a white solid (12.4 g). Yield 41% (ESI 402.0 $(M+H)^+$).

Step 3: ethyl (*E*)-2-(5-(2-ethoxyvinyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)- 4-methylpentanoate



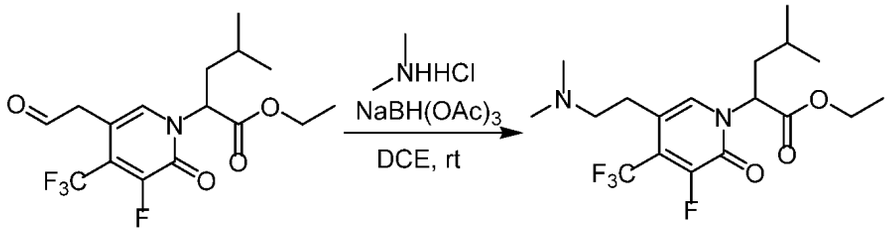
A mixture of ethyl 2-(5-bromo-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate (9.7 g, 24.12 mmol), (*E*)-2-(2-ethoxyvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5.7 g, 28.94 mmol), $Pd(PPh_3)_4$ (832 mg, 0.72 mmol,) and K_2CO_3 (6.7 g, 48.24 mmol) in 1,4-dioxane (100 mL) and water (10 mL) was stirred at 70°C under N_2 for 20 h. The reaction mixture was poured into 100 mL of water and extracted with EtOAc (100 mL x 2). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (pet ether: EtOAc 10:1) to provide ethyl (*E*)-2-(5-(2-ethoxyvinyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate (6.0 g). Yield 63% (ESI 394.1 $(M+H)^+$).

Step 4: ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate



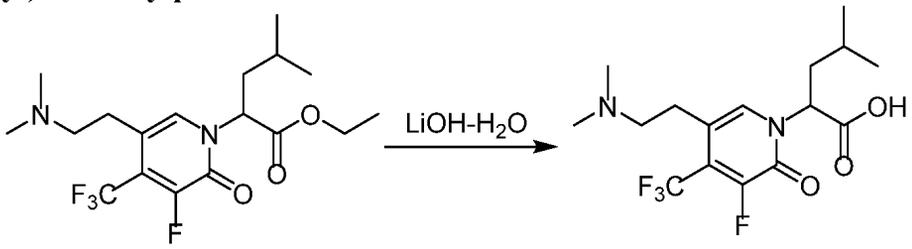
To a mixture of ethyl (*E*)-2-(5-(2-ethoxyvinyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate (6.0 g, 15.25 mmol) in DCM (50 mL) was added TFA (5 mL). The mixture was stirred at room temperature for 3 hours. LCMS showed that the reaction was completed. The mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc (100 mL), washed with saturated $NaHCO_3$ (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo* to give crude product ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate as a colorless oil (5.5 g) used directly in the next reaction without further purification. Yield 99% (ESI 366.1 $[M+H]^+$).

Step 5: ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate



To a mixture of ethyl 2-(3-fluoro-2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate (5.5 g, 15.06 mmol) in DCE (100 mL) at 25 °C was added dimethylamine hydrochloride (2.5 g, 30.12 mmol) and stirred for 1 hour. $NaBH(OAc)_3$ (6.4 g, 30.12 mmol) was added at 5 °C and stirred at 25 °C for 16 hours. The mixture was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to provide ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoate as a brown oil (4.5 g) Yield 76% (ESI 395.1 $[M+H]^+$).

Step 6: 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid



Ethyl 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-

methylpentanoate (4.5 g, 11.41 mmol) was treated with LiOH-H_2O (2.4 g, 57.05 mmol) in EtOH (10 mL) and water (2 mL) and the mixture was stirred at room temperature for 1 hour. The mixture was acidified with 1N HCl to pH = 5~6, concentrated and purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid as a white solid (3.7 g). Yield 89% (ESI 367.1 $(M+H)^+$).

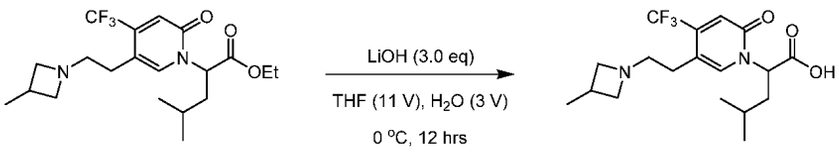
Preparation of 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid

Step 1: ethyl 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate



To a mixture of ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (16.0 g, 36.8 mmol, 1.00 *eq*) in DCE (100 mL) at 25 °C was added 3-methylazetidine (2.62 g, 36.8 mmol, 1.00 *eq*, HCl) and sodium triacetoxyborohydride (15.6 g, 73.7 mmol, 2.00 *eq*). The mixture was stirred at 0 °C for 10 mins, then 25 °C for 12 hrs. The mixture was diluted with H_2O (100 mL) and extracted with DCM (50.0 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 1 to 0: 1) provided ethyl 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (9.00 g, 22.3 mmol, 61% yield) as a yellow oil. 1H NMR: (400 MHz, MeOD) δ 7.86 (s, 1H), 6.90 (s, 1H), 5.52-5.56 (m, 1H), 4.08-4.12 (m, 2H), 3.73-3.74 (m, 4H), 3.59-3.61 (m, 2H), 3.81-3.20 (m, 2H), 2.79-2.81 (m, 3H), 2.05-2.09 (m, 2H), 1.86-1.89 (m, 4H), 1.30-1.50 (m, 7H), 1.25-1.29 (m, 6H), 0.95-0.98 (m, 6H).

Step 2: 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid

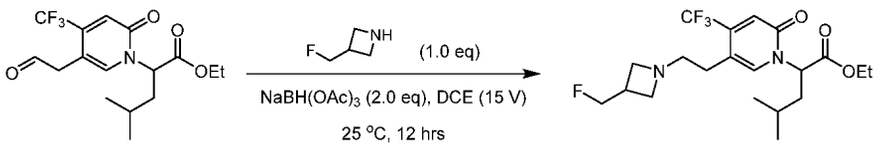


To a solution of ethyl 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (9.00 g, 19.0 mmol, 1.00 eq) in THF (80.0 mL) and

H_2O (8.00 mL) was added LiOH.H_2O (2.39 g, 57.0 mmol, 3.00 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hrs. The reaction mixture was adjusted to pH = 7 with aq.1M HCl and concentrated under reduced pressure. The resulting residue was purified by prep-HPLC (column: Phenomenex luna c18 250mm*100mm*10um; mobile phase: [water (0.05%HCl)-ACN]; B%: 9%-39%, 20min), concentrated under reduced pressure, then lyophilized to provide 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid (4.70 g, 12.0 mmol, 64% yield) as a white solid. 1H NMR: (400 MHz, MeOD) δ 7.79 (s, 1H), 6.87 (s, 1H), 5.60-5.64 (m, 1H), 4.20-4.30 (m, 2H), 3.75-3.85 (m, 2H), 3.35-3.40 (m, 2H), 2.85-2.89 (m, 3H), 2.02-2.09 (m, 2H), 1.26-1.35 (m, 4H), 0.92-0.96 (m, 6H).

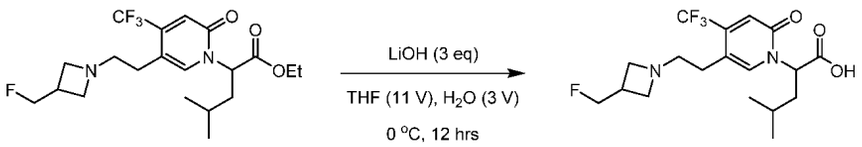
Preparation of 2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a mixture of ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (12.0 g, 24.1 mmol, 1.00 *eq*) in DCE (100 mL) at 25 °C was added 3-(fluoromethyl)azetidine (3.04 g, 24.1 mmol, 1.00 eq, HCl) and DIPEA (6.25 g, 48.3 mmol, 8.42 mL, 2.00 eq) stirred at 0 °C for 10 mins. Sodium triacetoxyborohydride (10.2 g, 48.3 mmol, 2 .00 eq) was added at 5 °C and then stirred at 25 °C for 12 hrs. The mixture was diluted with H2O (100 mL) and extracted with DCM (50.0 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide ethyl 2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (10.1 g, 24.0 mmol, 99.3% yield) as a yellow oil used without further purification.

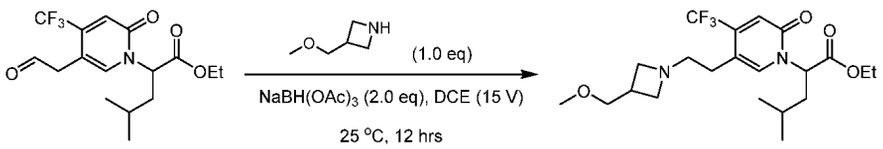
Step 2: 2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



To a solution of ethyl 2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (10.1 g, 24.0 mmol, 1.00 eq) in THF (80.0 mL) and H_2O (10.0 mL) was added $LiOH.H_2O$ (3.02 g, 72.0 mmol, 3.00 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hrs. The reaction mixture was adjusted to (pH = 7) with aq.1M HCl and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna c18 250mm*100mm*10um;mobile phase: [water(0.05%HCl)-ACN];B%: 6%-36%,20min) and concentrated under reduced pressure, then lyophilized to give 2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (4.50 g, 11.4 mmol, 47.7% yield) as a white solid. 1H NMR: (400 MHz, MeOD) δ 7.82 (s, 1H), 6.89 (s, 1H), 5.59-5.63 (m, 1H), 4.50-4.62 (m, 2H), 4.3-4.32 (m, 2H), 4.11-4.14 (m, 2H), 3.37-3.41 (m, 6H), 2.86-2.90 (m, 2H), 2.06-2.10 (m, 2H), 1.53-1.55 (m, 1H), 0.93-0.97 (m, 6H).

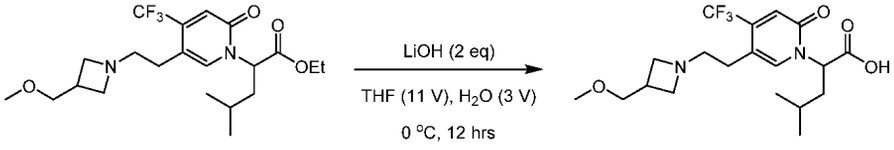
Preparation of 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a mixture of ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (11.0 g, 22.1 mmol, 1.00 *eq*) in DCE (100 mL) at 25 °C was added 3-(methoxymethyl)azetidine hydrochloride (3.05 g, 22.1 mmol, 1.00 *eq*) and DIPEA (5.73 g, 44.3 mmol, 7.72 mL, 2.00 *eq*) stirred at 0 °C for 10 mins. Sodium triacetoxyborohydride (9.40 g, 44.3 mmol, 2.00 *eq*) was added at 5 °C and stirred at 25 °C for 12 hrs. The mixture was diluted with H_2O (100 mL) and extracted with DCM (50.0 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide ethyl 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (9.50 g, 21.9 mmol, 99.0% yield) as a yellow oil used without further purification.

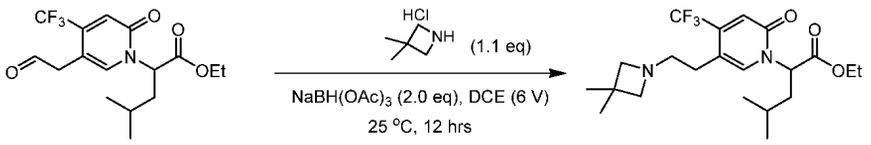
Step 2: 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



To a solution of ethyl 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (9.50 g, 21.9 mmol, 1.00 *eq*) in THF (80.0 mL) and H_2O (10.0 mL) was added $LiOH.H_2O$ (1.84 g, 43.9 mmol, 2.00 *eq*) at 0 °C. The mixture was stirred at 20 °C for 12 hrs. The reaction mixture was adjusted to (pH = 7) with aq.1M HCl and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna c18 250mm*100mm*10um;mobile phase: [water(0.05%HCl)-ACN];B%: 6%-36%,20min) and concentrated under reduced pressure, then lyophilized to give 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (5.10 g, 12.6 mmol, 57.4% yield) as a yellow solid. 1H NMR: (400 MHz, MeOD) δ 7.86 (s, 1H), 6.89 (s, 1H), 5.58-5.62 (m, 1H), 4.07-4.26 (m, 4H), 3.36-3.49 (m, 7H), 3.07 (s, 1H), 2.84-2.88 (m, 2H), 2.07-2.11 (m, 2H), 1.37-1.41 (m, 1H), 0.94-0.97 (m, 6H).

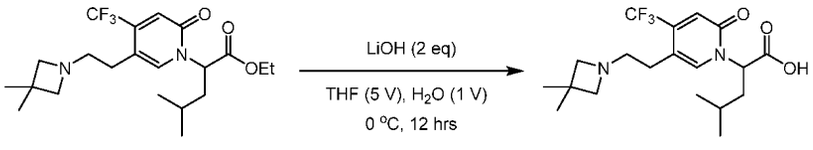
Preparation of 2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a mixture of ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (20 g, 46.1 mmol) in DCE (140 mL) at 25 °C was added 3,3-dimethylazetidine hydrochloride (6.16 g, 50.7 mmol, HCl) and DIPEA (11.9 g, 92.1 mmol, 16.1 mL). After stirring at 10 °C for 10 mins, $NaBH(OAc)_3$ (19.5 g, 92.1 mmol) was added at 5 °C and stirred at 25 °C for 12 hrs. The mixture was diluted with H_2O (200 mL) and the mixture was extracted with DCM (200 mL x 2). The combined organic phase was washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure provide ethyl 2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (20 g) as a yellow oil used without further purification.

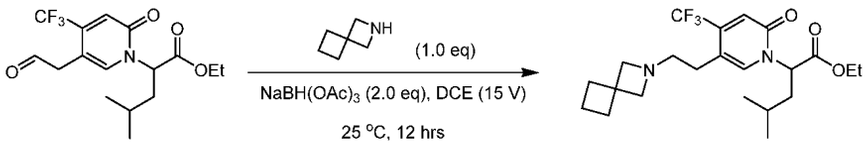
Step 2: 2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



To a mixture of ethyl 2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (20 g, 48.0 mmol) in THF (100 mL) and H_2O (20 mL) was added $LiOH.H_2O$ (4.03 g, 96.0 mmol) in one portion at 15 °C under N_2. The mixture was stirred at 15 °C for 2 hrs. The reaction mixture was adjusted to (pH = 6) with 1M HCl and then concentrated under reduced pressure. The residue was purified by prep-HPLC (HCl condition), concentrated under reduced pressure, then lyophilized to give 2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (6.55 g, 16.7 mmol, 28% yield) as pink solid. 1H NMR: (400 MHz, MeOD) δ 7.94 (s, 1H), 6.91 (s, 1H), 5.59-5.63 (dd, *J* = 4.0 Hz, 12 Hz, 1H), 4.02-4.04 (m, 2H), 3.85-3.92 (m, 2H), 3.34-3.49 (m, 2H), 2.83-2.96 (m, 2H), 2.04-2.20 (m, 2H), 1.39-1.48 (m, 4H), 1.32 (s, 3H), 0.95-0.97 (d, *J* = 8.0 Hz, 6H)

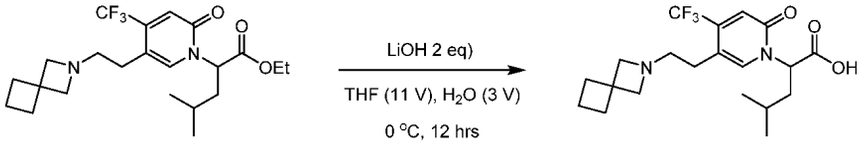
Preparation of 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a mixture of ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (11.0 g, 22.1 mmol, 70.0% purity, 1.00 *eq*) in DCE (100 mL) at 25 °C was added 2-azaspiro[3.3]heptane (2.96 g, 22.1 mmol, 1.00 *eq*, HCl) and DIPEA (5.73 g, 44.3 mmol, 7.72 mL, 2.00 *eq*). After stirring at 0 °C for 10 mins, sodium triacetoxyborohydride (9.40 g, 44.3 mmol, 2.00 *eq*) was added at 5 °C and stirred at 25 °C for 12 hrs. The mixture was diluted with H_2O (100 mL) and extracted with DCM (50.0 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide ethyl 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (9.49 g, 22.1 mmol, 99.9% yield) as a yellow oil used without further purification.

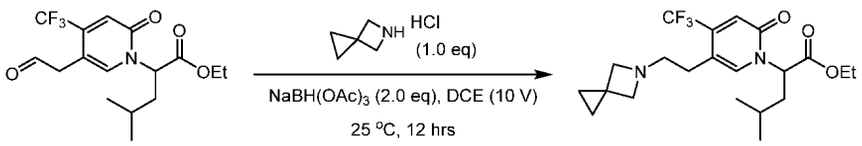
Step 2: 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



To a solution of ethyl 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (9.50 g, 22.1 mmol, 1.00 *eq*) in THF (80.0 mL) and H_2O (10.0 mL) was added $LiOH.H_2O$ (1.86 g, 44.3 mmol, 2.00 *eq*) at 0 °C. The mixture was stirred at 20 °C for 12 hrs. The reaction mixture was adjusted to (pH = 7) with aq.1M HCl and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna c18 250mm*100mm*10um;mobile phase: [water(0.05%HCl)-ACN];B%: 6%-36%,20min) and concentrated under reduced pressure, then lyophilized to give 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (5.50 g, 13.3 mmol, 60.0% yield) as a white solid. 1H NMR: (400 MHz, MeOD) δ 7.86 (s, 1H), 6.90 (s, 1H), 5.60-5.64 (m, 1H), 4.11-4.25 (m, 4H), 3.32-3.36 (m, 2H), 2.83-2.87 (m, 2H), 2.07-2.11 (m, 6H),1.86-1.90 (m, 1H), 1.37-1.39 (m, 1H), 0.94-0.97 (m, 6H).

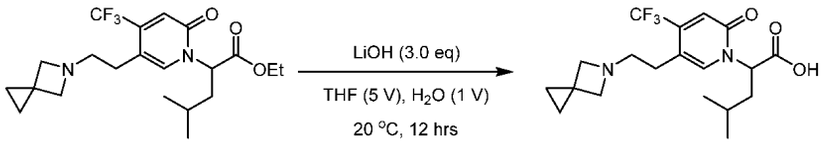
Preparation of 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a mixture of ethyl 4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (10.0 g, 20.1 mmol, 70.0% purity, 1.00 *eq*) in DCE (100 mL) at 25 °C was added 5-azaspiro[2.3]hexane (2.05 g, 17.1 mmol, 0.85 *eq*, HCl). After stirring at 0 °C for 10 mins, sodium triacetoxyborohydride (8.54 g, 40.3 mmol, 2.00 *eq*) was added, the mixture was stirred at 25 °C for 12 hrs. The mixture was diluted with H_2O (100 mL) and extracted with DCM (50.0 mL x 2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2, Petroleum ether: Ethyl acetate = 100: 1 to 0: 1) to provideethyl 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (5.10 g, 12.3 mmol, 61.0% yield) as a yellow oil.

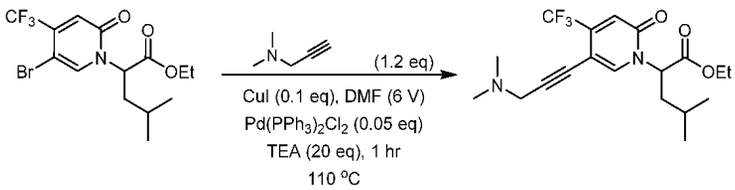
Step 2: 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



To a solution of ethyl 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (5.10 g, 12.3 mmol, 1.00 eq) in THF (30.0 mL) and H_2O (3.00 mL) was added $LiOH.H_2O$ (1.55 g, 36.9 mmol, 3.00 eq) at 0 °C. The mixture was stirred at 20 °C for 12 hrs. The reaction mixture was adjusted to (pH = 7) with aq.1M HCl and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna c18 250mm*100mm*10um;mobile phase: [water(0.05%HCl)-ACN];B%: 10%-40%,25min) and concentrated under reduced pressure, then lyophilized to give 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (2.40 g, 5.53 mmol, 44.9% yield) as a white solid. 1H NMR: (400 MHz, MeOD) δ 7.86 (s, 1H), 6.89 (s, 1H), 5.62 (t, *J* = 7.2Hz, 1H), 4.27 (s, 4H), 3.47-3.55 (m, 2H), 2.90-2.94 (m, 2H), 2.06-2.12 (m, 2H), 1.34-1.39 (m, 1H), 0.94-0.97 (m, 6H), 0.81 (s, 4H).

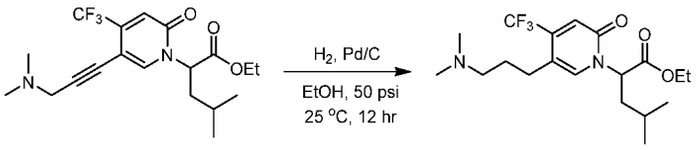
Preparation of 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid

Step 1: ethyl 2-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



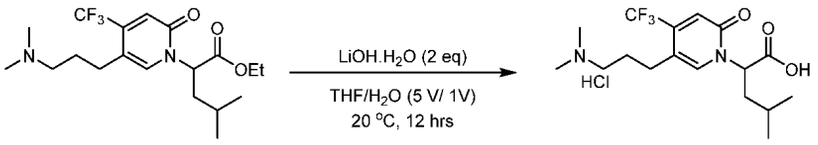
To a solution of ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (68.0 g, 177 mmol, 1.00 eq) in THF (408 mL) was added N,N-dimethylprop-2-yn-1-amine (19.1 g, 230 mmol, 24.4 mL, 1.3 eq), CuI (3.37 g, 17.7 mmol, 0.10 eq), $Pd(PPh_3)_2Cl_2$ (6.21 g, 8.85 mmol, 0.05 eq) and TEA (358 g, 3.54 mol, 493 mL, 20 eq). The reation mixture was stirred at 25 °C for 12 hrs. The reaction was diluted with ethyl acetate, washed twice with saturated ammonium chloride solution and once with brine. The combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude was purified by silica gel chromatography (Petroleum ether: Ethyl acetate=3 : 1) to give ethyl 2-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (20.0 g, 51.8 mmol, 29.2% yield) as a yellow oil.

Step 2: ethyl 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate



To a solution of ethyl 2-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (20.0 g, 51.8 mmol, 1 *eq*) in EtOH (200 mL) was added Pd/C (6.00 g, 2.59 mmol, 5% purity, 0.05 *eq*). The mixture was stirred under H_2 (50 psi) at 15 C for 24 hr. The reaction mixture was filtered and the filtrate concentrated to give ethyl 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (19.7 g, 44.4 mmol, 85.7% yield) as a yellow oil.

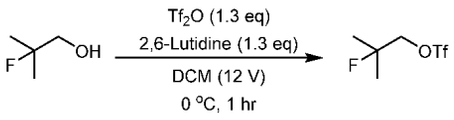
Step 3: 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid



To a solution of ethyl 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoate (19.7 g, 50.4 mmol, 1 eq) in THF (98.0 mL) and H_2O (20.0 mL) was added $LiOH.H_2O$ (4.23 g, 101 mmol, 2.00 eq) at 0 °C. The reaction mixture was warmed to 20 °C and stirred at 20 °C for 12 hrs. The reaction mixture was adjusted to pH = 7 with 1N aqueous HCl and concentrated under vacuum to give the crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 10 um); mobile phase: [water (0.05% HCl)-ACN]; B%: 15%-45%, 20 min)to provide 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (5.40 g, 13.5 mmol, 26.8% yield, HCl) as a white solid. ^{1}H NMR: 400 MHz D_2O δ: 7.71 (s, 1H), 7.00 (s,1H), 5.40-5.45 (d, J = 20 Hz, 1H), 3.13-3.17 (m, 2H), 2.84 (s, 6H), 2.65-2.67 (m, 2H), 1.95-1.99 (m, 4H), 1.25-1.30 (m, 1H), 0.86 (s, 9H)

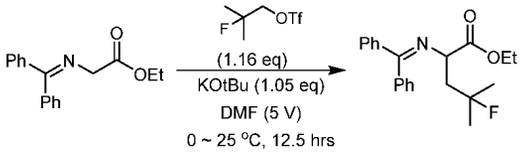
Preparation of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoic acid

Step 1: 2-fluoro-2-methylpropyl trifluoromethanesulfonate



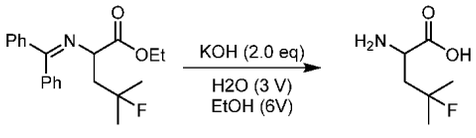
To a solution of alcohol (100 g, 1.09 mol, 1.00 eq) and 2,6-LUTIDINE (151 g, 1.41 mol, 164 mL, 1.30 eq) in DCM (1.20 L) was added Tf_2O (398 g, 1.41 mol, 233 mL, 1.30 eq) dropwise at 0 °C. The solution was stirred at 0 °C for 1 hr. The reaction mixture was washed with 1 N HCl (2 x 1.00 L) and sat.$NaHCO_3$ (2 x 1.00 L). The combined organic layer was dried over Na_2SO_4, filtered and concentrated under vacuum (150 mbar, 25 °C) to give 2-fluoro-2-methylpropyl trifluoromethanesulfonate (214 g) as a light yellow oil used without further purification.

Step 2: ethyl 2-((diphenylmethylene)amino)-4-fluoro-4-methylpentanoate



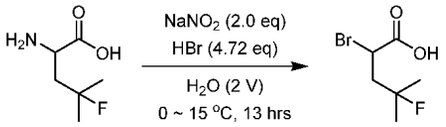
To a solution of KOtBu (97.0 g, 864 mmol, 1.05 eq) in DMF (1.10L) was added ethyl 2-((diphenylmethylene)amino)acetate (220 g, 823 mmol, 1.00 eq) at 0 °C. After stirring for 0.5 hr, 2-fluoro-2-methylpropyl trifluoromethanesulfonate (214 g, 955 mmol, 1.16 eq) was added. The reaction solution was warmed to 25 °C and stirred for 12 hrs. The reaction was poured into 5% aqueous NH_4Cl (0.80 L) and extracted with EtOAc (2.00 L and 1.00 L). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum to give the crude product. The crude product was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 100: 1 ~ 0 : 1) to provide ethyl 2-((diphenylmethylene)amino)-4-fluoro-4-methylpentanoate (220 g) as a light yellow oil.

Step 3: 2-amino-4-fluoro-4-methylpentanoic acid



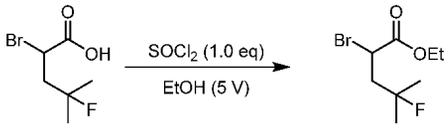
To a solution of ethyl 2-((diphenylmethylene)amino)-4-fluoro-4-methylpentanoate (220 g, 644 mmol, 1.00 eq) in EtOH (1.32 L) was added KOH (72.3 g, 1.29 mol, 2.00 eq) in H_2O (660 mL) at 25 °C. The reaction solution was stirred for 1 hr at 25 °C. The reaction was adjusted to pH=7 with HCl (1 M). The reaction solution was extracted with EtOAc (0.80 L x 2), the combined aqueous phase was concentrated under reduced pressure to give 2-amino-4-fluoro-4-methylpentanoic acid (203 g, 48% purity, HCl) as a white solid used without further purification. 1H NMR 400 MHz $CDCl_3$ δ: 4.00-4.03 (m, 1H), 2.19-2.23 (m, 2H), 1.43-1.50 (m, 6H).

Step 4: 2-bromo-4-fluoro-4-methylpentanoic acid



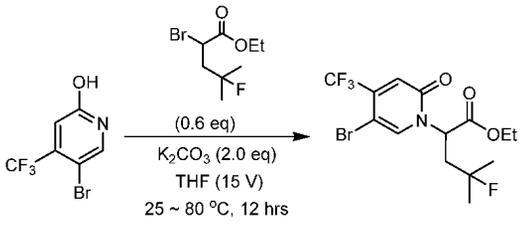
To a solution of 2-amino-4-fluoro-4-methylpentanoic acid (203 g, 1.09 mol, 1.00 eq, HCl) in HBr (4 M, 1.29 L, 40% purity, 4.72 eq) was added dropwise a solution of $NaNO_2$ (151 g, 2.19 mol, 2.00 eq) in H_2O (608 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hr, warmed to 15 °C and stirred at 15 °C for 12 hrs. The reaction mixture was extracted with MTBE (1.00 L and 500 mL). The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was dissolved in MTBE (50.0 mL) and concentrated under vacuum to give 2-bromo-4-fluoro-4-methylpentanoic acid (127 g) as a yellow oil used without further purification. 1H NMR: 400 MHz $CDCl_3$ δ: 4.61-4.65 (m, 1H), 4.41-4.44 (m, 1H), 2.70-2.76 (m, 2H), 2.44-2.48 (m, 2H), 1.21-1.48 (m, 6H).

Step 5: ethyl 2-bromo-4-fluoro-4-methylpentanoate



To a solution of 2-bromo-4-fluoro-4-methylpentanoic acid (127 g, 596 mmol, 1.00 eq) in EtOH (520 mL) was added $SOCl_2$ (70.9 g, 596 mmol, 43.2 mL, 1.00 eq) at 0 °C. The reaction solution was stirred for 2 hrs at 60 °C. The solution was poured into H_2O (400 mL) and extracted with MTBE (500 mL x 2). The combined organic was washed with brine (500 mL), dried over anhydrous Na2SO4, filtered and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography (SiO_2, petroleum ether:ethyl acetate = 100:1 to 10:1) to provide ethyl 2-bromo-4-fluoro-4-methylpentanoate (90.0 g) as a yellow oil. ^1H NMR: 400 MHz $CDCl_3$ δ: 4.38-4.42 (m, 1H), 4.21-4.26 (m, 2H), 2.69-2.76 (m, 1H), 2.25-2.26 (m, 1H), 0.85-1.39 (m, 9H).

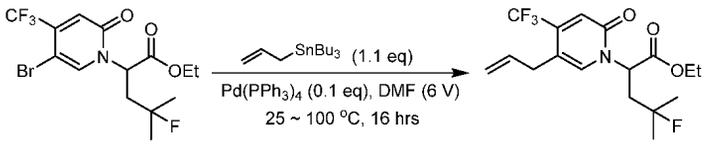
Step 6: ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate



To a solution of 5-bromo-4-(trifluoromethyl)pyridin-2-ol (60.0 g, 249 mmol, 1.00 eq) and K_2CO_3 (103 g, 747 mmol, 2.00 eq) in THF (900 mL) was added ethyl 2-bromo-4-fluoro-4-methylpentanoate

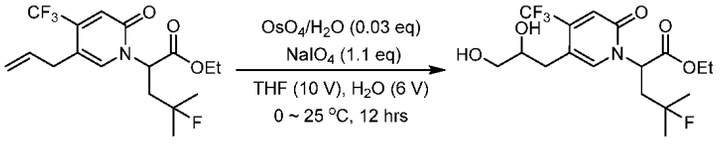
(151 g, 622 mmol, 2.50 eq) at 0 °C. The mixture was heated to 70 °C and stirred at 70 °C for 12 hrs. The reaction was poured into aqueous NH_4Cl (1.00 L) at 0 °C and extracted with MBTE (1.00 L and 500 mL). The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated under vacuum to give the crude product. The crude product was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 100 : 1 ~ 0 : 1) to give ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (40.0 g, 99.5 mmol) as a white solid. ^1H NMR: 400 MHz $CDCl_3$ δ: 7.66 (s, 1H), 6.94 (s, 1H), 5.48-5.51 (m, 1H), 4.22-4.27 (m, 2H), 2.56-2.65 (m, 1H), 2.30-2.32 (m, 1H), 1.26-1.59 (m, 9H).

Step 6: ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate



To a solution of ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (25.0 g, 62.2 mmol, 1.00 eq) and allyltributylstannane (24.5 g, 74.0 mmol, 22.7 mL, 1.10 eq) in DMF (150 mL) was added $Pd(PPh_3)_4$ (7.18 g, 6.22 mmol, 0.10 eq) in one portion at 25 °C under N_2. The mixture was heated to 100 °C and stirred at 100 °C for 12 hrs. The reaction mixture was poured into a solution of KF (10.0 eq) in H_2O (200 mL) and ethyl acetate (200 mL). The resulting suspension was stirred at 15 °C for 0.5 hr, filtered and the filtrate was extracted with ethyl acetate (300 mL and 200 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give the crude product. The crude product was purified by column chromatography (SiO_2, petroleum ether: ethyl acetate = 100 : 1 ~ 0 : 1) to afford ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (19.8 g, 54.5 mmol, 87.7 % yield) as a light yellow oil. ^1H NMR: 400 MHz $CDCl_3$ δ: 7.23 (s, 1H), 6.89 (s, 1H), 5.88-5.93 (m, 1H), 5.45-5.47 (m, 1H), 5.10-5.21 (m, 2H), 4.19-4.26 (m, 2H), 3.29-3.30 (m, 2H), 2.57-2.68 (m, 1H), 2.30-2.37 (m, 1H), 0.93-1.40 (m, 9H).

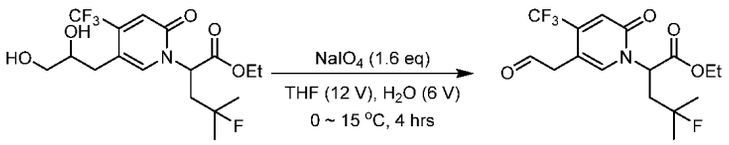
Step 7: ethyl 2-(5-(2,3-dihydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate



To a solution of ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (19.8 g, 54.5 mmol, 1.00 eq) in THF (198 mL) and H_2O (20.0 mL) was added $K_2OsO_4/2H_2O$ (602 mg, 1.64 mmol, 0.03 eq) at 0 °C. Then a solution of $NaIO_4$ (11.7 g, 54.5 mmol, 3.02 mL, 1.00 eq) in H_2O (100 mL) was added dropwise at 0 °C and the solution stirred at 0 °C for 2

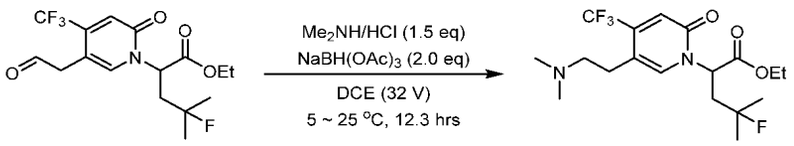
hrs. The solution was warmed to 25 °C and was stirred at 25 °C for 1 hr. The mixture was quenched with a sat.$Na_2S_2O_3$ solution (200 mL) and filtered. The filtrate was extracted with ethyl acetate (500 mL x 2), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give ethyl 2-(5-(2,3-dihydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (21.0 g, crude) as a brown oil used without further purification.

Step 8: ethyl 4-fluoro-4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate



To a solution of ethyl 2-(5-(2,3-dihydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (21.0 g, 52.9 mmol, 1.00 eq) in THF (252 mL) was added a solution of $NaIO_4$ (17.0 g, 79.3 mmol, 4.39 mL, 1.50 eq) in H_2O (100 mL) at 0 °C. The solution was stirred at 0 °C for 2 hrs, warmed to 25 °C and stirred at 25 °C for 2 hrs. The mixture was quenched with a sat. $Na_2S_2O_3$ solution (150 mL) and filtered. The filtrate was extracted with ethyl acetate (250 mL x 2) and the combined organic layer washed with 1 N HCl (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4 and filtered. AcOH (21.0 mL) was added to the filtrate and the solution concentrated under vacuum to give ethyl 4-fluoro-4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (21.0 g) as a brown oil used without further purification.

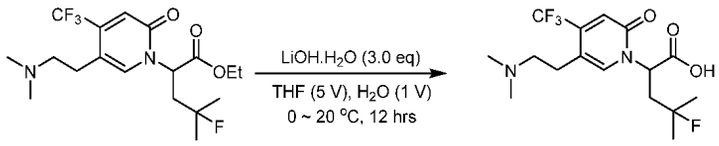
Step 9: ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate



To a solution of ethyl 4-fluoro-4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (13.3 g, 36.4 mmol, 1.00 *eq*) in DCE (80.0 mL) was added $NaBH(OAc)_3$ (15.4 g, 72.8 mmol, 2.00 eq) and DIEA (9.41 g, 72.8 mmol, 12.7 mL, 2.00 eq) at 25 °C. The solution was stirred at 25 °C for 20 mins, cooled to 5 °C and Me_2NH/HCl (4.45 g, 54.6 mmol, 1.50 *eq*) was added.. The reaction solution was warmed to 25 °C and stirred for 12 hrs. The reaction mixture was diluted with H_2O (50.0 mL) and was extracted with DCM (100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuumto give 6-6 (14.9 g, crude) as a brown oil. Compound ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-

(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate was used without further purification.

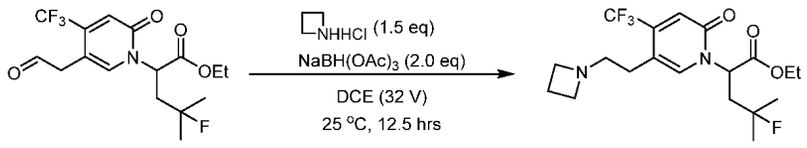
Step 10: 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoic acid



To a solution of ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (14.9 g, 37.8 mmol, 1.00 *eq*) in THF (75.0 mL) and H_2O (15.0 mL) was added $LiOH.H_2O$ (4.76 g, 113 mmol, 3.00 *eq*) at 0 °C. The reaction solution was warmed to 20 °C and stirred for 12 hrs. The reaction mixture was adjusted to pH = 7 with 1 N HCl (50.0 mL) and concentrated under vacuum to give the crude product. The crude product was purified by pre-HPLC (column: Agela DuraShell C18 250 * 80 mm * 10 um; mobile phase: [water (10 mM NH_4HCO_3) - ACN]; B%: 5% - 30%, 20min). Then the solution was concentrated under vacuum to give 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoic acid (2.00 g, 5.35 mmol, 14.2% yield, 98% purity) as a white solid. ^1H NMR: 400 MHz D_2O δ: 7.79 (s, 1H), 6.97 (s, 1H), 5.51-5.53 (m, 1H), 3.27-3.31 (m, 2H), 3.00-3.04 (m, 2H), 2.91 (s, 6H), 2.49-2.58 (m, 2H), 1.34 (t, J = 24.4 Hz, 6H).

Preparation of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoic acid

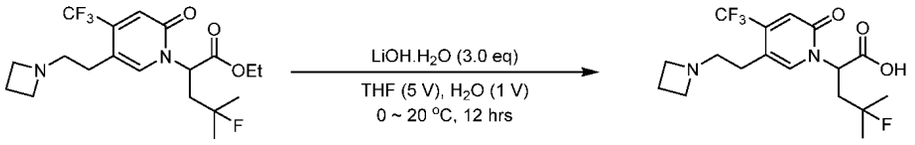
Step 1: ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate



To a solution of ethyl 4-fluoro-4-methyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (21.0 g, 57.5 mmol, 1.00 eq) in DCE (126 mL) was added $NaBH(OAc)_3$ (24.4 g, 115 mmol, 2.00 eq) at 25 °C. The solution was stirred at 25 °C for 20 mins, cooled to 5 °C and azetidine-HCl (5.38 g, 57.5 mmol, 1.00 eq) was added. The reaction solution was warmed to 25 °C and stirred for 12 hrs. The reaction mixture was diluted with H_2O (50.0 mL) and was extracted with DCM (100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-

(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (11.5 g, 25.2 mmol, 43.8% yield) as a brown oil. HNMR: 400 MHz $CDCl_3$ δ: 7.51 (s, 1H), 6.86 (s, 1H), 5.47-5.50 (m, 1H), 4.14-4.25 (m, 1H), 3.40-3.43 (m, 3H), 2.17-2.76 (m, 6H), 1.25-1.47 (m, 9H).

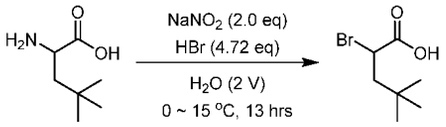
Step 2: 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoic acid



To a solution of ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate (11.5 g, 28.30 mmol, 1.00 eq) in THF (69.0 mL) and H_2O (36.0 mL) was added $LiOH.H_2O$ (4.75 g, 113.19 mmol, 3.00 eq) at 0 °C. The reaction solution was warmed to 20 °C and stirred for 12 hrs. The reaction mixture was adjusted to pH = 7 with 1 N HCl (50.0 mL) and concentrated under vacuum to give the crude product. The crude product was purified by reversed-phase HPLC (0.10 % $NH3•H_2O$) to give 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoic acid (5.00 g, 12.8 mmol, 45.1% yield) as an off-white solid. ^1H NMR: 400 MHz D_2O δ: 7.70 (s, 1H), 6.95 (s, 1H), 5.52 (s, 1H), 3.49-3.53 (m, 4H), 2.83-2.87 (m, 2H), 2.52-2.68 (m, 4H), 2.15-2.18 (m, 2H), 1.29-1.42 (m, 6H).

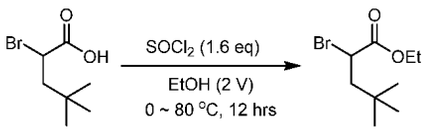
Preparation of ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate

Step 1: 2-bromo-4,4-dimethylpentanoic acid



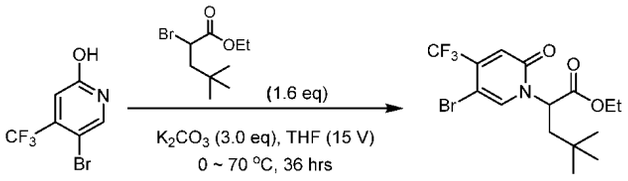
A solution of 2-amino-4,4-dimethylpentanoic acid (35.0 g, 241 mmol, 1.00 eq) in HBr (4 M, 284 mL, 40% purity, 4.72 eq) was added dropwise over $NaNO_2$ (16.6 g, 241 mmol, 1.00 eq) in H_2O (70.0 mL) at 0 °C. The mixture was stirred at 0 °C for 1 hr, warmed to 15 °C and stirred at 15 °C for 12 hrs. The reaction mixture was extracted with MTBE (20.0 mL). The organic layer was washed with brine (20.0 mL), dried over sodium sulfate, and concentrated under reduced pressure. The residue was dissolved in MTBE (20.0 mL) and concentrated under reduced pressure to give to give 2-bromo-4,4-dimethylpentanoic acid (31.0 g) as a yellow oil used without further purification. 1H NMR: 400 MHz $CDCl_3$ δ: 4.28-4.32 (m, 1H), 2.32-2.38 (m, 1H), 1.92-1.97 (m, 1H), 0.95 (s, 9 H).

Step 2: ethyl 2-bromo-4,4-dimethylpentanoate



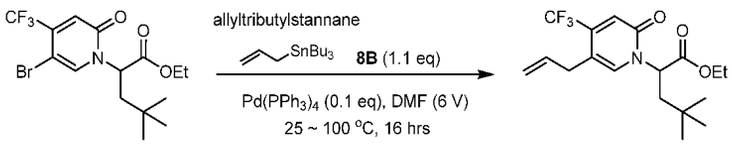
To a solution of 2-bromo-4,4-dimethylpentanoic acid (31.0 g, 148 mmol, 1.00 eq) in EtOH (62 mL) was added $SOCl_2$ (28.2 g, 237 mmol, 17.2 mL, 1.60 eq) at 0 °C. The solution was warmed to 80 °C and stirred for 12 hrs. The mixture was concentrated under reduced pressure and the residue was dissolve in MTBE (60 mL) and washed with aqueous $NaHCO_3$ (60 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated under vacuum to give ethyl 2-bromo-4,4-dimethylpentanoate (29.0 g, crude) as a yellow oil. 1H NMR: 400 MHz $CDCl_3$ δ: 4.20-4.30 (m, 3H), 2.33-2.40 (m, 1H), 1.89-1.94 (m, 1H), 1.29-1.32(m, 3H), 0.93 (s, 9H).

Step 3: ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate



To a solution of 5-bromo-4-(trifluoromethyl)pyridin-2-ol (22.0 g, 90.9 mmol, 1.00 eq) and K_2CO_3 (37.7 g, 273mmol, 3.00 eq) in THF (330 mL) was added ethyl 2-bromo-4,4-dimethylpentanoate (28.0 g, 118 mmol, 1.30 eq) at 0 °C. The mixture was heated to 70 °C and stirred for 14 hrs. The reaction was poured into water (400 mL) and extracted with MTBE (400 mL x 2). The combined organic phase was washed with brine (200 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate = 3 : 1) to give ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (23.0 g, 57.8 mmol, 63.5% yield) as a yellow oil.

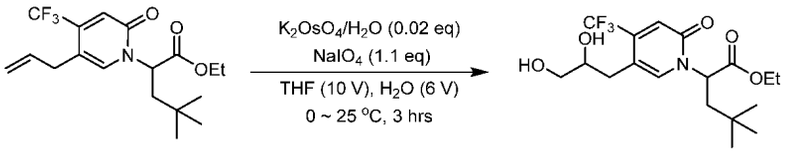
Step 4: ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate



To a mixture of ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (23.0 g, 57.8 mmol, 1.00 eq) and allyltributylstannane (21.0 g, 63.5 mmol, 19.5 mL, 1.10 eq) in DMF (132 mL) was added $Pd(PPh_3)_4$ (3.34 g, 2.89 mmol, 0.05 eq) in one portion at 20 °C. The reaction was purged with N_2 (3x) and stirred at 100 °C for 4 hrs under N_2. The reaction was dissolved in water (100 mL) and KF (23.0 g), extracted with MTBE (100 mL),dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (Petroleum ether:

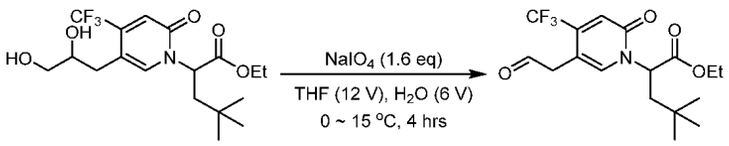
Ethyl acetate=3 : 1) to give ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (15.0 g, 41.74 mmol, 72.3% yield) as a yellow oil.

Step 5: ethyl 2-(5-(2,3-dihydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate



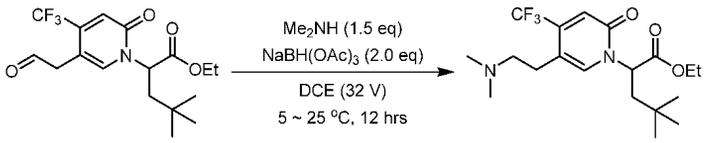
To a solution of ethyl 2-(5-allyl-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (15.0 g, 49.1 mmol, 1.00 eq) in H_2O (15.0 mL) and THF (150 mL) was added $K_2OsO_4.2H_2O$ (362 mg, 982. umol, 0.02 eq) at 0 °C. The solution was stirred at 0 °C for 15 mins. Then a solution of $NaIO_4$ (11.6 g, 54.0 mmol, 2.99 mL, 1.10 eq) in H_2O (15.0 mL) was added dropwise at 0 °C and was stirred for 2 hrs at 0 °C. The reaction was warmed to 25 °C and stirred for 12 hrs. The mixture was quenched with a saturated Na_2SO_3 solution, extracted with EtOAc (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give ethyl 2-(5-(2,3-dihydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (16.9 g, crude) as a yellow oil used without further purification.

Step 6: ethyl 4,4-dimethyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate



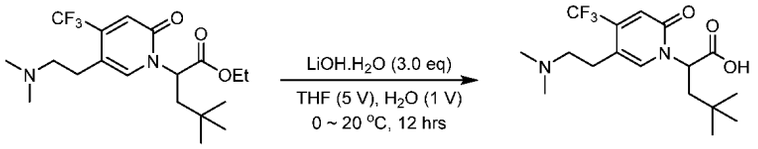
To a solution of ethyl 2-(5-(2,3-dihydroxypropyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (16.9 g, 43.0 mmol, 1.00 eq) in THF (200 mL) was added a solution of $NaIO_4$ (14.7 g, 68.7 mmol, 3.81 mL, 1.60 eq) in H_2O (100 mL) at 0 °C. The solution was stirred at 0 °C for 2 hrs, then warmed to 25 °C and stirred for 2 hrs. The mixture was quenched with a saturated Na_2SO_3solution and extracted with EtOAc (300 mL). The organic layer was washed with 1 N HCl solution and brine, then dried over anhydrous Na_2SO_4, filtered. AcOH was added to the filtrate and concentration under reduced pressure provided ethyl 4,4-dimethyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (16.8 g, crude) as a yellow oil used without further purification.

Step 7: ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate



To a solution of ethyl 4,4-dimethyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (8.40 g, 23.3 mmol, 1.00 eq) in DCE (268 mL) was added Me_2NH (2.84 g, 34.9 mmol, 1.50 eq) at 25 °C. The solution was stirred at 25 °C for 15 mins, then $NaBH(OAc)_3$ (9.85 g, 46.5 mmol, 2.00 eq) was added portion-wise at 5 °C, and the solution stirred at 25 °C for 12 hrs. The reaction mixture was diluted with H_2O (200 mL) and extracted with DCM (100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (7.30 g, crude) as a brown oil used without further purification.

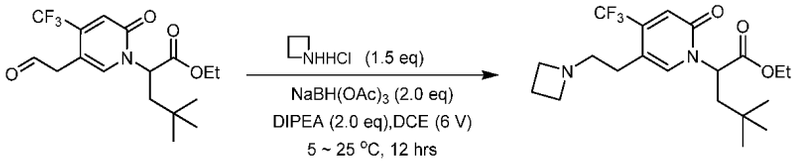
Step 8: 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid



To a solution of ethyl 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (7.30 g, 18.7 mmol, 1.00 eq) in THF (36.5 mL) and H_2O (7.30 mL) was added $LiOH.H_2O$ (1.57 g, 37.4 mmol, 2.00 eq) at 0 °C. The reaction mixture was warmed to 20 °C and stirred for 12 hrs. The reaction mixture was adjusted to pH = 7 with 1N aqueous HCl and concentrated under vacuum to give the crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*15um; mobile phase: [water (0.1%TFA)-ACN]; B%: 10%-35%, 20 min). Lyophilization give 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid (0.51 g, 511 umol, 2.74% yield, HCl) as a yellow solid. ^1H NMR: 400 MHz D_2O δ: 7.89 (s, 1H), 6.99 (s, 1H), 5.45-5.47 (d, J = 12.0 Hz, 1H), 3.25-3.29 (m, 2H), 2.98-3.03 (m, 1H), 2.92 (s, 6H), 2.18-2.22 (m, 1H), 1.98-2.04 (m, 2H), 0.78 (s, 9H)

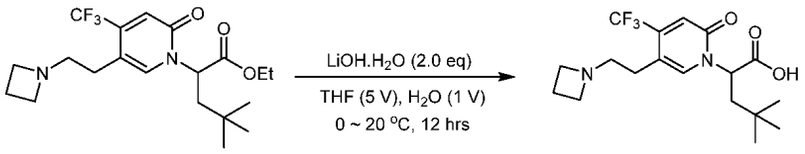
Preparation of ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoate

Step 1: ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate



To a solution of ethyl 4,4-dimethyl-2-(2-oxo-5-(2-oxoethyl)-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoate (8.40 g, 23.3 mmol, 1.00 eq) in DCE (268 mL) was added azetidine hydrochloride (3.26 g, 34.9 mmol, 1.50 eq) and DIPEA (6.01 g, 46.5 mmol, 8.10 mL, 2.00 eq) at 25 °C. The solution was stirred for 15 mins, then $NaBH(OAc)_3$ (9.85 g, 46.5 mmol, 2.00 eq) was added portion-wise at 5 °C, and the solution was stirred at 25 °C for 12 hrs. The reaction mixture was diluted with H_2O (200 mL) and extracted with DCM (100 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to give ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (10.9 g, crude) as a yellow oil used without further purification.

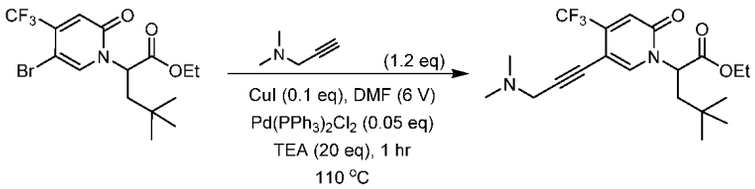
Step 2: 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid



To a solution of ethyl 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (10.9 g, 27.0 mmol, 1.00 eq) in THF (54.5 mL) and H_2O (10.9 mL) was added $LiOH.H_2O$ (2.27 g, 54.2 mmol, 2.00 eq) at 0 °C. The reaction mixture was warmed to 20 °C and stirred for 12 hrs. The reaction mixture was adjusted to pH = 7 with 1N aqueous HCl and concentrated under vacuum to give the crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*15um; mobile phase: [water (0.1%TFA)-ACN]; B%: 10%-35%, 23 min). Lyophilization provided 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid (0.32 g, 857 umol, 3.16% yield) as a white solid ^1H NMR: 400 MHz D_2O δ: 7.85 (s, 1H), 6.98 (s, 1H), 5.45 (s, 1H), 4.22 (m, 2H), 4.01-4.05 (m, 2H), 3.34-3.35 (m, 2H), 2.83 (m, 2H), 1.97-2.54 (m, 4H), 0.77 (s, 9H).

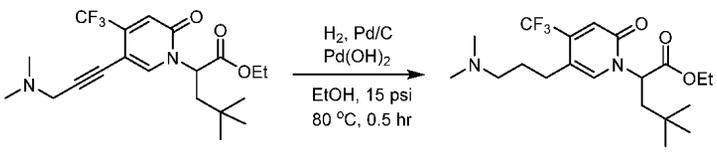
Preparation of 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid

Step 1: ethyl 2-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate



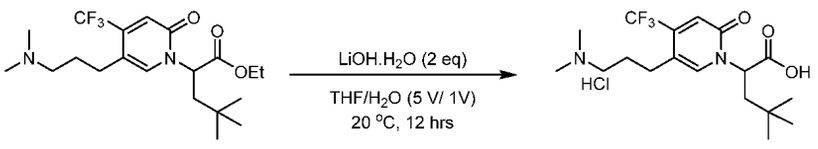
Ethyl 2-(5-bromo-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (1.00 g, 2.51 mmol, 1.00 eq), N,N-dimethylprop-2-yn-1-amine (251 mg, 3.01 mmol, 320 uL, 1.20 eq), TEA (5.08 g, 50.2 mmol, 6.99 mL, 20.0 eq), $Pd(PPh_3)_2Cl_2$ (88.1 mg, 126 umol, 0.05 eq) and CuI (47.8 mg, 251 umol, 0.10 eq) were added to a microwave tube in DMF (6 mL). The sealed tube was heated under microwave conditions at 110 °C for 1 hr. The reaction was poured into water and extracted with MTBE (100 mL x 2). The combined organic phase was washed with brine (50 mL x 2), dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue was purified by silica gel chromatography (Petroleum ether: Ethyl acetate= 5 :1) to give ethyl 2-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (0.52 g, 1.3 mmol, 52.5% yield) as a yellow oil.

Step 2: ethyl 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate



To a solution of ethyl 2-(5-(3-(dimethylamino)prop-1-yn-1-yl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (3.70 g, 9.24 mmol, 1.00 eq) in EtOH (170 mL) was added Pd/C (1.10 g) and $Pd(OH)_2$ (1.10 g). The mixture was stirred under H_2 (50 psi) at 80 °C for 0.5 hr. The reaction mixture was filtered and concentrated to give ethyl 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate used without further purification.

Step 3: 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid



To a solution of ethyl 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoate (3.70 g, 9.15 mmol, 1.00 eq) in THF (18.5 mL) and H_2O (3.70 mL) was added $LiOH.H_2O$ (768 mg, 18.3 mmol, 2.00 eq) at 0 °C. The reaction mixture was warmed to 20 °C and stirred for 12 hrs. The reaction mixture was adjusted to pH = 7 with 1N aqueous HCl and concentrated under vacuum to give the crude product. The crude product was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 15 um); mobile phase: [water(0.05%HCl)-ACN]; B%: 5%-35%, 20 min) to give 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid (2.2 g, 5.33 mmol, 58.25% yield) as a white solid. ^1H NMR: 400 MHz

D_2O δ: 7.83 (s, 1H), 7.00 (s,1H), 5.50-5.52 (m, 1H), 3.15-3.19 (m, 2H), 2.85 (s, 6H), 2.67-2.70 (m, 2H), 2.22-2.26 (m, 1H), 1.98-2.09 (m, 3H), 0.82 (s, 9H).

Example 3: Synthesis of examplary compounds of the invention

Prep-HPLC Methods

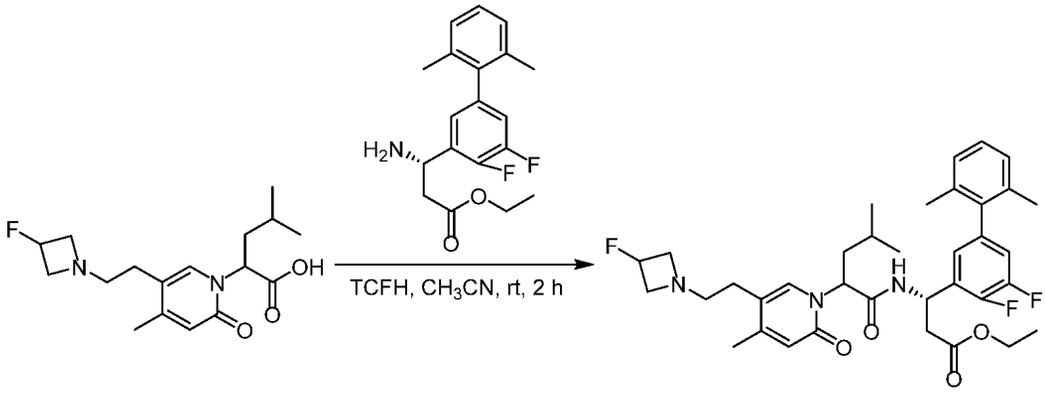
Crude samples were dissolved in MeOH and purified by prep HPLC using a Gilson 215 instrument, detection wavelength 214 nm:

Prep HPLC A: column: Xtimate C18, 21.2 * 250 mm, 10 μm; mobile phase: A water (10 mM ammonium hydrogen carbonate), B CH_3CN; gradient elution as in text; flow rate: 30 mL/min.

Prep HPLC B: column: Xtimate C18, 21.2 * 250 mm, 10 μm; mobile phase: A water (0.1% formic acid), B CH_3CN; gradient elution as in text; flow rate: 30 mL/min.

3-1. Preparation of (3*S*)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds D-P1 and D-P2)

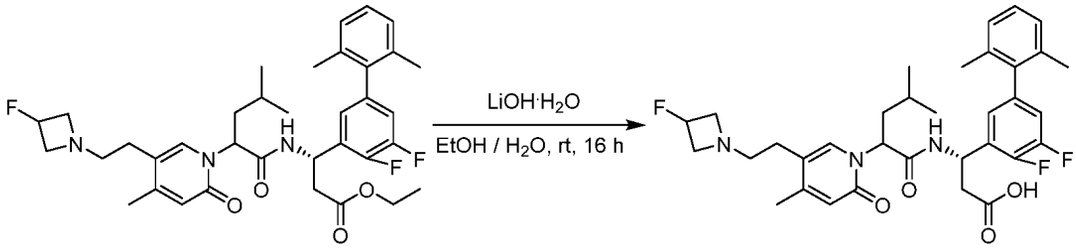
Step 1: (3*S*)-ethyl 3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (84 mg, 0.26 mmol), (*S*)-ethyl 3-amino-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)propanoate (173 mg, 0.52 mmol), TCFH (94 mg, 0.34 mmol), and NMI (0.30 mL, 3.76 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2

hours. The reaction mixture was poured into 100 mL of EtOAc, washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The reaction mixture was concentrated in vacuo and purified by reverse phase HPLC on a C18/40 g column (A: water/0.01%TFA, B: MeOH, 0~64%) to provide (3*S*)-ethyl 3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a white solid (131 mg). Yield 79% (ESI 640.2 $(M+H)^+$).

Step 2: (3*S*)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



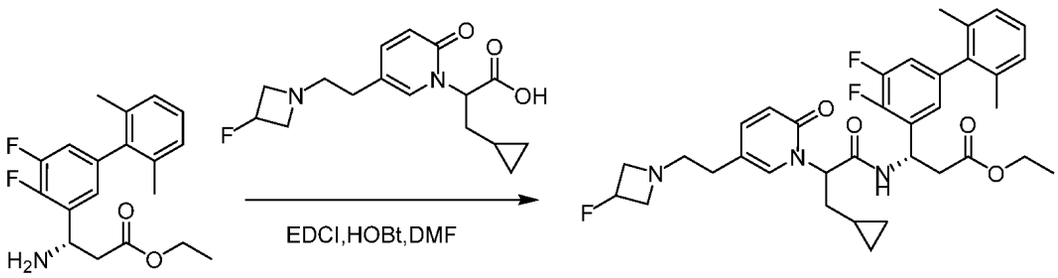
(3*S*)-ethyl 3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (131 mg, 0.20 mmol) was treated with LiOH monohydrate (72 mg, 1.71 mmol) in EtOH (12.5 mL) and H_2O (0.25 mL) at room temperature for 16 hours. The reaction mixture was acidified to pH 4~5 with concentrated HCl. The reaction mixture was concentrated *in vacuo* and purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **D-P1** (23 mg) and **D-P2** (23 mg) as white solids.

D-P1 ESI 612.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.46 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.07 (t, J = 6.0 Hz, 2H), 6.93 – 6.89 (m, 1H), 6.81 (d, J = 5.5 Hz, 1H), 6.27 (s, 1H), 5.59 – 5.54 (m, 2H), 5.28 – 5.12 (m, 1H), 4.07 – 3.94 (m, 2H), 3.74 – 3.60 (m, 2H), 3.05 – 2.99 (m, 2H), 2.79 – 2.69 (m, 2H), 2.65 – 2.59 (m, 2H), 2.20 (s, 3H), 1.99 (s, 3H), 1.92 (t, J = 7.0 Hz, 2H), 1.85 (s, 3H), 1.44 – 1.36 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H).

D-P2 ESI 612.2 $(M+H)^+$.^1H NMR (500 MHz, MeOD) δ 7.46 (s, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.07 (t, J = 6.0 Hz, 2H), 6.93 – 6.89 (m, 1H), 6.81 (d, J = 5.5 Hz, 1H), 6.27 (s, 1H), 5.59 – 5.54 (m, 2H), 5.28 – 5.12 (m, 1H), 4.07 – 3.94 (m, 2H), 3.75 – 3.60 (m, 2H), 3.06 – 2.98 (m, 2H), 2.79 – 2.69 (m, 2H), 2.65 – 2.59 (m, 2H), 2.20 (s, 3H), 1.99 (s, 3H), 1.92 (t, J = 7.0 Hz, 2H), 1.85 (s, 3H), 1.44 – 1.36 (m, 1H), 0.93 (d, J = 6.5 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H).

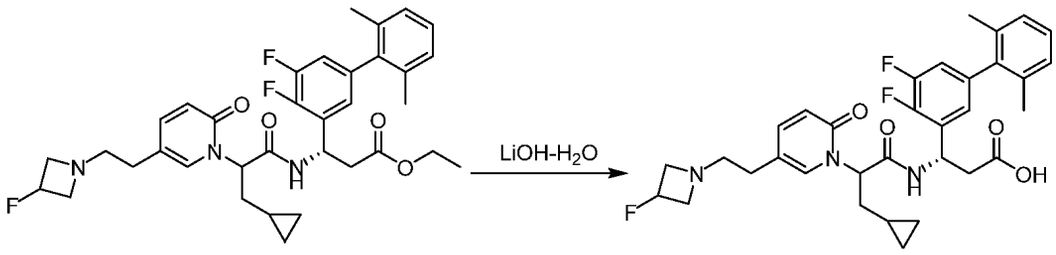
3-2. Preparation of (3*S*)-3-(3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanamido)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds E-P1 and E-P2)

Step 1: ethyl (3*S*)-3-(3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanamido)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (90 mg, 0.27 mmol), 3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanoic acid (125 mg, 0.40 mmol), HOBT (73 mg, 0.54 mmol), EDCI (104 mg, 0.54 mmol) and TEA (120 mg, 0.81 mmol) in DMF (2 mL) was stirred at 50 °C for 4 hours. The reaction mixture was concentrated in vacuo and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanamido)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (60 mg). Yield 35% (ESI 624.2 $(M+H)^+$).

Step 2: (3*S*)-3-(3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanamido)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(3-cyclopropyl-2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanamido)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (50 mg, 0.08 mmol) was treated with LiOH-H_2O (13 mg, 0.32 mmol) in MeOH (2 mL) and H_2O (0.5 mL)

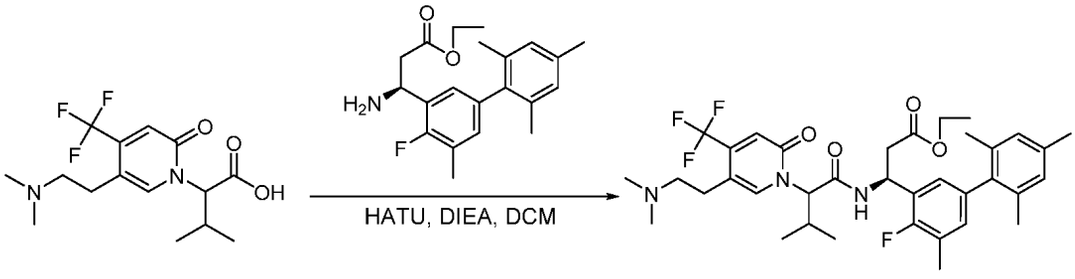
at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **E-P1** (1 mg) and **E-P2** (1 mg) as white solids.

E-P1 ESI 596.2(M+H)$^+$. ^{1}H NMR (500 MHz, MeOD) δ 7.47 (s, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.07 – 6.99 (m, 3H), 6.88 – 6.80 (m, 1H), 6.71 – 6.70 (m, 1H), 6.34 (d, *J* = 9.2 Hz, 1H), 5.45 (s, 2H), 5.19 – 5.03 (m, 1H), 3.96 – 3.84 (m, 2H), 3.57 (s, 2H), 2.97 – 2.96 (m, 2H), 2.67 (s, 2H), 2.50 (s, 2H), 1.91 (s, 5H), 1.79 (s, 3H), 0.55 (s, 1H), 0.35 – 0.34 (m, 2H), 0.07 – 0.00 (m, 2H).

E-P2 ESI 596.2(M+H)$^+$. ^{1}H NMR (500 MHz, MeOD) δ 7.49 (s, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.15 – 6.84 (m, 5H), 6.50 (d, *J* = 9.3 Hz, 1H), 5.57– 5.44 (m, 2H), 5.19– 5.07 (m, 1H), 3.95 – 3.59 (m, 3H), 2.99 (s, 2H), 2.59 – 2.54 (m, 4H), 2.15 – 2.12 (m, 1H), 1.99 – 1.95 (m, 8H), 0.52 – 0.47 (m, 1H), 0.25 – 0.23 (m, 2H), 0.01 – 0.05 (m, 2H).

3-3. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylbutanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (compounds F-P1 and F-P2)

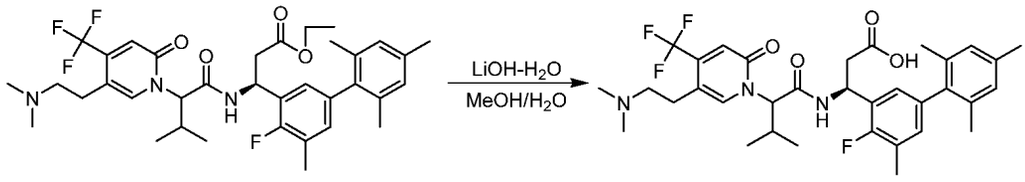
Step 1: (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylbutanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylbutanoic acid (150 mg, 0.45 mmol), (*S*)-ethyl 3-amino-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (154 mg, 0.45 mmol), HATU (205 mg, 0.54 mmol) and DIEA (175 mg, 1.35 mmol) in DCM (5 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 4: 1) to provide (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylbutanamido)-3-(4-fluoro-2',4',5,6'-

tetramethylbiphenyl-3-yl)propanoate as a brown oil (100 mg). Yield 33% (ESI 660.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylbutanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid



(3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylbutanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (100 mg, 0.15 mmol) was treated with LiOH-H_2O (32 mg, 0.75 mmol) in MeOH (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **F-P1** (30.0 mg) and **F-P2** (32.0 mg) as white solids.

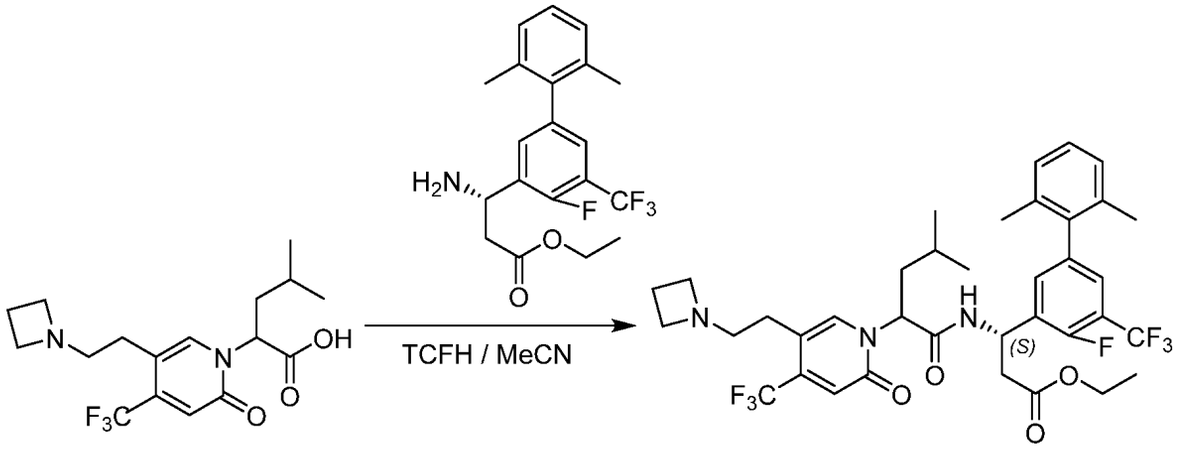
F-P1 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.95 (s, 1H), 6.89 (s, 1H), 6.84 – 6.76 (m, 3H), 6.67 (s, 1H), 5.65 – 5.54 (m, 1H), 5.26 (d, J = 11.3 Hz, 1H), 3.06 – 2.85 (m, 4H), 2.80 – 2.63 (m, 8H), 2.53 – 2.38 (m, 1H), 2.34 – 2.23 (m, 6H), 1.95 (s, 3H), 1.63 (s, 3H), 1.17 (d, J = 6.5 Hz, 3H), 0.80 (d, J = 6.5 Hz, 3H).

F-P2 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.11 – 7.95 (m, 1H), 7.02 – 6.83 (m, 5H), 5.76 (s, 1H), 5.24 (d, J = 10.9 Hz, 1H), 3.27 – 2.90 (m, 4H), 2.81 (d, J = 3.7 Hz, 6H), 2.66 – 2.36 (m, 3H), 2.31 (d, J = 5.7 Hz, 6H), 1.95 (t, J = 5.8 Hz, 6H), 0.95 (s, 3H), 0.82 – 0.66 (m, 3H).

3-4. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds G-P1 and G-P2)

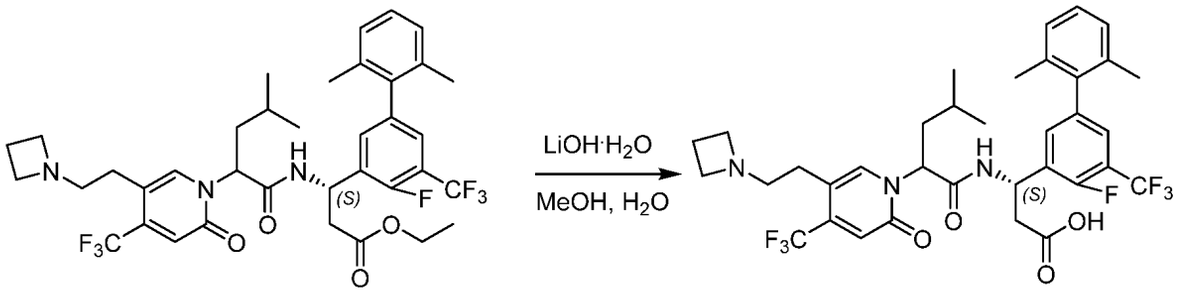
Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-

(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150 mg, 0.42 mmol), (*S*)-ethyl 3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (161 mg, 0.42 mmol), TCFH (235 mg, 0.84 mmol), and NMI (138 mg, 1.68 mmol) in acetonitrile (4 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as colorless oil (155 mg). Yield 51% (ESI 726.1 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (155 mg, 0.21 mmol) was treated with LiOH monohydrate (35 mg, 0.84 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The mixture was concentrated in vacuo and the residue was purified by

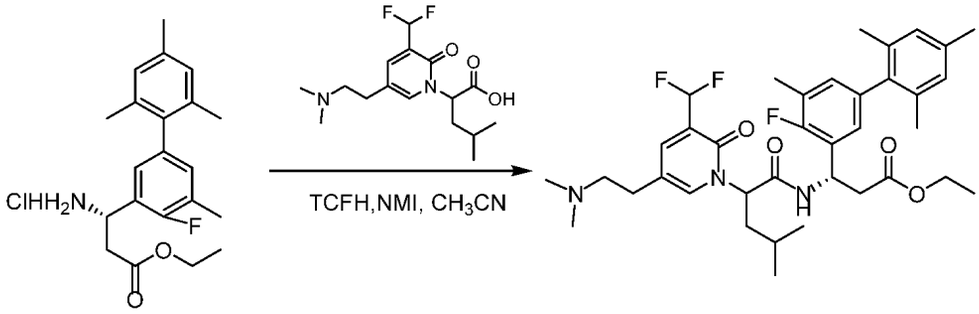
prep-HPLC A (30-65% MeCN) to give the diastereomeric products **G-P1** (37.8 mg) and **G-P2** (49.6 mg) as white solids.

G-P1 ESI 698.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.41 (d, *J* = 5.0 Hz, 1H), 7.36 – 7.27 (m, 1H), 7.21 – 7.09 (m, 3H), 6.74 (s, 1H), 5.71 – 5.54 (m, 2H), 4.04 (t, *J* = 8.1 Hz, 4H), 3.29 (t, *J* = 6.7 Hz, 2H), 2.86-2.82 (m, 2H), 2.78 – 2.68 (m, 2H), 2.50 – 2.36 (m, 2H), 2.08 – 1.93 (m, 5H), 1.86 (s, 3H), 1.44 – 1.41 (m, 1H), 1.13 – 0.79 (m, 6H).

G-P2 ESI 698.2 (M+H)+. ^1H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.50 – 7.44 (m, 1H), 7.41 – 7.33 (m, 1H), 7.22 – 7.18 (m, 1H), 7.14 (d, *J* = 7.4 Hz, 2H), 6.90 (s, 1H), 5.813 – 5.80 (m, 1H), 5.64 (t, *J* = 7.7 Hz, 1H), 4.13 (t, *J* = 8.0 Hz, 4H), 3.55 – 3.34 (m, 2H), 2.99 – 2.88 (m, 1H), 2.85 – 2.81 (m, 1H), 2.71 – 2.66 (m, 1H), 2.60 – 2.54 (m, 1H), 2.53 – 2.43 (m, 2H), 2.07 – 1.93 (m, 7H), 1.76 – 1.61 (m, 1H), 1.42 – 1.37 (m, 1H), 0.95 – 0.83 (m, 6H).

3-5. Preparation of ((3*S*)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds H-P1 and H-P2)

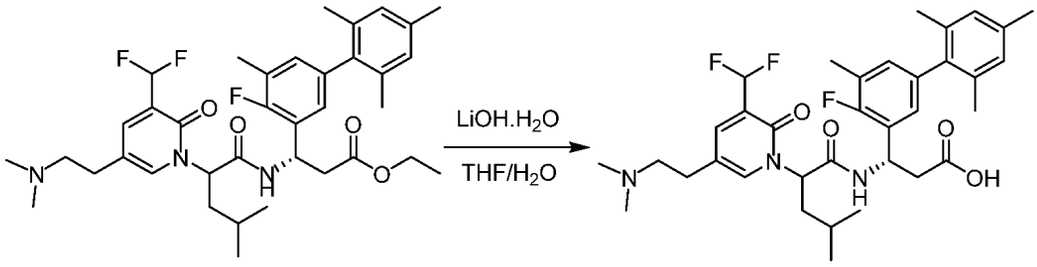
Step 1: ethyl (3*S*)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (120 mg, 0.35 mmol), 2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (138 mg, 0.42 mmol), TCFH (147 mg, 0.52 mmol) and NMI (86 mg, 1.05 mmol) in acetonitrile (5 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM:MeOH 4:1) to provide ethyl (3*S*)-3-(2-(3-

(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a brown solid (150 mg). Yield 65.2% (ESI 656.2 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid



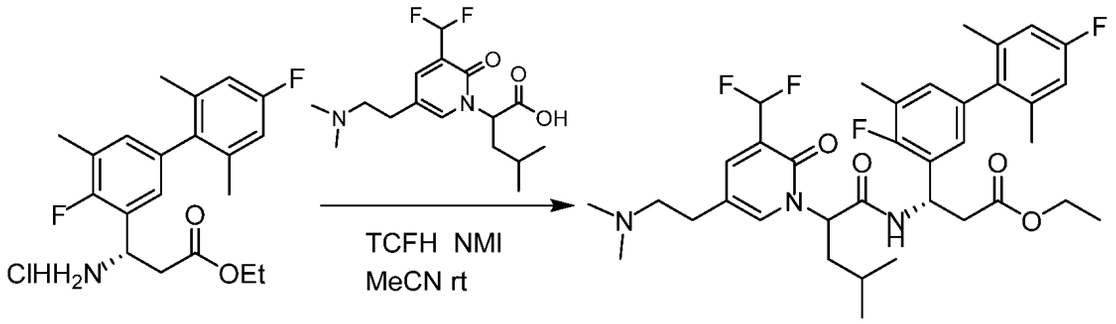
Ethyl (3*S*)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.23 mmol) was treated with LiOH-H_2O (95.5mg, 2.3 mmol) in THF (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-70% MeCN) to give the diastereomeric products **H-P1** (24.0 mg) and **H-P2** (33.0 mg) as white solids.

H-P1 ESI 628.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.71 (s, 2H), 6.78 (s, 2H), 6.76 – 6.62 (m, 2H), 6.42 (t, J = 55.1 Hz, 1H), 5.49 – 5.45 (m, 1H), 5.30 (t, J = 5.7 Hz, 1H), 3.20 – 3.10 (m, 1H), 3.09 – 3.02 (m, 1H), 2.83 – 2.70 (m, 2H), 2.61 (s, 6H), 2.58 – 2.50 (m, 1H), 2.48 – 2.39 (m, 1H), 2.22 – 2.10 (m, 6H), 1.94 – 1.84 (m, 2H), 1.83 (s, 3H), 1.73 (s, 3H), 1.36 – 1.29 (m, 1H), 0.89 – 0.78 (m, 6H).

H-P2 ESI 628.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.70 (s, 2H), 6.79 – 6.71 (m, 4H), 6.49 (t, J = 55.1 Hz, 1H), 5.50 – 5.45 (m, 2H), 3.30 – 3.23 (m, 1H), 3.18 – 3.13 (m, 1H), 2.85 – 2.74 (m, 2H), 2.70 (s, 6H), 2.54 – 2.43 (m, 1H), 2.39 – 2.29 (m, 1H), 2.18 (s, 6H), 1.93 – 1.85 (m, 1H), 1.83 (d, J = 5.9 Hz, 6H), 1.76 – 1.62 (m, 1H), 1.33 – 1.30 (m, 1H), 0.80 – 0.77 (m, 6H).

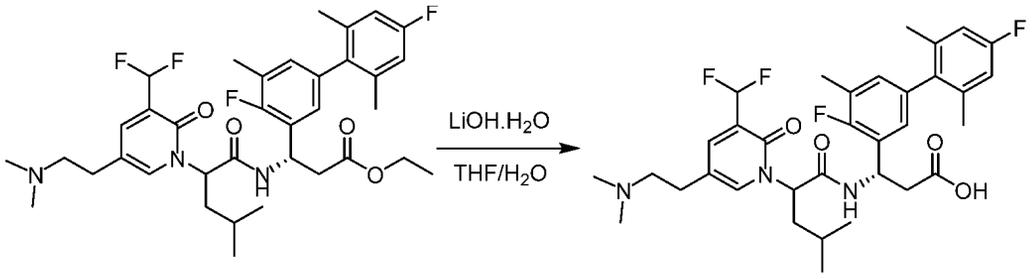
3-6. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds I-P1 and I-P2)

Step 1: ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid (120 mg, 0.39 mmol), ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (120 mg, 0.36 mmol), TCFH (120 mg, 0.54 mmol), and NMI (75 mg, 1.08 mmol) in acetonitrile (5 mL) was stirred at room temperature for 20 hours. The reaction mixture was concentrated in vacuo and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as brown solid (150 mg). Yield 63.2% (ESI 660.3 $(M+H)^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



Ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-(difluoromethyl)-5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (150 mg, 0.23 mmol) was treated with LiOH monohydrate (100 mg, 2.3 mmol) in EtOH (6 mL) and H_2O (0.8 mL) at 36°C for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-

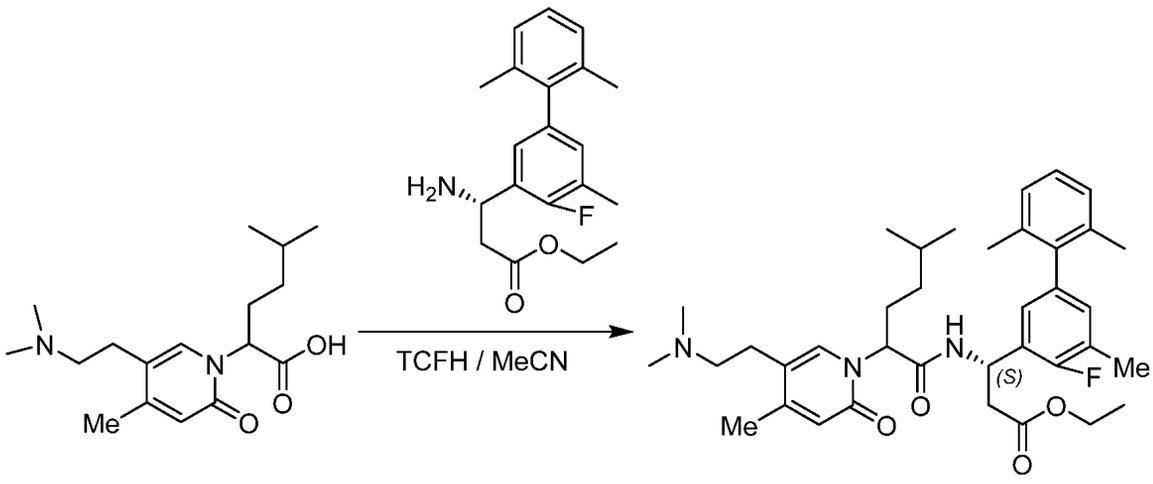
60% MeCN) to provide the diastereomeric products **I-P1** (20 mg) and **I-P2** (22 mg) as white solids.

I-P1 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 2H), 6.74 – 6.67 (m, 4H), 6.46 (t, *J* = 55.2 Hz, 1H), 5.48 – 5.44 (m, 1H), 5.33 – 5.30 (m, 1H), 3.20 – 3.16 (m, 1H), 3.12 – 3.04 (m, 1H), 2.84 – 2.73 (m, 2H), 2.65 (s, 6H), 2.59 – 2.42 (m, 2H), 2.17 (s, 3H), 1.95 – 1.83 (m, 5H), 1.78 (s, 3H), 1.39 – 1.29 (m, 1H), 0.85 – 0.75 (m, 6H).

I-P2 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.81 (s, 1H), 6.90 – 6.78 (m, 4H), 6.65 (t, *J* = 55.2 Hz, 1H), 5.63 – 5.57 (m, 2H), 3.48 – 3.38 (m, 1H), 3.32 – 3.23 (m, 1H), 3.02 – 2.87 (m, 2H), 2.83 (s, 6H), 2.67 – 2.54 (m, 1H), 2.50 – 2.41 (m, 1H), 2.32 (d, *J* = 1.6 Hz, 3H), 2.07 – 2.01 (m, 1H), 2.00 (d, *J* = 6.2 Hz, 6H), 1.88 – 1.76 (m, 1H), 1.50 – 1.39 (m, 1H), 0.96 – 0.86 (m, 6H).

3-7. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (compounds J-P1 and J-P2)

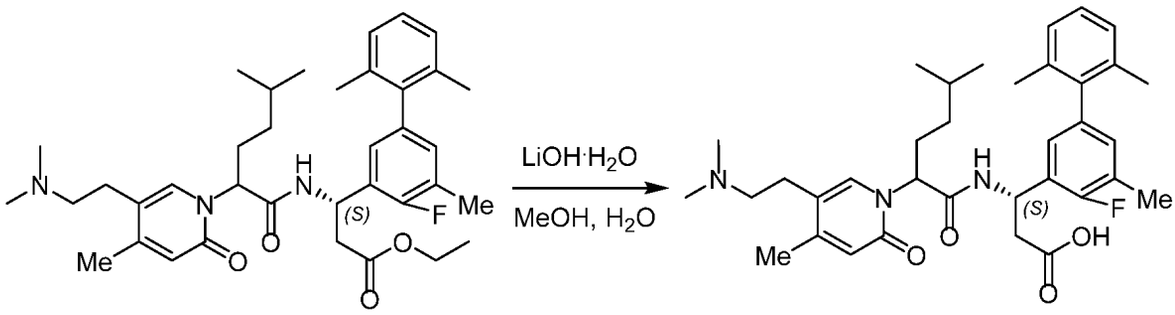
Step 1: (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanoic acid (150 mg, 0.49 mmol), (*S*)-ethyl 3-amino-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (161 mg, 0.49 mmol), TCFH (274 mg, 0.98 mmol), and NMI (201 mg, 2.45 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (3*S*)-ethyl 3-

(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate as colorless oil (170 mg). Yield 56% (ESI 620.2 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid



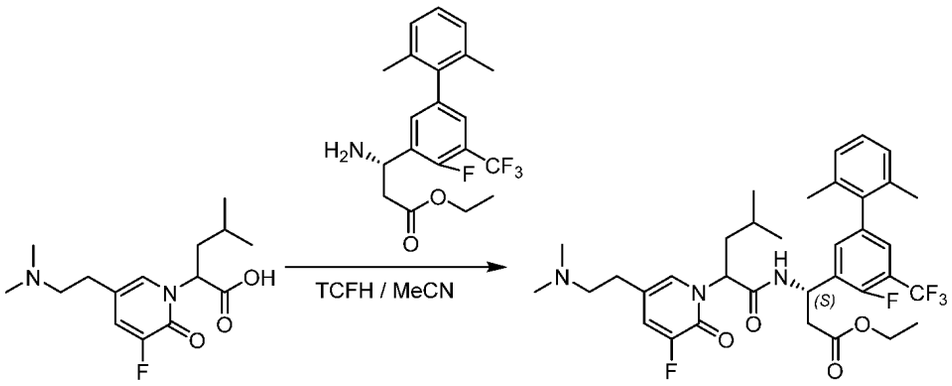
(3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (170 mg, 0.27 mmol) was treated with LiOH monohydrate (57 mg, 1.35 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction mixture was concentrated *in vacuo* and purified by prep-HPLC A (30-60% MeCN) to provide the diastereomeric products **J-P1** (50 mg) and **J-P2** (60.4 mg) as white solids.

J-P1 ESI 592.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.57 (s, 1H), 7.17 – 7.10 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.87 – 6.82 (m, 2H), 6.33 (s, 1H), 5.49 (t, *J* = 5.7 Hz, 1H), 5.39 (s, 1H), 3.26 – 3.05 (m, 2H), 2.88 (d, *J* = 7.9 Hz, 2H), 2.82 – 2.69 (m, 6H), 2.69 – 2.58 (m, 2H), 2.26 (t, *J* = 15.5 Hz, 6H), 2.22 – 2.10 (m, 1H), 1.97 (d, *J* = 16.6 Hz, 4H), 1.91 (s, 3H), 1.60 – 1.53 (m, 1H), 1.29 – 1.14 (m, 1H), 1.09 – 1.04 (m, 1H), 0.89-0.87 (m, 6H).

J-P2 ESI 592.3 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.55 (s, 1H), 7.15 – 7.07 (m, 3H), 6.91 (d, *J* = 6.9 Hz, 2H), 6.43 (s, 1H), 5.67 – 5.64 (m, 1H), 5.42 (t, *J* = 7.7 Hz, 1H), 3.31 – 3.25 (m, 1H), 3.25 – 3.14 (m, 1H), 2.99 – 2.88 (m, 2H), 2.86 (d, *J* = 17.8 Hz, 6H), 2.65 – 2.60 (m, 1H), 2.51 – 2.45 (m, 1H), 2.38 – 2.19 (m, 6H), 2.19 – 2.06 (m, 1H), 2.00 (s, 6H), 1.86 – 1.77 (m, 1H), 1.57 – 1.50 (m, 1H), 1.17 – 1.09 (m, 1H), 1.07 – 1.01 (m, 1H), 0.84 (t, *J* = 6.4 Hz, 6H).

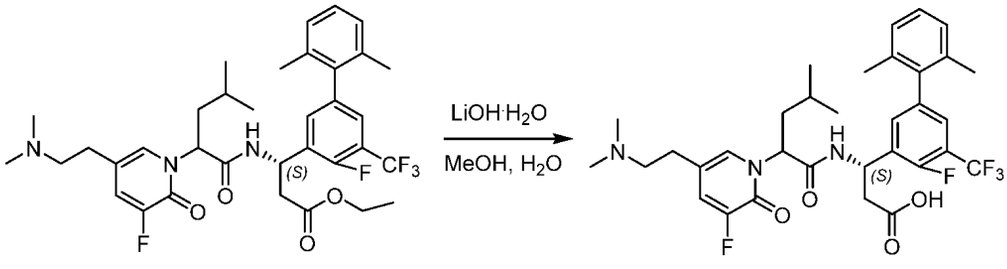
3-8. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds K-P1 and K-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (130 mg, 0.44 mmol), (*S*)-ethyl 3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (169 mg, 0.44 mmol), TCFH (246 mg, 0.88 mmol), and NMI (144 mg, 1.76 mmol) in acetonitrile (4 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated in vacuo and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as yellow oil (150 mg). Yield 51% (ESI 664.2 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



(3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (150 mg, 0.23 mmol) was treated with LiOH monohydrate (39 mg, 0.92 mmol) in MeOH (4 mL) and H_2O (1 mL) at 36°C for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction mixture was concentrated in vacuo and purified by prep-HPLC A (30-

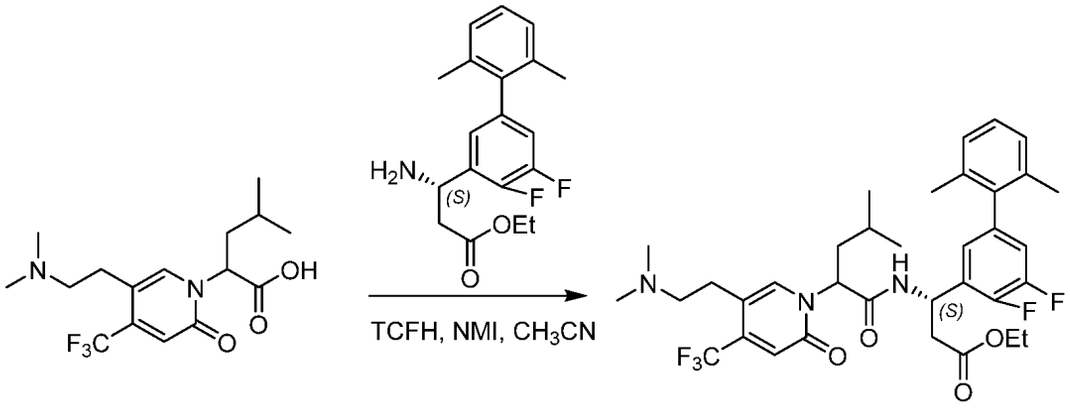
60% MeCN) to give the diastereomeric products **K-P1** (41 mg) and **K-P2** (46.8 mg) as white solids.

K-P1 ESI 636.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.53 (s, 1H), 7.47 – 7.44 (m, 1H), 7.33 – 7.28 (m, 2H), 7.23 – 7.17 (m, 1H), 7.16 – 7.08 (m, 2H), 5.65 – 5.61 (m, 1H), 5.46 (t, *J* = 5.7 Hz, 1H), 3.38 (d, *J* = 7.8 Hz, 1H), 3.24 – 3.17 (m, 1H), 2.95 – 2.84 (m, 2H), 2.82 – 2.64 (m, 7H), 2.60 – 2.54 (m, 1H), 2.08 – 1.97 (m, 5H), 1.94 (s, 3H), 1.43 (s, 1H), 0.96 – 0.91(m, 6H).

K-P2 ESI 636.2 (M+H)+. ^1H NMR (400 MHz, MeOD) δ 7.38 (s, 1H), 7.33 – 7.28 (m, 2H), 7.24 (d, *J* = 6.3 Hz, 1H), 7.12 – 6.99 (m, 3H), 5.55 – 5.49 (m, 2H), 3.36 – 3.25 (m, 1H), 3.18 – 3.12 (m, 1H), 2.91 – 2.79 (m, 1H), 2.73 (d, *J* = 11.7 Hz, 7H), 2.52 – 2.48 (m, 1H), 2.39 – 2.32 (m, 1H), 2.00 – 1.79 (m, 7H), 1.75 – 1.68 (m, 1H), 1.29 – 1.24 (m, 1H), 0.81 – 0.78 (m, 6H).

3-9. Preparation of (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds L-P1 and L-P2)

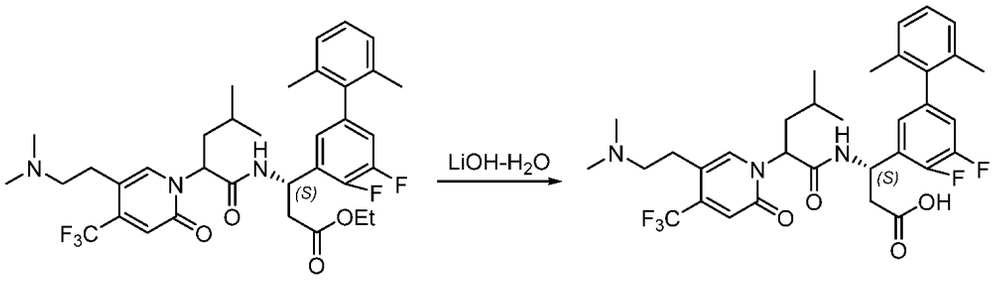
Step 1: ethyl (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100 mg, 0.29 mmol), ethyl (*S*)-3-amino-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (96 mg, 0.29 mmol), TCFH (100 mg, 0.34 mmol) and NMI (96.0 mg, 1.14 mmol) in CH_3CN (3 mL) was stirred at room temperature for 1.5 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 /

40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow solid (131 mg). Yield 68.1% (ESI 664.2 $[M+H]^+$).

Step 2: (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



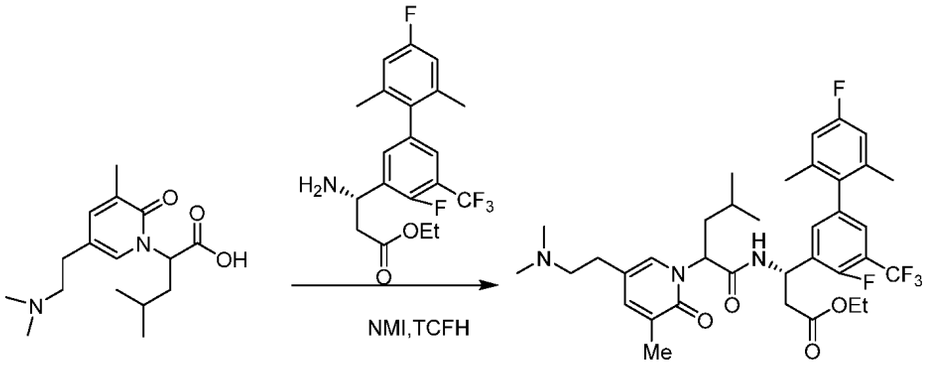
Ethyl (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (131.0 mg, 0.19 mmol) was treated with LiOH-H_2O (100.0 mg, 2.38 mmol) in THF (2 mL) and water (0.5 mL) at 30°C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric product **L-P1** (11.1 mg) and **L-P2** (19.0 mg) as white solids.

L-P1 ESI 636.1 $(M+H)^+$ ^1H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 7.05 – 6.92 (m, 3H), 6.83 – 6.76 (m, 2H), 6.63 (s, 1H), 5.58 – 5.45 (m, 2H), 3.03 – 2.96 (m, 2H), 2.84– 2.81 (m, 2H), 2.65 (s, 6H), 2.62 – 2.60 (m, 2H), 1.92 – 1.79 (m, 5H), 1.72 (s, 3H), 1.33 – 1.30 (m, 1H), 0.86 – 0.81 (m, 6H).

L-P2 ESI 636.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.07 – 6.97 (m, 3H), 6.90 – 6.80 (m, 3H), 6.77 (s, 1H), 5.63 – 5.59 (m, 1H), 5.49 (t, J = 7.6 Hz, 1H), 3.22 – 3.08(m, 2H), 2.88 (t, J = 6.9 Hz, 2H), 2.72 (s, 6H), 2.58 – 2.38 (m, 2H), 1.92 – 1.83 (m, 7H), 1.64 – 1.56 (m, 1H), 1.33 – 1.24 (m, 1H), 0.77 (d, J = 6.5 Hz, 6H).

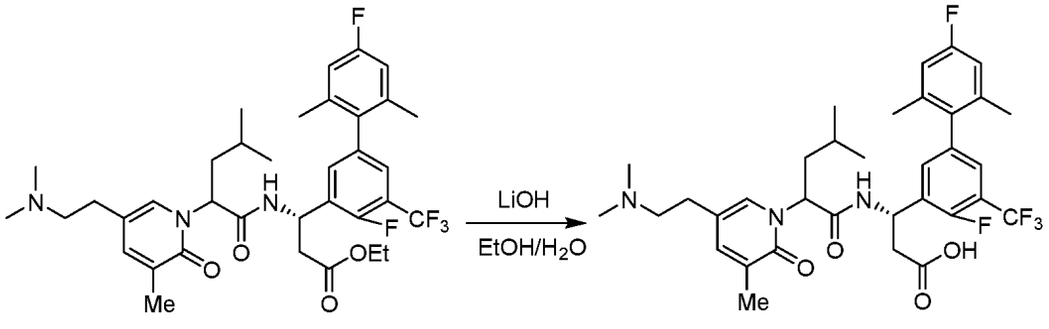
3-10. Preparation of (3*S*)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds M-P1 and M-P2)

Step 1: ethyl (3*S*)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (160 mg, 0.54 mmol), ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (260 mg, 0.64 mmol), TCFH (226 mg, 0.81 mmol), NMI (221.4 mg, 2.7 mmol) and CH_3CN (5 mL) was stirred at room temperature for 1 hour. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a colorless oil (180 mg). Yield 50% (ESI 678.3 $(M+H)^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



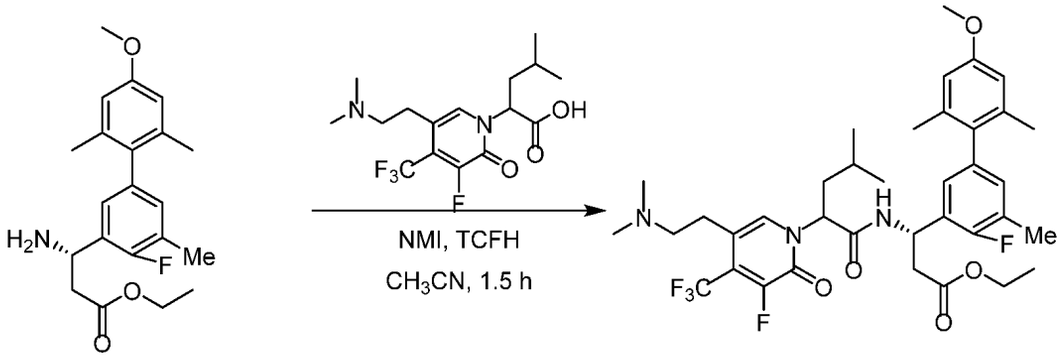
Ethyl (3*S*)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (180 mg, 0.26 mmol) was treated with LiOH-H_2O (39 mg, 0.92 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **M-P1** (50 mg) and **M-P2** (53.0 mg) as white solids.

M-P1 ESI 650.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.39 (s, 1H), 7.33 – 7.18 (m, 2H), 6.88 (d, J = 9.6 Hz, 2H), 5.56 – 5.47 (m, 2H), 3.28 – 3.17 (m, 2H), 2.84 – 2.69 (m, 9H), 2.63 – 2.57 (m, 1H), 2.06 – 1.92 (m, 8H), 1.86 (s, 3H), 1.48 – 1.38 (m, 1H), 0.95 – 0.90 (m, 6H).

M-P2 ESI 650.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.56 (s, 1H), 7.43 (s, 1H), 7.38 – 7.22 (m, 2H), 6.92 – 6.87 (m, 2H), 5.65 – 5.54 (m, 2H), 3.46 – 3.39 (m, 1H), 3.29 – 3.24 (m, 1H), 2.97 – 2.75 (m, 8H), 2.67 – 2.61 (m, 1H), 2.51 – 2.45 (m, 1H), 2.05 – 1.90 (m, 11H), 1.45 – 1.38 (m, 1H), 0.94 – 0.88 (m, 6H).

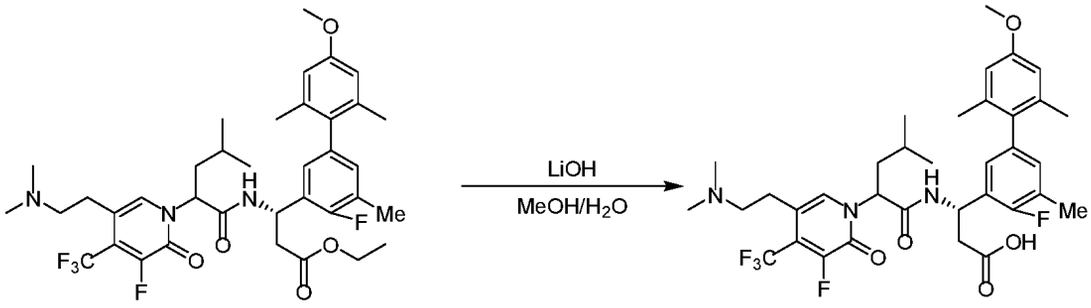
3-11. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds P-P1 and P-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (220 mg, 0.60 mmol), 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100 mg, 0.55 mmol), TCFH (230 mg, 0.82 mmol), and NMI (177 mg, 2.18 mmol) in acetonitrile (10 mL) was stirred at room temperature for 20 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (214 mg) as a white solid. Yield 56% (ESI 708.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (214 mg, 0.30 mmol) was treated with LiOH-H_2O (52 mg, 1.24 mmol) in MeOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **P-P1** (39.8 mg) and **P-P2** (48.6 mg) as white solids.

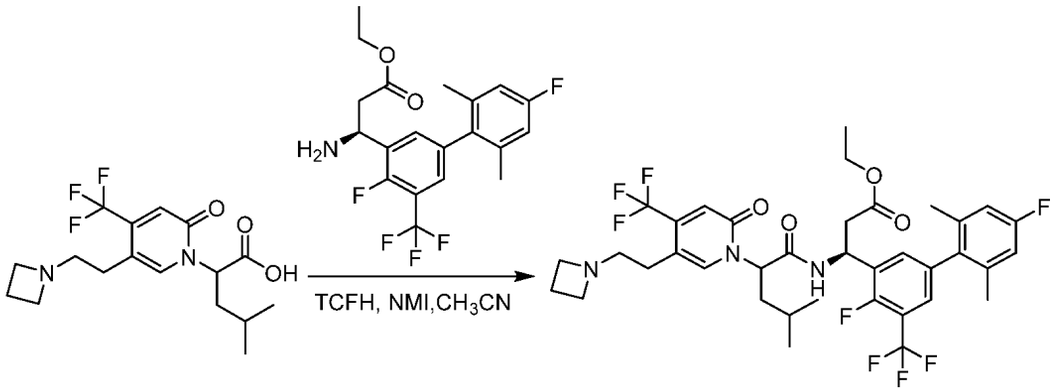
P-P1 ESI 680.4$(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.69 (s, 1H), 6.88 – 6.85(m, 2H), 6.64 (d, *J* = 10.6 Hz, 2H), 5.73 – 5.65 (m, 1H), 5.55 (t, *J* = 6.8 Hz, 1H), 4.92 (s, 3H), 3.79 (s, 3H), 3.17 – 2.92 (m, 4H), 2.82 – 2.69 (m, 7H), 2.29 (s, 3H), 2.10 – 1.94 (m, 5H), 1.83 (s, 1H), 1.51 – 1.41(m, 1H), 0.97 – 0.93 (m, 6H).

P-P2 ESI 680.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.60 (s, 1H), 6.91 (t, *J* = 7.1 Hz, 2H), 6.67 (s, 2H), 5.73 – 5.70 (m, 1H), 5.61 (t, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.23 – 3.18 (m,

2H), 3.18 – 2.95 (m, 2H), 2.83 (s, 6H), 2.65 – 2.61 (m, 1H), 2.52 – 2.47 (m, 1H), 2.32 (s, 3H), 2.11 – 1.95 (m, 7H), 1.72 – 1.66 (m, 1H), 1.45 – 1.41 (m, 1H), 0.94 – 0.85 (m, 6H).

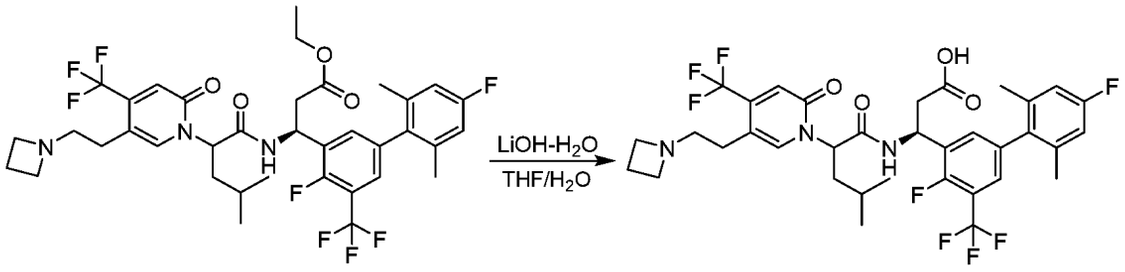
3-12. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds R-P1 and R-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100 mg, 0.28 mmol), ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (112 mg, 0.28 mmol), NMI (69 mg, 0.84 mmol) and TCFH (95 mg, 0.34 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue was purified by silica gel column (MeOH/DCM 7%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (180 mg). Yield 87% (ESI 744.1 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (180 mg, 0.24 mmol) was treated with LiOH-H_2O (50 mg, 1.20 mmol) in THF (3 mL), MeOH (2 mL) and H_2O (1 mL) at room temperature for 16 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **R-P1** (65.0 mg) and **R-P2** (35.0 mg) as white solids.

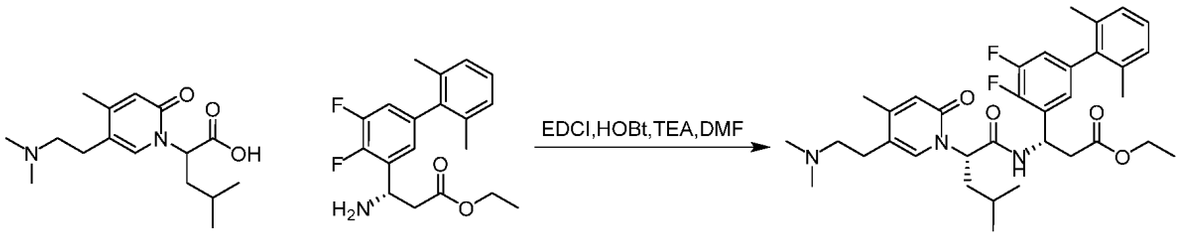
R-P1 ESI 716.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.40 – 7.32 (m, 2H), 6.90 – 6.86 (m, 2H), 6.75 (s, 1H), 5.64 – 5.60 (m, 2H), 4.07 (t, *J* = 8.1 Hz, 4H), 3.36 – 3.33 (m, 1H), 3.31 – 3.27 (m, 1H), 2.91 – 2.69 (m, 4H), 2.49 – 2.44 (m, 2H), 2.06 – 1.97 (m, 5H), 1.89 (s, 3H), 1.48 – 1.36 (m, 1H), 0.99 – 0.91 (m, 6H).

R-P2 ESI 716.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.45 – 7.38 (m, 2H), 6.92 (s, 1H), 6.90 (s, 2H), 5.82 – 5.78 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.15 (t, *J* = 7.9 Hz, 4H), 3.45 – 3.35 (m, 2H), 2.99 – 2.80 (m, 2H), 2.69 – 2.42 (m, 4H), 2.03 – 1.92 (m, 7H), 1.76 – 1.63 (m, 1H), 1.44 – 1.37 (m, 1H), 0.92 – 0.89 (m, 6H).

3-13. Preparation of (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds S-P1 and S-P2)

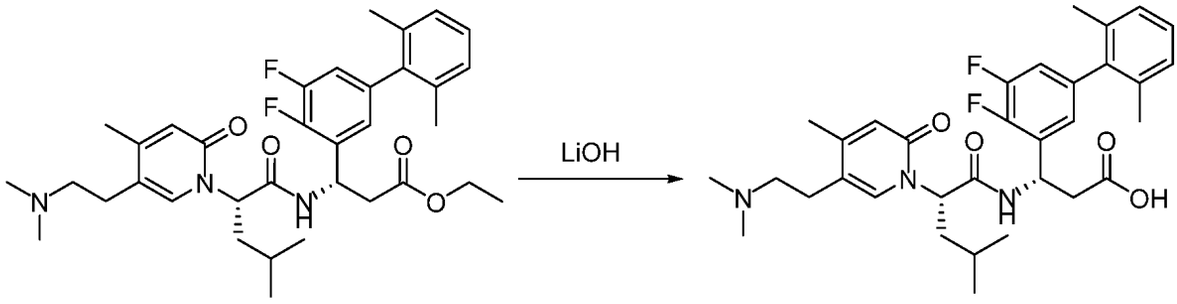
Step 1: ethyl (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-

methylpentanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid (80 mg, 0.27 mmol), ethyl (S)-3-amino-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (100 mg, 0.30 mmol), EDCI (77 mg, 0.41 mmol), TEA (0.2 mL) and HOBt (36mg, 0.27 mmol) in acetonitrile (10 mL) was stirred at room temperature for 20 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoate as yellow oil (75 mg). Yield 45% (ESI 610.3 $(M+H)^+$).

Step 2: (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



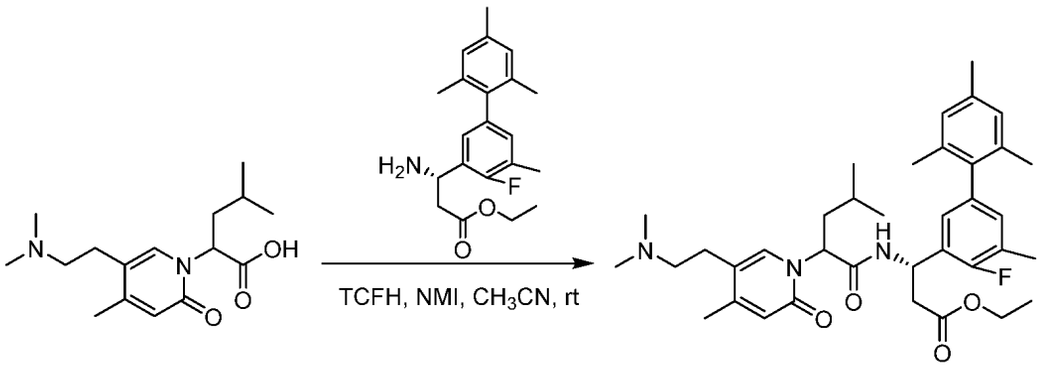
Ethyl (S)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoate (75 mg, 0.12 mmol) was treated with LiOH monohydrate (26 mg, 0.62 mmol) in MeOH (2 mL) and H_2O (1 mL) at room temperature for 2 h. The reaction mixture was acidified to pH 4~5 with 1N HCl. The mixture was concentrated in vacuo and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **S-P1** (28 mg) and **S-P2** (38 mg) as white solids.

S-P1 ESI 582.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.58 (s, 1H), 7.19 – 7.14 (m, 1H), 7.10 (d, *J* = 8.6 Hz, 2H), 6.96 – 6.90 (m, 1H), 6.83 (d, *J* = 5.8 Hz, 1H), 6.33 (s, 1H), 5.57 (s, 1H), 5.52 – 5.47 (m, 1H), 3.33 – 3.13 (m, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.79 (s, 6H), 2.72 – 2.60 (m, 2H), 2.26 (s, 3H), 2.03 – 1.90 (m, 8H), 1.40 (d, *J* = 7.3 Hz, 1H), 0.95 – 0.91 (m, 6H).

S-P2 ESI 582.2 $(M+H)^+$.^1H NMR (500 MHz, MeOD) δ 7.54 (s, 1H), 7.19 – 7.15 (m, 1H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.01 – 6.95 (m, 1H), 6.90 (d, *J* = 5.9 Hz, 1H), 6.42 (s, 1H), 5.67 – 5.64 (m, 1H), 5.61 – 5.55 (m, 1H), 3.24 – 3.18 (m, 1H), 2.97 – 2.84 (m, 8H), 2.63 (dd, *J* = 15.2, 4.2 Hz, 1H), 2.49 (dd, *J* = 15.2, 9.9 Hz, 1H), 2.27 (s, 3H), 2.02 (s, 6H), 1.99 – 1.93 (m, 1H), 1.81 – 1.73 (m, 1H), 1.41- 1.37 (m, 1H), 0.90 – 0.88 (m, 6H).

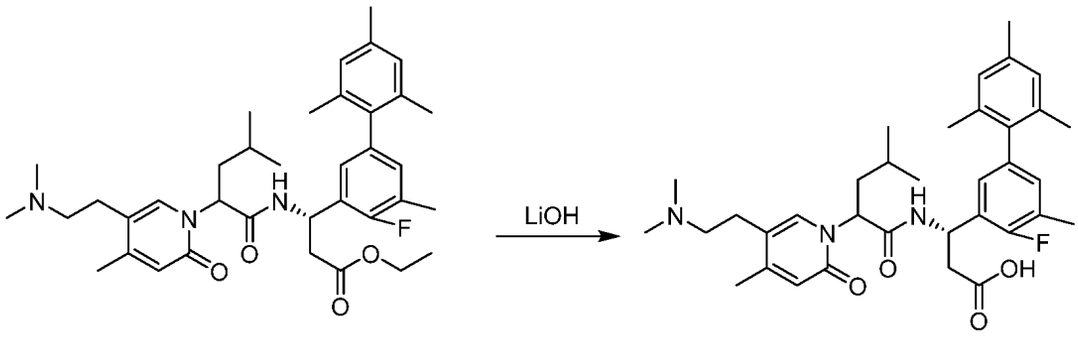
3-14. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds T-P1 and T-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (100.0 mg, 0.34 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (117.0 mg, 0.34 mmol), TCFH (190.4 mg, 0.68 mmol), NMI (115.5 mg, 1.36 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a white oil (95.0 mg). Yield 45% (ESI 620.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid



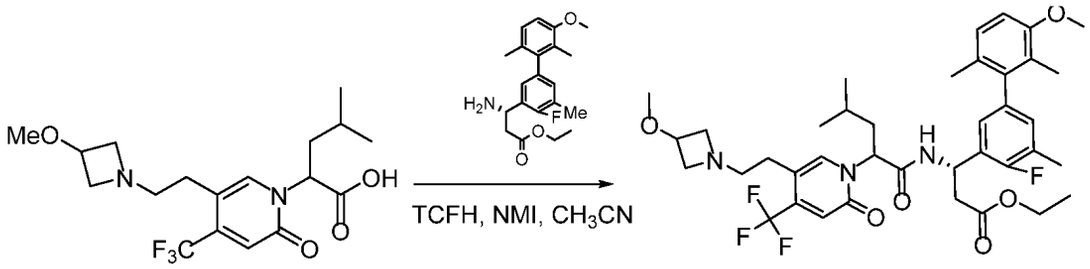
Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (95.0 mg, 0.15 mmol) was treated with LiOH-H_2O (25.2 mg, 0.60 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **T-P1** (26.2 mg) and **T-P2** (58.3 mg) as white solids.

T-P1 ESI 592.3$(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 6.89 (d, J = 3.6 Hz, 2H), 6.85 – 6.72 (m, 2H), 6.32 (s, 1H), 5.69 – 5.56 (m, 1H), 5.53 – 5.41 (m, 1H), 3.04 – 2.84 (m, 2H), 2.79 (t, J = 7.3 Hz, 2H), 2.71 – 2.51 (m, 8H), 2.36 – 2.17 (m, 9H), 2.06 – 1.88 (m, 5H), 1.83 (s, 3H), 1.51 – 1.30 (m, 1H), 1.02 – 0.82 (m, 6H).

T-P2 ESI 592.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.56 (s, 1H), 6.98 – 6.82 (m, 4H), 6.44 (s, 1H), 5.69 – 5.50 (m, 2H), 3.20 (d, J = 38.2 Hz, 2H), 2.85 (d, J = 33.5 Hz, 8H), 2.70 – 2.40 (m, 2H), 2.38 – 2.19 (m, 9H), 2.04 – 1.87 (m, 7H), 1.85 – 1.70 (m, 1H), 1.47 – 1.26 (m, 1H), 0.99 – 0.78 (m, 6H).

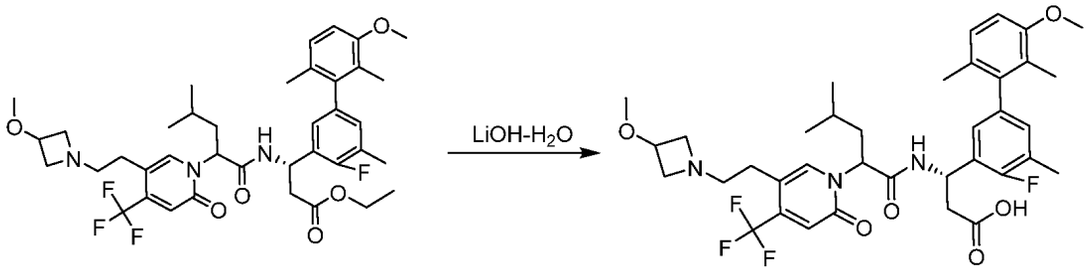
3-15. Preparation of (3*S*)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds N-P1 and N-P2)

Step 1: ethyl (3*S*)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (272 mg, 0.70 mmol, 1.25 *eq*), ethyl (*S*)-3-amino-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.56 mmol, 1.00 *eq*), NMI (0.5 mL) and TCFH (232 mg, 0.83 mmol, 1.50 *eq*) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to provide ethyl (3*S*)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (201 mg). Yield 49% (ESI 732.2 $[M+H]^+$).

Step 2: (3*S*)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



Ethyl (3*S*)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (201 mg, 0.27 mmol, 1.00 *eq*) was treated with LiOH-H_2O (44 mg, 1.08 mmol, 4.00 *eq*) in MeOH (10 mL) and H_2O (5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **N-P1** (31 mg) and **N-P2** (41 mg) as white solids.

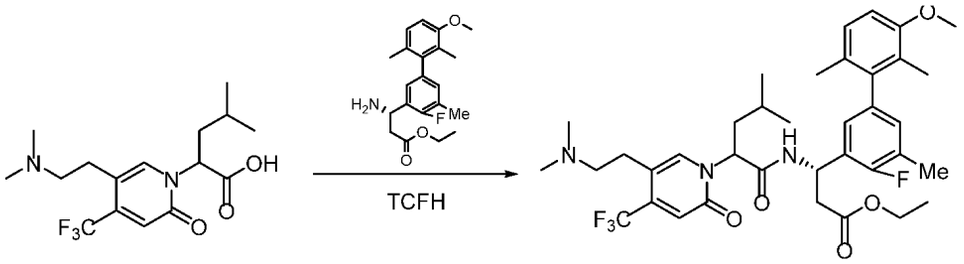
N-P1 ESI 704.4$(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.03 – 6.79 (m, 5H), 5.69 – 5.58 (m, 2H), 4.21 – 4.18 (m, 3H), 3.83 (s, 3H), 3.76 – 3.70 (m, 2H), 3.31 (s, 3H), 3.24

– 3.20 (m, 2H), 2.84 – 2.72 (m, 4H), 2.29(s, 3H), 1.98 (t, *J* = 7.6 Hz, 2H), 1.92 – 1.68 (m, 6H), 1.48 – 1.41 (m, 1H), 0.98 – 0.93 (m, 6H).

N-P2 ESI 704.4 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 7.01 – 6.80 (m, 4H), 5.74 – 5.62 (m, 2H), 4.24 (s, 3H), 3.84 (s, 3H), 3.75 – 3.66 (m, 2H), 3.31 (s, 3H), 3.30 – 3.15 (m, 2H), 2.85 – 2.63 (m, 4H), 2.33 (s, 3H), 2.09 – 1.89 (m, 4H), 1.86 (d, *J* = 3.1 Hz, 3H), 1.74 – 1.67 (m, 1H), 1.42 – 1.39 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 6H).

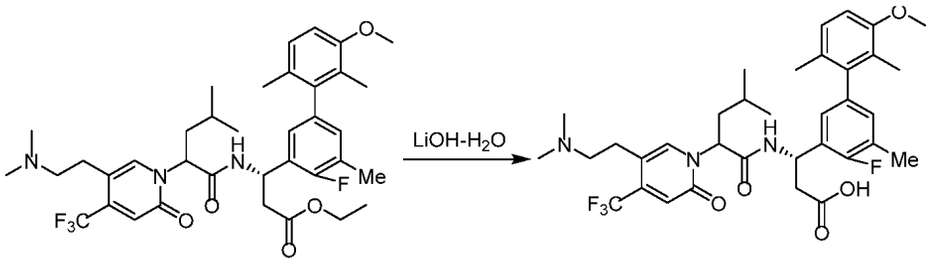
3-16. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds U-P1 and U-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (232 mg, 0.67 mmol, 1.20 *eq*), ethyl (*S*)-3-amino-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.56 mmol, 1.00 *eq*), NMI (0.5 mL) and TCFH (233 mg, 0.83 mmol, 1.50 *eq*) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH3CN) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (250 mg). Yield 65% (ESI 690.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



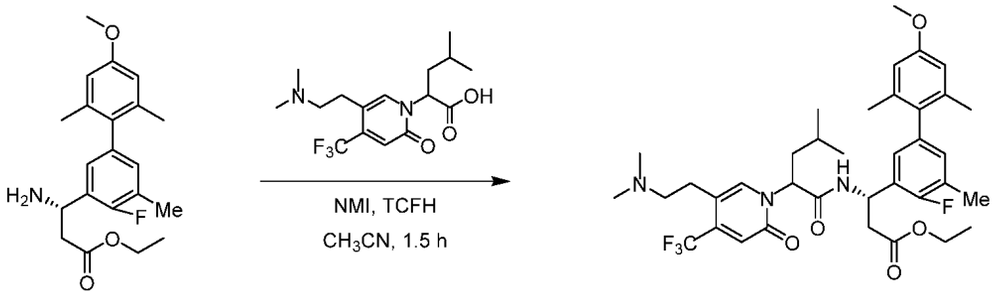
Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (250 mg, 0.32mmol, 1.00 *eq*) was treated with LiOH-H_2O (19 mg, 0.81 mmol, 2.50 *eq*) in MeOH (5 mL) and H_2O (0.5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **U-P1** (40.0 mg) and **U-P2** (55.0 mg) as white solids.

U-P1 ESI 662.3$(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.90(s, 1H), 7.04 – 6.99 (m, 1H), 6.86 – 6.76 (m, 4H), 5.70 – 5.66 (m, 1H), 5.58 – 5.55 (m, 1H), 3.83 (s, 3H), 3.15 – 3.03 (m, 2H), 2.97 – 2.93 (m, 2H), 2.74– 2.69 (m, 8H), 2.29 (s, 3H), 2.00 – 1.96 (m, 2H), 1.92 – 1.67 (m, 6H), 1.48 – 1.41 (m, 1H), 0.97 – 0.93 (m, 6H).

U-P2 ESI 662.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.84(s, 1H), 7.05 (d, J = 8.5 Hz, 1H), 7.03 – 6.79 (m, 4H), 5.73 – 5.69 (m, 1H), 5.61 (t, J = 7.7 Hz, 1H), 3.84 (s, 3H), 3.33 – 3.22 (m, 2H), 3.01– 2.98 (m, 2H), 2.82 (s, 6H), 2.67– 2.62 (m, 1H), 2.55– 2.49 (m, 1H), 2.32 (s, 3H), 2.24 – 1.88 (m, 4H), 1.86 (d, J = 3.1 Hz, 3H), 1.81 – 1.60 (m, 1H), 1.45 – 1.37 (m, 1H), 0.90 – 0.88 (m, 6H).

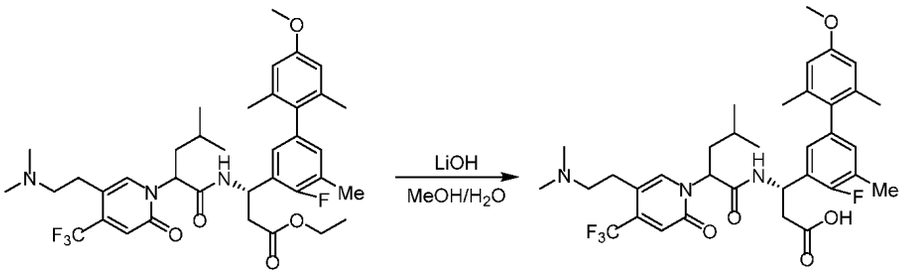
3-17. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds V-P1 and V-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acidd (170 mg, 0.49 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (176 mg, 0.49 mmol), NMI (160 mg, 1.96 mmol) and TCFH (205.8 mg, 0.74 mmol) in CH_3CN (10 mL) was stirred at room temperature for 1.5 hours. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 9:1) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (131 mg). Yield 39% (ESI 690.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



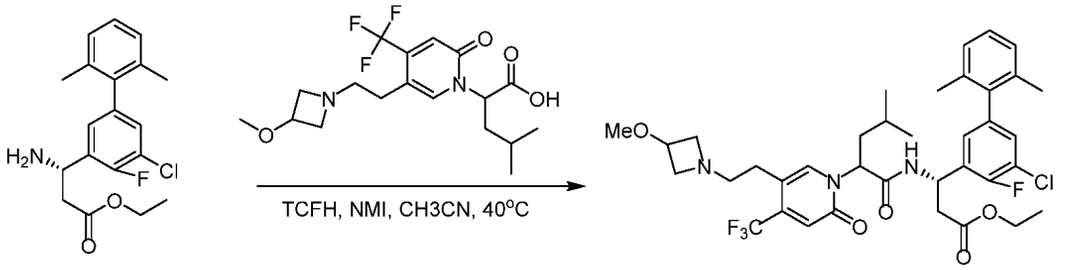
Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (131 mg, 0.19 mmol) was treated with LiOH-H_2O (32 mg, 0.76 mmol) in MeOH (10 mL) and H_2O (5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **V-P1** (24 mg) and **V-P2** (15 mg) as white solids.

V-P1 ESI 662.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.90 (s, 1H), 6.85 (t, *J* = 7.6 Hz, 2H), 6.76 (s, 1H), 6.63 (d, *J* = 18.7 Hz, 2H), 5.68 (t, *J* = 7.9 Hz, 1H), 5.57 – 5.54 (m, 1H), 3.80 (s, 3H), 3.12 – 3.02 (m, 2H), 2.98 – 2.90 (m, 2H), 2.90 – 2.46 (m, 8H), 2.28 (s, 3H), 2.06 – 1.94 (m, 5H), 1.80 (s, 3H), 1.48 – 1.41 (m, 1H), 0.97 – 0.93 (m, 6H).

V-P2 ESI 662.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.87 (s, 1H), 6.92 – 6.90 (m, 3H), 6.67 (s, 2H), 5.73-5.70 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.80 (s, 3H), 3.30 – 3.20 (m, 2H), 3.01 – 2.97 (m, 2H), 2.83 (s, 6H), 2.70 – 2.59 (m, 1H), 2.55 – 2.50 (m,1H), 2.32 (s, 3H), 1.98 (d, *J* = 4.0 Hz, 7H), 1.73 – 1.68 (m, 1H), 1.43 – 1.36 (m, 1H), 0.90 – 0.88 (m, 6H).

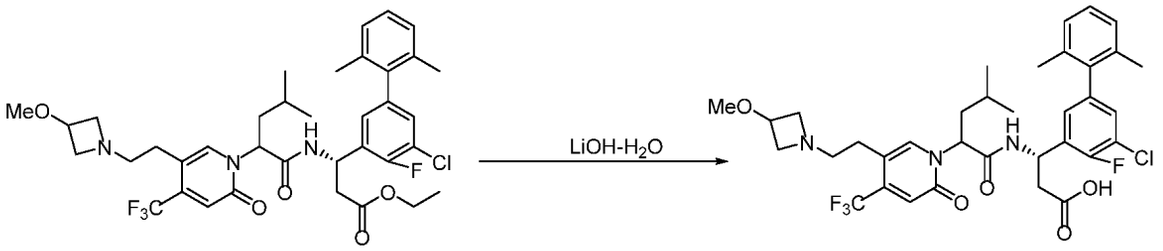
3-18. Preparation of (3*S*)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds W-P1 and W-P2)

Step 1: ethyl (3*S*)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (167 mg, 0.43 mmol), ethyl (*S*)-3-amino-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.43 mmol), TCFH (182 mg, 0.65 mmol) and NMI (176 mg, 2.15 mmol) in CH_3CN (4 mL) was stirred at 40°C for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (150 mg). Yield 48% (ESI 722.2 $(M+H)^+$).

Step 2: (3*S*)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



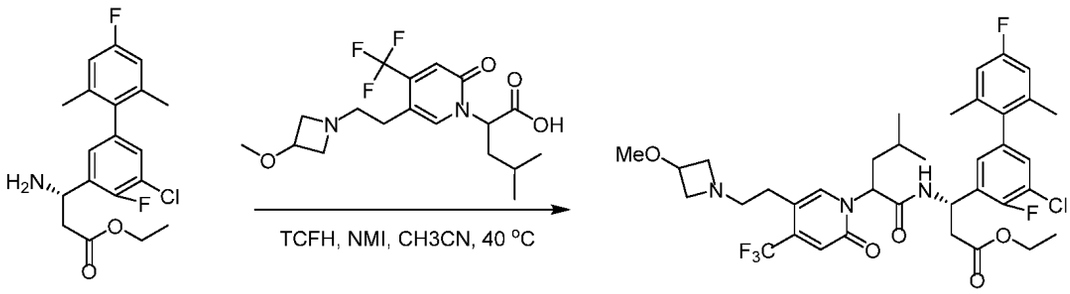
Ethyl (3S)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (150 mg, 0.21 mmol) was treated with LiOH-H_2O (42 mg, 1 mmol) in MeOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **W-P1** (46 mg) and **W-P2** (57 mg) as white solids.

W-P1 ESI 694.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.21 – 7.00 (m, 5H), 6.74 (s, 1H), 5.72 – 5.50 (m, 2H), 4.27 – 4.08 (m, 3H), 3.80 – 3.61 (m, 2H), 3.31 (s, 3H), 3.26 – 3.09 (m, 2H), 2.86 – 2.70 (m, 4H), 2.09 – 1.93 (m, 5H), 1.84 (s, 3H), 1.50 – 1.37 (m, 1H), 1.04 – 0.83 (m, 6H).

W-P2 ESI 694.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.26 – 7.06 (m, 5H), 6.90 (s, 1H), 5.79 – 5.70 (m, 1H), 5.63 (t, J = 7.7 Hz, 1H), 4.44 – 4.22 (m, 3H), 3.98 – 3.76 (m, 2H), 3.41 – 3.34 (m, 5H), 2.99 – 2.74 (m, 2H), 2.70 – 2.49 (m, 2H), 2.08 – 1.89 (m, 7H), 1.77 – 1.62 (m, 1H), 1.48 – 1.32 (m, 1H), 0.90 (d, J = 6.4 Hz, 6H).

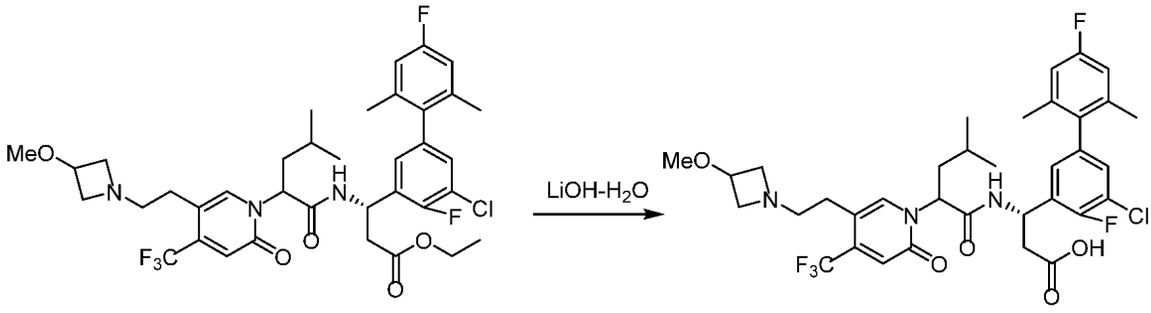
3-19. Preparation of (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds X-P1 and X-P2)

Step 1: (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate ethyl



A mixture of 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (160 mg, 0.41 mmol), ethyl (*S*)-3-amino-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.41 mmol), TCFH (174 mg, 0.62 mmol) and NMI (168 mg, 2.05 mmol) in CH_3CN (4 mL) was stirred at 40 °C for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoateas a yellow oil (150 mg). Yield 49% (ESI 740.2 $(M+H)^+$).

Step 2: (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



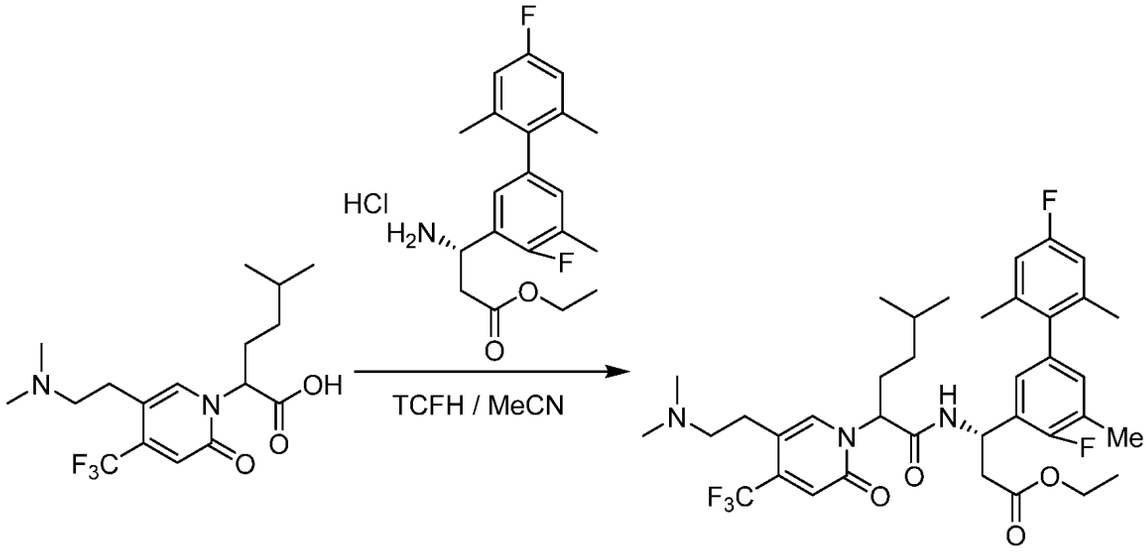
Ethyl (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (150 mg, 0.20 mmol) was treated with LiOH-H_2O (42 mg, 1 mmol) in MeOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **X-P1** (35 mg) and **X-P2** (49 mg) as white solids.

X-P1 ESI 712.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.13 (d, *J* = 6.6 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.90 – 6.79 (m, 2H), 6.74 (s, 1H), 5.72 – 5.48 (m, 2H), 4.26 – 4.07 (m, 3H), 3.80 – 3.64 (m, 2H), 3.32 (s, 3H), 3.19 (t, *J* = 6.2 Hz, 2H), 2.86 – 2.71 (m, 4H), 2.08 – 1.95 (m, 5H), 1.86 (d, *J* = 4.4 Hz, 3H), 1.51 – 1.36 (m, 1H), 1.01 – 0.88 (m, 6H).

X-P2 ESI 712.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.25 – 7.16 (m, 1H), 7.15 – 7.05 (m, 1H), 6.93 – 6.83 (m, 3H), 5.81 – 5.68 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.44 – 4.23 (m, 3H), 3.95 – 3.78 (m, 2H), 3.40 – 3.34 (m, 5H), 3.00 – 2.75 (m, 2H), 2.70 – 2.47 (m, 2H), 2.08 – 1.93 (m, 7H), 1.76 – 1.64 (m, 1H), 1.47 – 1.33 (m, 1H), 0.96 – 0.84 (m, 6H).

3-20. Preparation of (3S)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanamido)propanoic acid (compounds Y-P1 and Y-P2)

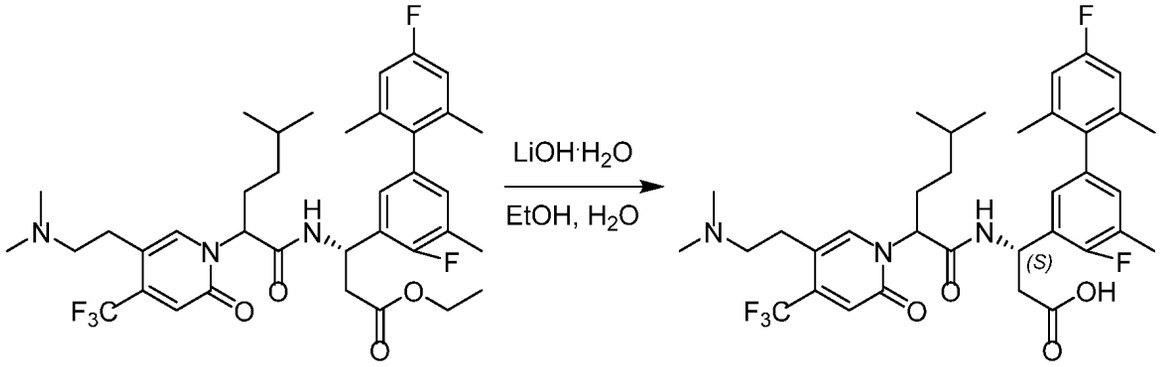
Step 1: (3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanoic acid (273 mg, 0.75 mmol), (*S*)-ethyl 3-amino-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate hydrochloride (164 mg, 0.39 mmol), TCFH (211 mg, 0.75 mmol), and NMI (0.45 mL, 5.70 mmol) in acetonitrile (9 mL) was stirred at room temperature for 16 hours. The reaction mixture was concentrated *in vacuo* and purified by

reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~80%) to provide (3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)propanoate as a brown solid (262 mg). Yield 97% (ESI 692.3 $(M+H)^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2 (dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)propanoic acid



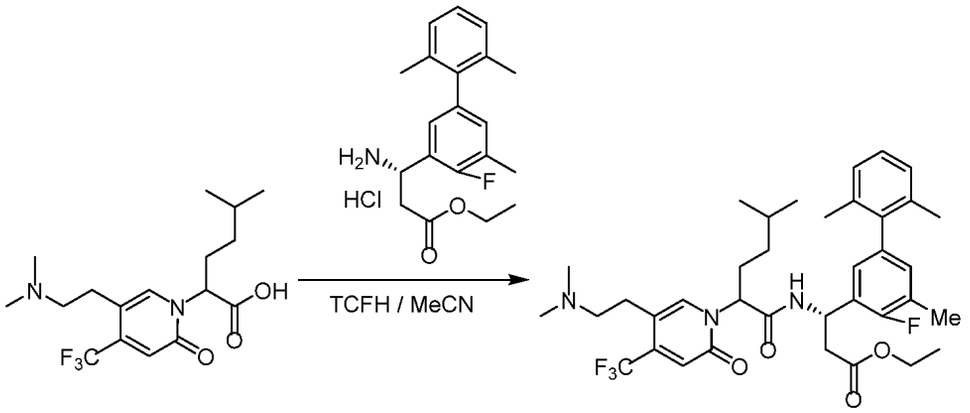
(3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)propanoate (262 mg, 0.38 mmol) was treated with LiOH monohydrate (80 mg, 1.90 mmol) in EtOH (6 mL) and H_2O (0.10 mL) at 36°C for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction mixture was concentrated *in vacuo* and purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **Y-P1** (68 mg) and **Y-P2** (66 mg) as white solids.

Y-P1 ESI 664.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 6.87 – 6.85 (m, 1H), 6.83 – 6.78 (m, 2H), 6.76 – 6.73 (m, 1H), 6.70 (s, 1H), 5.56 – 5.52 (m, 1H), 5.50 – 5.46 (m, 1H), 3.10 – 3.03 (m, 2H), 2.95 – 2.91 (m, 2H), 2.75 – 2.66 (m, 8H), 2.26 (d, J = 1.2 Hz, 3H), 2.22 – 2.14 (m, 1H), 2.00 – 1.92 (m, 4H), 1.78 (s, 3H), 1.60 – 1.53 (m, 1H), 1.29 – 1.18 (m, 1H), 1.13 – 1.04 (m, 1H), 0.88 (d, J = 2.8 Hz, 3H), 0.86 (d, J = 2.8 Hz, 3H).

Y-P2 ESI 664.2 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.92 (s, 1H), 6.95 – 6.93 (m, 1H), 6.91 – 6.88 (m, 1H), 6.87 (s, 1H), 6.82 (s, 1H), 6.80 (s, 1H), 5.72 – 5.68 (m, 1H), 5.47 (t, J = 7.6 Hz, 1H), 3.24 – 3.12 (m, 2H), 3.02 – 2.93 (m, 2H), 2.78 (t, J = 5.8 Hz, 6H), 2.67 – 2.62 (m, 1H), 2.58 – 2.52 (m, 1H), 2.30 (d, J = 1.6 Hz, 3H), 2.13 – 2.04 (m, 1H), 2.00 (s, 3H), 1.99 (s, 3H), 1.84 – 1.75 (m, 1H), 1.52 – 1.44 (m, 1H), 1.15 – 0.99 (m, 2H), 0.80 (d, J = 4.0 Hz, 3H), 0.77 (d, J = 4.5 Hz, 3H).

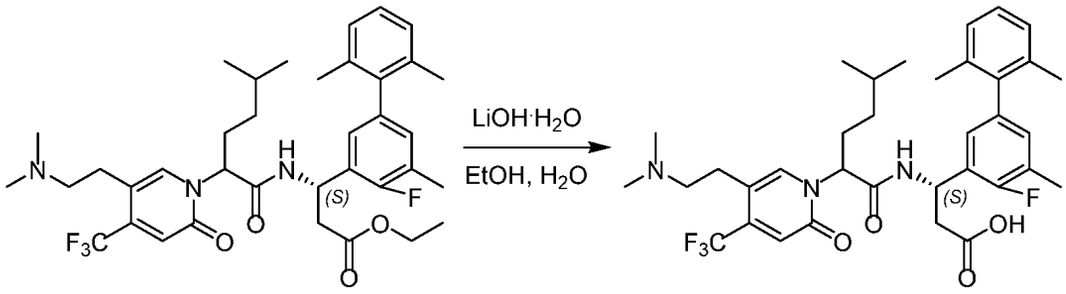
3-21. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds Z-P1 and Z-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanoic acid (283 mg, 0.78 mmol), (*S*)-ethyl 3-amino-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate hydrochloride (170 mg, 0.46 mmol), TCFH (248 mg, 0.88 mmol), and NMI (0.21 mL, 2.63 mmol) in acetonitrile (10 mL) was stirred at room temperature for 20 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate as a brown solid (223 mg). Yield 71% (ESI 674.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



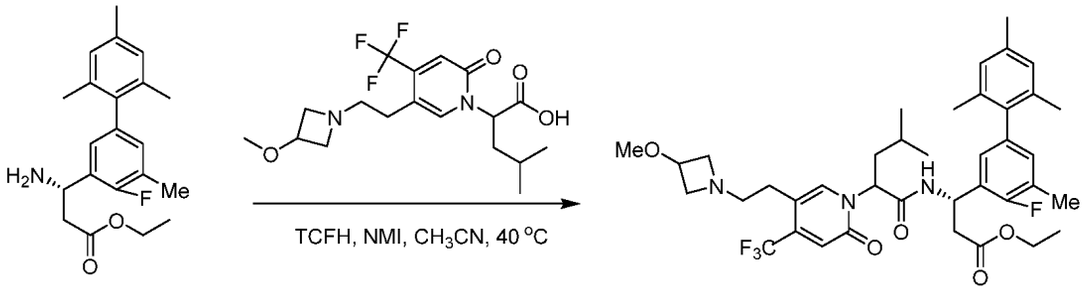
(3S)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-5-methylhexanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (223 mg, 0.33 mmol) was treated with LiOH monohydrate (35 mg, 0.82 mmol) in EtOH (6 mL) and H_2O (0.08 mL) at 36 °C for 1 h. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction mixture was concentrated *in vacuo* and purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **Z-P1** (60 mg) and **Z-P2** (59 mg) as white solids.

Z-P1 ESI 646.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 6.8 Hz, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.89 – 6.87 (m, 1H), 6.84 (d, *J* = 7.0 Hz, 1H), 6.71 (s, 1H), 5.57 – 5.54 (m, 1H), 5.51 – 5.47 (m, 1H), 3.12 – 3.02 (m, 2H), 2.93 (t, *J* = 7.9 Hz, 2H), 2.74 (s, 6H), 2.73 – 2.69 (m, 2H), 2.27 (d, *J* = 1.4 Hz, 3H), 2.24 – 2.14 (m, 1H), 2.02 – 1.90 (m, 4H), 1.79 (s, 3H), 1.61 – 1.51 (m, 1H), 1.27 – 1.18 (m, 1H), 1.13 – 1.03 (m, 1H), 0.88 (d, *J* = 2.4 Hz, 3H), 0.86 (d, *J* = 2.4 Hz, 3H).

Z-P2 ESI 646.3 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.13 – 7.05 (m, 3H), 6.94 – 6.88 (m, 3H), 5.73 – 5.69 (m, 1H), 5.45 (t, *J* = 7.6 Hz, 1H), 3.27 – 3.15 (m, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.80 (s, 6H), 2.66 – 2.61 (m, 1H), 2.55 – 2.49 (m, 1H), 2.31 (d, *J* = 1.2 Hz, 3H), 2.14 – 2.05 (m, 1H), 1.99 (d, *J* = 2.6 Hz, 6H), 1.82 – 1.73 (m, 1H), 1.56 – 1.46 (m, 1H), 1.16 – 0.99 (m, 2H), 0.81 (t, *J* = 6.5 Hz, 6H).

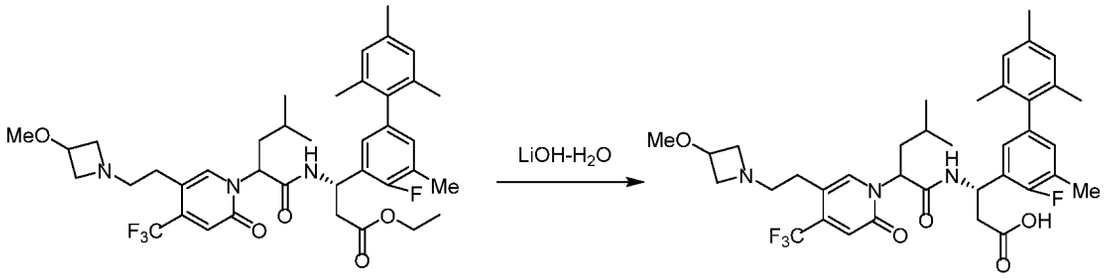
3-22. Preparation of (3*S*)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AA-P1 and AA-P2)

Step 1: ethyl (3*S*)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (168 mg, 0.43 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.43 mmol), TCFH (182 mg, 0.65 mmol) and NMI (177 mg, 2.2 mmol) in CH_3CN (4 mL) was stirred at 40 °C for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (160 mg). Yield 51% (ESI 716.2 $(M+H)^+$).

Step 2: (3*S*)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



Ethyl (3*S*)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (160 mg, 0.22 mmol) was treated with LiOH-H_2O (42 mg, 1 mmol) in MeOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **AA-P1** (46 mg) and **AA-P2** (61 mg) as white solids.

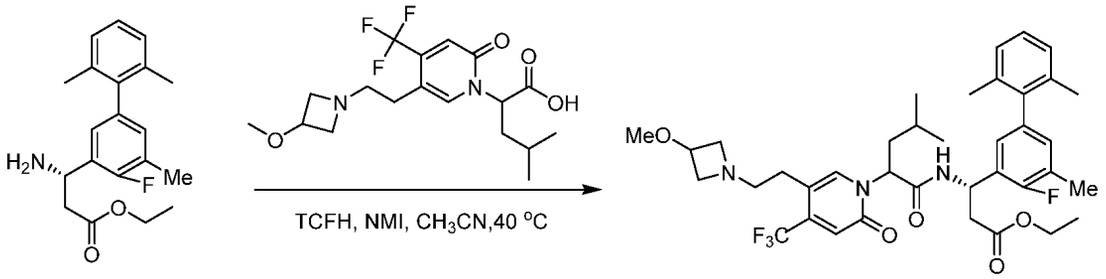
AA-P1 ESI 688.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 6.97 – 6.81 (m, 4H), 6.75 (s, 1H), 5.75 – 5.52 (m, 2H), 4.20 – 4.00 (m, 3H), 3.61 (d, *J* = 11.2 Hz, 2H), 3.30 (s,

3H), 3.14 (t, *J* = 6.9 Hz, 2H), 2.87 – 2.66 (m, 4H), 2.29 (s, 6H), 2.04 – 1.90 (m, 5H), 1.80 (s, 3H), 1.50 – 1.38 (m, 1H), 1.05 – 0.88 (m, 6H).

AA-P2 ESI 688.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 6.97 – 6.84 (m, 5H), 5.80 – 5.69 (m, 1H), 5.62 (t, *J* = 7.7 Hz, 1H), 4.46 – 4.21 (m, 3H), 3.93 – 3.76 (m, 2H), 3.40 – 3.34 (m, 5H), 3.04 – 2.76 (m, 2H), 2.70 – 2.45 (m, 2H), 2.38 – 2.21 (m, 6H), 2.07 – 1.88 (m, 7H), 1.75 – 1.61 (m, 1H), 1.49 – 1.33 (m, 1H), 1.03 – 0.83 (m, 6H).

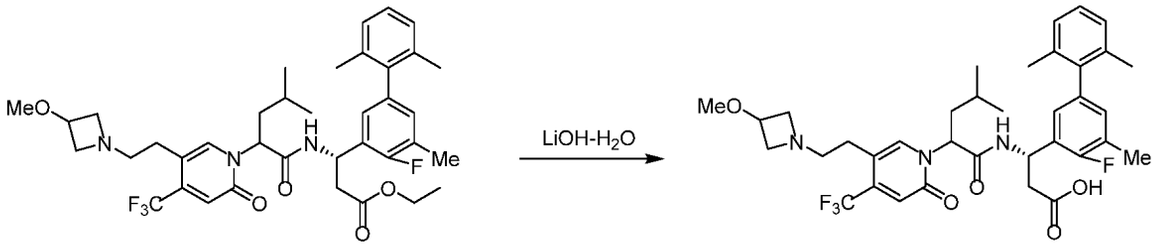
3-23. Preparation of (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AB-P1 and AB-P2)

Step 1: ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (180 mg, 0.46 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.46 mmol), TCFH (193 mg, 0.69 mmol) and NMI (188 mg, 2.3 mmol) in CH_3CN (4 mL) was stirred at 40 °C for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (140 mg). Yield 43% (ESI 702.1 $(M+H)^+$).

Step 2: (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



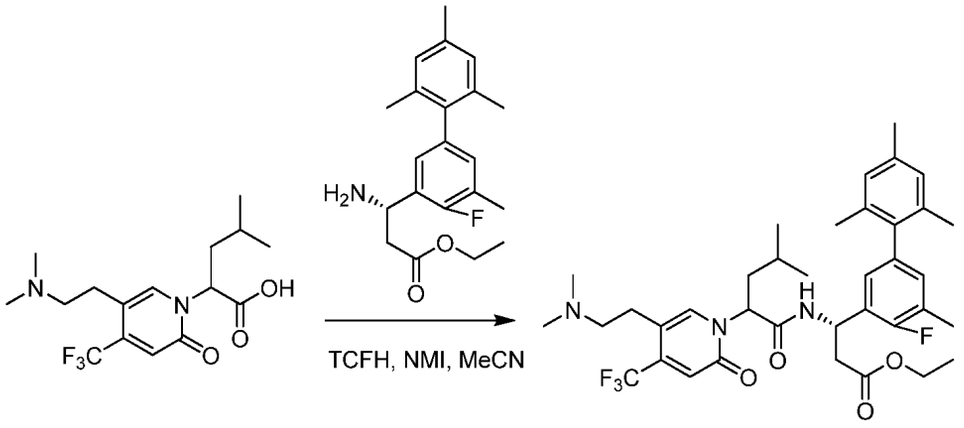
Ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (140 mg, 0.20 mmol) was treated with LiOH-H_2O (42 mg, 1 mmol) in MeOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **AB-P1** (34 mg) and **AB-P2** (46 mg) as white solids.

AB-P1 ESI 674.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.16 – 6.98 (m, 3H), 6.88 (t, J = 7.5 Hz, 2H), 6.76 (s, 1H), 5.74 – 5.53 (m, 2H), 4.24 – 4.04 (m, 3H), 3.70 – 3.53 (m, 2H), 3.30 (s, 3H), 3.14 (t, J = 7.1 Hz, 2H), 2.84 – 2.66 (m, 4H), 2.30 (s, 3H), 2.03 – 1.91 (m, 5H), 1.84 (s, 3H), 1.52 – 1.34 (m, 1H), 1.14 – 0.86 (m, 6H).

AB-P2 ESI 674.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.20 – 7.06 (m, 3H), 7.00 – 6.86 (m, 3H), 5.84 – 5.71 (m, 1H), 5.62 (t, J = 7.7 Hz, 1H), 4.46 – 4.22 (m, 3H), 3.97 – 3.75 (m, 2H), 3.42 – 3.34 (m, 5H), 3.00 – 2.76 (m, 2H), 2.69 – 2.45 (m, 2H), 2.34 (d, J = 1.7 Hz, 3H), 2.09 – 1.92 (m, 7H), 1.71 – 1.59 (m, 1H), 1.49 – 1.35 (m, 1H), 1.04 – 0.83 (m, 6H).

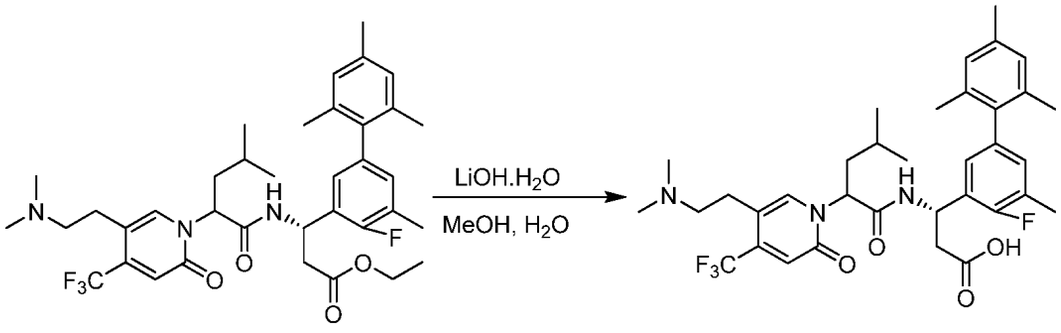
3-24. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (compounds AC-P1 and AC-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150 mg, 0.43 mmol, 1.0 *eq*), (*S*)-ethyl 3-amino-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (148 mg, 0.361 mg, 1.29 mmol, 3 *eq*), TCHF (361 mg, 1.29 mmol, 3 *eq*) and NMI (176 mg, 2.15 mmol, 5.0 *eq*) in CH_3CN (5 mL) was stirred at room temperature for 16 hours. LCMS showed that the reaction was completed. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate as a yellow solid (130 mg). Yield 45% (ESI 674.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid



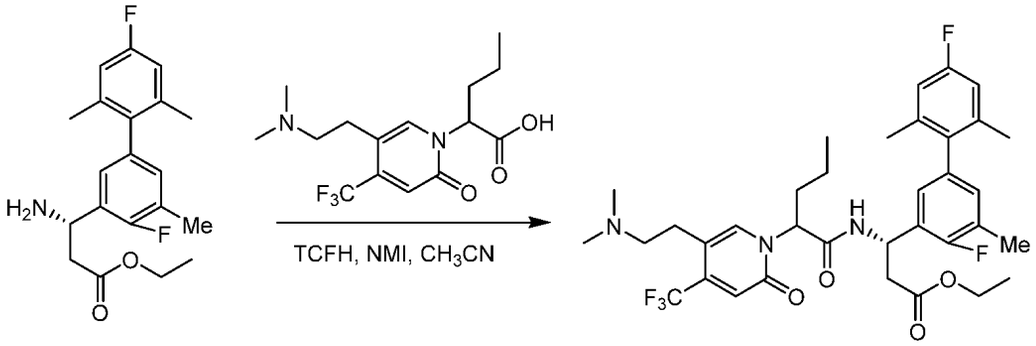
(3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (130 mg, 0.19 mmol, 1.0 *eq*) was treated with LiOH-H_2O (40 mg, 0.95 mmol, 5.0 *eq*) in MeOH (4 mL) and water (1 mL) at 28 °C for 1 hour. LCMS showed that the reaction was completed. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo*

and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AC-P1** (42 mg) and **AC-P2** (34 mg) as white solids.

AC-P1 ESI 646.3 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 6.89 (s, 1H), 6.84 (d, *J* = 8.0 Hz, 3H), 6.74 (s, 1H), 5.68 (t, *J* = 8.0 Hz, 1H), 5.57-5.54 (m, 1H), 3.12-3.06 (m, 2H), 2.95 (d, *J* = 7.4 Hz, 2H), 2.78 – 2.67 (m, 8H), 2.29 (d, *J* = 4.2 Hz, 6H), 2.02 – 1.93 (m, 5H), 1.77 (s, 3H), 1.47-1.41 (m, 1H), 0.97-0.93 (m, 6H).
AC-P2 ESI 646.3 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 6.90 (d, *J* = 5.8 Hz, 5H), 5.73-5.70 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.30 – 3.17 (m, 2H), 3.00 (t, *J* = 6.5 Hz, 2H), 2.82 (s, 6H), 2.66-2.60 (m, 1H), 2.55-2.49 (m, 1H), 2.31 (d, *J* = 7.7 Hz, 6H), 2.01-1.96 (m, 7H), 1.76 – 1.66 (m, 1H), 1.43-1.36 (m, 1H), 0.93 – 0.84 (m, 6H).

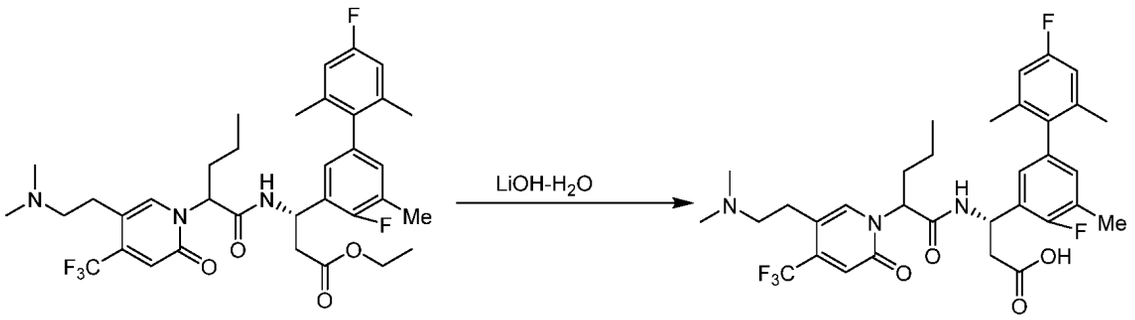
3-25. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoic acid (compounds AD-P1 and AD-P2)

Step 1: ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.43 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (174 mg, 0.52 mmol), TCFH (180 mg, 0.64 mmol) and NMI (70 mg, 0.86 mmol) in CH_3CN (5 mL) was stirred at 20 °C for 2 hours. The reaction mixture was concentrated *in vacuo* and purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate as a yellow oil (200 mg). Yield 70% (ESI 664.3 $(M+H)^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoic acid



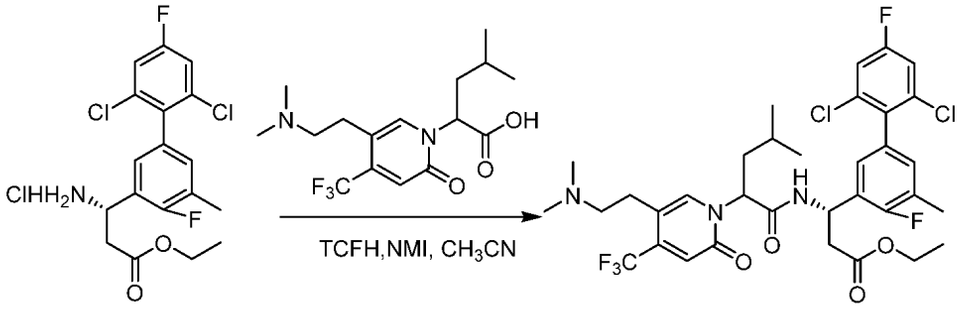
Ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate (200 mg, 0.3 mmol) was treated with LiOH-H_2O (37 mg, 0.9 mmol) in MeOH (2 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AD-P1** (57 mg) and **AD-P2** (51 mg) as white solids.

AD-P1 ESI 636.2$(M+H)^+$. ^{1}H NMR (500 MHz, MeOD) δ 7.90 (s, 1H), 6.89 – 6.77 (m, 4H), 6.74 (s, 1H), 5.58 – 5.55 (m, 2H), 3.16 – 3.13 (m, 2H), 2.98 – 2.95 (m, 2H), 2.81 (s, 6H), 2.75 – 2.72 (m, 2H), 2.29 (s, 3H), 2.18 – 2.12 (m, 1H), 2.01 – 2.00 (m, 4H), 1.82 (m, 3H), 1.36 – 1.31 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

AD-P2 ESI 636.2$(M+H)^+$. ^{1}H NMR (500 MHz, MeOD) δ 7.84 (s, 1H), 6.93 – 6.89 (m, 3H), 6.84 (d, J = 9.6 Hz, 2H), 5.72 – 5.69 (m, 1H), 5.52 (t, J = 7.6 Hz, 1H), 3.28 – 3.22 (m, 2H), 3.02 – 2.99 (m, 2H), 2.83 (s, 6H), 2.65 – 2.61 (m, 1H), 2.55 – 2.50 (m, 1H), 2.32 (t, J = 6.4 Hz, 3H), 2.10 – 2.05 (m, 1H), 2.01 (s, 6H), 1.84 – 1.79 (m, 1H), 1.25 – 1.23 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H).

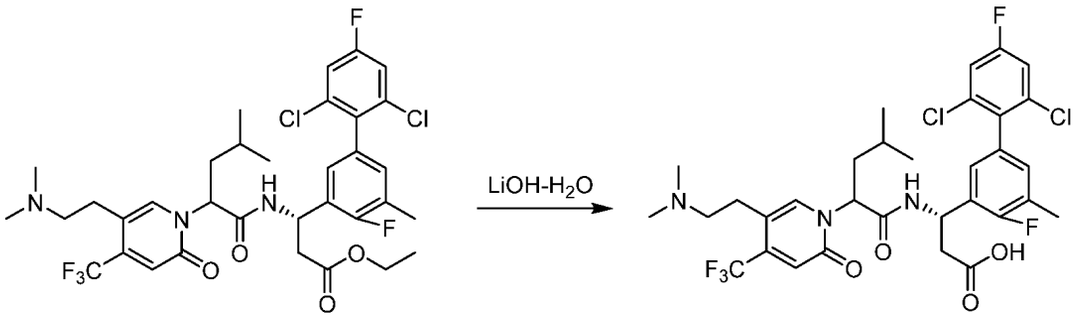
3-26. Preparation of (3*S*)-3-(2',6'-dichloro-4,4'-difluoro-5-methyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AE-P1 and AE-P2)

Step 1: ethyl (3*S*)-3-(2',6'-dichloro-4,4'-difluoro-5-methyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2',6'-dichloro-4,4'-difluoro-5-methyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (450 mg, 1.06 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (370 mg, 1.06 mmol), TCFH (356 mg, 1.27 mmol) and NMI (261 mg, 3.18 mmol) in CH_3CN (10 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM:MeOH 4: 1) to provide ethyl (3*S*)-3-(2',6'-dichloro-4,4'-difluoro-5-methyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a brown solid (610 mg). Yield 80% (ESI 718.0 $(M+H)^+$).

Step 2: (3*S*)-3-(2',6'-dichloro-4,4'-difluoro-5-methyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



Ethyl (3*S*)-3-(2',6'-dichloro-4,4'-difluoro-5-methyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (110 mg, 0.15 mmol) was treated with LiOH-H_2O (32 mg, 0.75 mmol) in THF (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction

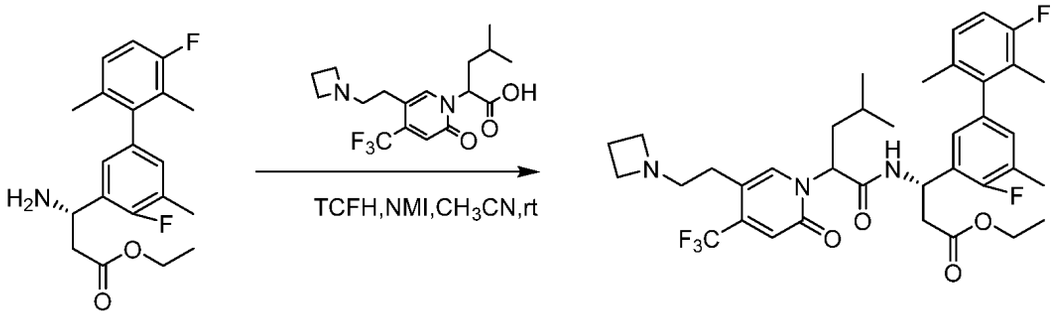
mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to provide the diastereomeric products **AE-P1** (29.0 mg) and **AE-P2** (31.0 mg) as white solids.

AE-P1 ESI 690.0 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.38 – 7.5 (m, 1H), 7.29 -7.25 (m, 1H), 6.99 (t, *J* = 7.5 Hz, 2H), 6.77 (s, 1H), 5.71 (t, *J* = 8.0 Hz, 1H), 5.60 – 5.56 (m, 1H), 3.05 – 2.91 (m, 4H), 2.80 – 2.60 (m, 8H), 2.29 (t, *J* = 0.8 Hz, 3H), 1.99 (t, *J* = 7.5 Hz, 2H), 1.49 – 1.42 (m, 1H), 0.98 – 0.93 (m, 6H).

AE-P2 ESI 690.0 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.37 (t, *J* = 9.0 Hz, 2H), 7.09 – 7.03 (m, 2H), 6.92 (s, 1H), 5.76 – 5.72 (m, 1H), 5.65 (t, *J* = 7.7 Hz, 1H), 3.29 – 3.10 (m, 2H), 3.00 (t, *J* = 6.6 Hz, 2H), 2.80 (s, 6H), 2.66 – 2.61 (m, 1H), 2.56 – 2.50 (m, 1H), 2.34 (d, *J* = 1.4 Hz, 3H), 2.01 – 1.94 (m, 1H), 1.77 – 1.61 (m, 1H), 1.43 – 1.37 (m, 1H), 0.90 – 0.87 (m, 6H).

3-27. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AF-P1 and AF-P2)

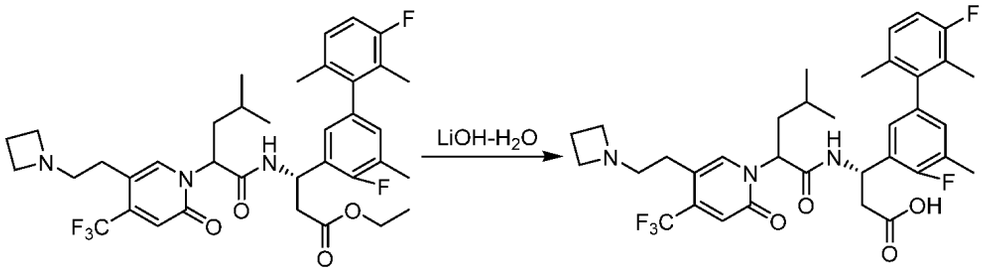
Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (120.0 mg, 0.34 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (122.4 mg, 0.34 mmol), TCFH (190.4 mg, 0.68 mmol), NMI (115.5 mg, 1.36 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified

by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white oil (90.0 mg). Yield 38% (ESI 690.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



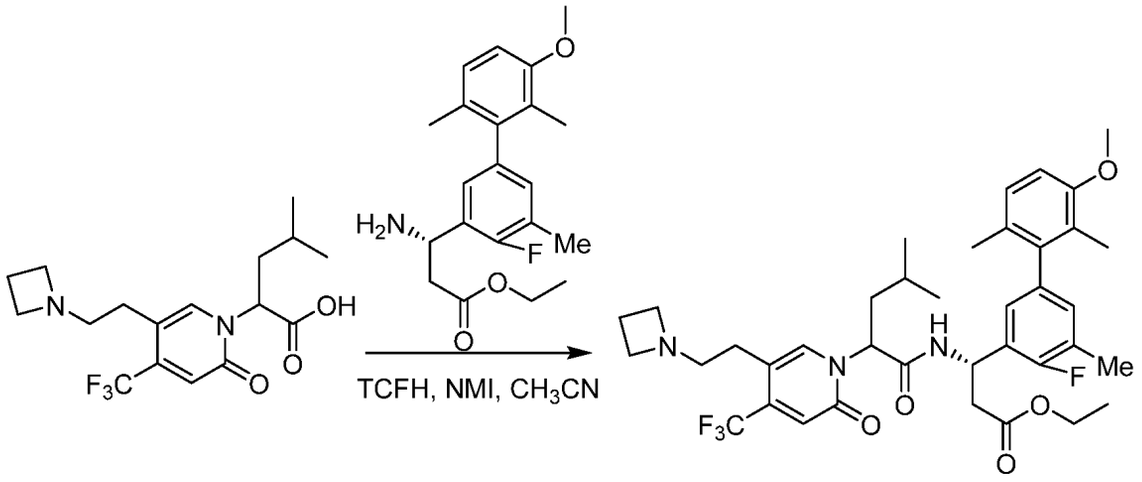
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (90 mg, 0.13 mmol) was treated with LiOH-H_2O (22 mg, 0.52 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to provide the diastereomeric products **AF-P1** (15 mg) and **AF-P2** (15 mg) as white solids.

AF-P1 ESI 662.2$(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.14 – 7.01 (m, 1H), 7.00 – 6.84 (m, 3H), 6.79 (d, *J* = 7.3 Hz, 1H), 5.70 – 5.51 (m, 2H), 4.13 – 3.94 (m, 4H), 3.28 – 3.18 (m, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 2.72 (d, *J* = 6.5 Hz, 2H), 2.54 – 2.37 (m, 2H), 2.31 (s, 3H), 2.06 – 1.95 (m, 3H), 1.96 – 1.70 (m, 5H), 1.50 – 1.32 (m, 1H), 1.01 – 0.83 (m, 6H).

AF-P2 ESI 662.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.19 – 7.04 (m, 1H), 7.03 – 6.82 (m, 4H), 5.85 – 5.70 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 4.13 (t, *J* = 7.5 Hz, 4H), 3.41 (s, 2H), 2.94 (d, *J* = 15.8 Hz, 1H), 2.87 – 2.73 (m, 1H), 2.70 – 2.58 (m, 1H), 2.56 – 2.40 (m, 3H), 2.35 (d, *J* = 1.5 Hz, 3H), 2.00 (t, *J* = 7.6 Hz, 4H), 1.94 – 1.85 (m, 3H), 1.73 – 1.57 (m, 1H), 1.48 – 1.36 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H).

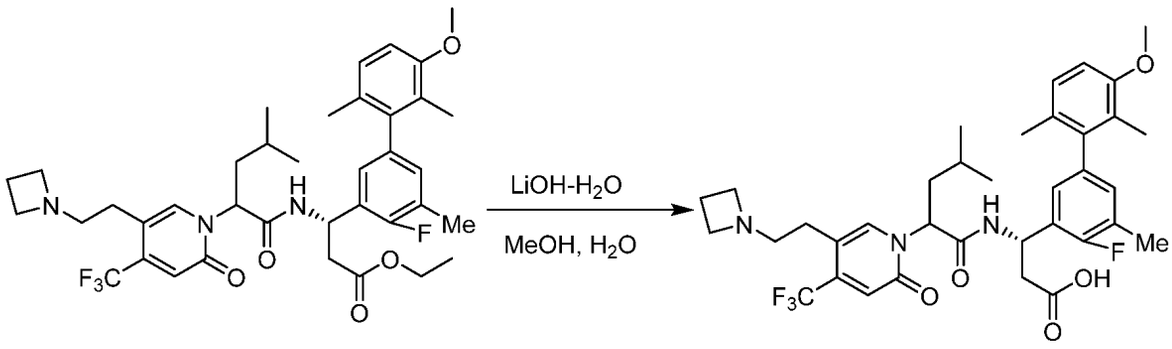
3-28. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AG-P1 and AG-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (160 mg, 0.44 mmol, 1.0 *eq*), ethyl (*S*)-3-amino-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (158 mg, 0.44 mmol, 1.0 *eq*) , N,N,N,N- Tetramethylchloroformamidinium hexafluorophosphate (246 mg, 0.88 mmol, 2 *eq*) and NMI (144 mg, 1.76 mmol, 4.0 *eq*) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. LCMS showed that the reaction was completed. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (170 mg). Yield 55% (ESI 702.1 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (170 mg, 0.24 mmol, 1.0 *eq*) was treated with LiOH-H_2O (40 mg, 0.96 mmol, 4.0 *eq*) in MeOH (4 mL) and water (1 mL) at 30°C for 1 hour. LCMS showed that the reaction was completed. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to provide the diastereomeric products **AG-P1** (50.8 mg) and **AG-P2** (60 mg) as white solids.

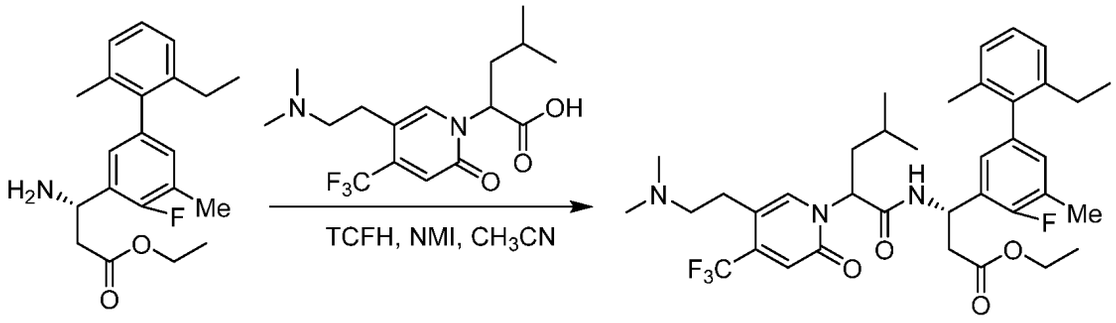
AG-P1 ESI 674.3 (M+H)+. ^{1}H NMR (500 MHz, MeOD) δ 7.83 (s, 1H), 7.03 (t, *J* = 7.8 Hz, 1H), 6.92 – 6.76 (m, 4H), 5.63-5.59 (m, 2H), 4.03 – 3.97 (m, 4H), 3.83 (s, 3H), 3.32 – 3.24 (m, 2H), 2.86 (t, *J* = 6.7 Hz, 2H), 2.72 – 2.70 (m, 2H), 2.49 – 2.37 (m, 2H), 2.30 (s, 3H), 1.99 (t, *J* = 7.6 Hz, 2H), 1.89 (d, *J* = 37.2 Hz, 3H), 1.78 (d, *J* = 34.9 Hz, 3H), 1.49 – 1.34 (m, 1H), 0.96 – 0.92 (m, 6H).

AG-P2 ESI 674.2 (M+H)+. ^{1}H NMR (500 MHz, MeOD) δ 7.74 (s, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 6.94-6.89 (m, 3H), 6.84 (d, *J* = 8.4 Hz, 1H), 5.79-5.76 (m, 1H), 5.60 (t, *J* = 7.6 Hz, 1H), 4.14 (t, *J* = 8.0 Hz, 4H), 3.84 (d, *J* = 1.1 Hz, 3H), 3.50 – 3.40 (m, 1H), 3.36 (d, *J* = 9.5 Hz, 1H), 2.94 (d, *J* = 16.2 Hz, 1H), 2.86 – 2.76 (m, 1H), 2.69 – 2.61 (m, 1H), 2.57 – 2.44 (m, 3H), 2.34 (d, *J* = 1.3 Hz, 3H), 2.05 – 1.96 (m, 1H), 1.93 (d, *J* = 6.2 Hz, 3H), 1.86 (d, *J* = 4.9 Hz, 3H), 1.68-1.63 (m, 1H), 1.45-1.40 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 6H).

3-29. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AH-P1 and AH-P2)

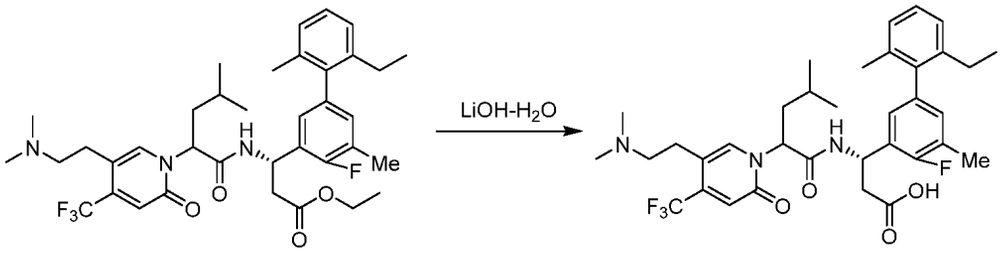
Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-

yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.43 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (101 mg, 0.52 mmol), TCFH (180 mg, 0.64 mmol) and NMI (70 mg, 0.86 mmol) in CH_3CN (5 mL) was stirred at 20 °C for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (180 mg). Yield 62% (ESI 674.2 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



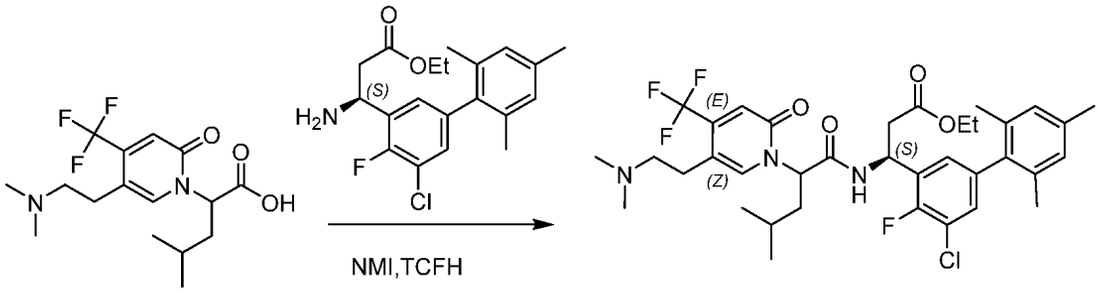
Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-ethyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.22 mmol) was treated with LiOH-H_2O (28 mg, 0.66 mmol) in MeOH (2 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AH-P1** (66 mg) and **AH-P2** (46 mg) as white solids.

AH-P1 ESI 646.3(M+H)$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.16 – 7.05 (m, 3H), 6.90 – 6.86 (m, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 5.70 – 5.57 (m, 2H), 3.09 (d, *J* = 7.1 Hz, 2H), 2.95 (d, *J* = 7.2 Hz, 2H), 2.75 – 2.70 (m, 8H), 2.34 – 2.29 (m, 4H), 2.20 – 2.18 (m, 1H), 2.00 – 1.96 (m, 3H), 1.79 (s, 1H), 1.47 – 1.39 (m, 1H), 1.02 – 0.92 (m, 8H), 0.83 (t, *J* = 7.5 Hz, 2H).

AH-P2 ESI 646.3(M+H)$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (d, *J* = 6.6 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.12 – 7.07 (m, 2H), 6.96 – 6.89 (m, 3H), 5.74 – 5.70 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 3.31– 3.14 (m, 2H), 3.00 (t, *J* = 6.7 Hz, 2H), 2.81 (d, *J* = 1.2 Hz, 6H), 2.62 – 2.61 (m, 1H), 2.57 – 2.44 (m, 1H), 2.36 – 2.31 (m, 5H), 2.00 – 1.97 (m, 4H), 1.71 – 1.65 (m, 1H), 1.42 – 1.37 (m, 1H), 1.02 – 0.98 (m, 3H), 0.88 (d, *J* = 6.5 Hz, 6H).

3-30. Preparation of (3*S*)-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AI-P1 and AI-P2)

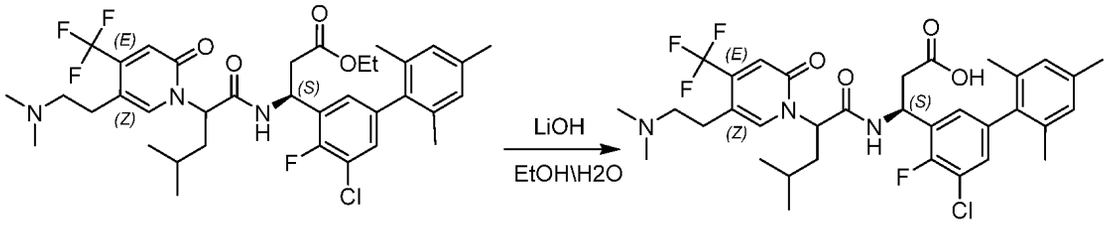
Step 1: ethyl (3*S*)-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (120 mg, 0.34 mmol), ethyl (*S*)-3-amino-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (145 mg, 0.40 mmol), TCFH (142 mg, 0.51 mmol), NMI (139.4 mg, 1.7 mmol) in CH_3CN (4 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue was by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-

oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a red oil (175 mg). Yield 74% (ESI 694.2 $(M+H)^+$).

Step 2: (3*S*)-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



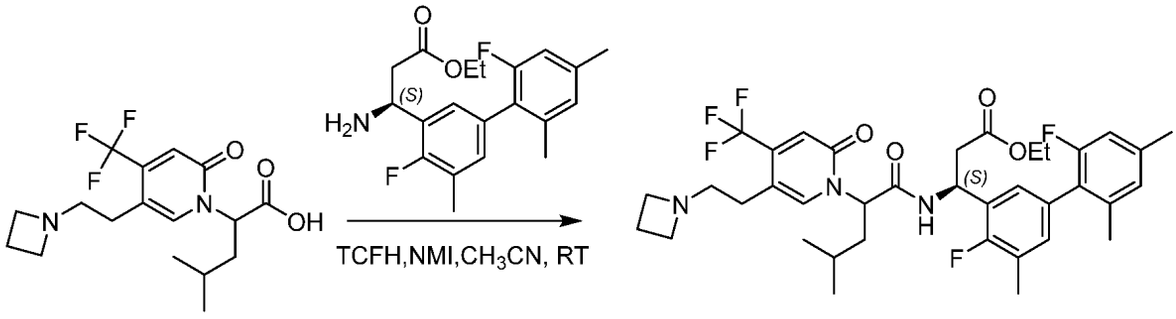
Ethyl (3*S*)-3-(5-chloro-4-fluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (175 mg, 0.25 mmol) was treated with LiOH-H_2O (52.5 mg, 1.25 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AI-P1** (29 mg) and **AI-P2** (23 mg) as white solids.

AI-P1 ESI 666.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.08 – 7.06 (m, 1H), 7.01 – 6.98 (m, 1H), 6.92 (s, 1H), 6.87 (s, 1H), 6.71 (s, 1H), 5.70 – 5.65 (m, 1H), 5.56 – 5.62 (m, 1H), 3.17 – 2.89 (m, 4H), 2.82 – 2.63 (m, 8H), 2.30 (s, 3H), 2.08 – 1.91 (m, 5H), 1.76 (s, 3H), 1.52 – 1.38 (m, 1H), 1.03 – 0.83 (m, 6H).

AI-P2 ESI 666.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.16 – 7.13 (m, 1H), 7.08 – 67.05 (m, 1H), 6.93 (s, 2H), 6.89 (s, 1H), 5.77 – 5.54 (m, 2H), 3.28 – 3.17 (m, 2H), 3.02 – 2.98 (m, 2H), 2.83 (s, 6H), 2.71 – 2.47 (m, 2H), 2.31 (s, 3H), 2.11 – 1.87 (m, 7H), 1.83 – 1.64 (m, 1H), 1.46 – 1.23 (m, 1H), 1.06 – 0.62 (m, 6H).

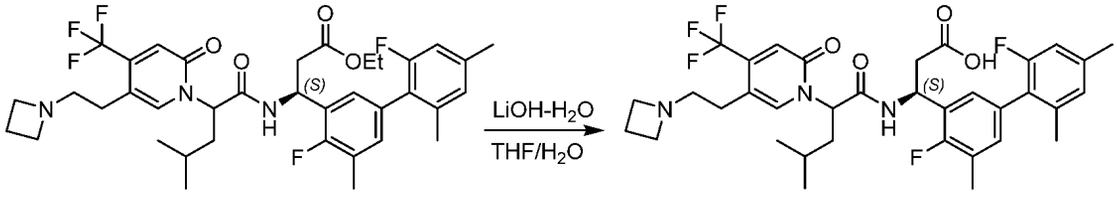
3-31. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2',4-difluoro-4',5,6'-trimethylbiphenyl-3-yl)propanoic acid (compounds AJ-P1 and AJ-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150 mg, 0.42 mmol), ethyl (S)-3-amino-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (145 mg, 0.42 mmol), TCFH (141 mg, 0.50 mmol) and NMI (104 mg, 1.26 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM:MeOH 4: 1) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoateas a white solid (130 mg). Yield 45% (ESI 690.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2',4-difluoro-4',5,6'-trimethylbiphenyl-3-yl)propanoic acid



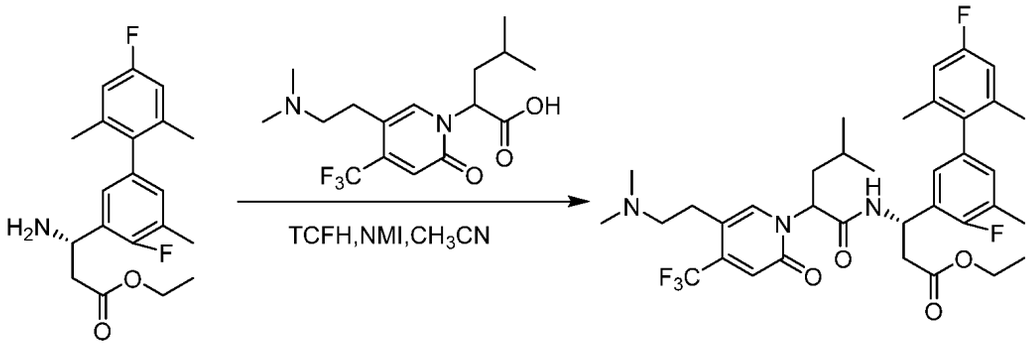
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2',4-difluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (130 mg, 0.19 mmol) was treated with LiOH-H_2O (40 mg, 0.95 mmol) in THF (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AJ-P1** (30.0 mg) and **AJ-P2** (29.7 mg) as white solids.

AJ-P1 ESI 662.2 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 6.99 (t, *J* = 6.3 Hz, 2H), 6.92 (s, 1H), 6.79 (t, *J* = 4.9 Hz, 2H), 5.68 (t, *J* = 8.0 Hz, 1H), 5.59 (t, *J* = 6.6 Hz, 1H), 4.00 – 3.96 (m, 4H), 3.30 – 3.25 (m, 2H), 2.85 (t, *J* = 6.9 Hz, 2H), 2.72 – 2.70 (m, 2H), 2.44 – 2.37 (m, 2H), 2.35 (s, 3H), 2.29 (d, *J* = 1.2 Hz, 3H), 2.05 (s, 3H), 2.00 (t, *J* = 7.6 Hz, 2H), 1.45 – 1.40 (m, 1H), 0.95 (t, J = 7.1 Hz, 6H).

AJ-P2 ESI 662.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.08 (d, *J* = 6.5 Hz, 1H), 7.04 (d, *J* = 6.9 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.82 (d, *J* = 10.4 Hz, 1H), 5.78 – 5.74 (m, 1H), 5.64 (t, *J* = 7.7 Hz, 1H), 4.11 (t, *J* = 8.0 Hz, 4H), 3.44 – 3.38 (m, 1H), 2.96 – 2.89 (m, 1H), 2.84 – 2.76 (m, 1H), 2.67 – 2.62 (m, 1H), 2.57 – 2.43 (m, 3H), 2.35 – 2.33 (m, 6H), 2.11 (s, 3H), 2.02 – 1.94 (m, 1H), 1.71 – 1.64 (m, 1H), 1.44 – 1.30 (m, 2H), 0.91 – 0.88 (m, 6H).

3-32. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AK-P1 and AK-P2)

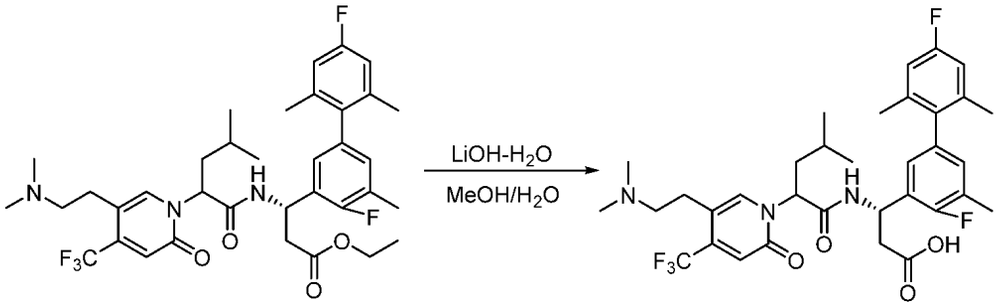
Step 1: ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.43 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (180 mg, 0.51 mmol), TCFH (240 mg, 0.86 mmol) and NMI (106 mg, 1.29 mmol) in CH_3CN (5 mL) was stirred at 20 °C for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide

ethyl (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a yellow oil (120 mg). Yield 41% (ESI 678.1 $(M+H)^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



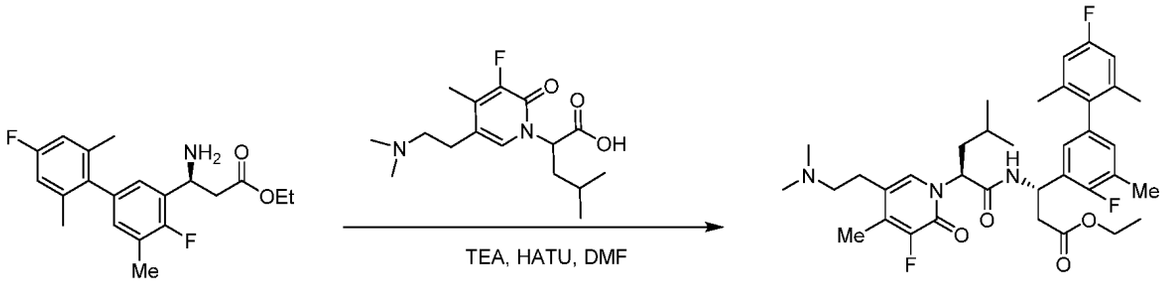
Ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (100 mg, 0.14 mmol) was treated with LiOH-H_2O (18 mg, 0.44 mmol) in MeOH (2 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to provide the diastereomeric products **AK-P1** (36 mg) and **AK-P2** (32 mg) as white solids.

AK-P1 ESI 650.3$(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 6.88 – 6.74 (m, 5H), 5.69 (t, J = 8.1 Hz, 1H), 5.58 – 5.54 (m, 1H), 3.19 – 3.07 (m, 2H), 3.02 – 2.95 (m, 2H), 2.84 – 2.67 (m, 8H), 2.30 (t, J = 8.2 Hz, 3H), 2.03 – 1.94 (m, 5H), 1.80 (d, J = 9.4 Hz, 3H), 1.48 – 1.39 (m, 1H), 0.97 – 0.88 (m, 6H).

AK-P2 ESI 650.2$(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 6.93 – 6.83 (m, 5H), 5.71 – 5.62 (m, 2H), 3.19 (s, 2H), 3.00 – 2.97 (m, 2H), 2.80 (s, 6H), 2.67 – 2.57 (m, 2H), 2.32 (d, J = 1.5 Hz, 3H), 2.01 – 1.93 (m, 7H), 1.79 – 1.74 (m, 1H), 1.42 – 1.35 (m, 1H), 0.90 – 0.87 (m, 6H).

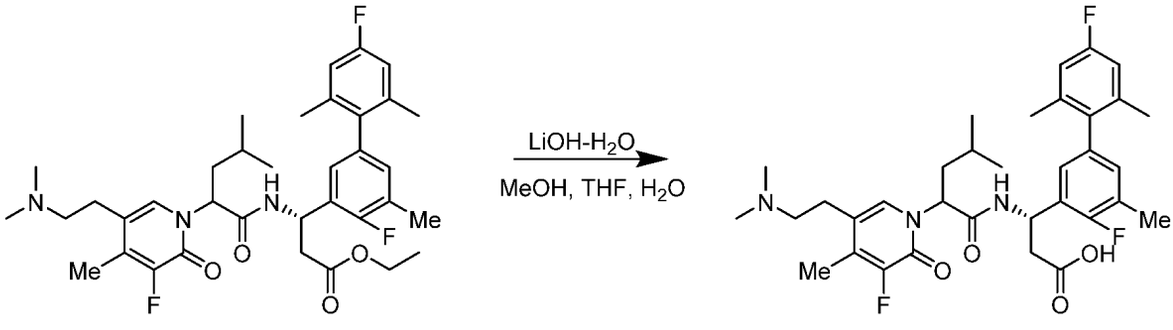
3-33. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AL-P1 and AL-P2)

Step 1: ethyl (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoate



To a solution of 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid (1g, 3.20 mmol) and HATU (2.434 g, 6.40 mmol) in DMF (16.01 mL) was added TEA (0.892 mL, 6.40 mmol) at room temperature. After stirring for 5 minutes, ethyl (S)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.668 g, 4.80 mmol) in 5.0 mL DMF was added to the solution. The reaction mixture was dilluted with 200 mL of water and 10 mL of brine. The mixture was washed (EtOAc; 200 mL X 3). The combined organic phase was dried over Na_2SO4, conentrated and purified by silica gel column (DCM: MeOH 10: 1) to provide ethyl (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoate (1.76 g, 86% yield) as pinkish oil. (ESI 642 $(M+H)^+$)

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid

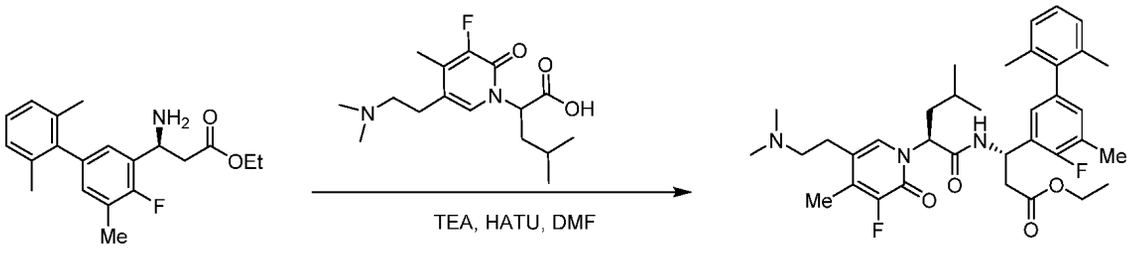


Ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (1.65 g, 2.6 mmol, 1.0 *eq*) was treated with LiOH monohydrate (391 mg, 9.3 mmol, 4.0 *eq*) in methanol (5 mL), THF (5 mL) and H_2O (5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl aqueous solution, concentrated *in vacuo* and the residue was purified by prep HPLC A to provide the diastereomeric products **AL-P1** (383 mg) and **AL-P2** (239 mg) as white solids.

AL-P1 ESI 614.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.48 (s, 1H), 6.86 – 6.81 (m, 4H), 5.66 – 5.60 (m, 1H), 5.50 – 5.47 (m, 1H), 3.22 – 3.12 (m, 2H), 2.93 – 2.89 (m, 2H), 2.77 (s, 6H), 2.72 – 2.61 (m, 2H), 2.29 (d, J = 1.6 Hz, 3H), 2.25 (d, J = 2.8 Hz, 3H), 2.00 – 1.93 (m, 5H), 1.88 (s, 3H), 1.46 – 1.36 (m, 1H), 0.95 – 0.90 (m, 6H).

AL-P2 ESI 614.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.43 (s, 1H), 6.88 (dd, J = 24.6, 8.2 Hz, 4H), 5.66 – 5.57 (m, 2H), 3.27 – 3.13 (m, 2H), 2.97 – 2.93 (m, 2H), 2.86 (s, 6H), 2.62 – 2.57 (m, 1H), 2.51 – 2.39 (m, 1H), 2.33 (d, J = 1.7 Hz, 3H), 2.25 (d, J = 2.7 Hz, 3H), 2.05 – 1.93 (m, 7H), 1.80 – 1.73 (m, 1H), 1.41 – 1.34 (m, 1H), 0.91 – 0.89 (m, 6H).

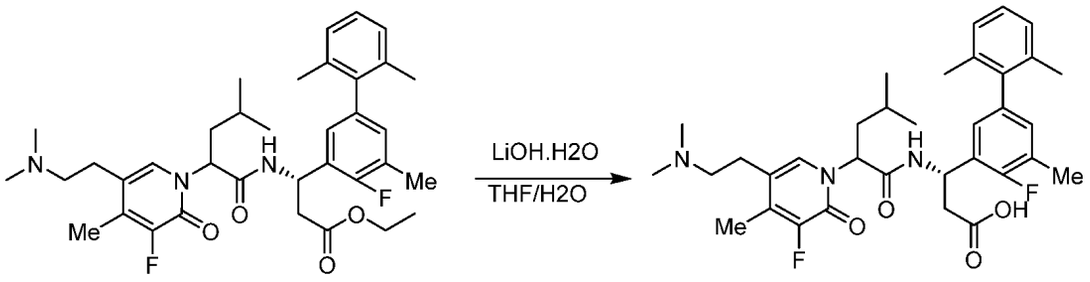
3-34. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AM-P1 and AM-P2)



To a solution of 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid (1g, 3.20 mmol) and HATU (2.434 g, 6.40 mmol) in DMF (16.01 mL) was added TEA (0.892 mL, 6.40 mmol) at room temperature. After stirring for 5 minutes, ethyl (S)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.668 g, 4.80 mmol) in 5.0 mL DMF was added to the solution. The reaction mixture was dilluted with 200 mL of water and 10 mL of brine. The mixture was washed (EtOAc; 200 mL X 3). The combined organic phase was dried over Na_2SO4, conentrated and purified by silica gel column (DCM: MeOH 10: 1) to provide ethyl (S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-

biphenyl]-3-yl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoate (1.76 g, 86% yield) as pinkish oil. (ESI 642 $(M+H)^+$)

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



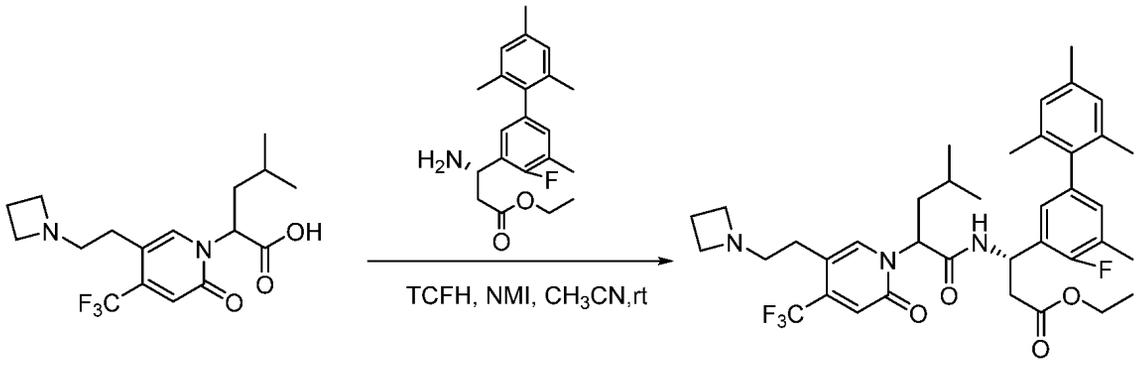
Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (1.2 g, 1.93 mmol) was treated with LiOH-H_2O (162 mg, 3.85 mmol) in THF (12 mL) and H_2O (2 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue was purified by purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AM-P1** (482 mg) and **AM-P2** (237mg) as white solids.

AM-P1 ESI 596.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.47 (s, 1H), 7.16 – 7.01 (m, 3H), 6.90 – 6.79 (m, 2H), 5.68 – 5.64 (m, 1H), 5.51 – 5.48 (m, 1H), 3.17 – 3.08 (m, 2H), 2.92 – 2.88 (m, 2H), 2.76 (s, 6H), 2.72 – 2.44 (m, 2H), 2.29 (s, 3H), 2.23 (d, J = 2.6 Hz, 3H), 1.99 – 1.94 (m, 5H), 1.87 (s, 3H), 1.42 – 1.38 (m, 1H), 0.94 – 0.90 (m, 6H).

AM-P2 ESI 596.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.39 (s, 1H), 7.15 – 7.08 (m, 3H), 6.93 – 6.90 (m, 2H), 5.67 – 5.60 (m, 2H), 3.32 – 3.28 (m, 1H), 3.22 – 3.16 (m, 1H), 2.96 – 2.92 (m, 2H), 2.84 (s, 6H), 2.63 – 2.58 (m, 1H), 2.50 – 2.43 (m, 1H), 2.32 (d, J = 1.6 Hz, 3H), 2.24 (d, J = 2.8 Hz, 3H), 2.01 – 1.93 (m, 7H), 1.78 – 1.71 (m, 1H), 1.41 – 1.34 (m, 1H), 0.90(d, J = 6.8 Hz, 6H).

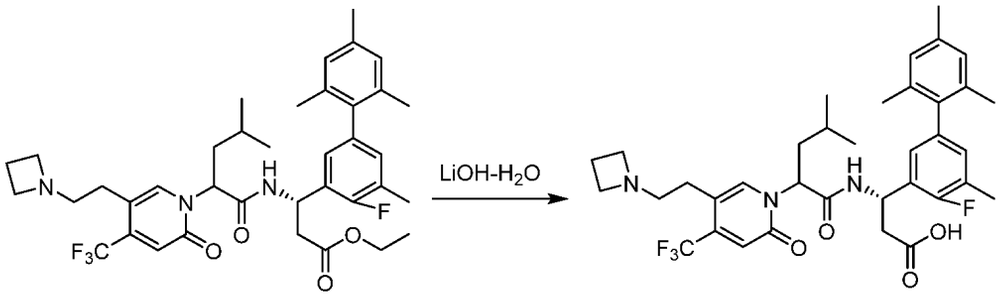
3-35. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AN-P1 and AN-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150 mg, 0.41 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (141 mg, 0.41 mmol), TCFH (230 mg, 0.82 mmol), NMI (135 mg, 1.64 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a white oil (90 mg). Yield 32% (ESI 686.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid



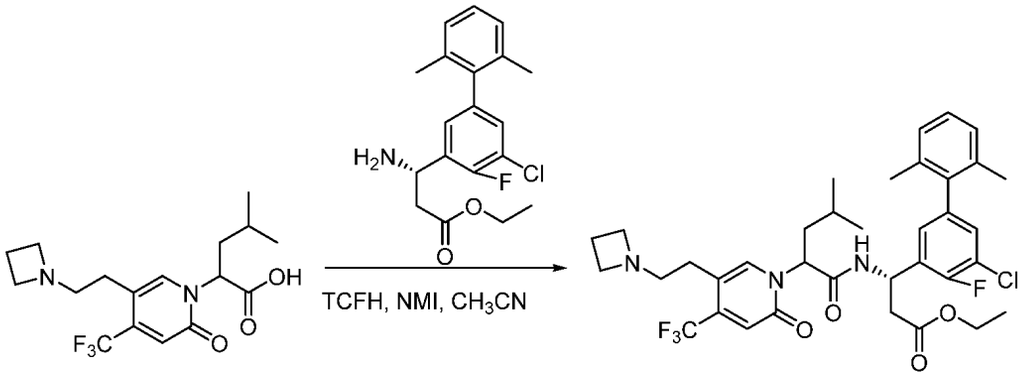
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (90 mg, 0.14 mmol) was treated with LiOH-H_2O (24 mg, 0.56 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AN-P1** (22 mg) and **AN-P2** (22 mg) as white solids.

AN-P1 ESI 658.3$(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 6.96 – 6.83 (m, 4H), 6.80 (s, 1H), 5.73 – 5.50 (m, 2H), 4.03 (s, 4H), 3.15 (s, 2H), 2.86 (t, *J* = 6.7 Hz, 2H), 2.77 – 2.62 (m, 2H), 2.51 – 2.38 (m, 2H), 2.30 (s, 6H), 2.09 – 1.91 (m, 5H), 1.85 (s, 3H), 1.49 – 1.30 (m, 1H), 1.04 – 0.83 (m, 6H).

AN-P2 ESI 658.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 6.92 (t, *J* = 7.5 Hz, 5H), 5.84 – 5.72 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 4.14 (s, 4H), 3.42 (s, 2H), 2.94 (d, *J* = 16.0 Hz, 2H), 2.87 – 2.59 (m, 2H), 2.56 – 2.41 (m, 2H), 2.37 – 2.25 (m, 6H), 2.05 – 1.88 (m, 7H), 1.72 – 1.59 (m, 1H), 1.47 – 1.34 (m, 1H), 0.96 – 0.82 (m, 6H).

3-36. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AO-P1 and AO-P2)

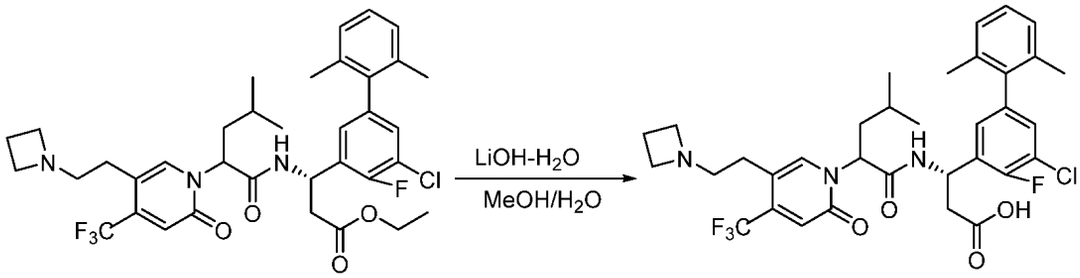
Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150 mg, 0.42 mmol), ethyl (*S*)-3-amino-3-(5-chloro-4-fluoro-2',6'-

dimethyl-[1,1'-biphenyl]-3-yl)propanoate (154 mg, 0.42 mmol), TCFH (180 mg, 0.63 mmol) and NMI (100 mg, 1.26 mmol) in CH_3CN (5 mL) was stirred at 40°C for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (150 mg). Yield 52.8% (ESI 692.0 $(M+H)^+$).

Step 2: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



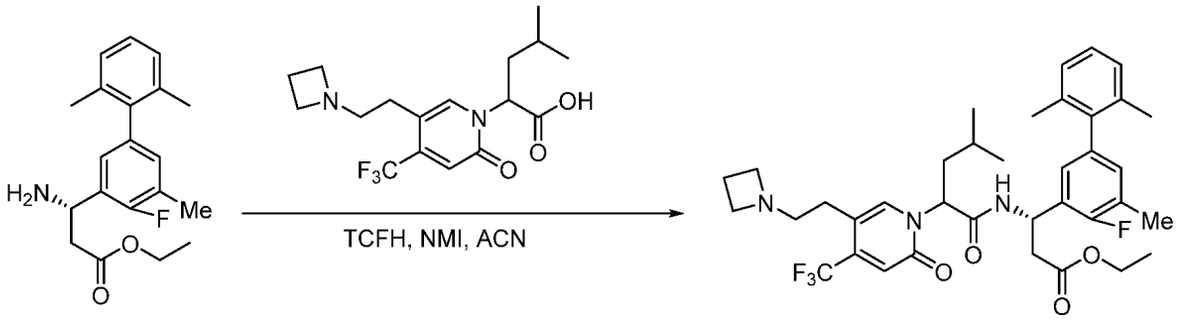
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.22 mmol) was treated with LiOH-H_2O (95.5 mg, 2.3 mmol) in MeOH (4 mL) and H_2O (4 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **AO-P1** (29 mg) and **AO-P2** (34 mg) as white solids.

AO-P1 ESI 664.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.11 – 6.90 (m, 5H), 6.65 (s, 1H), 5.60 – 5.40 (m, 2H), 3.91 (t, *J* = 8.2 Hz, 4H), 3.21 – 3.11 (m, 2H), 2.73 (t, *J* = 7.0 Hz, 2H), 2.67 – 2.55 (m, 2H), 2.41 – 2.25 (m, 2H), 1.96 – 1.83 (m, 5H), 1.77 (s, 3H), 1.36 – 1.24 (m, 1H), 0.88 – 0.77 (m, 6H).

AO-P2 ESI 664.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.26 – 7.07 (m, 5H), 6.90 (s, 1H), 5.86 – 5.74 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 4.14 (t, *J* = 7.9 Hz, 4H), 3.49 – 3.36 (m, 2H), 3.01 – 2.74 (m, 2H), 2.71 – 2.62 (m, 1H), 2.59 – 2.43 (m, 3H), 2.12 – 1.91 (m, 7H), 1.77 – 1.58 (m, 1H), 1.49 – 1.32 (m, 1H), 0.90 (d, J = 6.6 Hz, 6H).

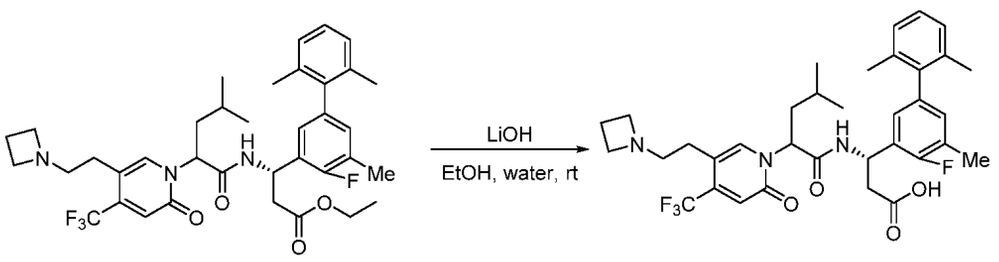
3-37. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AP-P1 and AP-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (262 mg, 0.73 mmol, 1.20 *eq*), ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.61 mmol, 1.00 *eq*), NMI (0.5 mL) and TCFH (255mg, 0.91 mmol, 1.50 *eq*) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (300 mg). Yield 73.5% (ESI 672.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (300 mg, 0.45 mmol, 1.00 *eq*) was treated with LiOH-H_2O (100 mg, 2.38 mmol, 5.00 *eq*) in MeOH (5

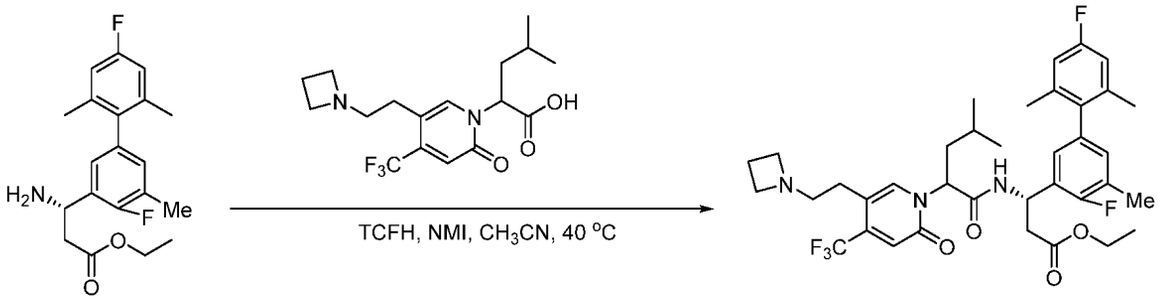
mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give **AP-P1** (30 mg) and **AP-P2** (50 mg) as white solids.

AP-P1 ESI 644.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.17 – 7.02 (m, 3H), 6.96 – 6.85 (m, 2H), 6.80 (s, 1H), 5.71– 5.56 (m, 2H), 4.13 – 3.94 (m, 4H), 3.33 – 3.29 (m, 2H), 2.86 (t, J = 6.7 Hz, 2H), 2.71 (d, J = 6.1 Hz, 2H), 2.48 – 2.40 (m, 2H), 2.31 (d, J = 1.7 Hz, 3H), 2.07 – 1.92 (m, 5H), 1.89 (s, 3H), 1.45 – 1.39 (m, 1H), 0.99 – 0.84 (m, 6H).

AP-P2 ESI 644.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.12 – 7.08 (m, 3H), 6.97 – 6.91(m, 3H), 5.79 – 5.76 (m, 1H), 5.61 (t, J = 7.6 Hz, 1H), 4.14 (t, J = 7.5 Hz, 4H), 3.53 – 3.34 (m, 2H), 2.94 (d, J = 15.6 Hz, 1H), 2.88 – 2.71 (m, 1H), 2.68 – 2.63 (m, 1H), 2.54 – 2.44 (m, 3H), 2.34 (s, 3H), 2.02 – 1.96 (m, 7H), 1.75 – 1.54 (m, 1H), 1.45 – 1.39 (m, 1H), 0.90 (d, J = 6.4 Hz, 6H).

3-38. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AQ-P1 and AQ-P2)

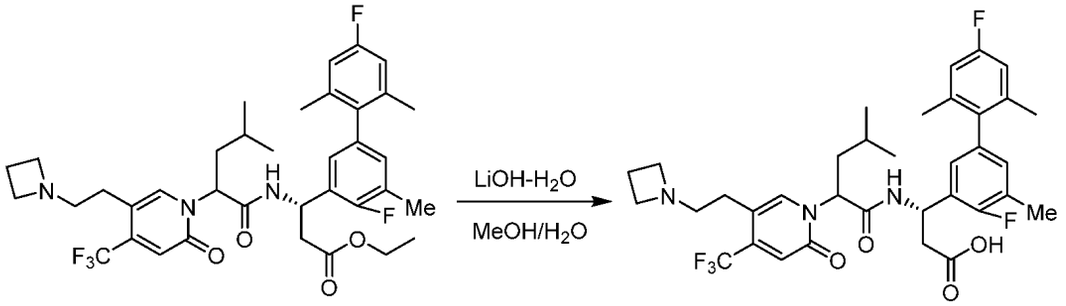
Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (165 mg, 0.46 mmol), ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (160 mg, 0.46 mmol), TCFH (193 mg, 0.69 mmol) and NMI (188 mg, 2.3 mmol) in CH_3CN (4 mL) was stirred at 40 °C for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-

(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow oil (200 mg). Yield 62% (ESI 690.2 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



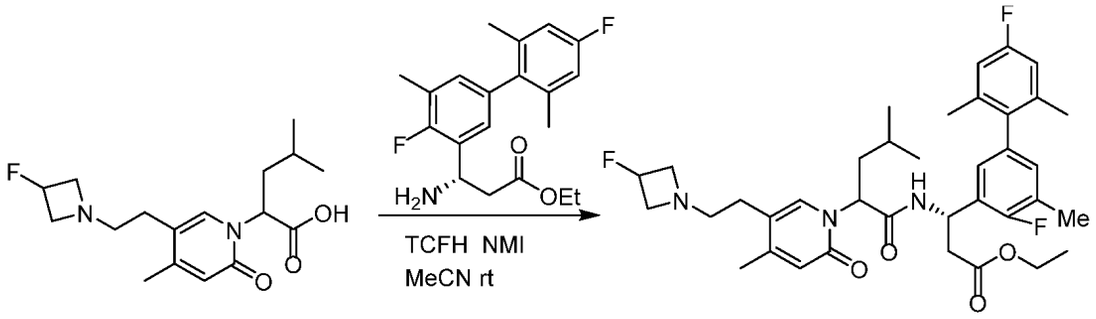
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.29 mmol) was treated with LiOH-H_2O (42 mg, 1 mmol) in MeOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **AQ-P1** (54 mg) and **AQ-1-P2** (53 mg) as white solids.

AQ-P1 ESI 662.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 6.94 – 6.74 (m, 5H), 5.72 – 5.55 (m, 2H), 4.05 (t, J = 8.0 Hz, 4H), 3.33 – 3.25 (m, 2H), 2.86 (t, J = 7.1 Hz, 2H), 2.77 – 2.64 (m, 2H), 2.55 – 2.38 (m, 2H), 2.30 (s, 3H), 2.06 – 1.94 (m, 5H), 1.87 (s, 3H), 1.53 – 1.34 (m, 1H), 1.01 – 0.86 (m, 6H).

AQ-P2 ESI 662.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.78 (s, 1H), 6.98 – 6.89 (m, 3H), 6.85 (d, J = 9.6 Hz, 2H), 5.80 – 5.70 (m, 1H), 5.63 (t, J = 7.6 Hz, 1H), 4.14 (s, 4H), 3.52 – 3.36 (m, 2H), 2.97 – 2.43 (m, 6H), 2.33 (s, 3H), 2.06 – 1.93 (m, 7H), 1.77 – 1.63 (m, 1H), 1.49 – 1.29 (m, 1H), 0.96 – 0.84 (m, 6H).

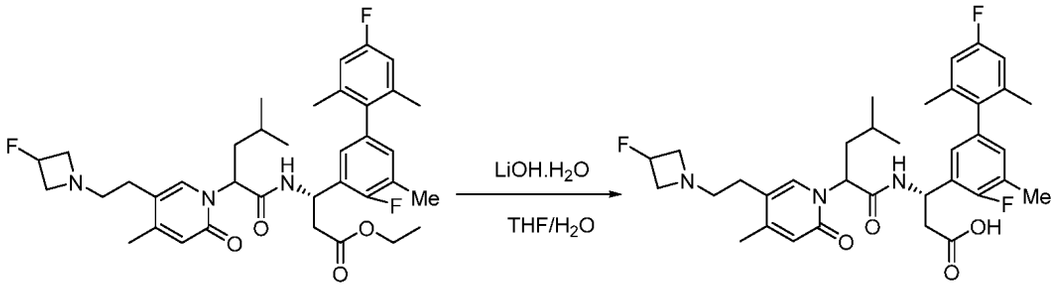
3-39. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AR-P1 and AR-P2)

Step 1: ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (112 mg, 0.34 mmol), ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (100 mg, 0.29 mmol), TCFH (120 mg, 0.43 mmol) and NMI (71 mg, 0.87 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (150 mg). Yield 79.7% (ESI 654.3 $(M+H)^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



Ethyl ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (150 mg, 0.23 mmol) was treated with LiOH-H_2O (100 mg, 2.3 mmol) in THF (3 mL) and H_2O (3 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the

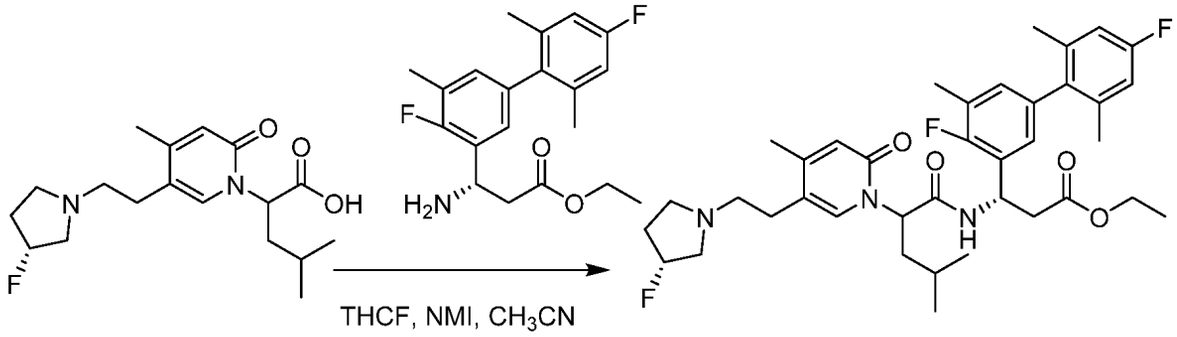
residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **AR-P1** (43 mg) and **AR-P2** (36 mg) as white solids.

AR-P1 ESI 626.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.49 (s, 1H), 6.92 – 6.68 (m, 4H), 6.30 (s, 1H), 5.74 – 5.52 (m, 2H), 5.30 – 5.12 (m, 1H), 4.15 – 3.90 (m, 2H), 3.75 – 3.57 (m, 2H), 3.05 – 3.00 (m, 2H), 2.85 – 2.62 (m, 3H), 2.32 – 2.27 (m, 4H), 2.22 (d, *J* = 1.2 Hz, 3H), 1.99 (s, 3H), 1.96 – 1.92 (m, 2H), 1.85 (s, 3H), 1.45 – 1.35 (m, 1H), 0.96 – 0.91 (m, 6H).

AR-P2 ESI 626.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.33 (s, 1H), 6.87 – 6.81 (m, 4H), 6.30 (s, 1H), 5.62 – 5.43 (m, 2H), 5.34 – 5.08 (m, 1H), 4.37 – 4.12 (m, 2H), 4.00 – 3.76 (m, 2H), 3.19 – 3.11 (m, 2H), 2.79 – 2.67 (m, 1H), 2.62 – 2.36 (m, 3H), 2.20 (d, *J* = 1.6 Hz, 3H), 2.12 (s, 3H), 1.89 (s, 6H), 1.85 – 1.75 (m, 1H), 1.69 – 1.58 (m, 1H), 1.32 – 1.21 (m, 1H), 0.82 – 0.72 (m, 6H).

3-40. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AS-P1 and AS-P2)

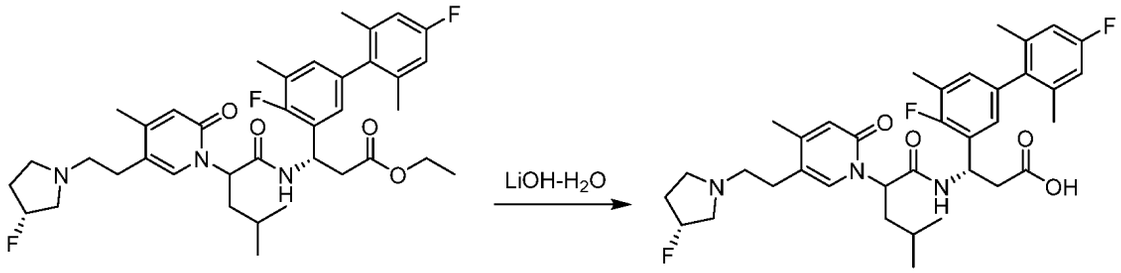
Step 1: (3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (120 mg, 0.36 mmol), (*S*)-ethyl 3-amino-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (123 mg, 0.36 mmol),TCFH (114 mg, 0.41 mmol) and NMI (84 mg, 1.02 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM:MeOH 4:1) to provide (3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-

(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a white solid (120 mg). Yield 51% (ESI 668.2 $(M+H)^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



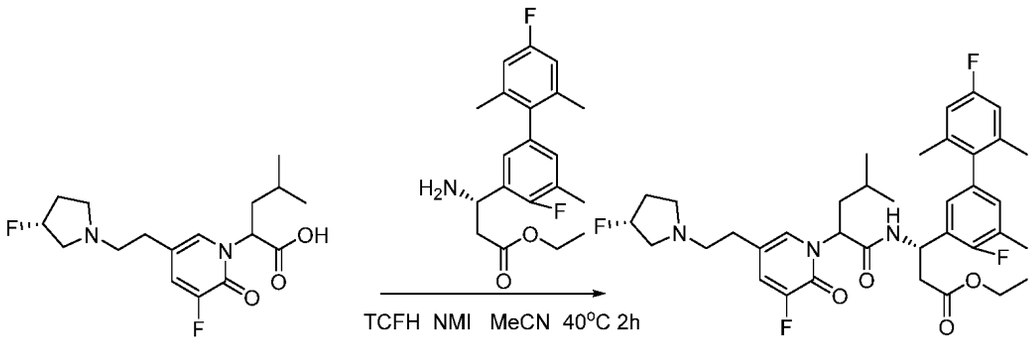
(3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (120 mg, 0.18 mmol)) was treated with LiOH-H_2O (32 mg, 0.75 mmol) in THF (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **AS-P1** (28.0 mg) and **AS-P2** (43.0 mg) as white solids.

AS-P1 ESI 640.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.56 (s, 1H), 6.84 – 6.79 (m, 4H), 6.26 (s, 1H), 5.65 – 5.60 (m, 1H), 5.55 – 5.50 (m, 1H), 5.35 – 5.52 (m, 1H), 3.38 – 3.33 (m, 1H), 3.32 – 2.66 (m, 9H), 2.39 – 2.11 (m, 8H), 1.98 – 1.92 (m, 5H), 1.81 (s, 3H), 1.46-1.39 (m, 1H), 0.96 – 0.91 (m, 6H).

AS-P2 ESI 640.3 (M+H)+. ^1H NMR (400 MHz, MeOD) δ 7.57 (s, 1H), 6.90 – 6.82 (m, 4H), 6.42 (s, 1H), 5.64 -5.58 (m, 2H), 5.40 – 5.24 (m, 1H), 3.51 – 3.37 (m, 3H), 3.32 – 3.10 (m, 3H), 2.92 – 2.76 (m, 2H), 2.68 – 2.55 (m, 2H), 2.40 – 2.21 (m, 8H), 2.05 – 1.88 (m, 7H), 1.80 – 1.73 (m, 1H), 1.41 – 1.34 (m, 1H), 0.96 – 0.87 (m, 6H).

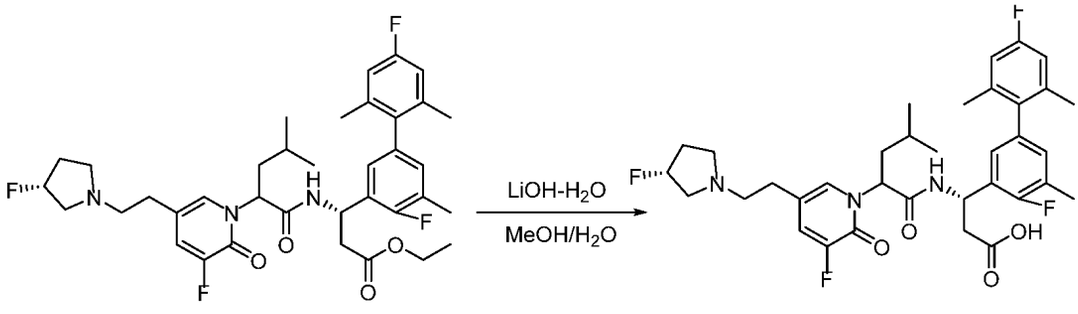
3-41. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AT-P1 and AT-P2)

Step 1: ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (120 mg, 0.35 mmol), ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (140 mg, 0.42 mmol), TCFH (117 mg, 0.42 mmol) and NMI (86 mg, 1.05 mmol) in CH_3CN (5 mL) was stirred at 40 °C for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (150 mg). Yield 63.8% (ESI 672.3 $(M+H)^+$).

Step 2: ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



Ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (150 mg, 0.22 mmol) was treated with LiOH-H_2O (94 mg, 2.2 mmol) in MeOH (5 mL) and H_2O (5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with

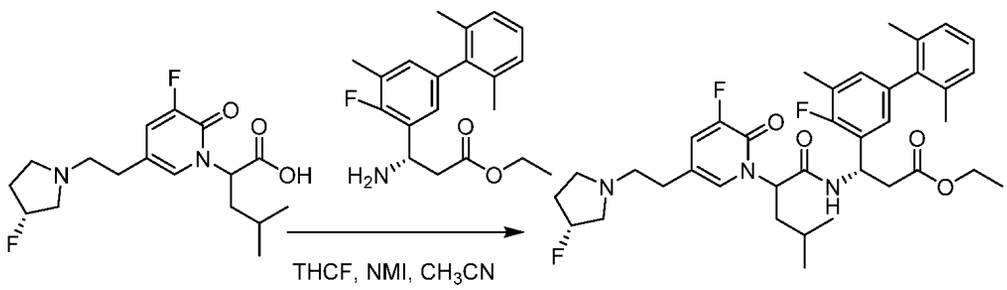
1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **AT-P1** (28 mg) and **AT-P2** (37 mg) as white solids.

AT-P1 ESI 644.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.37 (d, J = 10.1 Hz, 1H), 6.92 – 6.77 (m, 4H), 5.74 – 5.62 (m, 1H), 5.57 – 5.46 (m, 1H), 5.27 (d, *J* = 53.4 Hz, 1H), 3.29 – 2.96 (m, 6H), 2.84 – 2.56 (m, 4H), 2.40 – 2.10 (m, 5H), 2.07 – 1.90 (m, 5H), 1.87 (s, 3H), 1.49 – 1.38 (m, 1H), 1.03 – 0.89 (m, 6H).

AT-P2 ESI 644.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.49 (s, 1H), 7.41 (d, J = 10.3 Hz, 1H), 6.97 – 6.76 (m, 4H), 5.67 (t, *J* = 7.7 Hz, 1H), 5.62 – 5.52 (m, 1H), 5.33 (d, *J* = 55.0 Hz, 1H), 3.69 – 3.34 (m, 6H), 2.92 – 2.77 (m, 2H), 2.65 – 2.43 (m, 2H), 2.30 (d, *J* = 17.3 Hz, 5H), 2.10 – 1.89 (m, 7H), 1.86 – 1.74 (m, 1H), 1.48 – 1.34 (m, 1H), 0.95 – 0.86 (m, 6H).

3-42. Preparation of (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds AU-P1 and AU-P2)

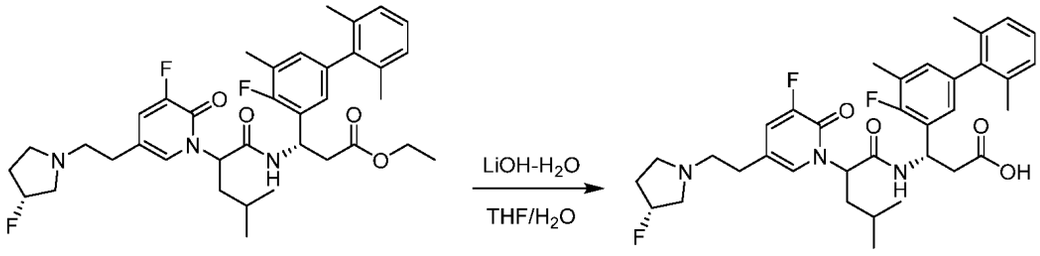
Step 1: ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanoic acid (150 mg, 0.44 mmol), ethyl (S)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (144 mg, 0.44 mmol), TCFH (148 mg, 0.53 mmol), NMI (108 mg, 1.32 mmol) in CH_3CN (4 mL) was stirred at room temperature for 1 hour. LCMS showed that the reaction was completed. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/120g column (A: water 10 mM NH_4HCO_3, B: CH3CN, 0~100%) to provide ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-

yl)-4-methylpentanamido)propanoate as a colorless oil (130 mg). Yield 45% (ESI 654.2 $(M+H)^+$).

Step 2: (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid

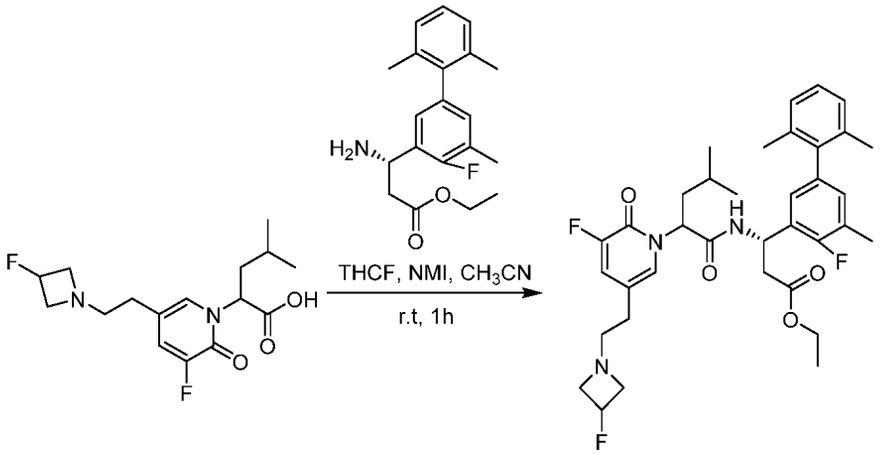


Ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (130 mg, 0.20 mmol) was treated with LiOH-H_2O (83 mg, 2.0 mmol) in THF (2 mL) and H_2O (1 mL) at 35 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AU-P1** (33 mg) and **AU-P2** (53 mg) as white solids.

AU-P1 ESI 626.2 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.51 (s, 1H), 7.38 – 7.35 (m, 1H), 7.15 – 7.06 (m, 3H), 6.88 – 6.81 (m, 2H), 5.73 – 5.68 (m, 1H), 5.53 – 5.50 (m, 1H), 5.35 – 5.19 (m, 1H), 3.44 – 3.35 (m, 1H), 3.30 – 3.08 (m, 5H), 2.80 – 2.65 (m, 4H), 2.37 – 2.18 (m, 5H), 1.98 – 1.95 (m, 5H), 1.88 (s, 3H), 1.47 – 1.40 (m, 1H), 097 – 0.93 (m, 6H).
AU-P2 ESI 626.2 (M+H)+. ^{1}H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.41 – 7.38 (m, 1H), 7.14 – 7.07 (m, 3H), 6.93 – 6.90 (m, 2H), 5.70 – 5.66 (m, 1H), 5.61 – 5.58 (m, 1H), 5.40 – 5.25 (m, 1H), 3.65 – 3.37 (m, 5H), 3.30 – 3.25 (m, 1H), 2.91 – 2.79 (m, 2H), 2.64 – 2.48 (m, 2H), 2.39 – 2.25 (m, 5H), 2.00 – 1.94 (m, 7H), 1.84 – 1.75 (m, 1H), 1.43 – 1.35 (m, 1H), 0.92 – 0.89 (m, 6H).

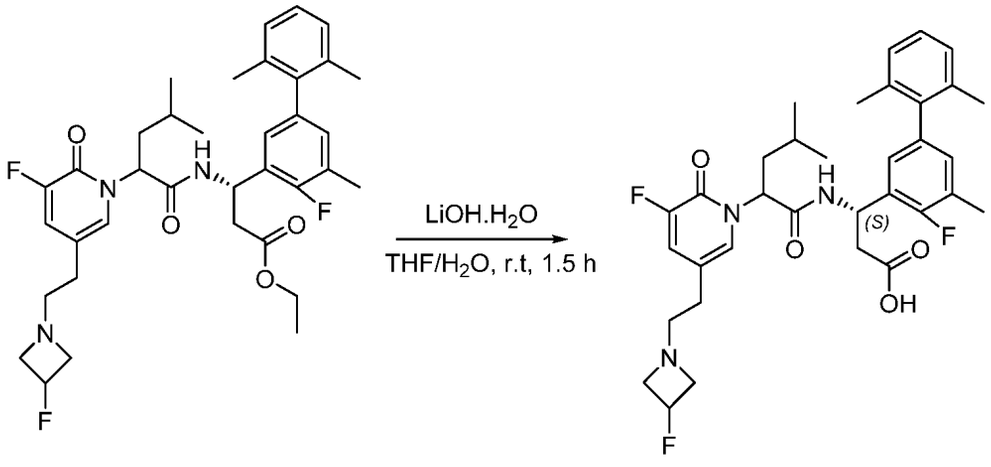
3-43. Preparation of (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds AV-P1 and AV-P2)

Step 1: ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (142 mg, 0.43 mmol), 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (120 mg, 0.36 mmol), TCHF (151 mg, 0.54 mmol) and NMI (147.6 mg, 1.8 mmol) in CH_3CN (4 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow solid(110 mg). Yield 48% (ESI 640.2 $[M+H]^+$).

Step 2: (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



Ethyl (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (110 mg, 0.17 mmol) was treated with LiOH-H_2O (36 mg, 0.86 mmol) in THF (20 mL) and water (8 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The

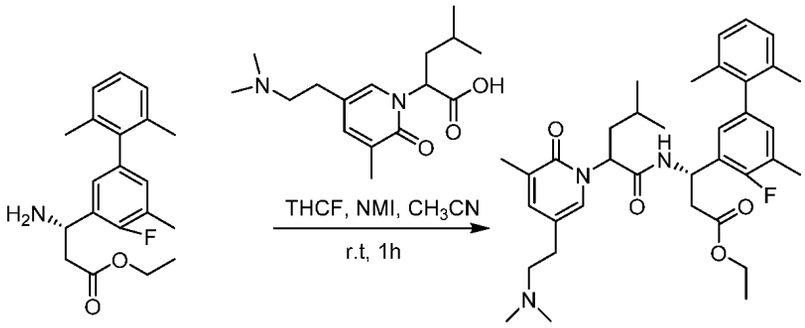
solvent was removed *in vacuo* and the residue was purified by preparotary HPLC B to give the diastereomeric product **AV-P1** (40 mg) and **AV-P2** (39 mg) as white solids.

AV-P1 ESI 612.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.76 (s, 0.18H, FA), 7.50 – 7.27 (m, 2H), 7.23 – 7.02 (m, 3H), 6.96 – 6.75 (m, 2H), 5.69 (t, *J* = 8.0 Hz, 1H), 5.50 (t, *J* = 6.1 Hz, 1H), 5.20 (d, *J* = 57.4 Hz, 1H), 4.11 (s, 1H), 3.95 (s, 1H), 3.75 – 3.53 (m, 2H), 3.21 – 3.05 (m, 2H), 2.85 – 2.52 (m, 4H), 2.30 (s, 3H), 2.05 – 1.82 (m, 8H), 1.56 – 1.32 (m, 1H), 1.06 – 0.83 (m, 6H).

AV-P2 ESI 612.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.36 (s, 0.27H, FA), 7.51 – 7.29 (m, 2H), 7.09 (t, *J* = 7.6 Hz, 3H), 6.94 (t, *J* = 7.0 Hz, 2H), 5.80 – 5.58 (m, 2H), 5.57 – 5.18 (m, 1H), 4.54 – 4.21 (m, 2H), 4.16 – 3.93 (m, 2H), 3.39 (d, *J* = 5.5 Hz, 2H), 2.83 – 2.48 (m, 4H), 2.33 (d, *J* = 1.6 Hz, 3H), 2.00 (s, 7H), 1.88 – 1.66 (m, 1H), 1.54 – 1.26 (m, 1H), 1.23 – 0.69 (m, 6H).

3-44. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds AW-P1 and AW-P2)

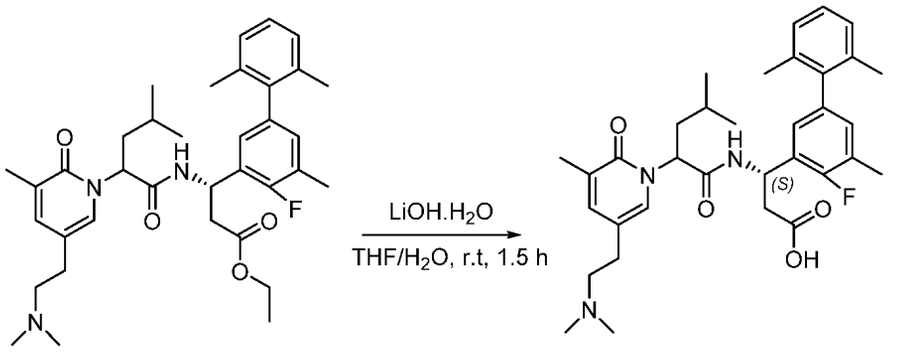
Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (130.0 mg, 0.44 mmol), 2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (145.0 mg, 0.44 mmol), TCHF (131 mg, 0.47 mmol) and NMI (96.0 mg, 1.17 mmol) in CH_3CN (4 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-

2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (130 mg). Yield 48.6% (ESI 606.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid

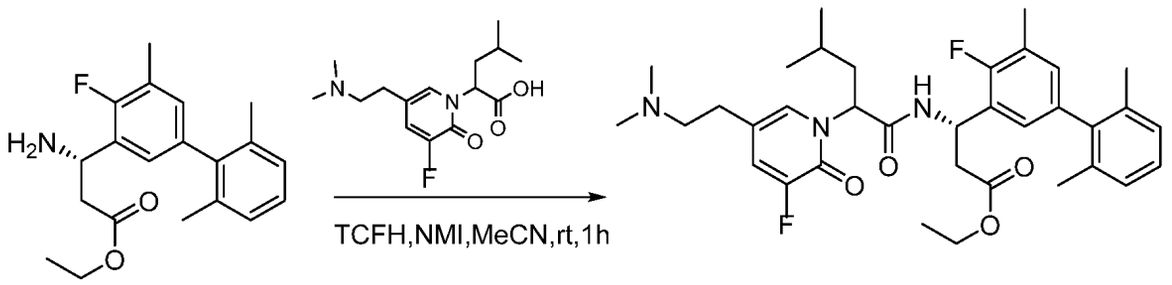


Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (130.0 mg, 0.21 mmol) was treated with LiOH-H_2O (46.0 mg, 1.0 mmol) in THF (6 mL) and water (3 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 1 N HCl. The solvent was removed *in vacuo* and the residue was purified by Prep HPLC A (30-60% MeCN) to give the diastereomeric products **AW-P1** (30.3 mg) and **AW-P2** (46.0 mg) as white solids.

AW-P1 ESI 578.3 $(M+H)^+$.^{1}H NMR (400 MHz, MeOD) δ 7.46 (s, 1H), 7.43 (s, 1H),7.17 – 7.07 (m, 3H), 6.88 – 6.86 (m, 1H), 6.74 – 6.71 (m, 1H), 5.57 – 5.54 (m, 1H), 5.36 (t, *J* = 5.0 Hz, 1H), 3.38 – 3.5 (m, 1H), 3.19 – 3.06 (m, 1H), 2.83 – 2.77 (m, 2H), 2.67 (s, 6H), 2.64 – 2.59 (m, 1H), 2.53 – 2.47 (m, 1H), 2.30 (d, *J* = 1.7 Hz, 3H), 2.05 (s, 3H), 1.98 – 1.93 (m, 8H), 1.48 – 1.39 (m, 1H), 0.95 – 0.89 (m, 6H).
AW-P2 ESI 578.3 $(M+H)^+$.^{1}H NMR (400 MHz, MeOD) δ 7.51 (s, 1H), 7.41 (s, 1H), 7.17 – 7.02 (m, 3H), 6.89 – 6.87 (m, 1H), 6.81 – 6.79 (m, 1H), 5.64 – 5.60 (m, 1H), 5.55 – 5.51 (m, 1H), 3.45 – 3.38 (m, 1H), 3.30 – 3.23 (m, 1H), 2.97 – 2.72 (m, 8H), 2.61 – 2.56 (m, 1H), 2.45 – 2.39 (m, 1H), 2.31 (d, *J* = 1.8 Hz, 3H), 2.06 – 1.80 (m, 11H), 1.46 – 1.39 (m, 1H), 0.94 – 0.88 (m, 6H).

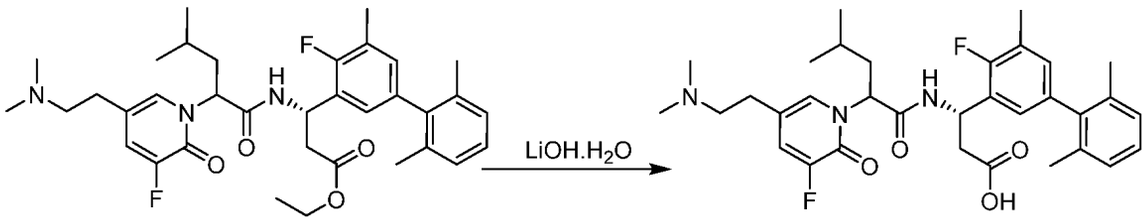
3-45. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (compounds AX-P1 and AX-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (109 mg, 0.36 mmol), (*S*)-ethyl 3-amino-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (120 mg, 0.36 mmol), TCFH (114 mg, 0.41 mmol) and NMI (84 mg, 1.02 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM:MeOH 4:1) to provide (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate as a white solid (130 mg). Yield 59% (ESI 610.2 $(M+H)^+$).

Step 2: (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid



(3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (130 mg, 0.21 mmol)) was treated with LiOH-H_2O (32 mg, 0.75 mmol) in THF (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by pre-HPLC A (30-60% MeCN) to give the diastereomeric products **AX-P1** (32.0 mg) and **AX-P2** (35.0 mg) as white solids.

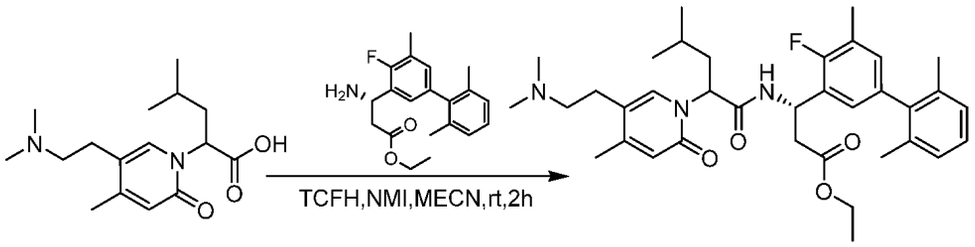
AX-P1 ESI 582.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.48 (s, 1H), 7.40 (d, J = 10.2 Hz, 1H), 7.15 – 7.08 (m, 3H), 6.86 (d, J = 6.8 Hz, 1H), 6.78 (d, J = 6.4 Hz, 1H), 5.67 (t, J = 8.1

Hz, 1H), 5.43 (t, *J* = 5.5 Hz, 1H), 3.18 – 3.13 (m, 1H), 3.03 – 2.99 (m, 1H), 2.81 – 2.77 (m, 2H), 2.68 – 2.53 (m, 8H), 2.29 (s, 3H), 2.00 – 1.94 (m, 5H), 1.92 (s, 3H), 1.45 – 1.39 (m, 1H), 0.96 – 0.90 (m, 6H).

AX-P2 ESI 582.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.43 – 7.40 (m, 1H), 7.15 – 7.07 (m, 3H), 6.91 (d, *J* = 6.9 Hz, 2H), 5.66 – 5.58 (m, 2H), 3.41 - 3.34 (m, 1H), 3.28 – 3.22 (m, 1H), 2.99 – 2.91 (m, 1H), 2.85 – 2.81 (m, 7H), 2.61 – 2.55 (m, 1H), 2.47-2.41 (m, 1H), 2.32 (d, *J* = 1.8 Hz, 3H), 2.04 – 1.97 (m, 7H), 1.85 – 1.77 (m, 1H), 1.44 – 1.36 (m, 1H), 0.92 – 0.89 (m, 6H).

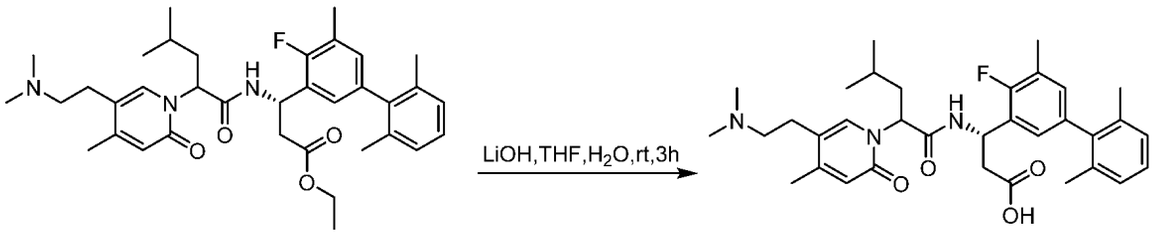
3-46. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (compounds AZ-P1 and AZ-P2)

Step 1: ethyl (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (100 mg, 0.34 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (112 mg, 0.34 mmol), TCFH (115 mg, 0.41 mmol), NMI (84 mg, 1.02 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM:MeOH 4:1) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (90 mg). Yield 44% (ESI 606.2 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid



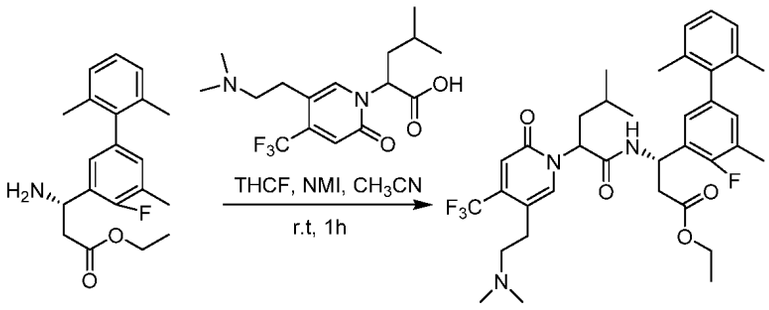
Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (90 mg, 0.15 mmol)) was treated with LiOH-H_2O (32 mg, 0.75 mmol) in THF (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **AZ-P1** (30.0 mg) and **AZ-P2** (26.0 mg) as white solids.

AZ-P1 ESI 578.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.57 (s, 1H), 7.18 – 7.03 (m, 3H), 6.86 – 6.81 (m, 2H), 6.35 (s, 1H), 5.59 – 5.55 (m, 1H), 5.49 – 5.46 (m, 1H), 3.25 – 3.16 (m, 1H), 3.13 – 3.108 (m, 1H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.75 (s, 6H), 2.70 – 2.59 (m, 2H), 2.29 (d, *J* = 1.5 Hz, 3H), 2.26 (s, 3H), 1.99 – 1.94 (m, 5H), 1.90 (s, 3H), 1.46 – 1.37 (m, 1H), 0.94 – 0.89 (m, 6H).

AZ-P2 ESI 578.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.55 (s, 1H), 7.15 – 7.07 (m, 3H), 6.90 (d, *J* = 6.9 Hz, 2H), 6.43 (s, 1H), 5.65 – 5.56 (m, 2H), 3.31 – 3.28 (m, 1H), 3.22 – 3.15 (m, 1H), 2.98 – 2.88 (m, 2H), 2.84 (s, 6H), 2.63 – 2.59 (m, 1H), 2.50 – 2.44 (m, 1H), 2.32 (d, *J* = 1.5 Hz, 3H), 2.26 (s, 3H), 2.03 – 1.91 (m, 7H), 1.80 – 1.72 (m, 1H), 1.42 – 1.32 (m, 1H), 0.90 – 0.88 (m, 6H).

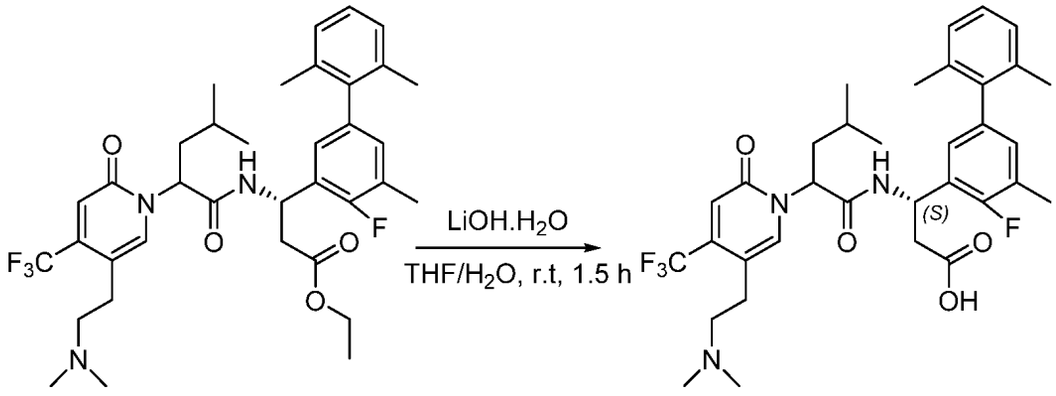
3-47. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds BA-P1 and BA-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (95.0 mg, 0.29 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100.0 mg, 0.29 mmol), TCHF (97.0 mg, 0.35 mmol) and NMI (71.0 mg, 0.87 mmol) in CH_3CN (4 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40 g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (100.0 mg). Yield 52.3% (ESI 660.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



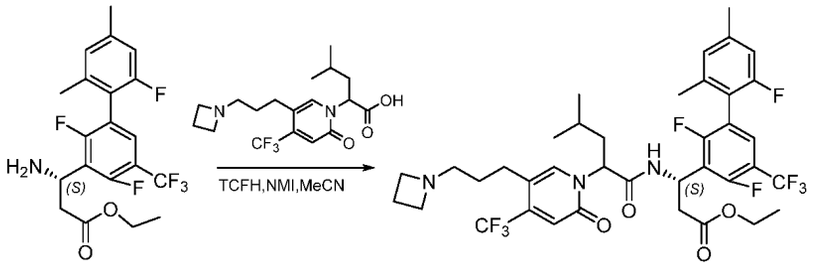
Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (100.0 mg, 0.15 mmol) was treated with LiOH-H_2O (32.0 mg, 0.75 mmol) in THF (3 mL) and water (1 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **BA-P1** (16.4 mg) and **BA-P2** (12.5 mg) as white solids.

BA-P1 ESI 632.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.77 (s, 1H), 7.03 – 6.86 (m, 3H), 6.79 – 6.70 (m, 2H), 6.64 (s, 1H), 5.56 (t, *J* = 8.0 Hz, 1H), 5.48 – 5.38 (m, 1H), 2.98 – 2.92 (m, 2H), 2.83 – 2.78 (m, 2H), 2.62-2.59 (m, 8H), 2.17 (s, 3H), 1.87 (d, *J* = 11.3 Hz, 5H), 1.71 (s, 3H), 1.34 – 1.30 (m, 1H), 0.85 – 0.81 (m, 6H).

BA-P2 ESI 632.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.71 (s, 1H), 7.03 – 6.95 (m, 3H), 6.82 – 6.77 (m, 3H), 5.60 – 5.57 (m, 1H), 5.49 (t, *J* = 7.7 Hz, 1H), 3.15 – 3.06 (m, 2H), 2.88 (t, *J* = 6.6 Hz, 2H), 2.70 (s, 6H), 2.54 – 2.50 (m, 1H), 2.42 – 2.37 (m, 1H), 2.21 (s, 3H), 1.90 – 1.85 (m, 7H), 1.62 – 1.52 (m, 1H), 1.33 – 1.22 (m, 1H), 0.79 – 0.77 (m, 6H).

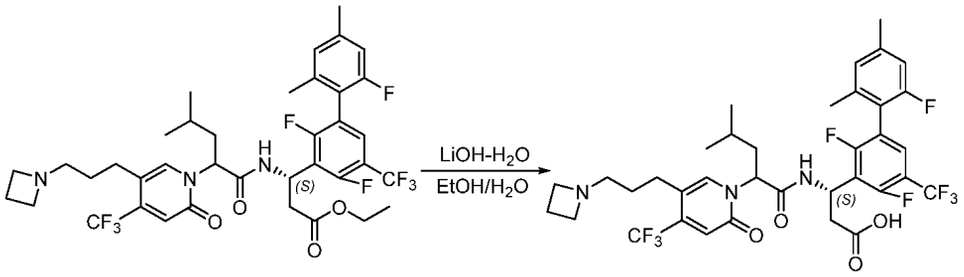
3-48. Preparation of (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds HD-P1 and HD-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100 mg, 0.28 mmol), (3*S*)-ethyl 3-amino-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (120 mg, 0.29 mmol), NMI (71 mg, 0.87 mmol) and TCFH (98 mg, 0.35 mmol) in CH_3CN (4 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (110 mg). Yield 52 % (ESI 776.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



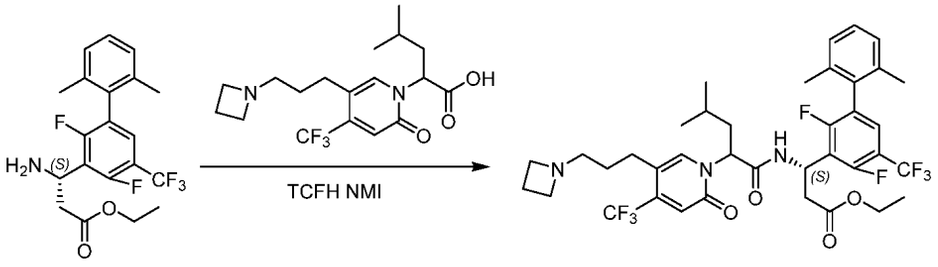
(3*S*)-ethyl 3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (110 mg, 0.14 mmol) was treated with LiOH-H_2O (24 mg, 0.56 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **HD-P1** (27 mg) and **HD-P2** (28 mg) as white solids.

HD-P1 ESI 748.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 7.53 – 7.43 (m, 1H), 6.98 (s, 1H), 6.90 – 6.73 (m, 2H), 5.81 – 5.71 (m, 2H), 4.05 (t, *J* = 8.1 Hz, 4H), 3.14 (t, *J* = 7.7 Hz, 2H), 3.01 – 2.89 (m, 1H), 2.84 – 2.53 (m, 3H), 2.51 – 2.30 (m, 5H), 2.18 – 1.90 (m, 5H), 1.90 – 1.66 (m, 2H), 1.46 – 1.23 (m, 1H), 1.06 – 0.86 (m, 6H).

HD-P2 ESI 748.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.00 (s, 1H), 6.93 – 6.75 (m, 2H), 5.89 – 5.73 (m, 1H), 5.69 – 5.62 (m, 1H), 4.17 – 3.93 (m, 4H), 3.21 – 3.00 (m, 2H), 2.94 – 2.84 (m, 1H), 2.75 – 2.56 (m, 3H), 2.51 – 2.30 (m, 5H), 2.10 (d, *J* = 11.8 Hz, 3H), 1.98 – 1.55 (m, 4H), 1.42 – 1.22 (m, 1H), 0.92 – 0.80 (m, 6H).

3-49. Preparation of (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HE-P1 and HE-P2)

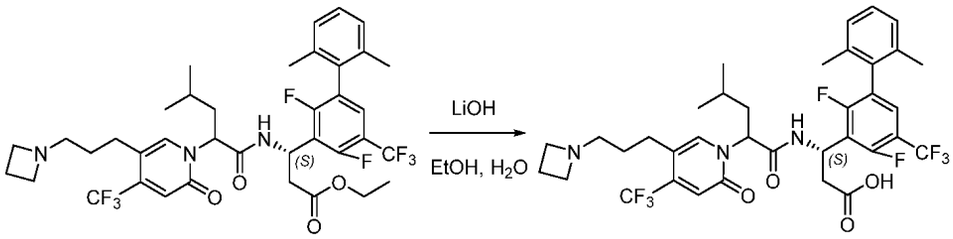
Step 1: ethyl (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (116 mg, 0.29 mmol), 2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-

1(2H)-yl)-4-methylpentanoic acid (100 mg, 0.27 mmol), TCFH (151 mg, 0.54 mmol) and NMI (110 mg, 1.35 mmol) in CH_3CN (2 mL) was stirred at 25 °C for 2 hr. The solvent was concentrated *in vacuo* and the residue was purified The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (120 mg). Yield 58.6 % (ESI 758.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



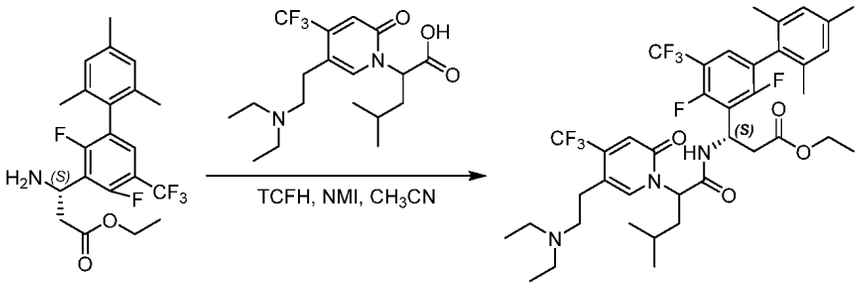
Ethyl (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (120 mg, 0.16 mmol) was treated with $LiOH-H_2O$ (13 mg, 0.32 mmol) in EtOH (2 mL) and H_2O (0.5 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (40-65% CH_3CN) to give the diastereomeric products **HE-P1** (40 mg) and **HE-P2** (42 mg) as yellow solids.

HE-P1 ESI 730.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.23 – 7.16 (m, 1H), 7.14 – 7.08 (m, 2H), 6.78 (s, 1H), 5.78 – 5.70 (m, 2H), 3.88 (s, 4H), 3.05 – 2.91 (m, 3H), 2.76 – 2.70 (m, 1H), 2.66 – 2.57 (m, 2H), 2.41 – 2.32 (m, 2H), 2.09 – 1.91 (m, 6H), 1.90 (s, 3H), 1.77 – 1.69 (m, 1H), 1.36 – 1.30 (m, 1H), 0.99 – 0.85 (m, 6H).

HE-P2 ESI 730.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.15 (d, *J* = 7.4 Hz, 2H), 6.84 (s, 1H), 5.85 – 5.79 (m, 1H), 5.63 (t, *J* = 7.6 Hz, 1H), 4.08 (s, 4H), 3.18 – 3.05 (m, 2H), 2.95 – 2.87 (m, 1H), 2.71 – 2.59 (m, 3H), 2.48 – 2.39 (m, 2H), 2.02 (d, *J* = 5.7 Hz, 6H), 1.95 – 1.78 (m, 3H), 1.70 – 1.60 (m, 1H), 1.34 – 1.27 (m, 1H), 0.90 – 0.82 (m, 6H).

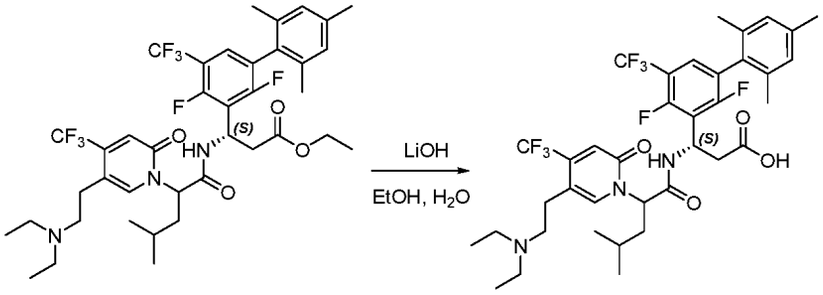
3-50. Preparation of (3*S*)-3-(2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HF-P1 and HF-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (125 mg, 0.3 mmol), 2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (120 mg, 0.32 mmol), TCFH (150 mg, 0.54 mmol) and NMI (110 mg, 1.35 mmol) in CH_3CN (2.5 mL) was stirred at 50 °C for 30 mins. The reaction was concentrated *in vacuo* and the residue purifiedThe reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3S)-3-(2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (140 mg). Yield 60.3 % (ESI 774.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



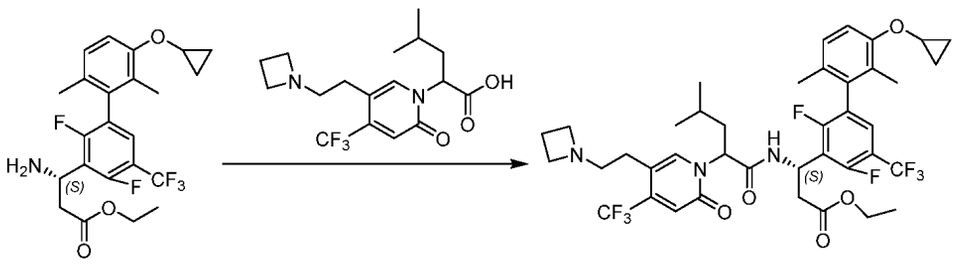
Ethyl (3*S*)-3-(2-(5-(2-(diethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (140 mg, 0.18 mmol) was treated with LiOH-H_2O (23 mg, 0.54 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (35-60% CH_3CN) to give the diastereomeric products **HF-P1** (46 mg) and **HF-P2** (50 mg) as white solids.

HF-P1 ESI 746.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 4.0 Hz, 2H), 6.82 (s, 1H), 5.79 – 5.67 (m, 2H), 3.25 – 3.11 (m, 6H), 3.04 – 2.88 (m, 3H), 2.78 – 2.69 (m, 1H), 2.29 (s, 3H), 2.06 – 1.91 (m, 5H), 1.86 (s, 3H), 1.42 – 1.35 (m, 1H), 1.28 (t, *J* = 7.3 Hz, 6H), 0.94 (t, *J* = 6.5 Hz, 6H).

HF-P2 ESI 746.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 6.96 (s, 2H), 6.88 (s, 1H), 5.82 – 5.64 (m, 2H), 3.29 – 3.15 (m, 6H), 2.96 (t, *J* = 7.7 Hz, 2H), 2.91 – 2.82 (m, 1H), 2.70 (d, *J* = 15.0 Hz, 1H), 2.31 (s, 3H), 1.98 (d, *J* = 4.2 Hz, 6H), 1.92 – 1.79 (m, 1H), 1.77 – 1.67 (m, 1H), 1.36 – 1.23 (m, 7H), 0.93 – 0.82 (m, 6H).

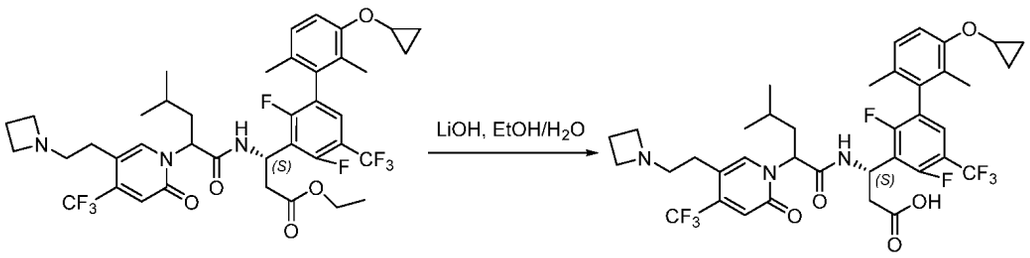
3-51. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds HG-P1 and HG-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (3*S*)-ethyl 3-amino-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (150 mg, 0.33 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (119 mg, 0.33 mmol), TCFH (174 mg, 0.62 mmol) and NMI (82 mg, 1.0 mmol) in MeCN (5mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 97: 3) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a colorless oil (130 mg). Yield 53% (ESI 800.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



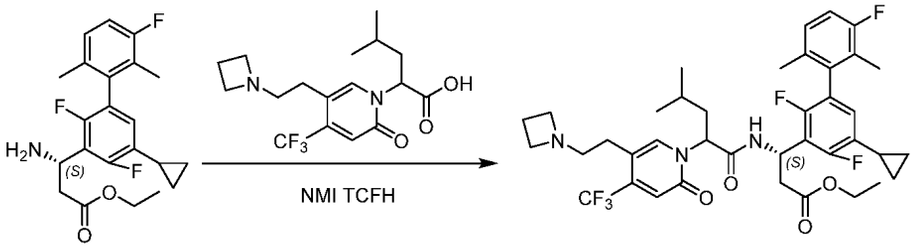
(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3'-cyclopropoxy-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (120 mg, 0.16 mmol) was treated with LiOH-H_2O (35 mg, 0.9 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated *in vacuo* and the residue purifiedThe reaction was concentrated in vacuo and the residue purifiedby prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **HG-P1** (30.1 mg) and **HG-P2** (42.0 mg) as white solids.

HG-P1 ESI 772.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 6.85 (s, 1H), 5.71-5.68 (m, 2H), 4.04 (t, *J* = 8.0 Hz, 4H), 3.82 – 3.73 (m, 1H), 3.29 – 3.18 (m, 2H), 2.92 (dd, *J* = 15.0, 8.7 Hz, 1H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.77 – 2.69 (m, 1H), 2.48 – 2.37 (m, 2H), 2.04 – 1.85 (m, 5H), 1.81 – 1.69 (m, 3H), 1.38 (dd, *J* = 13.7, 7.2 Hz, 1H), 0.93 (t, *J* = 6.2 Hz, 6H), 0.78 (dd, *J* = 11.2, 5.2 Hz, 2H), 0.70 (t, *J* = 6.8 Hz, 2H).

HG-P2 ESI 772.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 13.3 Hz, 1H), 5.90 (dd, *J* = 10.8, 4.2 Hz, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.12 (t, *J* = 8.0 Hz, 4H), 3.79-3.75 (m, 1H), 3.48 – 3.33 (m, 2H), 3.01 – 2.76 (m, 3H), 2.60 (dd, J = 15.5, 4.1 Hz, 1H), 2.53 – 2.35 (m, 2H), 2.02 – 1.85 (m, 4H), 1.81 (d, *J* = 3.2 Hz, 3H), 1.76 – 1.67 (m, 1H), 1.34-1.30 (m, 1H), 1.02 – 0.81 (m, 6H), 0.81-0.75 (m, 2H), 0.70 (d, *J* = 3.1 Hz, 2H).

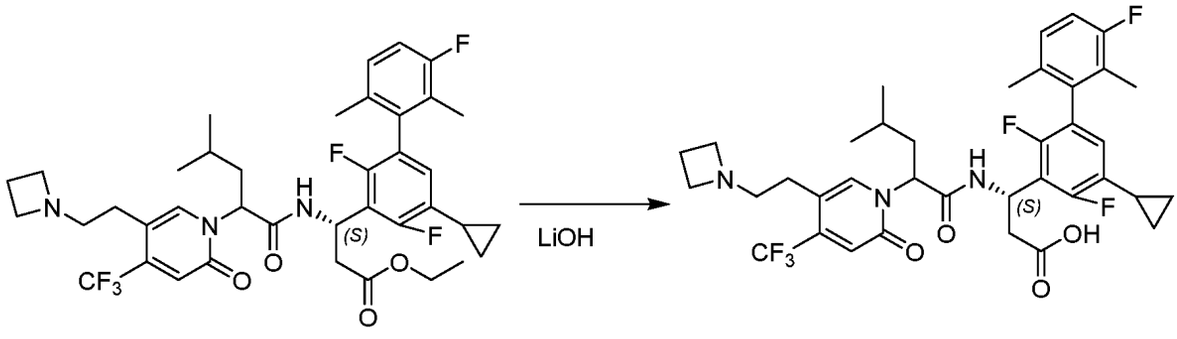
3-52. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HH-P1 and HH-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (120 mg, 0.3 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (108 mg, 0.3 mmol), *TCFH* (126 mg, 0.45 mmol) and NMI (123 mg, 1.5 mmol) in CH_3CN (3 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 20~95%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (140 mg). Yield 62% (ESI 734.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



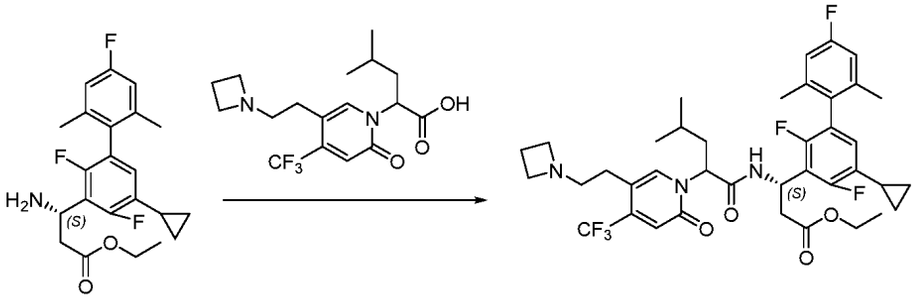
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (140 mg, 0.19 mmol) was treated with LiOH-H_2O (24 mg, 0.57 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (20-85% MeCN) to give the diastereomeric products **HH-P1** (35 mg) and **HH-P2** (58 mg) as white solids.

HH-P1 ESI 706.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.12 – 7.03 (m, 1H), 7.00 – 6.91 (m, 1H), 6.87 (s, 1H), 6.62 (t, *J* = 8.0 Hz, 1H), 5.80 – 5.58 (m, 2H), 4.00 (t, *J* = 7.7 Hz, 4H), 3.30 – 3.19 (m, 2H), 2.97 – 2.78 (m, 3H), 2.71 – 2.62 (m, 1H), 2.49 – 2.34 (m, 2H), 2.13 – 1.76 (m, 9H), 1.46 – 1.33 (m, 1H), 1.00 – 0.86 (m, 8H), 0.66 (d, *J* = 4.8 Hz, 2H).

HH-P2 ESI 706.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.70 (s, 1H), 7.14 – 7.04 (m, 1H), 7.02 – 6.87 (m, 2H), 6.67 (t, *J* = 8.1 Hz, 1H), 5.98 – 5.86 (m, 1H), 5.62 (t, *J* = 7.7 Hz, 1H), 4.11 (t, *J* = 8.1 Hz, 4H), 3.45 – 3.33 (m, 2H), 2.99 – 2.71 (m, 3H), 2.60 – 2.36 (m, 3H), 2.17 – 2.03 (m, 1H), 2.00 – 1.86 (m, 7H), 1.80 – 1.67 (m, 1H), 1.41 – 1.29 (m, 1H), 1.06 – 0.94 (m, 2H), 0.93 – 0.82 (m, 6H), 0.72 – 0.62 (m, 2H).

3-53. Preparation of (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HI-P1 and HI-P2)

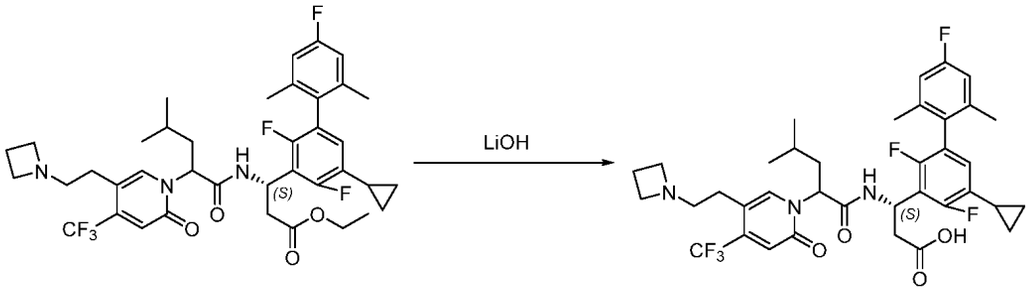
Step 1: ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (150 mg, 0.42 mmol), ethyl (S)-3-amino-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (162 mg, 0.42 mmol), NMI (0.14mL) and TCFH (141 mg, 0.504 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (30-90% CH_3CN) to provide ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (160 mg). Yield 52% (ESI 734.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-

yl)propanoic acid



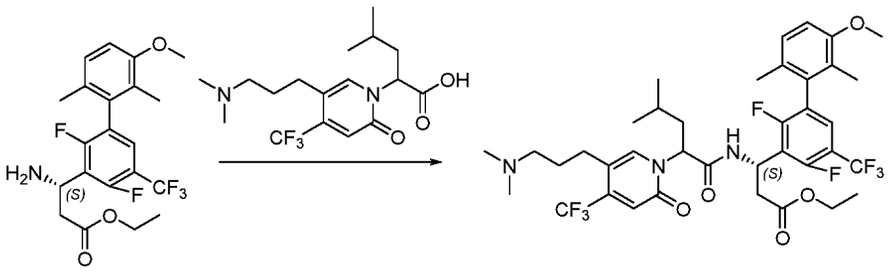
Ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4,4'-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoate (160 mg, 0.22 mmol) was treated with LiOH-H_2O (46 mg, 1.1 mmol) in MeOH (4 mL) and H_2O (0.4 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-70% CH_3CN) to give the diastereomeric products **HI-P1** (44.0 mg) and **HI-P2** (36.0 mg) as white solids.

HI-P1 ESI 706.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 6.91 – 6.79 (m, 3H), 6.61 (t, *J* = 8.2 Hz, 1H), 5.82 – 5.71 (m, 1H), 5.67 (t, *J* = 8.1 Hz, 1H), 4.01 (t, *J* = 8.1 Hz, 4H), 3.28 – 3.22 (m, 2H), 2.94 – 2.79 (m, 3H), 2.72 – 2.60 (m, 1H), 2.49 – 2.34 (m, 2H), 2.11 – 1.87 (m, 9H), 1.45 – 1.33 (m, 1H), 1.04 – 0.85 (m, 8H), 0.70 – 0.60 (m, 2H).

HI-P2 ESI 706.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 6.93 (s, 1H), 6.86 (d, *J* = 9.6 Hz, 2H), 6.66 (t, *J* = 8.1 Hz, 1H), 5.98 – 5.85 (m, 1H), 5.62 (t, *J* = 7.7 Hz, 1H), 4.12 (t, *J* = 8.1 Hz, 4H), 3.44 – 3.34 (m, 2H), 2.97 – 2.72 (m, 3H), 2.58 – 2.36 (m, 3H), 2.14 – 2.04 (m, 1H), 2.02 – 1.88 (m, 7H), 1.80 – 1.66 (m, 1H), 1.46 – 1.26 (m, 1H), 1.07 – 0.96 (m, 2H), 0.94 – 0.81 (m, 6H), 0.72 – 0.63 (m, 2H).

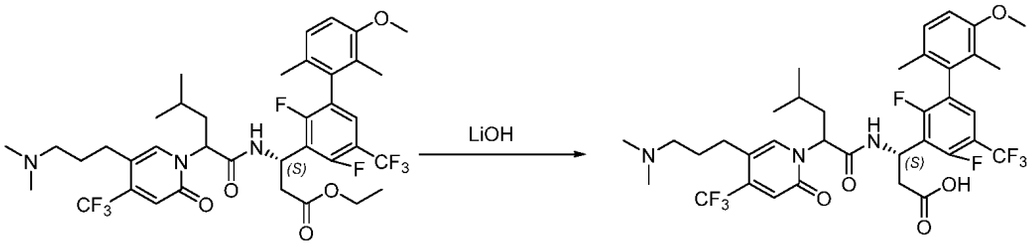
3-54. Preparation of (3S)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds HJ-P1 and HJ-P2)

Step 1: ethyl (3S)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (150 mg, 0.41 mmol), ethyl (3S)-3-amino-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (176 mg, 0.41 mmol), NMI (0.15mL) and TCFH (141 mg, 0.507 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (30-90% CH_3CN) to provide ethyl (3S)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (160 mg). Yield 52% (ESI 776.3 $[M+H]^+$).

Step 2: (3S)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



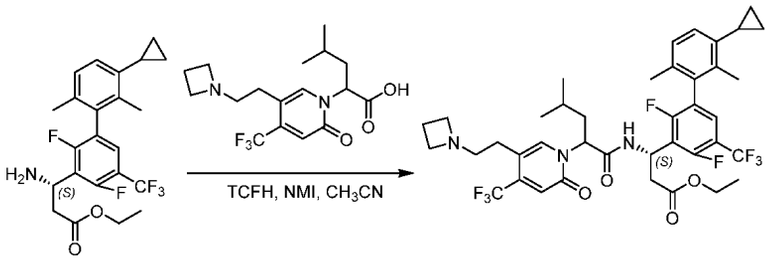
Ethyl (3S)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (160 mg, 0.21 mmol) was treated with LiOH-H_2O (46 mg, 1.1 mmol) in MeOH (4 mL) and H_2O (0.4 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-70% CH_3CN) to give the diastereomeric products **HJ-P1** (36.0 mg) and **HJ-P2** (41.0 mg) as white solids.

HJ-P1 ESI 748.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.12 – 7.03 (m, 1H), 6.89 (d, J = 8.3 Hz, 1H), 6.80 (s, 1H), 5.82 – 5.67 (m, 2H), 3.82 (s, 3H), 3.08 (t, J = 8.1 Hz, 2H), 2.98 – 2.91 (m, 1H), 2.80 (s, 6H), 2.75 – 2.58 (m, 3H), 2.10 – 1.69 (m, 10H), 1.35 (s, 1H), 0.93 (d, J = 6.6 Hz, 6H).

HJ-P2 ESI 748.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 1H), 6.85 (s, 1H), 5.88 – 5.77 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.84 (s, 3H), 3.15 – 2.95 (m, 2H), 2.96 – 2.84 (m, 1H), 2.79 (s, 6H), 2.70 – 2.58 (m, 3H), 2.11 – 1.83 (m, 9H), 1.72 – 1.57 (m, 1H), 1.42 – 1.17 (m, 1H), 0.97 – 0.70 (m, 6H).

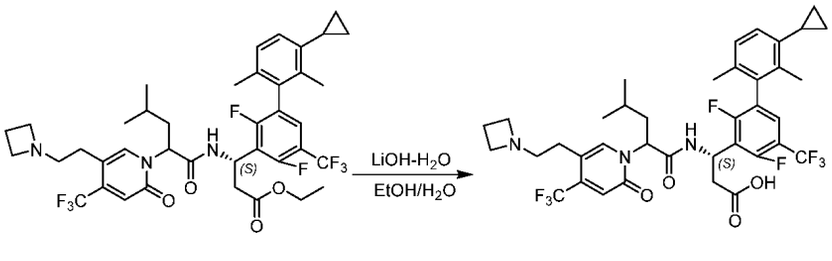
3-55. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HK-P1 and HK-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (210.0 mg, 0.48 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (136.9 mg, 0.38 mmol), TCFH (134.7 mg, 0.48 mmol) and NMI (118.2 mg, 1.44 mmol) in CH_3CN (5 mL) was stirred at room temperature for 16 hours. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (100.0 mg). Yield 34% (ESI 784.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



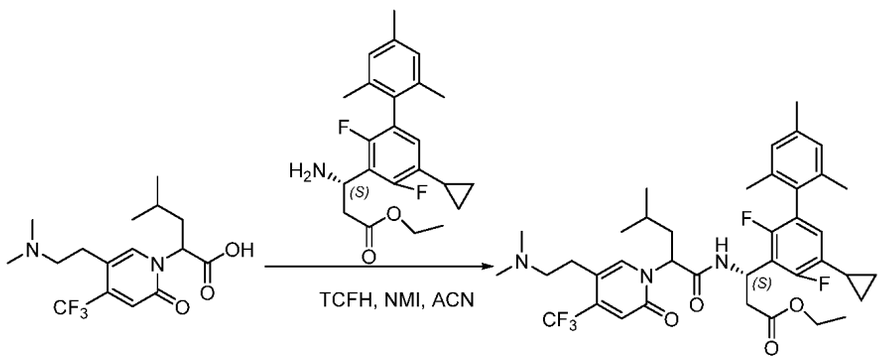
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (100.0 mg, 0.13 mmol) was treated with LiOH-H_2O (16.4 mg, 0.39 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **HK-P1** (5.6 mg) and **HK-P2** (48.8 mg) as white solids.

HK-P1 ESI 756.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (d, *J* = 3.7 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.07 – 6.97 (m, 2H), 6.86 (d, *J* = 3.2 Hz, 1H), 5.78 – 5.65 (m, 2H), 4.04 (t, *J* = 8.1 Hz, 4H), 3.29 – 3.21 (m, 2H), 2.96 – 2.88 (m, 1H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.77 – 2.70 (m, 1H), 2.51 – 2.35 (m, 2H), 2.11 – 1.96 (m, 4H), 1.97 – 1.82 (m, 5H), 1.44 – 1.31 (m, 1H), 0.96 – 0.89 (m, 8H), 0.65 – 0.54 (m, 2H).

HK-P2 ESI 756.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.08 – 7.00 (m, 2H), 6.91 (s, 1H), 5.91 (d, *J* = 8.6 Hz, 1H), 5.67 – 5.61 (m, 1H), 4.12 (t, *J* = 8.1 Hz, 4H), 3.344 – 3.32 (m, 2H), 2.97 – 2.74 (m, 3H), 2.64 – 2.57 (m, 1H), 2.51 – 2.39 (m, 2H), 2.10 (d, *J* = 2.5 Hz, 3H), 1.99 – 1.86 (m, 5H), 1.76 – 1.67 (m, 1H), 1.40 – 1.28 (m, 1H), 0.96 – 0.83 (m, 8H), 0.65 – 0.57 (m, 2H).

3-56. Preparation of (3*S*)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds HL-P1 and HL-P2)

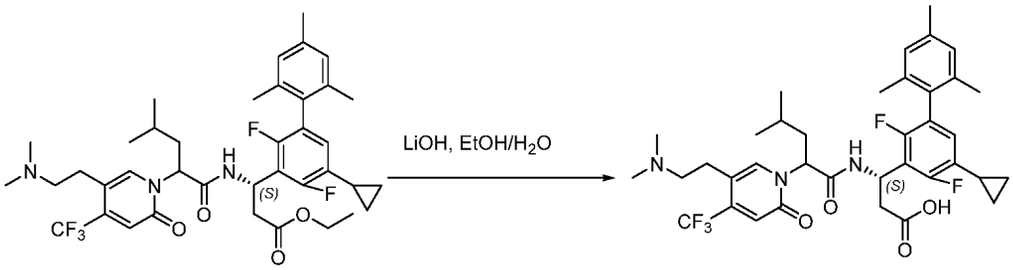
Step 1: (3*S*)-ethyl 3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of (*S*)-ethyl 3-amino-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)propanoate (120 mg, 0.31 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-

1(2H)-yl)-4-methylpentanoic acid (108 mg, 0.31 mmol), TCFH (174 mg, 0.62 mmol) and NMI (82 mg, 1.0 mmol) in MeCN (5mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 97: 3) to provide (3*S*)-ethyl 3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a colorless oil (130 mg). Yield 59% (ESI 718.3 $(M+H)^+$).

Step 2: (3*S*)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



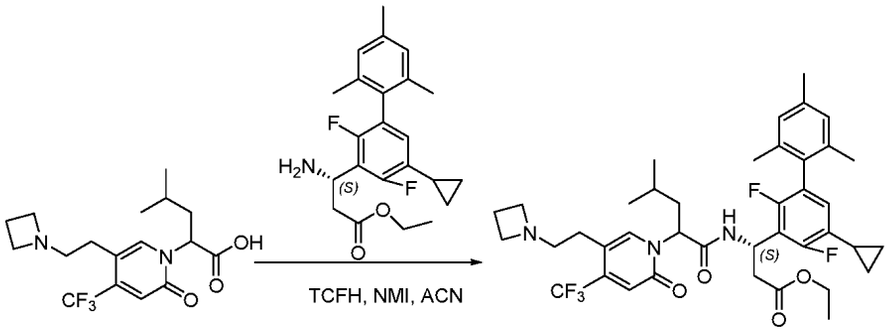
(3*S*)-ethyl 3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (130 mg, 0.18 mmol) was treated with LiOH-H_2O (38 mg, 0.9 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **HL-P1** (50.2 mg) and **HL-P2** (41.8 mg) as white solids.

HL-P1 ESI 690.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 6.88 (t, *J* = 18.3 Hz, 3H), 6.56 (t, *J* = 7.8 Hz, 1H), 5.71 (dd, *J* = 15.9, 7.0 Hz, 2H), 3.08 (d, *J* = 7.9 Hz, 2H), 3.00 – 2.81 (m, 3H), 2.84 – 2.55-2.50 (m, 7H), 2.27 (s, 3H), 2.09 – 2.00 (m, 1H), 1.96 (dd, *J* = 14.8, 7.0 Hz, 2H), 1.92 (s, 3H), 1.84 (s, 3H), 1.40-1.38 (m, 1H), 0.93 (t, *J* = 6.5 Hz, 8H), 0.63 (d, *J* = 5.1 Hz, 2H).

HL-P2 ESI 690.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 6.88 (t, *J* = 18.3 Hz, 3H), 6.56 (t, *J* = 7.8 Hz, 1H), 5.71 (dd, *J* = 15.9, 7.0 Hz, 2H), 3.08 (d, *J* = 7.9 Hz, 2H), 3.00 – 2.81 (m, 3H), 2.84 – 2.55-2.50 (m, 7H), 2.27 (s, 3H), 2.09 – 2.00 (m, 1H), 1.96 (dd, *J* = 14.8, 7.0 Hz, 2H), 1.92 (s, 3H), 1.84 (s, 3H), 1.40-1.37 (m, 1H), 0.93 (t, *J* = 6.5 Hz, 8H), 0.63 (d, *J* = 5.1 Hz, 2H).

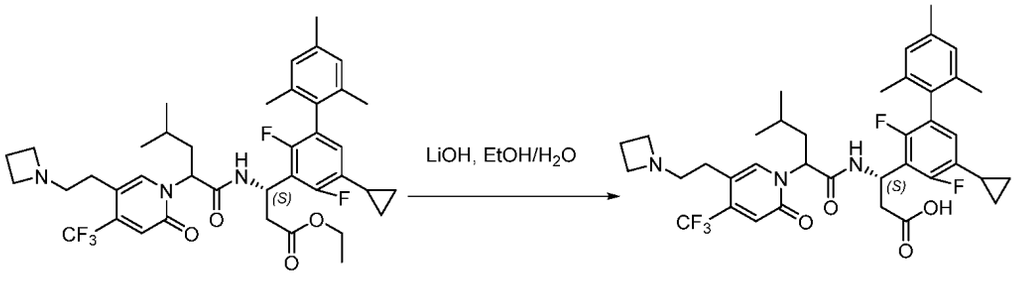
3-57. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)propanoic acid (compounds HM-P1 and HM-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)propanoate



A mixture of (*S*)-ethyl 3-amino-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)propanoate (120 mg, 0.31 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (112 mg, 0.31 mmol), TCFH (174 mg, 0.62 mmol) and NMI (82 mg, 1.0 mmol) in MeCN (5mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 97: 3) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)propanoate as a colorless oil (120 mg). Yield 53% (ESI 730.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)propanoic acid



(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(5-cyclopropyl-2,4-difluoro-2',4',6'-trimethylbiphenyl-3-yl)propanoate (120 mg, 0.16 mmol) was treated with LiOH-H_2O (35 mg, 0.9 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **HM-P1** (30.2 mg) and **HM-P2** (31.8 mg) as white solids.

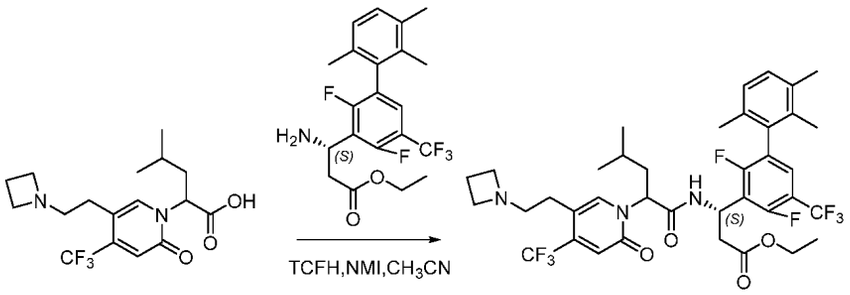
HM-P1 ESI 702.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 6.97 – 6.79 (m, 3H), 6.58 (t, *J* = 8.1 Hz, 1H), 5.84 – 5.61 (m, 2H), 4.00 (t, *J* = 8.1 Hz, 4H), 3.30 – 3.21 (m, 2H), 2.88-2.85 (m, 3H),

2.67 (dd, *J* = 14.8, 4.8 Hz, 1H), 2.48 – 2.37 (m, 2H), 2.28 (d, *J* = 6.4 Hz, 3H), 2.13 – 1.96 (m, 3H), 1.90 (d, *J* = 21.3 Hz, 6H), 1.46 – 1.31 (m, 1H), 0.94 -0.90(m, 8H), 0.64-0.62 (m, 2H).

HM-P2 ESI 702.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.70 (s, 1H), 7.00 – 6.86 (m, 3H), 6.63 (t, J = 8.2 Hz, 1H), 5.93 (dd, *J* = 11.4, 3.5 Hz, 1H), 5.62 (t, *J* = 7.7 Hz, 1H), 4.11 (t, *J* = 8.0 Hz, 4H), 3.50 – 3.33 -3.30(m, 2H), 2.97 – 2.76 (m, 3H), 2.47-2.45 (m, 3H), 2.29 (s, 3H), 2.08-2.05 (m, 1H), 2.00 – 1.89 (m, 7H), 1.74-1.70 (m, 1H), 1.37 -1.35(m, 1H), 1.04 – 0.95 (m, 2H), 0.88 (dd, *J* = 11.4, 6.6 Hz, 6H), 0.67-0.65 (m, 2H).

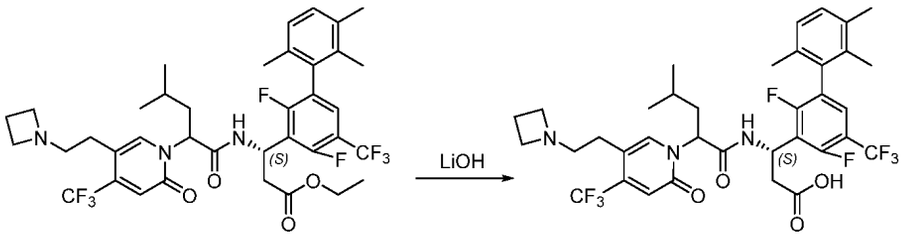
3-58. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HN-P1 and HN-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (120.0 mg, 0.33 mmol), ethyl (3*S*)-3-amino-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (138.3 mg, 0.33 mmol), TCFH (184.8 mg, 0.66 mmol) and NMI (108.2 mg, 1.32 mmol) in CH_3CN (10 mL) was stirred at room temperature for 1 hour. The reaction was concentrated in vacuo and the residue purified by silica gel column (DCM: MeOH 4: 1) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a brown solid (125.0 mg). Yield 50% (ESI 758.7 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



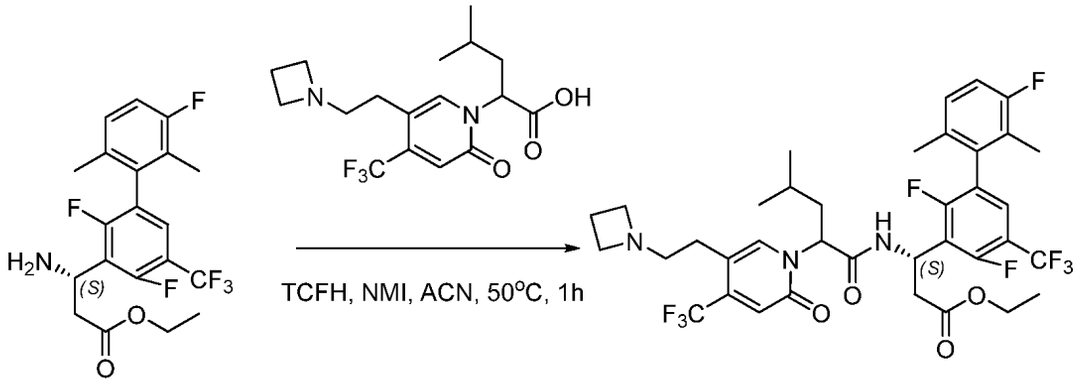
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (122 mg, 0.16 mmol)) was treated with LiOH-H_2O (26.9 mg, 0.64 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **HN-P1** (36.1 mg) and **HN-P2** (37.6 mg) as white solids.

HN-P1 ESI 730.7$(M+H)^+$. 1H NMR (400 MHz, DMSO) δ 9.29 (d, *J* = 6.4 Hz, 1H), 7.72 (s, 1H), 7.50 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 5.1 Hz, 1H), 5.58 – 5.50 (m, 1H), 5.44 (s, 1H), 3.18 – 3.03 (m, 5H), 2.98 – 2.79 (m, 3H), 2.39 – 2.30 (m, 2H), 2.23 (d, *J* = 6.6 Hz, 3H), 1.99 – 1.63 (m, 10H), 1.28 (d, *J* = 35.1 Hz, 1H), 0.90 – 0.70 (m, 6H).

HN-P2 ESI 730.7 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.91 (s, 1H), 5.98 – 5.84 (m, 1H), 5.63 (d, *J* = 7.7 Hz, 1H), 4.12 (t, *J* = 8.1 Hz, 4H), 3.43 – 3.34 (m, 2H), 2.92 – 2.77 (m, 3H), 2.63 – 2.53 (m, 1H), 2.53 – 2.42 (m, 2H), 2.29 (s, 3H), 1.98 – 1.85 (m, 7H), 1.77 – 1.66 (m, 1H), 1.39 – 1.27 (m, 1H), 0.92 – 0.76 (m, 6H).

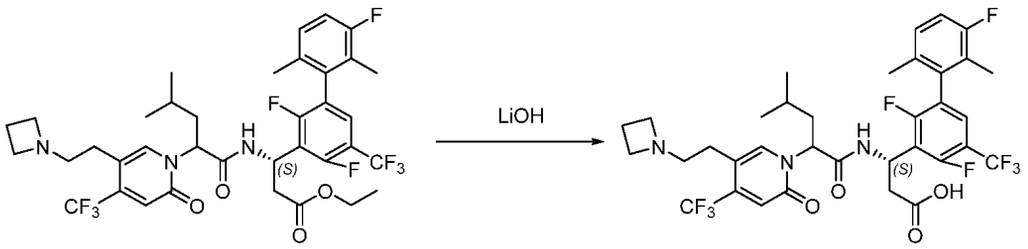
3-59. Preparation of (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds HO-P1 and HO-P2)

Step 1: (3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (3S)-ethyl 3-amino-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (100 mg, 0.24 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (86 mg, 0.24 mmol), NMI (59 mg, 0.72 mmol) and TCFH (101 mg, 0.36 mmol) in CH_3CN (5 mL) was stirred at 50°C for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 12:1) to provide (3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (116 mg). Yield 63.8 % (ESI 762.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



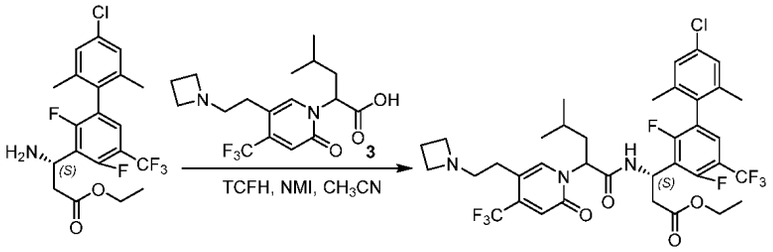
(3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (116 mg, 0.15 mmol) was treated with LiOH-H_2O (18.9 mg, 0.45 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **HO-P1** (34 mg) and **HO-P2** (26 mg) as white solids.

HO-P1 ESI 734.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 6.3 Hz, 1H), 7.02 (t, J = 8.9 Hz, 1H), 6.84 (s, 1H), 5.76 – 5.65 (m, 2H), 4.05 (t, J = 8.1 Hz, 4H), 3.29 – 3.18 (m, 2H), 2.96 – 2.87 (m, 1H), 2.84 (t, J = 6.9 Hz, 2H), 2.79– 2.72 (m, 1H), 2.49– 2.41 (m, 2H), 1.99– 1.89 (m, 8H), 1.39– 1.33 (m, 1H), 0.96 – 0.91 (m, 6H).

HO-P2 ESI 734.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.21 – 7.12 (m, 1H), 7.05 (t, *J* = 9.0 Hz, 1H), 6.91 (s, 1H), 5.92 – 5.86 (m, 1H), 5.64 (t, *J* = 7.7 Hz, 1H), 4.11 (t, *J* = 8.1 Hz, 4H), 3.39 – 3.31 (m, 2H), 2.93 – 2.75 (m, 3H), 2.66 – 2.59 (m, 1H), 2.49 – 2.41 (m, 2H), 2.00 (s, 3H), 1.96 – 1.86 (m, 4H), 1.76 – 1.71 (m, 1H), 1.36 – 1.29 (m, 1H), 0.91 – 0.86 (m, 6H).

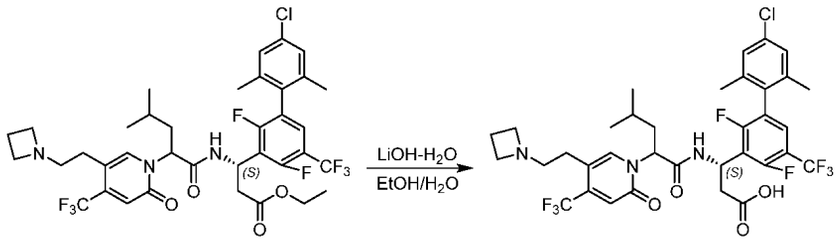
3-60. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-chloro-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HP-P1 and HP-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-chloro-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4'-chloro-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (120.0 mg, 0.28 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100.9 mg, 0.28 mmol), TCFH (95.4 mg, 0.34 mmol) and NMI (115.0 mg, 1.40 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-chloro-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (80.0 mg). Yield 37% (ESI 778.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-chloro-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



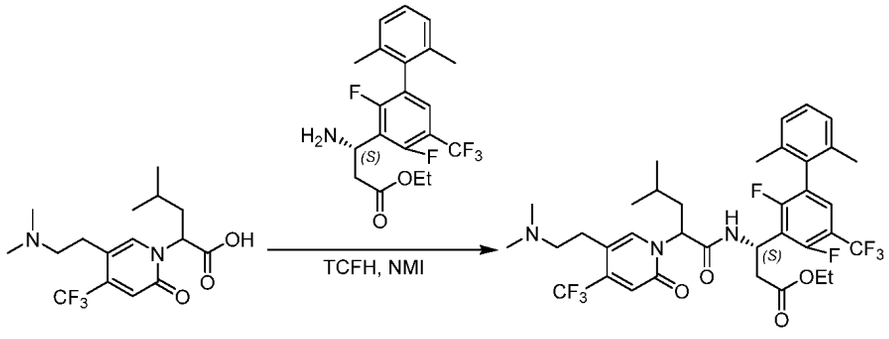
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-chloro-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (80.0 mg, 0.10 mmol) was treated with LiOH-H_2O (12.6 mg, 0.30 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **HP-P1** (12.5 mg) and **HP-P2** (24.5 mg) as white solids.

HP-P1 ESI 750.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.17 (s, 2H), 6.85 (s, 1H), 5.80 – 5.62 (m, 2H), 4.06 (t, *J* = 8.1 Hz, 4H), 3.39 – 3.32 (m, 1H), 3.28 – 3.21 (m, 1H), 2.98 – 2.65 (m, 4H), 2.55 – 2.36 (m, 2H), 2.07 – 1.95 (m, 5H), 1.93 (s, 3H), 1.48 – 1.30 (m, 1H), 0.93 (t, *J* = 6.5 Hz, 6H).

HP-P2 ESI 750.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.20 (s, 2H), 6.92 (s, 1H), 5.92 – 5.86 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.12 (t, *J* = 8.1 Hz, 4H), 3.47 – 3.32(m, 2H), 2.99 – 2.72 (m, 3H), 2.64 – 2.57 (m, 1H), 2.50 – 2.40 (m, 2H), 2.02 (d, *J* = 1.8 Hz, 6H), 1.97 – 1.85 (m, 1H), 1.79 – 1.65 (m, 1H), 1.40 – 1.28 (m, 1H), 0.91 – 0.85 (m, 6H).

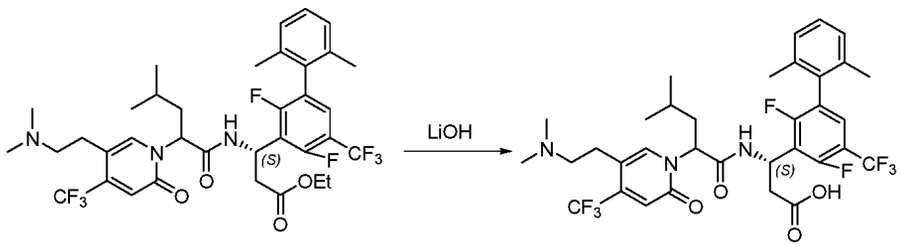
3-61. Preparation of (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyr -idin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds HQ-P1 and HQ-P2)

Step 1: ethyl (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (86 mg, 0.23 mmol), ethyl (S)-3-amino-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (92.0 mg, 0.23 mmol), TCFH (78.0 mg, 0.28 mmol) and NMI (38.0 mg, 0.46 mmol) in CH_3CN (4 mL) was stirred at room temperature for 2 hrs. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl) -2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a yellow solid (90.0 mg). Yield 53.4% (ESI 732.2 $[M+H]^+$).

Step 2: (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



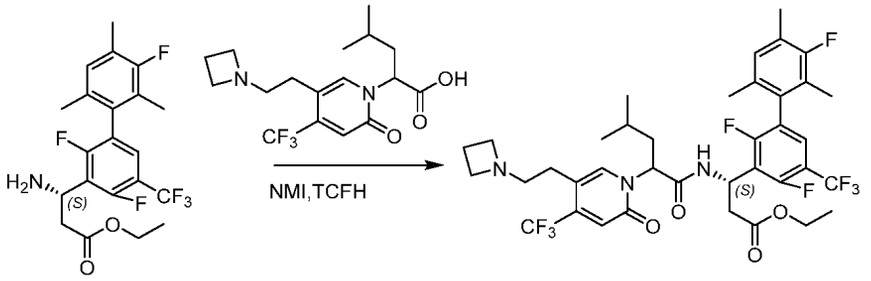
Ethyl (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (90.0 mg, 0.12 mmol) was treated with LiOH-H_2O (29.0 mg, 0.68 mmol) in EtOH (3 mL) and water (1 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by Prep HPLC A (30-80% MeCN) to give the diastereomeric products **HQ-P1** (15.1 mg) and **HQ-P2** (35.4 mg) as white solids.

HQ-P1 ESI 704.2 $(M+H)^+$ ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.15 – 7.03 (m, 2H), 6.82 (s, 1H), 5.76 – 5.60 (m, 2H), 3.12-3.09 (m, 2H), 2.98-2.92 (m, 3H), 2.78-2.72 (m, 7H), 2.09 – 1.92 (m, 5H), 1.90 (s, 3H), 1.49 – 1.31 (m, 1H), 0.99 – 0.89 (m, 6H).

HQ-P2 ESI 704.2 $(M+H)^+$ ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.44 (t, J = 7.7 Hz, 1H), 7.26 – 7.17 (t, J = 16.0 Hz, 1H), 7.14 (d, J = 7.6 Hz, 2H), 6.90 (s, 1H), 5.84-5.80 (m, 1H), 5.66 (t, J = 7.6 Hz, 1H), 3.26-3.18 (m, 2H), 2.97 (t, J = 7.3 Hz, 2H), 2.90 – 2.75 (m, 7H), 2.68-2.65 (m, 1H), 2.02 (d, J = 3.1 Hz, 6H), 1.96 – 1.82 (m, 1H), 1.77-1.72 (m, 1H), 1.34-1.29 (m, 1H), 0.90-0.85 (m, 6H).

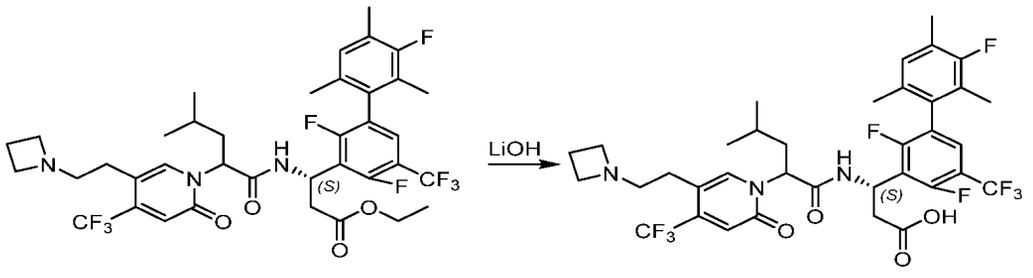
3-62. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HR-P1 and HR-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(2,3',4-trifluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (90 mg, 0.21 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (81 mg, 0.21mmol), NMI (0.2 mL) and TCFH (88 mg, 0.32 mmol) in CH_3CN (3 mL) was stirred at room temperature for 2 hours. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provideethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a white solid (80 mg). Yield 50% (ESI 776.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (80 mg, 0.1 mmol) was treated with LiOH-H_2O (13 mg, 0.3 mmol) in MeOH (2.0 mL) and H_2O (0.5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5~6 with

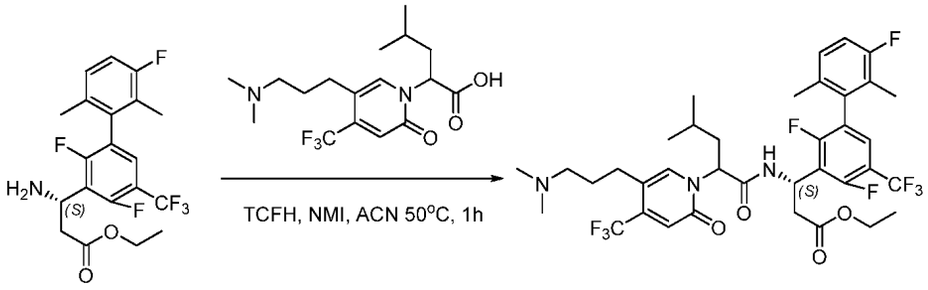
1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (50-80% CH_3CN) to give the diastereomeric products **HR-P1** (22.0 mg) and **HR-P2** (25.0 mg) as white solids.

HR-P1 ESI 748.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.40 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 7.9 Hz, 1H), 6.85 (d, J = 3.0 Hz, 1H), 5.78 – 5.60 (m, 2H), 4.04 (t, J = 8.0 Hz, 4H), 3.29 – 3.20 (m, 2H), 2.95 – 2.80 (m, 3H), 2.77 – 2.68 (m, 1H), 2.51 – 2.37 (m, 2H), 2.25 (d, J = 1.6 Hz, 3H), 2.09 – 1.75 (m, 8H), 1.37 (s, 1H), 0.93 (t, J = 6.4 Hz, 6H).

HR-P2 ESI 748.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.91 (s, 1H), 5.87 – 5.82 (m, 1H), 5.63 (t, J = 7.7 Hz, 1H), 4.12 (t, J = 7.8 Hz, 4H), 3.45 – 3.34 (m, 2H), 2.95 – 2.74 (m, 3H),), 2.64 – 2.56 (m, 1H), 2.50 – 2.36 (m, 2H), 2.27 (d, J = 1.5 Hz, 3H), 2.02 – 1.83 (m, 7H),), 1.78 – 1.65 (m, 1H),), 1.40 – 1.26 (m, 1H),), 0.93 – 0.84 (m, 6H).

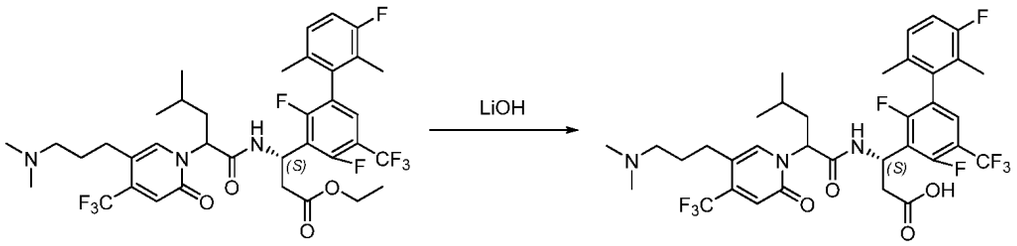
3-63. Preparation of (3S)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds HS-P1 and HS-P2)

Step 1: (3S)-ethyl 3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (3S)-ethyl 3-amino-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (100 mg, 0.24 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (86 mg, 0.24 mmol), NMI (59 mg, 0.72 mmol) and TCFH (101 mg, 0.36 mmol) in CH_3CN (5 mL) was stirred at 50°C for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 15:1) to provide (3S)-ethyl 3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (110 mg). Yield 60.4 % (ESI 764.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



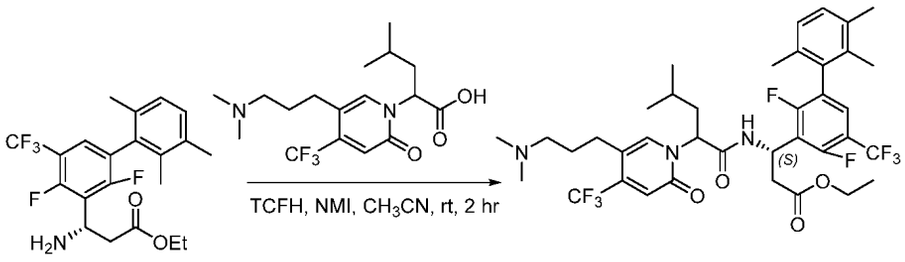
(3S)-ethyl 3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (110 mg, 0.14 mmol) was treated with LiOH-H_2O (18.1mg, 0.43 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **HS-P1** (29 mg) and **HS-P2** (30 mg) as white solids.

HS-P1 ESI 736.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO) δ 9.23 (d, J = 6.5 Hz, 1H), 7.73 (s, 1H), 7.61 (t, J = 6.9 Hz, 1H), 7.21 – 7.11 (m, 2H), 6.71 (s, 1H), 5.64 – 5.53 (m, 1H), 5.45 – 5.41 (m, 1H), 2.98 – 2.81 (m, 3H), 2.47 – 2.35 (m, 2H), 2.31-2.26 (m, 2H), 2.16 (s, 6H), 1.93 – 1.73 (m, 8H), 1.61 – 1.55 (m, 2H), 1.32 – 1.29 (m, 1H), 0.92 – 0.83 (m, 6H).

HS-P2 ESI 736.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.20 – 7.12 (m, 1H), 7.04 (t, J = 9.0 Hz, 1H), 6.85 (s, 1H), 5.85 – 5.69 (m, 1H), 5.64 (t, J = 7.7 Hz, 1H), 3.11 – 2.96 (m, 2H), 2.96 – 2.89 (m, 1H), 2.79 (s, 6H), 2.70 – 2.60 (m, 3H), 2.05 – 1.84 (m, 9H), 1.70 – 1.60 (m, 1H), 1.36 – 1.26 (m, 1H), 0.89 – 0.82 (m, 6H).

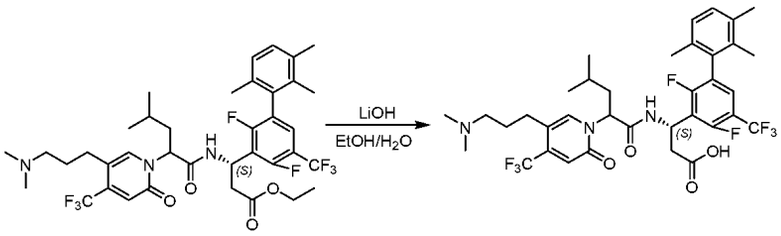
3-64. Preparation of (3S)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (HT-P1 and HT-P2)

Step 1: ethyl (3S)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (3S)-3-amino-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (160 mg, 0.39 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (153 mg, 0.42 mmol), TCFH (218 mg, 0.78 mmol) and NMI (160 mg, 1.95 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO3, B: CH_3OH, 0~85%) to provide ethyl (3S)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a yellow solid (120 mg). Yield 43.9 % (ESI 760.3 $[M+H]^+$).

Step 2: (3S)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



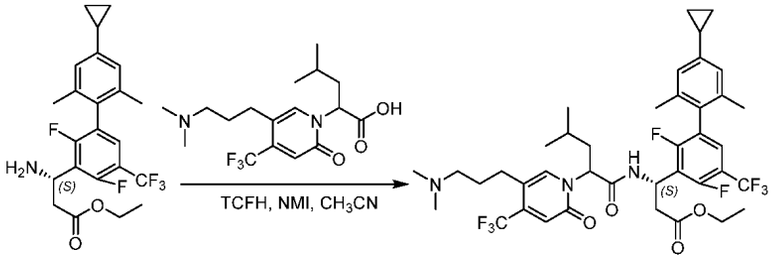
(3S)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (120 mg, 0.17 mmol) was treated with LiOH-H_2O (22 mg, 0.52 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 2 hr. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-65% CH_3CN) to give the diastereomeric products **HT-P1** (20 mg) and **HT-P2** (23 mg) as white solids.

HT-P1 ESI 732.2 $(M+H)^+$. ^1H NMR (400 MHz, DMSO) δ 9.22 (d, J = 6.3 Hz, 1H), 7.73 (s, 1H), 7.49 (t, J = 7.4 Hz, 1H), 7.14 (m, J = 7.7 Hz, 1H), 7.04 (t, J = 8.0 Hz, 1H), 6.72 (d, J = 5.5 Hz, 1H), 5.68 – 5.54 (m, 1H), 5.46 (d, J = 6.1 Hz, 1H), 3.44 (m, 1H), 2.97 (m, J = 16.3, 8.5 Hz, 1H), 2.90 – 2.75 (m, 1H), 2.46 – 2.34 (m, 2H), 2.31 – 2.22 (m, 5H), 2.16 (s, 6H), 1.84 (m, J = 18.7, 9.9 Hz, 5H), 1.73 (d, J = 29.3 Hz, 3H), 1.63 – 1.49 (m, 2H), 1.27 (m, J = 13.6, 6.8 Hz, 1H), 0.85 (m, J = 10.1, 6.6 Hz, 6H).

HT-P2 ESI 732.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.14 (d, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 6.87 (s, 1H), 5.84 (m, *J* = 9.8, 4.5 Hz, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 3.15 – 2.97 (m, 2H), 2.94 – 2.83 (m, 1H), 2.80 (s, 6H), 2.72 – 2.57 (m, 3H), 2.30 (d, *J* = 2.3 Hz, 3H), 2.09 – 1.85 (m, 9H), 1.66 (m, *J* = 14.1, 7.2 Hz, 1H), 1.33 (m, *J* = 13.1, 6.6 Hz, 1H), 0.95 – 0.71 (m, 6H).

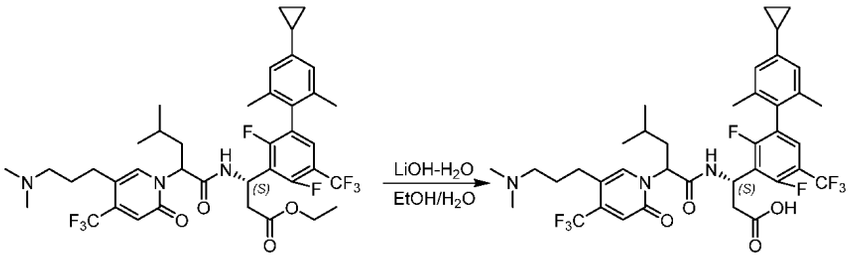
3-65. Preparation of (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds HU-P1 and HU-P2)

Step 1: ethyl (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (140.0 mg, 0.32 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (116.0 mg, 0.32 mmol), TCFH (106.6 mg, 0.38 mmol) and NMI (131.4 mg, 1.60 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a light yellow solid (150.0 mg). Yield 60% (ESI 786.3 $[M+H]^+$).

Step 2: (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



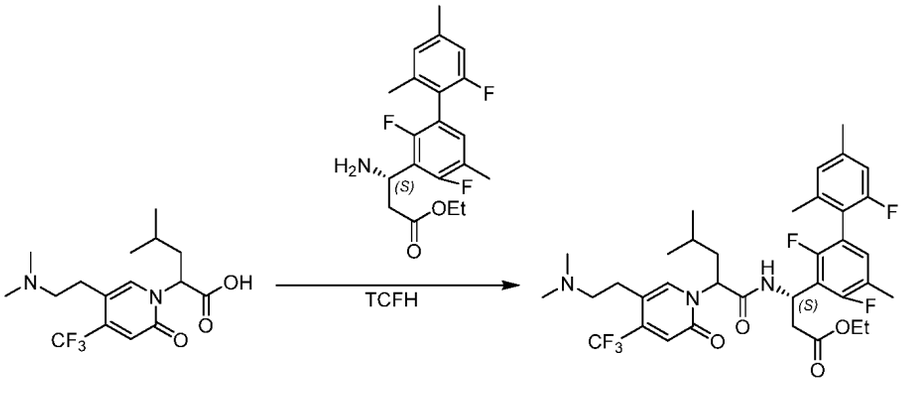
Ethyl (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (150.0 mg, 0.19 mmol) was treated with LiOH-H_2O (23.9 mg, 0.57 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **HU-P1** (54.5 mg) and **HU-P2** (50.5 mg) as white solids.

HU-P1 ESI 758.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 6.87 – 6.76 (m, 3H), 5.81 – 5.67 (m, 2H), 3.12 – 3.04 (m, 2H), 2.98 – 2.90 (m, 1H), 2.79 (s, 6H), 2.76 – 2.57 (m, 3H), 2.11 – 1.79 (m, 11H), 1.41 – 1.27 (m, 1H), 0.99 – 0.89 (m, 8H), 0.71 – 0.65 (m, 2H).

HU-P2 ESI 758.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 6.85 (s, 3H), 5.85 – 5.79 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.13 – 2.94 (m, 2H), 2.93 – 2.84 (m, 1H), 2.79 (s, 6H), 2.70 – 2.57 (m, 3H), 2.09 – 1.81 (m, 10H), 1.70 – 1.58 (m, 1H), 1.36 – 1.26 (m, 1H), 0.99 – 0.92 (m, 2H), 0.89 – 0.83 (m, 6H), 0.72 – 0.65 (m, 2H).

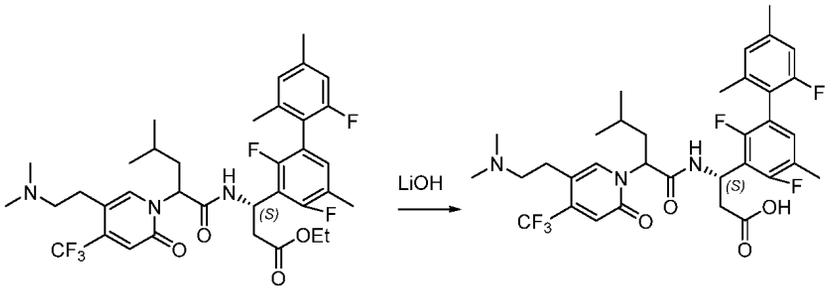
3-66. Preparation of (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HV-P1 and HV-P2)

Step 1: ethyl (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (142 mg, 0.41 mmol), ethyl (3S)-3-amino-3-(2,2',4-trifluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (150.0 mg, 0.41 mmol), TCFH (137.0 mg, 0.48 mmol) and NMI (67.0 mg, 0.81 mmol) in CH_3CN (4 mL) was stirred at room temperature for 2 hrs. The reaction mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido) -3-(2,2',4-trifluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (160.0 mg). Yield 56.1% (ESI 696.2 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid

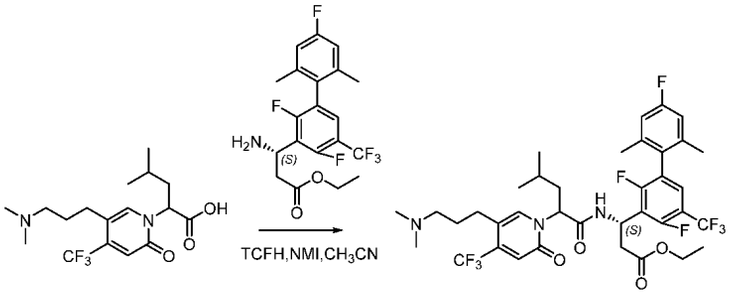


Ethyl (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (160.0 mg, 0.23 mmol) was treated with LiOH-H_2O (50.0 mg, 1.15 mmol) in EtOH (3 mL) and water (1 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by Prep HPLC A (30-80% MeCN) to give the diastereomeric products **HV-P1** (41.3 mg) and **HV-P2** (45.5 mg) as white solids.

HV-P1 ESI 668.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.02 – 6.89 (m, 2H), 6.83-6.77 (m, 2H), 5.77 – 5.64 (m, 2H), 3.11-3.07 (m, 2H), 2.97-2.91 (m, 3H), 2.74-2.66 (m, 7H), 2.33 (s, 3H), 2.23 (s, 3H), 2.06-1.96 (m, 5H), 1.42-1.39 (m, 1H), 0.95-0.92 (m, 6H).
HV-P2 ESI 668.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.03 (t, J = 8.2 Hz, 1H), 6.93 (d, J = 16.0 Hz, 2H), 6.82 (d, J = 10.3 Hz, 1H), 5.87-5.82 (m, 1H), 5.67-5.63 (m, 1H), 3.23-3.13 (m, 2H), 2.98-2.95 (m, 2H), 2.82-2.79 (m, 7H), 2.57 – 2.51 (m, 1H), 2.34 (s, 3H), 2.27 (s, 3H), 2.08 (d, J = 6.1 Hz, 3H), 1.95-1.88 (m, 1H), 1.79-1.70 (m, 1H), 1.40 – 1.25 (m, 1H), 0.93 – 0.80 (m, 6H).

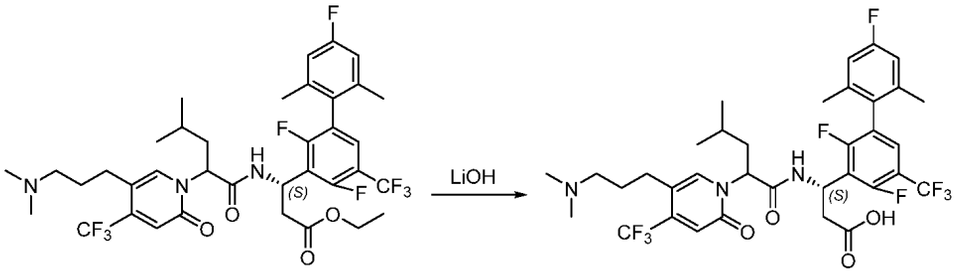
3-67. Preparation of (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds HW-P1 and HW-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100.0 mg, 0.28 mmol), ethyl (*S*)-3-amino-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (117.3 mg, 0.28 mmol), TCFH (156.8 mg, 0.56 mmol) and NMI (91.8 mg, 1.12 mmol) in CH_3CN (10 mL) was stirred at room temperature for 1 hour. The reaction was concentrated in vacuo and the residue purified by silica gel column (DCM: MeOH 4: 1) to provide ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a brown solid (150.0 mg). Yield 71% (ESI 764.7 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



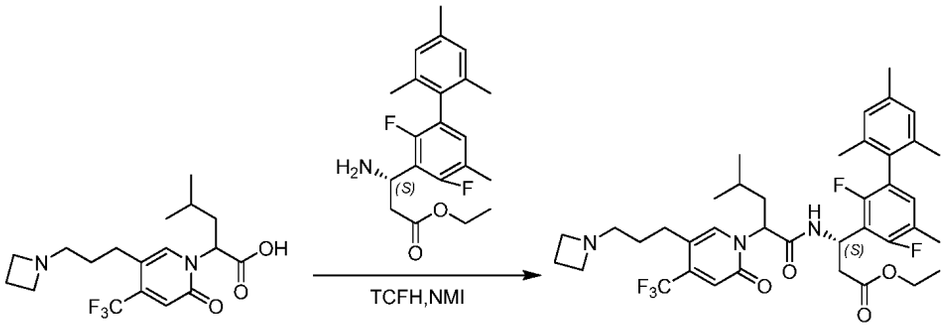
Ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.20 mmol)) was treated with LiOH-H_2O (33.6 mg, 0.80 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **HW-P1** (60.1 mg) and **HW-P2** (50.0 mg) as white solids.

HW-P1 ESI 736.6 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 9.3 Hz, 2H), 6.80 (s, 1H), 5.78 – 5.67 (m, 2H), 3.14 – 3.02 (m, 2H), 3.01 – 2.88 (m, 1H), 2.80 (s, 6H), 2.75 – 2.55 (m, 3H), 2.12 – 1.84 (m, 10H), 1.34 (s, 1H), 0.94 (d, *J* = 6.6 Hz, 6H).

HW-P2 ESI 736.6 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 6.96 – 6.80 (m, 3H), 5.86 – 5.75 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.14 – 2.97 (m, 2H), 2.97 – 2.85 (m, 1H), 2.79 (s, 6H), 2.71 – 2.50 (m, 3H), 2.07 – 1.87 (m, 8H), 1.67 – 1.52 (m, 1H), 1.35 – 1.25 (m, 1H), 0.93 – 0.77 (m, 6H).

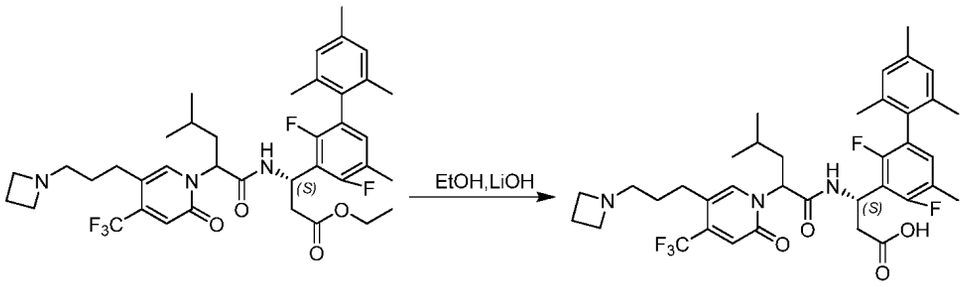
3-68. Preparation of (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (compounds HX-P1 and HX-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100 mg, 0.27 mmol), (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (97 mg, 0.27 mmol), NMI (0.5 mL) and TCFH (378 mg, 1.35 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-90% CH_3CN) to provide (3*S*)-ethyl 3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate as a white solid (140 mg). Yield 73% (ESI 718.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid



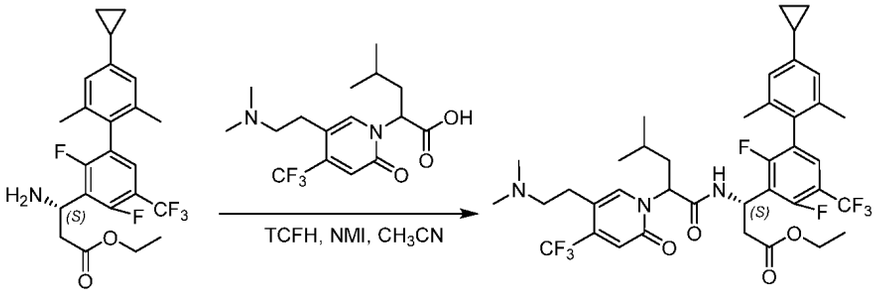
(3*S*)-ethyl 3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (140 mg, 0.20 mmol) was treated with LiOH-H_2O (76 mg, 1.80 mmol) in MeOH (5 mL) and H_2O (0.5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-70% CH_3CN) to give the diastereomeric products **HX-P1** (41.0 mg) and **HX-P2** (40.0 mg) as white solids.

HX-P1 ESI 690.3$(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 6.91 – 6.83 (m, 3H), 6.79 (s, 1H), 5.84 – 5.66 (m, 2H), 4.05 (t, *J* = 8.2 Hz, 4H), 3.14 (t, *J* = 7.5 Hz, 2H), 3.04 – 2.89 (m, 1H), 2.73 – 2.56 (m, 3H), 2.49 – 2.35 (m, 2H), 2.28 (s, 3H), 2.23 (s, 3H), 2.00 (t, *J* = 7.6 Hz, 2H), 1.91 (d, *J* = 21.2 Hz, 6H), 1.86 – 1.69 (m, 2H), 1.40 – 1.27 (m, 1H), 0.98 – 0.87 (m, 6H).

HX-P2 ESI 690.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.78 (s, 1H), 6.97 – 6.79 (m, 4H), 5.91 – 5.81 (m, 1H), 5.56 (t, *J* = 7.5 Hz, 1H), 4.16 – 3.95 (m, 4H), 3.17 – 2.97 (m, 2H), 2.93 – 2.81 (m, 1H), 2.70 – 2.51 (m, 3H), 2.48 – 2.37 (m, 2H), 2.29 (s, 3H), 2.27 (s, 3H), 2.04 – 1.69 (m, 9H), 1.65 – 1.52 (m, 1H), 1.41 – 1.22 (m, 1H), 0.94 – 0.78 (m, 6H).

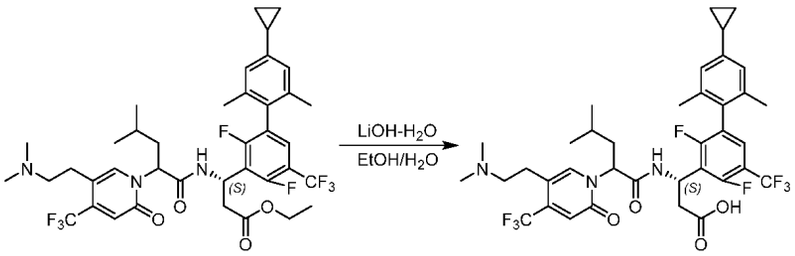
3-69. Preparation of (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds HY-P1 and HY-P2)

Step 1: ethyl (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (140.0 mg, 0.29 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (101.0 mg, 0.29 mmol), TCFH (97.6 mg, 0.35 mmol) and NMI (71.4 mg, 0.87 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a light yellow solid (130.0 mg). Yield 57% (ESI 772.3 $[M+H]^+$).

Step 2: (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



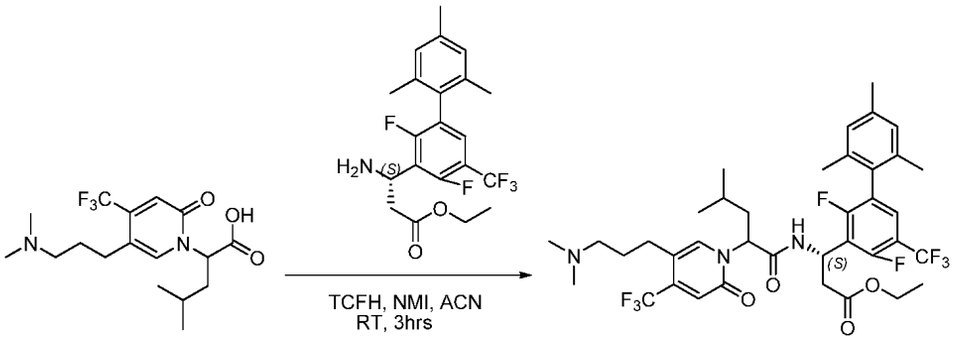
Ethyl (3*S*)-3-(4'-cyclopropyl-2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (130.0 mg, 0.17 mmol) was treated with LiOH-H_2O (21.4 mg, 0.51 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 5~6 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **HY-P1** (40 mg) and **HY-P2** (50.3 mg) as white solids.

HY-P1 ESI 744.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 4.5 Hz, 3H), 5.73 – 5.67 (m, 2H), 3.17 – 3.01 (m, 2H), 2.99 – 2.89 (m, 3H), 2.79 – 2.68 (m, 7H), 2.05 – 1.91 (m, 5H), 1.91 – 1.79 (m, 4H), 1.44 – 1.33 (m, 1H), 0.98 – 0.91 (m, 8H), 0.72 – 0.64 (m, 2H).

HY-P2 ESI 744.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 6.90 (s, 1H), 6.85 (s, 2H), 5.85 – 5.78 (m, 1H), 5.65 (t, *J* = 7.8 Hz, 1H), 3.27 – 3.12 (m, 2H), 2.96 (t, *J* = 7.1 Hz, 2H), 2.89 – 2.75 (m, 7H), 2.70 – 2.62 (m, 1H), 1.97 (d, *J* = 3.3 Hz, 6H), 1.94 – 1.83 (m, 2H), 1.79 – 1.65 (m, 1H), 1.38 – 1.24 (m, 1H), 1.01 – 0.92 (m, 2H), 0.91 – 0.84 (m, 6H), 0.75 – 0.63 (m, 2H).

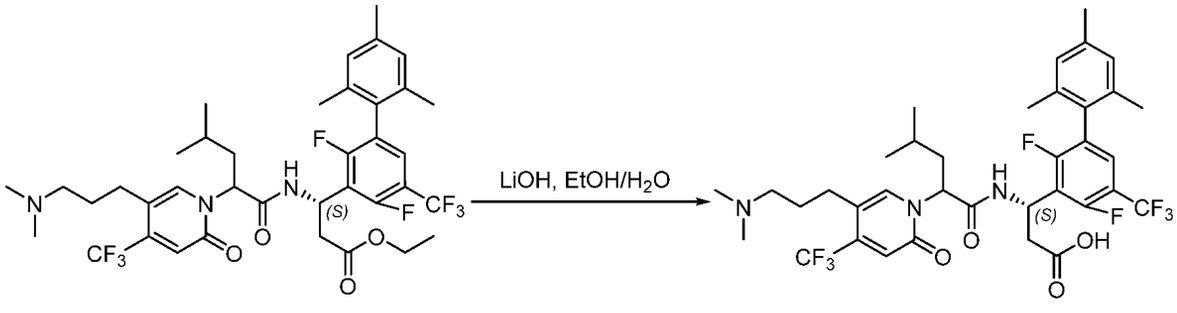
3-70. Preparation of (*3S*)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds HZ-P1 and HZ-P2)

Step 1: (*3S*)-ethyl 3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (208 mg, 0.50 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (180 mg, 0.50 mmol), TCFH (280 mg, 1.0 mmol) and NMI (123 mg, 1.5 mmol) in MeCN (5 mL) was stirred at room temperature for 3 hrs. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 97: 3) to provide (3*S*)-ethyl 3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a colorless oil (200 mg). Yield 53% (ESI 760.3 $(M+H)^+$).

Step 2: (*3S*)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



(3*S*)-ethyl 3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (200 mg, 0.26 mmol) was treated with LiOH-H_2O (55 mg, 1.3 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified

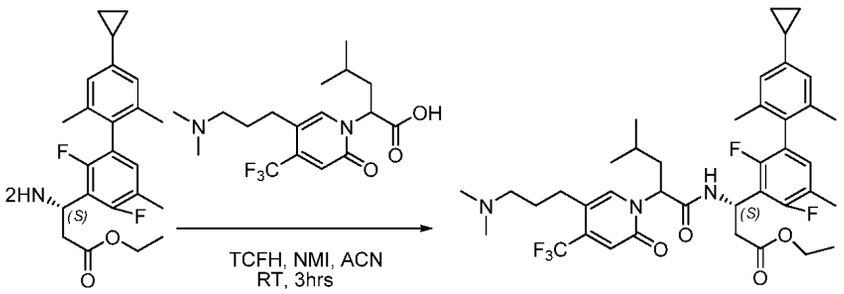
to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **HZ-P1** (7.0 mg) and **HZ-P2** (62.0 mg) as white solids.

HZ-P1 ESI 732.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 6.94 (s, 2H), 6.80 (s, 1H), 5.79 – 5.70 (m, 2H), 3.14 – 3.07 (m, 2H), 2.95-2.90 (m, 1H), 2.81 (s, 6H), 2.72 – 2.58 (m, 3H), 2.30 (s, 3H), 2.11 – 1.92 (m, 7H), 1.87 (s, 3H), 1.34 (s, 1H), 0.94 (d, *J* = 6.5 Hz, 6H).

HZ-P2 ESI 732.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 6.97 (s, 2H), 6.85 (s, 1H), 5.82-5.80 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.15 – 2.95 (m, 2H), 2.89-2.85 (m, 1H), 2.79 (s, 6H), 2.63 -2.60(m, 3H), 2.31 (s, 3H), 2.08 – 1.83 (m, 9H), 1.72 – 1.58 (m, 1H), 1.31-1.25 (m, 1H), 0.86-0.82 (m, 6H).

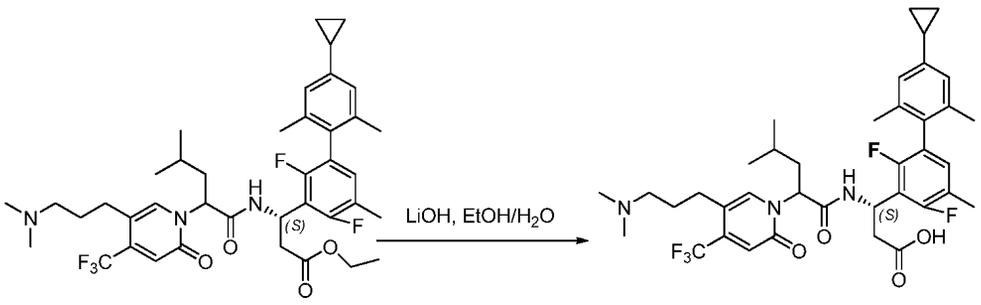
3-71. Preparation of (*3S*)-3-(4'-cyclopropyl-2,4-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds IA-P1 and IA-P2)

Step 1: (*3S*)-ethyl 3-(4'-cyclopropyl-2,4-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of (*S*)-ethyl 3-amino-3-(4'-cyclopropyl-2,4-difluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (107 mg, 0.28 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (100 mg, 0.28 mmol), TCFH (157 mg, 0.56 mmol) and NMI (69 mg, 0.84 mmol) in MeCN (5 mL) was stirred at room temperature for 3 hrs. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM:MeOH 97: 3) to provide (*3S*)-ethyl 3-(4'-cyclopropyl-2,4-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a colorless oil (100 mg). Yield 49% (ESI 732.3 $(M+H)^+$).

Step 2: (*3S*)-3-(4'-cyclopropyl-2,4-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



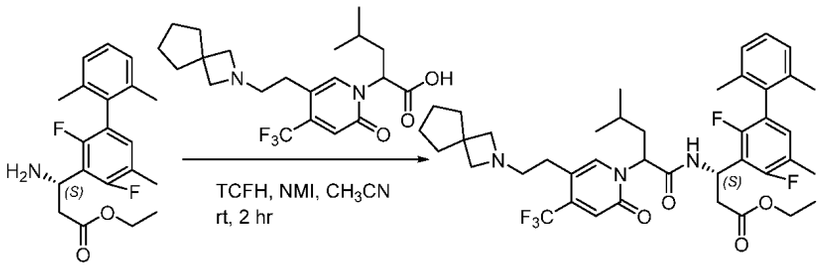
(*3S*)-ethyl 3-(4'-cyclopropyl-2,4-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (100 mg, 0.14 mmol) was treated with LiOH-H_2O (27 mg, 0.65 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **IA-P1** (37.3 mg) and **IA-P2** (38.5 mg) as white solids.

IA-P1 ESI 704.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.78 (d, *J* = 13.1 Hz, 1H), 6.84 (t, *J* = 8.0 Hz, 1H), 6.79-6.75 (m, 3H), 5.78 – 5.67 (m, 2H), 3.10 – 3.00 (m, 2H), 2.93 -2.90(m, 1H), 2.77 (s, 6H), 2.69 – 2.59 (m, 3H), 2.24 (d, *J* = 18.1 Hz, 3H), 2.08 – 1.97 (m, 3H), 1.97 – 1.74 (m, 8H), 1.34-1.30 (m, 1H), 1.02 – 0.82 (m, 8H), 0.72 – 0.56 (m, 2H).

IA-P2 ESI 704.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 6.89 (t, *J* = 8.2 Hz, 1H), 6.82 (d, *J* = 16.3 Hz, 3H), 5.84-5.80 (m, 1H), 5.57 (t, *J* = 7.5 Hz, 1H), 3.01-3.00 (m, 2H), 2.85 -2.83(m, 1H), 2.77 (s, 6H), 2.68 – 2.59 (m, 2H), 2.53-2.51 (m, 1H), 2.26 (s, 3H), 2.05 – 1.83 (m, 10H), 1.62-1.60 (m, 1H), 1.34-1.30 (m, 1H), 1.03 – 0.91 (m, 2H), 0.86-0.83 (m, 6H), 0.71 – 0.64 (m, 2H).

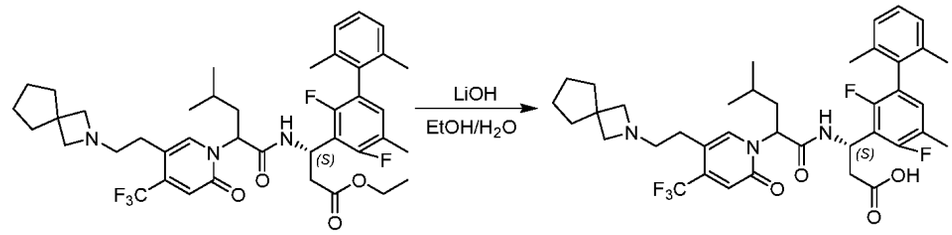
3-72. Preparation of (3S)-3-(2-(5-(2-(2-azaspiro[3.4]octan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (IB-P1 and IB-P2)

Step 1: ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.4]octan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (S)-3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (140 mg, 0.40 mmol), 2-(5-(2-(2-azaspiro[3.4]octan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (182 mg, 0.54 mmol), TCFH (224 mg, 0.80 mmol) and NMI (164 mg, 2.0 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO3, B: CH_3OH, 0~85%) to provide ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.4]octan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (130 mg). Yield 43.3 % (ESI 744.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(2-azaspiro[3.4]octan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3- yl)propanoic acid



Ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.4]octan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (130 mg, 0.17 mmol) was treated with LiOH-H_2O (22 mg, 0.52 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 2 hr. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-65% CH_3CN) to give the diastereomeric products **IB-P1** (48 mg) and **IB-P2** (65 mg) as white solids.

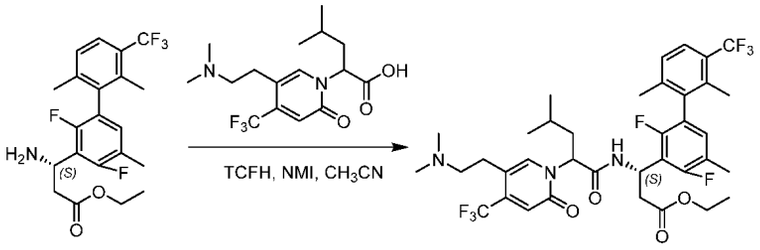
IB-P1 ESI 716.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.18 (m, J = 24.2, 7.1 Hz, 3H), 6.94 (m, J = 14.9, 6.5 Hz, 2H), 5.87 (m, J = 9.8, 4.8 Hz, 1H), 5.75 (m, J = 9.4, 6.8 Hz, 1H), 3.95 (d, J = 9.1 Hz, 4H), 3.38 (m, 1H), 3.32 (m, J = 7.3 Hz, 1H), 3.03 (m, J = 15.2, 9.9 Hz, 1H), 2.93 (t, J = 6.7 Hz, 2H), 2.70 (m, J = 15.3, 4.9 Hz, 1H), 2.31 (s, 3H), 2.11 – 1.98 (m, 8H), 1.92 (d, J = 6.3 Hz, 4H), 1.75 – 1.56 (m, 4H), 1.51 – 1.38 (m, 1H), 0.99 (m, J = 6.6, 1.2 Hz, 6H).

IB-P2 ESI 716.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.71 (s, 1H), 7.22 – 7.05 (m, 3H), 6.99 – 6.73 (m, 2H), 5.92 (m, J = 11.5, 3.4 Hz, 1H), 5.62 (t, J = 7.7 Hz, 1H), 3.99 (s, 4H), 3.43 – 3.31 (m, 2H), 2.95

– 2.75 (m, 3H), 2.47 (m, *J* = 16.1, 3.6 Hz, 1H), 2.28 (s, 3H), 2.01 (d, *J* = 5.5 Hz, 6H), 1.91 (m, *J* = 26.9, 12.0, 7.3 Hz, 5H), 1.74 – 1.56 (m, 5H), 1.44 – 1.26 (m, 1H), 0.89 (m, *J* = 9.1, 6.6 Hz, 6H).

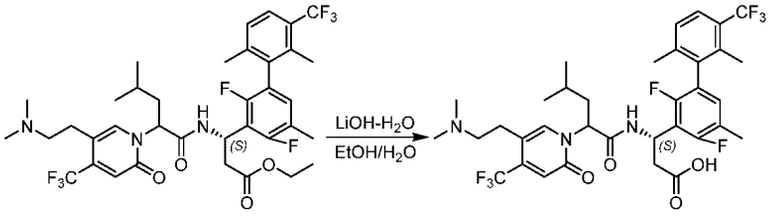
3-73. Preparation of (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds IC-P1 and IC-P2)

Step 1: ethyl (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (170.0 mg, 0.41 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (142.8 mg, 0.49 mmol), TCFH (137.5 mg, 0.76 mmol) and NMI (68.8 mg, 1.64 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a light yellow solid (210.0 mg). Yield 69% (ESI 746.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



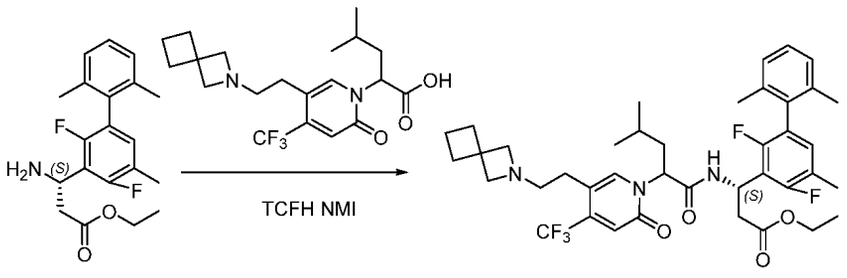
Ethyl (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate

(210.0 mg, 0.28 mmol) was treated with LiOH-H_2O (35.2 mg, 0.84 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **IC-P1** (53.3 mg) and **IC-P2** (78.3 mg) as white solids.

IC-P1 ESI 718.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.87 (d, *J* = 3.6 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 8.1 Hz, 1H), 6.83 (s, 1H), 5.75 – 5.64 (m, 2H), 3.18 – 3.01 (m, 2H), 3.00 – 2.85 (m, 3H), 2.79 – 2.64 (m, 7H), 2.25 (s, 3H), 2.10 – 1.94 (m, 8H), 1.46 – 1.33 (m, 1H), 0.96 – 0.90 (m, 6H).
IC-P2 ESI 718.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 1H), 6.96 (t, *J* = 8.2 Hz, 1H), 6.90 (s, 1H), 5.86 – 5.80 (m, 1H), 5.66 – 5.60 (m, 1H), 3.28 – 3.10 (m, 2H), 3.01 – 2.94 (m, 2H), 2.86 – 2.74 (m, 7H), 2.62 – 2.55 (m, 1H), 2.29 (s, 3H), 2.12 (s, 3H), 2.07 (d, *J* = 3.9 Hz, 3H), 1.97 – 1.82 (m, 1H), 1.80 – 1.66 (m, 1H), 1.39 – 1.28 (m, 1H), 0.90 – 0.82 (m, 6H).

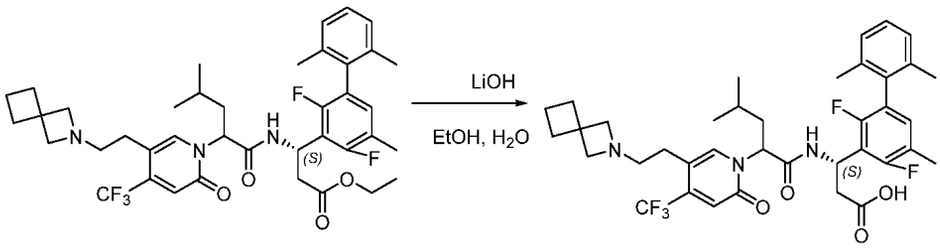
3-74. Preparation of (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds ID-P1 and ID-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (S)-3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (220 mg, 0.63 mmol), 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (240 mg, 0.6 mmol), TCFH (336 mg, 1.2 mmol) and NMI (246 mg, 3.0 mmol) in CH_3CN (4 mL) was stirred at 25 °C for 16 hr. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (310 mg). Yield 70.8 % (ESI 730.4 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



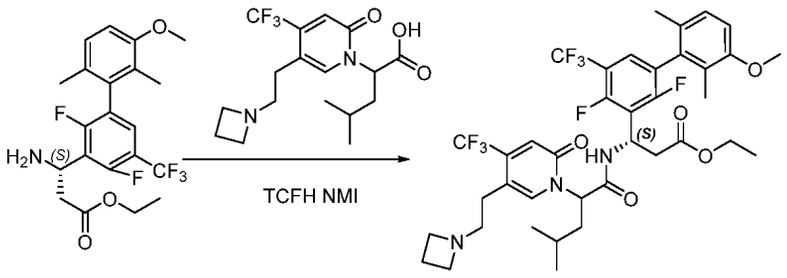
Ethyl (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (310 mg, 0.42 mmol) was treated with LiOH-H_2O (54 mg, 1.28 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 30 min. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (40-60% CH_3CN) to give the diastereomeric products **ID-P1** (72 mg) and **ID-P2** (96 mg) as white solids.

ID-P1 ESI 702.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.18 – 7.03 (m, 3H), 6.94 – 6.83 (m, 2H), 5.83 – 5.75 (m, 1H), 5.69 (t, *J* = 7.9 Hz, 1H), 3.96 (s, 4H), 3.28 – 3.13 (m, 2H), 3.02 – 2.91 (m, 1H), 2.85 (s, 2H), 2.64 (d, *J* = 15.1 Hz, 1H), 2.24 (t, *J* = 7.4 Hz, 7H), 2.04 – 1.89 (m, 8H), 1.88 – 1.76 (m, 2H), 1.43 – 1.33 (m, 1H), 0.98 – 0.88 (m, 6H).

ID-P2 ESI 702.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.71 (s, 1H), 7.19 – 7.07 (m, 3H), 6.97 – 6.88 (m, 2H), 5.95 – 5.86 (m, 1H), 5.61 (t, *J* = 7.7 Hz, 1H), 4.10 (s, 4H), 3.41 – 3.31 (m, 2H), 2.95 – 2.74 (m, 3H), 2.52 – 2.39 (m, 1H), 2.36 – 2.17 (m, 7H), 2.01 (d, *J* = 6.7 Hz, 6H), 1.98 – 1.89 (m, 1H), 1.90 – 1.79 (m, 2H), 1.75 – 1.64 (m, 1H), 1.42 – 1.33 (m, 1H), 0.93 – 0.83 (m, 6H).

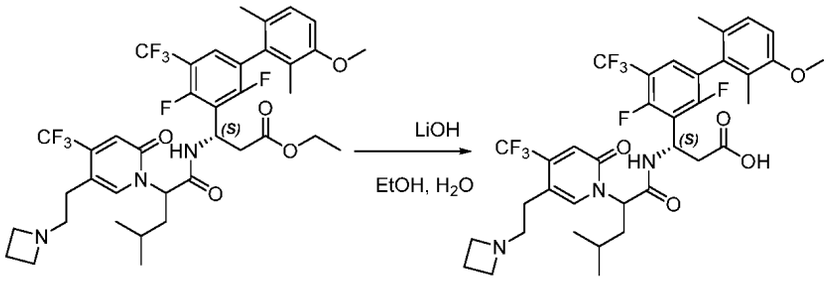
3-75. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IE-P1 and IE-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3S)-3-amino-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (150 mg, 0.35 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (150 mg, 0.41 mmol), TCFH (213 mg, 0.76 mmol) and NMI (156 mg, 1.9 mmol) in CH_3CN (3 mL) was stirred at 50 °C for 30 min. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoateas a yellow solid (180 mg). Yield 66.4 % (ESI 774.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



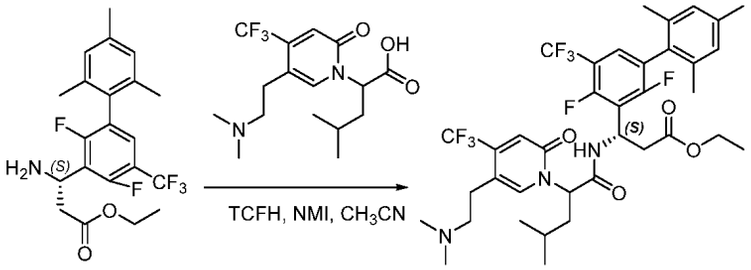
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (180 mg, 0.23 mmol) was treated with LiOH-H_2O (30 mg, 0.7 mmol) in EtOH (2 mL) and H_2O (0.5 mL) at room temperature for 30 min. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (35-60% CH_3CN) to give the diastereomeric products **IE-P1** (46 mg) and **IE-P2** (53 mg) as white solids.

IE-P1 ESI 746.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.93 – 6.83 (m, 2H), 5.76 – 5.65 (m, 2H), 4.04 (t, *J* = 7.9 Hz, 4H), 3.83 (s, 3H), 3.29 – 3.19 (m, 2H), 2.95 – 2.88 (m, 1H), 2.84 (t, *J* = 6.7 Hz, 2H), 2.76 – 2.69 (m, 1H), 2.48 – 2.39 (m, 2H), 2.04 – 1.95 (m, 2H), 1.85 (t, *J* = 30.1 Hz, 6H), 1.41 – 1.32 (m, 1H), 0.93 (t, *J* = 6.5 Hz, 6H).

IE-P2 ESI 746.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 6.3 Hz, 2H), 5.96 – 5.84 (m, 1H), 5.64 (t, *J* = 7.7 Hz, 1H), 4.12 (t, *J* = 8.1 Hz, 4H), 3.84 (s, 3H), 3.43 – 3.31 (m, 2H), 2.96 – 2.74 (m, 3H), 2.69 – 2.57 (m, 1H), 2.53 – 2.39 (m, 2H), 1.98 – 1.82 (m, 7H), 1.76 – 1.65 (m, 1H), 1.39 – 1.27 (m, 1H), 0.92 – 0.83 (m, 6H).

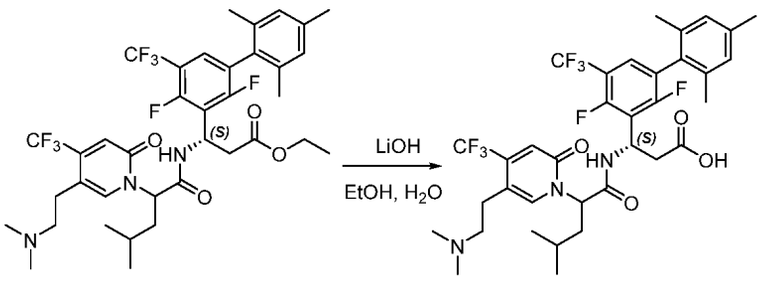
3-76. Preparation of (3S)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds IF-P1 and IF-P2)

Step 1: ethyl (3S)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (210 mg, 0.5 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (200 mg, 0.57 mmol), TCFH (364 mg, 1.3 mmol) and NMI (246 mg, 3.0 mmol) in CH_3CN (4 mL) was stirred at 50 °C for 1 hr. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3*S*)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoateas a yellow solid (330 mg). Yield 88.5 % (ESI 746.3 $[M+H]^+$).

Step 2: (3S)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



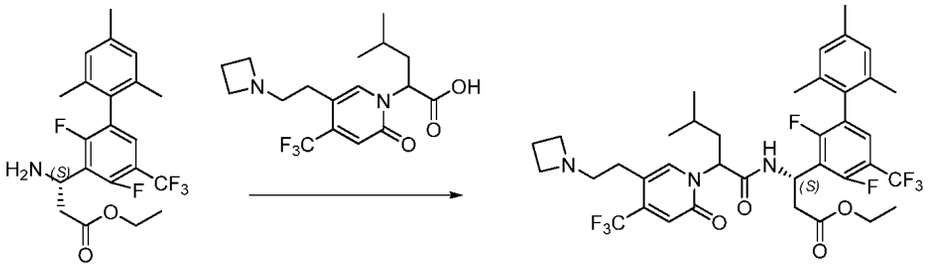
Ethyl (3S)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (330 mg, 0.44 mmol) was treated with LiOH-H_2O (56 mg, 1.34 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 30 min. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-58% CH_3CN) to give the diastereomeric products **IF-P1** (96 mg) and **IF-P2** (94 mg) as white solids.

IF-P1 ESI 718.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.34 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 3.7 Hz, 2H), 6.82 (s, 1H), 5.76 – 5.65 (m, 2H), 3.12 – 3.04 (m, 2H), 2.99 – 2.88 (m, 3H), 2.80 – 2.70 (m, 7H), 2.29 (s, 3H), 2.06 – 1.92 (m, 5H), 1.86 (s, 3H), 1.44 – 1.33 (m, 1H), 0.93 (t, J = 7.0 Hz, 6H).

IF-P2 ESI 718.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.41 (t, J = 7.6 Hz, 1H), 6.97 (s, 2H), 6.89 (s, 1H), 5.85 – 5.76 (m, 1H), 5.66 (t, J = 7.8 Hz, 1H), 3.25 – 3.09 (m, 2H), 2.96 (t, J = 7.2 Hz, 2H), 2.90 – 2.81 (m, 1H), 2.79 (s, 6H), 2.71 – 2.62 (m, 1H), 2.31 (s, 3H), 1.98 (d, J = 3.1 Hz, 6H), 1.93 – 1.81 (m, 1H), 1.76 – 1.67 (m, 1H), 1.36 – 1.27 (m, 1H), 0.92 – 0.82 (m, 6H).

3-77. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds IG-P1 and IG-P2)

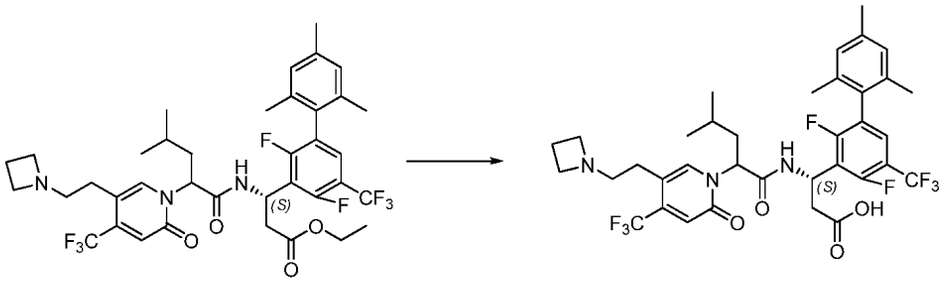
Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (150 mg, 0.41 mmol), (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (173 mg, 0.41 mmol), NMI (0.5 mL) and TCFH (364 mg, 1.30 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (30-90% CH_3CN) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-

methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a white solid (150 mg). Yield 54% (ESI 758.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



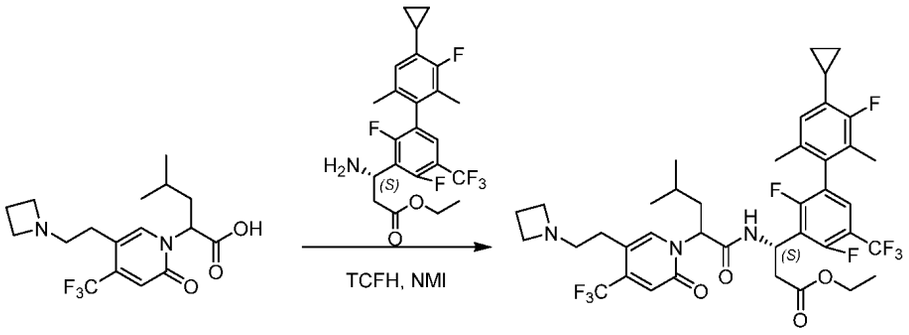
(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (150 mg, 0.19 mmol) was treated with LiOH-H_2O (42 mg, 1.00 mmol) in MeOH (4 mL) and H_2O (0.4 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-70% CH_3CN) to give the diastereomeric products **IG-P1** (33.0 mg) and **IG-P2** (51.0 mg) as white solids.

IG-P1 ESI 730.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.37 (t, J = 7.5 Hz, 1H), 6.95 (s, 2H), 6.85 (s, 1H), 5.79 – 5.65 (m, 2H), 4.03 (t, J = 8.1 Hz, 4H), 3.27 – 3.20 (m, 2H), 3.00 – 2.69 (m, 4H), 2.50 – 2.38 (m, 2H), 2.30 (s, 3H), 2.05 – 1.83 (m, 8H), 1.52 – 1.28 (m, 1H), 0.93 (t, J = 6.4 Hz, 6H).

IG-P2 ESI 730.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.43 (t, J = 7.6 Hz, 1H), 6.97 (s, 2H), 6.91 (s, 1H), 6.00 – 5.83 (m, 1H), 5.63 (t, J = 7.7 Hz, 1H), 4.11 (t, J = 8.0 Hz, 4H), 3.50 – 3.33 (m, 2H), 2.99 – 2.75 (m, 3H), 2.69 – 2.57 (m, 1H), 2.49 – 2.37 (m, 2H), 2.31 (s, 3H), 2.02 – 1.84 (m, 7H), 1.77 – 1.64 (m, 1H), 1.46 – 1.19 (m, 1H), 1.03 – 0.80 (m, 6H).

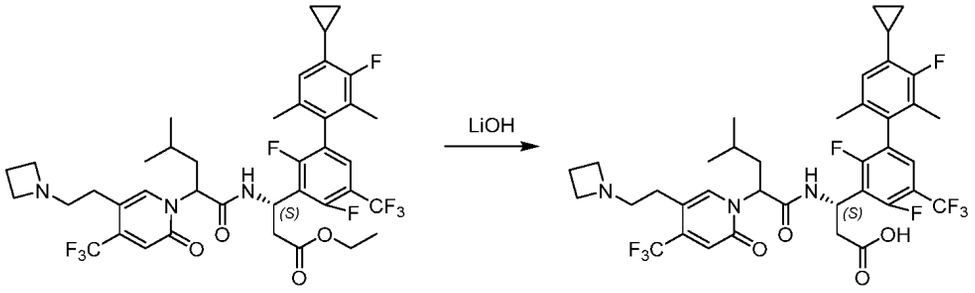
3-78. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IH-P1 and IH-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(4'-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (80 mg, 0.17 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (120 mg, 0.33 mmol), TCFH(74 mg, 0.26 mmol), and 1-methylimidazole (57 mg, 0.70 mmol) in acetonitrile (5 mL) was stirred at room temperature for 2 hours. The mixture was purified by reverse phase HPLC on a C18 / 40g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (100 mg) as a brown solid. Yield 71.4 % (ESI 802.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (100 mg, 0.13 mmol) was treated with LiOH-H_2O (27 mg, 0.65 mmol) in MeOH (5 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 6~7 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **IH-P1** (13.8 mg) and **IH-P2** (16.7 mg) as white solids.

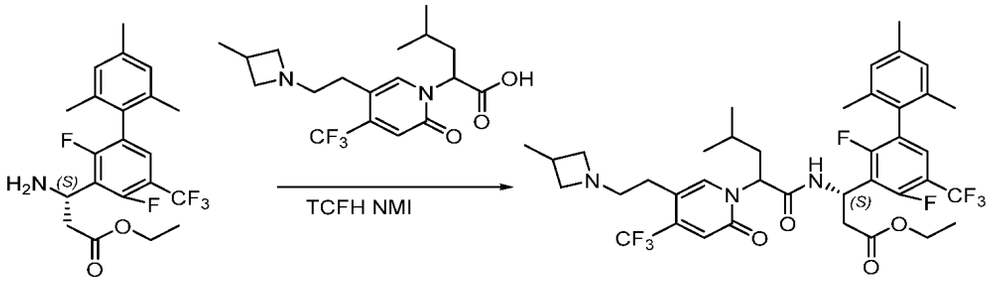
IH-P1 ESI 774.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.39 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 4.6 Hz, 1H), 6.71 – 6.68 (m, 1H), 5.74 – 5.67 (m, 2H), 4.02 (t, J = 7.8 Hz, 4H), 3.30 – 3.26

(m, 2H), 2.93 – 2.70 (m, 4H), 2.48 – 2.38 (m, 2H), 2.12 – 1.96 (m, 3H), 1.93 – 1.91 (m, 3H), 1.86 – 1.82 (m, 3H), 1.41 – 1.36 (m, 1H), 1.01– 0.92 (m, 8H), 0.75 – 0.69 (m, 2H).

IH-P2 ESI 774.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.46 (t, J = 7.6 Hz, 1H), 6.92 (s, 1H), 6.72 (d, J = 7.2 Hz, 1H), 5.87– 5.91 (m, 1H), 5.63 (t, J = 7.6 Hz, 1H), 4.12 (t, J = 8.0 Hz, 4H), 3.44 – 3.33 (m, 2H), 2.93 – 2.77 (m, 3H), 2.63– 2.58 (m, 1H), 2.49 – 2.41 (m, 2H), 2.13– 2.06 (m, 1H), 1.95 – 1.88 (m, 7H), 1.75 – 1.68 (m, 1H), 1.37 – 1.29 (m, 1H), 1.02 – 0.97 (m, 2H), 0.91 – 0.86(m, 6H), 0.77 – 0.74 (m, 2H) .

3-79. Preparation of (3*S*)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoic acid (compounds II-P1 and II-P2)

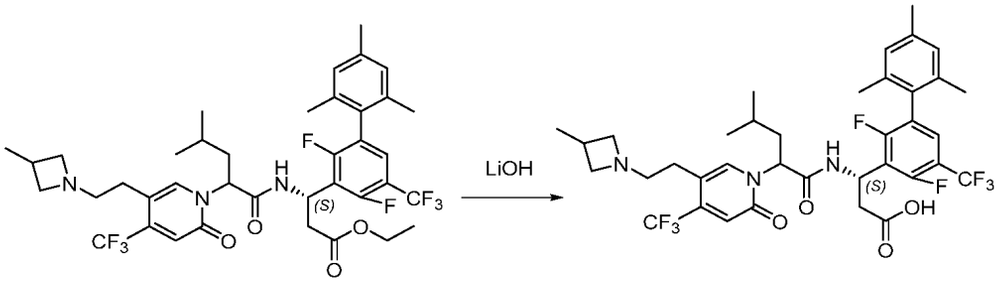
Step 1: ethyl (3*S*)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (120 mg, 0.29 mmol), 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid (108 mg, 0.29 mmol), *TCFH* (120 mg, 0.43 mmol) and NMI (119 mg, 1.45 mmol) in CH_3CN (3 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 20~95%) to provide ethyl (3*S*)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate as a light yellow solid (150 mg). Yield 67% (ESI 772.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-

yl)pentanamido)propanoic acid

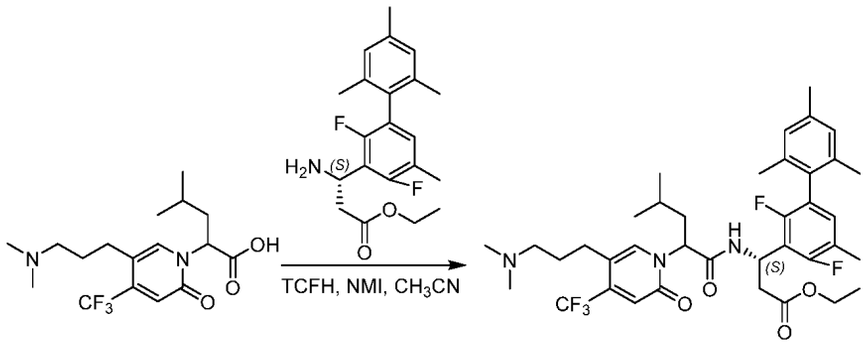


Ethyl (3*S*)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate (150 mg, 0.19 mmol) was treated with LiOH-H_2O (24 mg, 0.57 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (20-85% MeCN) to give the diastereomeric products **II-P1** (33 mg) and **II-P2** (49 mg) as white solids.

II-P1 ESI 744.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 6.95 (s, 2H), 6.84 (s, 1H), 5.77 – 5.61 (m, 2H), 4.12 (t, *J* = 9.2 Hz, 2H), 3.67 (t, *J* = 8.8 Hz, 2H), 3.28 – 3.20 (m, 2H), 3.00 – 2.78 (m, 4H), 2.76 – 2.67 (m, 1H), 2.30 (s, 3H), 2.05 – 1.95 (m, 5H), 1.89 (s, 3H), 1.45 – 1.30 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 3H), 0.96 – 0.84 (m, 6H).
II-P2 ESI 744.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 1H), 6.98 (s, 2H), 6.91 (s, 1H), 5.89 – 5.82 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.20 (d, *J* = 9.9 Hz, 2H), 3.75 (s, 2H), 3.45 – 3.34 (m, 2H), 3.02 – 2.85 (m, 4H), 2.65 – 2.53 (m, 1H), 2.31 (s, 3H), 2.03 – 1.84 (m, 7H), 1.75 – 1.65 (m, 1H), 1.42 – 1.18 (m, 4H), 0.95 – 0.85 (m, 6H).

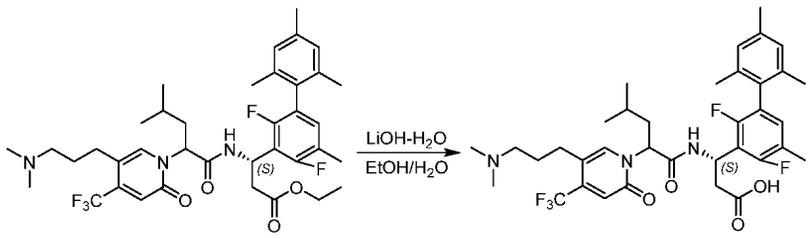
3-80. Preparation of (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds IJ-P1 and IJ-P2)

Step 1: ethyl (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (120.0 mg, 0.33 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (119.6 mg, 0.33 mmol), *TCFH* (138.9 mg, 0.50 mmol) and NMI (81.3 mg, 0.99 mmol) in CH_3CN (3 mL) was stirred at 50°C for 0.5hour. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a light yellow solid (160.0 mg). Yield 68% (ESI 706.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



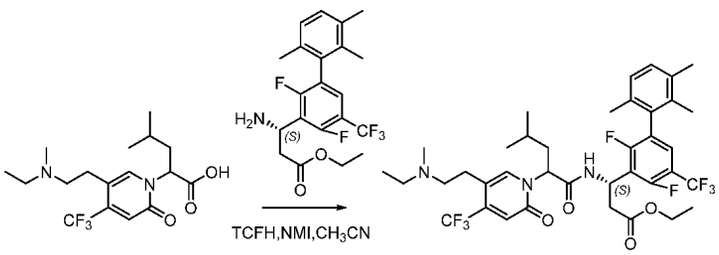
Ethyl (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (160.0 mg, 0.23 mmol) was treated with LiOH-H_2O (29.0 mg, 0.69 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **IJ-P1** (52.0 mg) and **IJ-P2** (44.0 mg) as white solids.

IJ-P1 ESI 678.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 6.94 – 6.75 (m, 4H), 5.78 – 5.72 (m, 2H), 3.09 – 3.02 (m, 2H), 2.98 – 2.90 (m, 1H), 2.78 (s, 6H), 2.73 – 2.59 (m, 3H), 2.28 (s, 3H), 2.23 (s, 3H), 2.11 – 1.96 (m, 3H), 1.97 – 1.81 (m, 7H), 1.41 – 1.26 (m, 1H), 0.95 – 0.91 (m, 6H).

IJ-P2 ESI 678.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 6.98 – 6.80 (m, 4H), 5.88 – 5.82 (m, 1H), 5.57 (t, *J* = 7.5 Hz, 1H), 3.08 – 2.92 (m, 2H), 2.91 – 2.73 (m, 7H), 2.72 – 2.45 (m, 3H), 2.28 (d, *J* = 10.7 Hz, 6H), 2.03 – 1.88 (m, 9H), 1.66 – 1.58 (m, 1H), 1.39 – 1.27 (m, 1H), 0.90 – 0.83 (m, 6H).

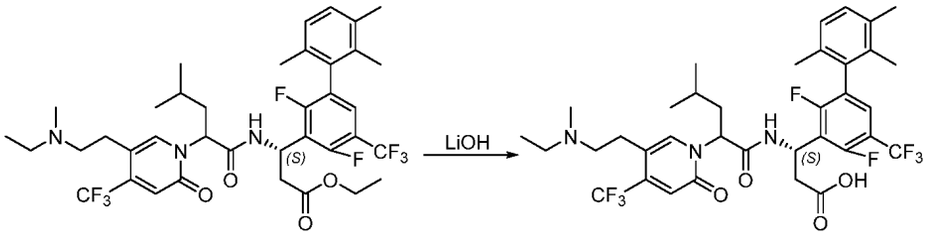
3-81. Preparation of (3*S*)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds IK-P1 and IK-P2)

Step 1: ethyl (3*S*)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100.0 mg, 0.28 mmol), ethyl (3S)-3-amino-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (116.2 mg, 0.28 mmol), TCFH (156.8 mg, 0.56 mmol) and NMI (91.8 mg, 1.12 mmol) in CH_3CN (10 mL) was stirred at room temperature for 1 hour. The reaction was concentrated in vacuo and the residue purified by silica gel column (DCM:MeOH 4: 1) to provide ethyl (3*S*)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a brown solid (110.0 mg). Yield 52% (ESI 760.7 $(M+H)^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



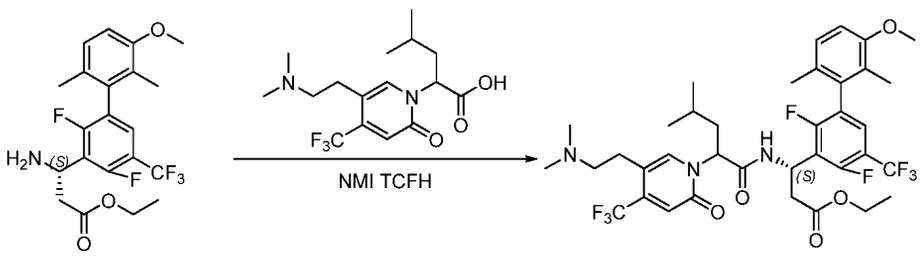
Ethyl (3*S*)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (110 mg, 0.14 mmol) was treated with LiOH-H_2O (23.5 mg, 0.56 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **IK-P1** (34.1 mg) and **IK-P2** (29.4 mg) as white solids.

IK-P1 ESI 732.7$(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 7.04 – 6.96 (m, 1H), 6.82 (d, J = 4.5 Hz, 1H), 5.78 – 5.66 (m, 2H), 3.19 – 3.05 (m, 4H), 3.00 – 2.85 (m, 3H), 2.80 – 2.70 (m, 4H), 2.26 (d, J = 2.0 Hz, 3H), 2.03 – 1.87 (m, 5H), 1.81 (d, J = 15.0 Hz, 3H), 1.43 – 1.32 (m, 1H), 1.26 (d, J = 7.3 Hz, 3H), 0.93 (d, J = 6.9 Hz, 6H).

IK-P2 ESI 732.7 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 7.8 Hz, 1H), 7.03 (d, J = 7.9 Hz, 1H), 6.88 (s, 1H), 5.85 – 5.75 (m, 1H), 5.71 – 5.61 (m, 1H), 3.27 – 3.09 (m, 4H), 3.00 – 2.84 (m, 3H), 2.79 (s, 3H), 2.72 – 2.62 (m, 1H), 2.28 (d, J = 2.1 Hz, 3H), 1.98 – 1.79 (m, 7H), 1.82 – 1.68 (m, 1H), 1.41 – 1.22 (m, 4H), 0.92 – 0.78 (m, 6H).

3-82. Preparation of (3*S*)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds IL-P1 and IL-P2)

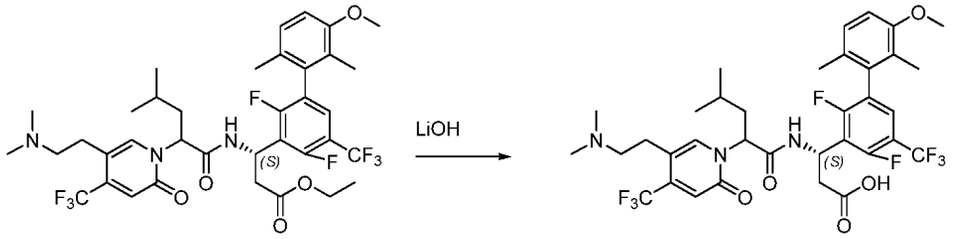
Step 1: (3*S*)-ethyl 3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (122 mg, 0.35 mmol), (3*S*)-ethyl 3-amino-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (150 mg, 0.35 mmol), NMI (86 mg, 1.05 mmol) and TCFH (147 mg, 0.53 mmol) in CH_3CN (4 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: CH_3CN, 0~100%) to provide (3*S*)-ethyl 3-(2,4-

difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (180 mg). Yield 68 % (ESI 762.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



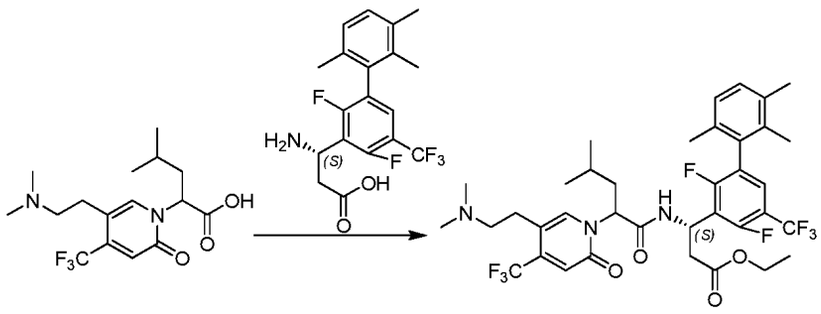
(3*S*)-ethyl 3-(2,4-difluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (180 mg, 0.24 mmol) was treated with LiOH-H_2O (40 mg, 0.96 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **IL-P1** (47 mg) and **IL-P2** (57 mg) as white solids.

IL-P1 ESI 734.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.12 – 7.05 (m, 1H), 6.92 – 6.81 (m, 2H), 5.78 – 5.63 (m, 2H), 3.82 (s, 3H), 3.19 – 3.04 (m, 2H), 3.02 – 2.87 (m, 3H), 2.83 – 2.69 (m, 7H), 2.09 – 1.93 (m, 2H), 1.93 – 1.73 (m, 6H), 1.45 – 1.33 (m,1H), 0.93 (t, *J* = 7.1 Hz, 6H).

IL-P2 ESI 734.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 8.2 Hz, 1H), 7.00 – 6.84 (m, 2H), 5.86 – 5.77 (m, 1H), 5.66 (t, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 3.26 – 3.06 (m, 2H), 3.01 – 2.71 (m, 9H), 2.78 – 2.50 (m, 1H), 2.02 – 1.80 (m, 7H), 1.80 – 1.55 (m, 1H), 1.53 – 1.22 (m, 1H), 0.97 – 0.77 (m, 6H).

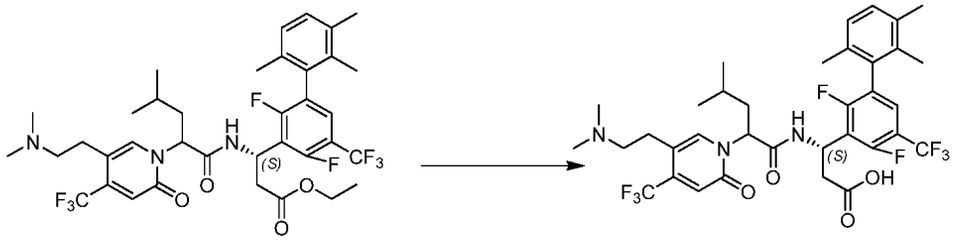
3-83. Preparation of (3*S*)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds IM-P1 and IM-P2)

Step 1: (3*S*)-ethyl 3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (100 mg, 0.29 mmol), (3*S*)-ethyl 3-amino-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (120 mg, 0.29 mmol), NMI (0.5 mL) and TCFH (378 mg, 1.35 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-90% CH_3CN) to provide (3*S*)-ethyl 3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a white solid (130 mg). Yield 60% (ESI 746.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



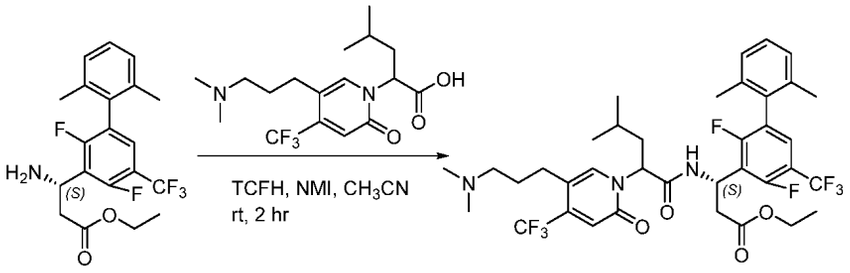
(3*S*)-ethyl 3-(2,4-difluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (130 mg, 0.17 mmol) was treated with LiOH-H_2O (42 mg, 1.00 mmol) in MeOH (4 mL) and H_2O (0.5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-70% CH_3CN) to give the diastereomeric products **IM-P1** (35.0 mg) and **IM-P2** (30.0 mg) as white solids.

IM-P1 ESI 718.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.33 (s, 1H), 7.10 (d, J = 7.6 Hz, 1H), 7.05 – 6.95 (m, 1H), 6.83 (d, J = 4.1 Hz, 1H), 5.76 – 5.62 (m, 2H), 3.17 – 3.02 (m, 2H), 2.98 – 2.86 (m, 3H), 2.75 (d, J = 14.0 Hz, 7H), 2.27 (d, J = 2.8 Hz, 3H), 2.04 – 1.88 (m, 5H), 1.82 (d, J = 15.0 Hz, 3H), 1.43 – 1.23 (m, 1H), 1.00 – 0.86 (m, 6H).

IM-P2 ESI 718.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.90 (s, 1H), 5.89 – 5.76 (m, 1H), 5.65 (t, *J* = 7.8 Hz, 1H), 3.26 – 3.11 (m, 2H), 2.97 (t, *J* = 7.0 Hz, 2H), 2.90 – 2.75 (m, 7H), 2.73 – 2.60 (m, 1H), 2.29 (s, 3H), 2.00 – 1.84 (m, 7H), 1.80 – 1.66 (m, 1H), 1.39 – 1.23 (m, 1H), 0.95 – 0.82 (m, 6H).

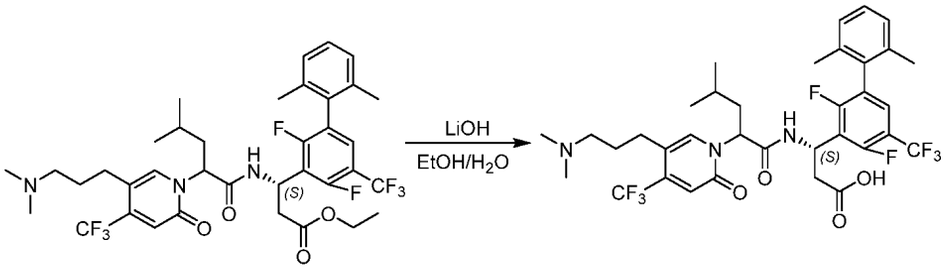
3-84. Preparation of (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (IN-P1 and IN-P2)

Step 1: ethyl (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (S)-3-amino-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (136 mg, 0.34 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (120 mg, 0.30 mmol), TCFH (168 mg, 0.60 mmol) and NMI (123 mg, 1.5 mmol) in CH_3CN (2 mL) was stirred at room temperature for 2 hours. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: CH_3OH, 0~85%) to provide ethyl (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a yellow oil (120 mg). Yield 43.3 % (ESI 746.3 $[M+H]^+$).

Step 2: (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



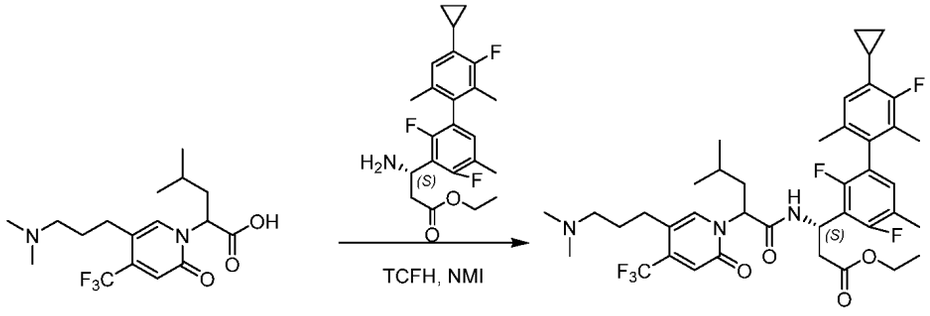
Ethyl (3S)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (120 mg, 0.16 mmol) was treated with LiOH-H_2O (17 mg, 0.40 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 2 hrs. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-65% CH_3CN) to give the diastereomeric products **IN-P1** (33 mg) and **IN-P2** (36 mg) as white solids.

IN-P1 ESI 718.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 7.38 (m, *J* = 7.6 Hz, 1H), 7.16 (m, *J* = 7.7, 6.3 Hz, 3H), 6.80 (s, 1H), 5.75 (m, *J* = 16.2, 8.0 Hz, 2H), 3.10 (s, 2H), 2.95 (m, *J* = 15.7, 9.3 Hz, 1H), 2.81 (s, 6H), 2.77 – 2.59 (m, 3H), 2.08 – 1.89 (m, 10H), 1.34 (s, 1H), 0.94 (d, *J* = 6.6 Hz, 6H).

IN-P2 ESI 718.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.43 (m, *J* = 7.6 Hz, 1H), 7.27 – 7.09 (m, 3H), 6.85 (s, 1H), 5.82 (m, *J* = 10.0, 4.8 Hz, 1H), 5.62 (m, *J* = 7.6 Hz, 1H), 3.17 – 2.97 (m, 2H), 2.91 – 2.80 (m, 3H), 2.80 (s, 4H), 2.69 – 2.54 (m, 3H), 2.20 – 1.81 (m, 9H), 1.73 – 1.53 (m, 1H), 1.31 (m, *J* = 13.3, 6.6 Hz, 1H), 0.86 (m, *J* = 9.8, 6.7 Hz, 6H).

3-85. Preparation of (3*S*)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid

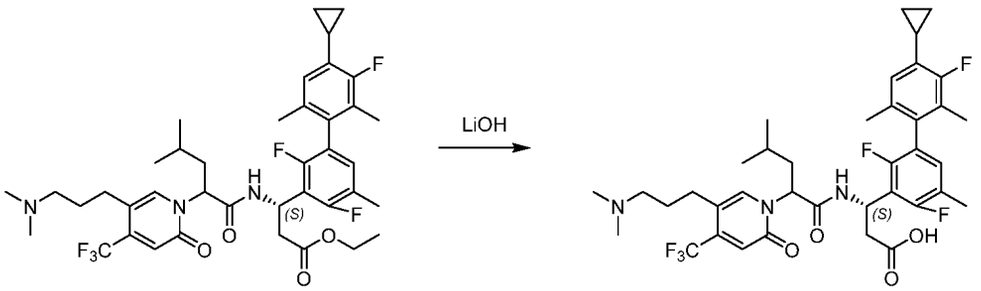
Step 1: ethyl (3*S*)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(4'-cyclopropyl-2,3',4-trifluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (197 mg, 0.48 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (160 mg, 0.44 mmol), *TCFH*(185 mg, 0.66 mmol), and 1-methylimidazole (144 mg, 1.76 mmol) in acetonitrile (8 mL) was stirred at room temperature for 2 hours. The mixture was purified by reverse phase HPLC on a C18 / 40g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4'-cyclopropyl-2,3',4-

trifluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (230 mg) as a yellow solid. Yield 70.0% (ESI 750.3 $(M+H)^+$).

Step 2: (3*S*)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



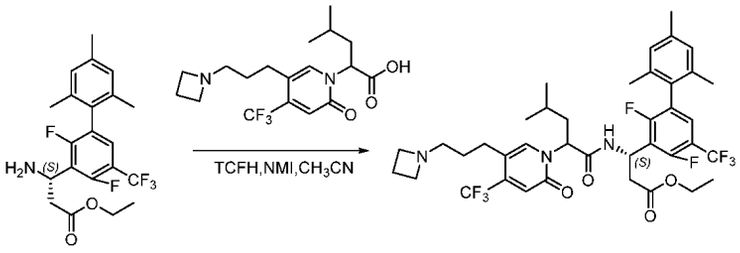
Ethyl (3*S*)-3-(4'-cyclopropyl-2,3',4-trifluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (230 mg, 0.31 mmol) was treated with LiOH-H_2O (51.6 mg, 1.23 mmol) in MeOH (5 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 6~7 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **IO-P1** (79.7 mg) and **IO-P2** (60.6 mg) as white solids.

IO-P1 ESI 722.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 6.86 (t, J = 8.2 Hz, 1H), 6.80 (d, J = 3.5 Hz, 1H), 6.65 – 6.63 (m, 1H), 5.77 – 5.71(m, 2H), 3.07 (t, J = 7.8 Hz, 2H), 2.96 – 2.90 (m, 1H), 2.79 (s, 6H), 2.73 – 2.59 (m, 3H), 2.23 (s, 3H), 2.12 – 1.82 (m, 11H), 1.38 – 1.32 (m, 1H), 1.01 – 0.92 (m, 8H), 0.77 – 0.70(m, 2H).

IO-P2 ESI 722.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 6.90 (t, J = 8.2 Hz, 1H), 6.85 (s, 1H), 6.67 (d, J = 7.3 Hz, 1H), 5.85 – 5.85 (m, 1H), 5.57 (t, J = 6.9 Hz, 1H), 3.14 – 3.11 (m, 2H), 2.89 – 2.78 (m, 7H), 2.68 – 2.52 (m, 3H), 2.27 (s, 3H), 2.14 – 1.89 (m, 10H), 1.66 – 1.57 (m, 1H), 1.36 – 1.29 (m, 1H), 1.03 – 0.92 (m, 2H), 0.86 (t, J = 7.8 Hz, 6H), 0.76 – 0.70 (m, 2H),.

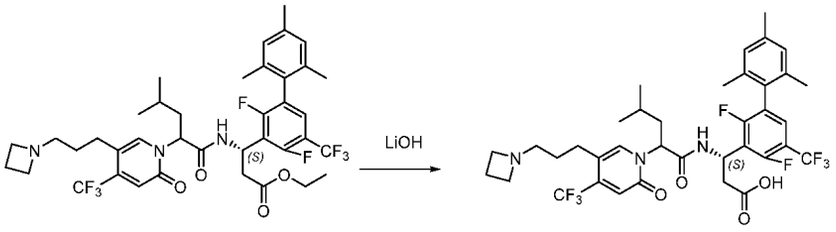
3-86. Preparation of (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IP-P1 and IP-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (112.0 mg, 0.27 mmol), 2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100.0 mg, 0.27 mmol), TCFH (151.2 mg, 0.54 mmol) and NMI (88.6 mg, 1.08 mmol) in CH_3CN (8 mL) was stirred at room temperature for 1 hour. The reaction was concentrated in vacuo and the residue purified by silica gel column (DCM: MeOH 4: 1) to provide ethyl (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a brown solid (130.0 mg). Yield 63% (ESI 772.6 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



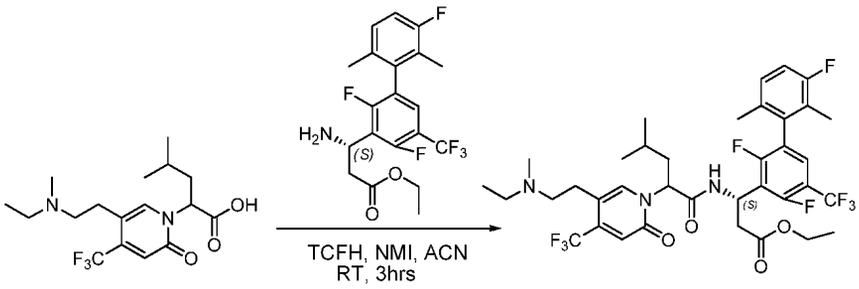
Ethyl (3*S*)-3-(2-(5-(3-(azetidin-1-yl)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (130 mg, 0.17 mmol)) was treated with LiOH-H_2O (28.6 mg, 0.68 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **IP-P1** (38.0 mg) and **IP-P2** (42.0 mg) as white solids.

IP-P1 ESI 744.7 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.94 (s, 1H), 6.79 (s, 2H), 5.74 (d, *J* = 4.1 Hz, 2H), 4.08 (t, *J* = 7.7 Hz, 4H), 3.21 – 3.11 (m, 2H), 2.97 – 2.89 (m, 1H), 2.71 – 2.58 (m, 3H), 2.45 (s, 2H), 2.30 (s, 3H), 2.06 – 1.91 (m, 5H), 1.83 (d, *J* = 43.4 Hz, 5H), 1.34 (s, 1H), 0.93 (d, *J* = 6.5 Hz, 6H).

IP-P2 ESI 744.7 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.78 (s, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 55.2 Hz, 3H), 5.87 – 5.78 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 4.15 – 3.99 (m, 4H), 3.19 – 2.97 (m, 2H), 2.94 – 2.82 (m, 1H), 2.69 – 2.54 (m, 3H), 2.50 – 2.37 (m, 2H), 2.31 (s, 3H), 2.03 – 1.71 (m, 9H), 1.73 – 1.53 (m, 1H), 1.39 – 1.20 (m, 1H), 0.89 – 0.72 (m, 6H).

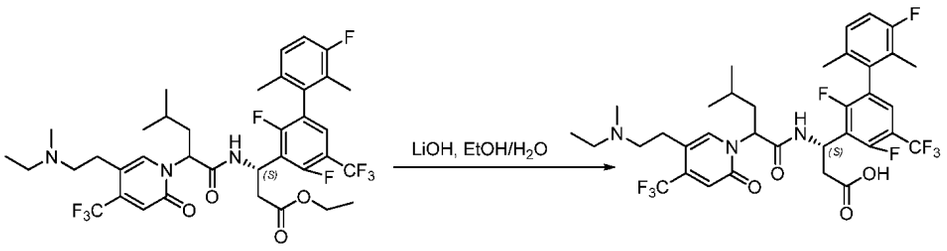
3-87. Preparation of (*3S*)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds IQ-P1 and IQ-P2)

Step 1: (*3S*)-ethyl 3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (*3S*)-ethyl 3-amino-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (118 mg, 0.28 mmol), 2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (100 mg, 0.28 mmol), TCFH (157 mg, 0.56 mmol) and NMI (69 mg, 0.84 mmol) in MeCN (5 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 97: 3) to provide (*3S*)-ethyl 3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a colorless oil (120 mg). Yield 55% (ESI 764.3 $(M+H)^+$).

Step 2: (*3S*)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



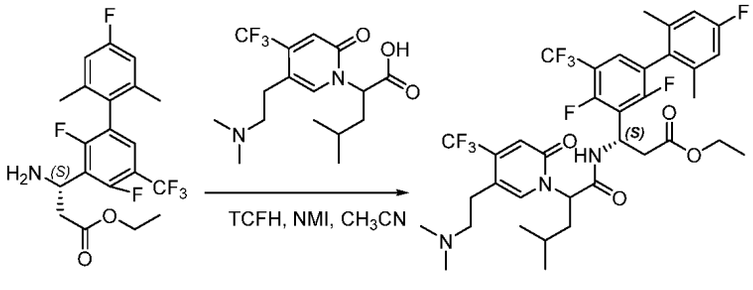
(*3S*)-ethyl 3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (100 mg, 0.13 mmol) was treated with LiOH-H_2O (27 mg, 0.65 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **IQ-P1** (30.3 mg) and **IQ-P2** (23.1 mg) as white solids.

IQ-P1 ESI 736.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.39 (t, *J* = 7.2 Hz 1H), 7.13-7.10 (m, 1H), 7.01 (t, *J* = 8.8 Hz 1H), 6.81 (d, *J* = 2.0 Hz, 1H), 5.72-5.68 (m, 2H), 3.15-3.08 (m, 4H), 2.97-2.92 (m, 3H), 2.79-2.74 (m, 4H), 2.02-1.87 (m, 8H), 1.38-1.35 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.93-0.90 (m, 6H).

IQ-P2 ESI 736.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.23 – 7.11 (m, 1H), 7.04 (t, *J* = 8.9 Hz, 1H), 6.88 (s, 1H), 5.78-5.75 (m, 1H), 5.68 (t, *J* = 7.8 Hz, 1H), 3.28 – 3.08 (m, 4H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.90 – 2.84 (m, 1H), 2.80 (s, 3H), 2.72-2.70 (m, 1H), 2.00 (d, *J* = 3.2 Hz, 3H), 1.93-1.90 (m, 3H), 1.86-1.83 (m, 1H), 1.80 – 1.68 (m, 1H), 1.37 – 1.22 (m, 4H), 0.87 -0.85(m, 6H).

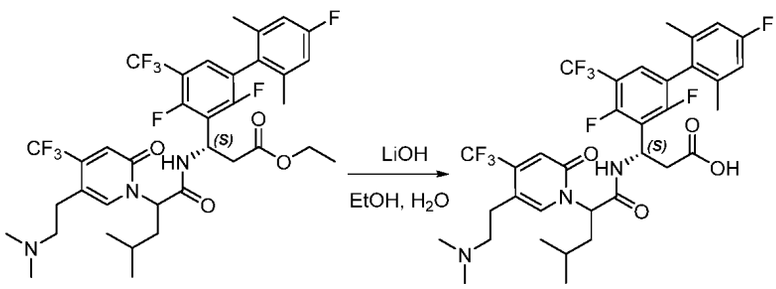
3-88. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IR-P1 and IR-P2)

Step 1: ethyl (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (S)-3-amino-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (100 mg, 0.24 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (100 mg, 0.29 mmol), TCFH (150 mg, 0.52 mmol) and NMI (106 mg, 1.3 mmol) in CH_3CN (3 mL) was stirred at 50 °C for 1 hr. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (110 mg). Yield 61.1 % (ESI 750.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



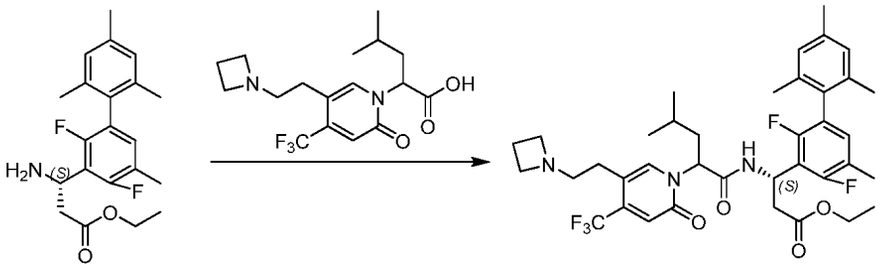
Ethyl (3S)-3-(2,4-difluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (110 mg, 0.15 mmol) was treated with LiOH-H_2O (13 mg, 0.3 mmol) in EtOH (2 mL) and H_2O (0.5 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (35-60% CH_3CN) to give the diastereomeric products **IR-P1** (32 mg) and **IR-P2** (39 mg) as white solids.

IR-P1 ESI 722.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.41 (t, J = 7.5 Hz, 1H), 6.95 – 6.86 (m, 2H), 6.84 (s, 1H), 5.79 – 5.62 (m, 2H), 3.12 (s, 2H), 3.02 – 2.88 (m, 3H), 2.85 – 2.68 (m, 7H), 2.11 – 1.84 (m, 8H), 1.45 – 1.36 (m, 1H), 1.02 – 0.88 (m, 6H).

IR-P2 ESI 722.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.46 (t, J = 7.6 Hz, 1H), 6.92 (d, J = 9.9 Hz, 3H), 5.80 (dd, J = 9.9, 5.6 Hz, 1H), 5.65 (t, J = 7.7 Hz, 1H), 3.25 – 3.14 (m, 2H), 2.96 (t, J = 7.0 Hz, 2H), 2.91 – 2.73 (m, 7H), 2.67 (d, J = 13.7 Hz, 1H), 2.03 (d, J = 2.6 Hz, 6H), 1.93 – 1.84 (m, 1H), 1.78 – 1.69 (m, 1H), 1.36 – 1.27 (m, 1H), 0.95 – 0.79 (m, 6H).

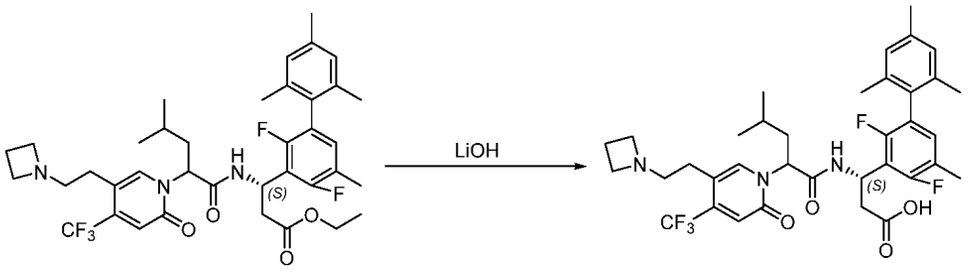
3-89. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (compounds IS-P1 and IS-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (240 mg, 0.66 mmol), (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (240 mg, 0.66 mmol), NMI (0.5 mL) and TCFH (378 mg, 1.35 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (30-90% CH_3CN) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate as a white solid (290 mg). Yield 62% (ESI 704.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid



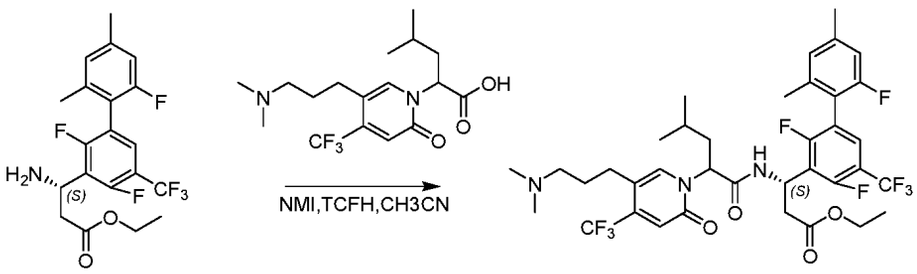
(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (290 mg, 0.41 mmol) was treated with LiOH-H_2O (86 mg, 2.05 mmol) in MeOH (5 mL) and H_2O (0.5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-70% CH_3CN) to give the diastereomeric products **IS-P1** (66.0 mg) and **IS-P2** (93.0 mg) as white solids.

IS-P1 ESI 675.9(M+H)$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 6.90 (s, 2H), 6.86 (s, 2H), 5.83 – 5.71 (m, 1H), 5.67 (t, *J* = 6.1 Hz, 1H), 3.99 (t, *J* = 8.1 Hz, 4H), 3.27 – 3.18 (m, 2H), 2.94 – 2.78 (m, 3H), 2.72 – 2.60 (m, 1H), 2.47 – 2.34 (m, 2H), 2.26 (d, *J* = 15.9 Hz, 6H), 2.06 – 1.93 (m, 5H), 1.90 (s, 3H), 1.50 – 1.29 (m, 1H), 0.92 (t, *J* = 6.1 Hz, 6H).

IS-P2 ESI 676.0 (M+H)$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.68 (s, 1H), 7.02 – 6.85 (m, 4H), 5.97 – 5.87 (m, 1H), 5.61 (t, *J* = 7.7 Hz, 1H), 4.11 (t, *J* = 8.1 Hz, 4H), 3.47 – 3.32 (m, 2H), 2.97 – 2.72 (m, 3H), 2.54 – 2.39 (m, 3H), 2.28 (d, *J* = 6.5 Hz, 6H), 2.00 – 1.87 (m, 7H), 1.79 – 1.66 (m, 1H), 1.46 – 1.26 (m, 1H), 0.94 – 0.80 (m, 6H).

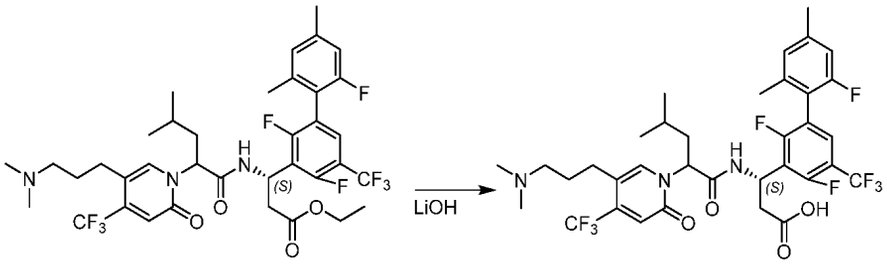
3-90. Preparation of Preparation of (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IT-P1 and IT-P2)

Step 1: ethyl ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (120.0 mg, 0.29 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (105.0 mg, 0.29 mmol), TCFH (123.2 mg, 0.44 mmol) and NMI (118.9 mg, 1.45 mmol) in CH_3CN (3 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (160.0 mg). Yield 73% (ESI 764.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid

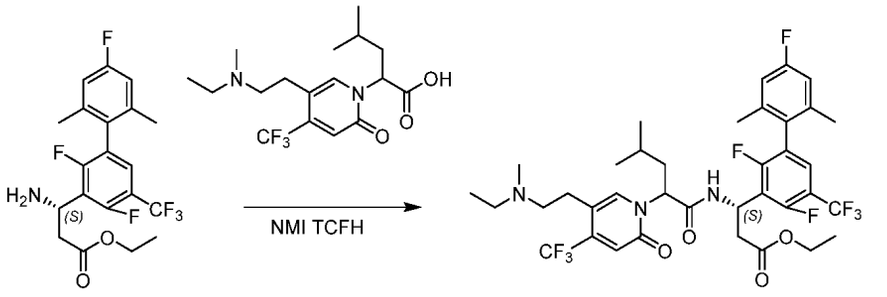


Ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (160.0 mg, 0.21 mmol) was treated with LiOH-H_2O (26.5 mg, 0.63 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **IT-P1** (30.0 mg) and **IT-P2** (49.0 mg) as white solids.

IT-P1 ESI 736.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 7.52 – 7.43 (m, 1H), 6.98 (s, 1H), 6.90 – 6.75 (m, 2H), 5.84 – 5.67 (m, 2H), 3.08 (t, *J* = 8.1 Hz, 2H), 2.97 – 2.87 (m, 1H), 2.83 – 2.55 (m, 9H), 2.35 (s, 3H), 2.13 – 1.82 (m, 7H), 1.40 – 1.27 (m, 1H), 0.97 – 0.90 (m, 6H).
IT-P2 ESI 736.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.00 (s, 1H), 6.93 – 6.80 (m, 2H), 5.84 – 5.75 (m, 1H), 5.70 – 5.60 (m, 1H), 3.15 – 2.96 (m, 2H), 2.93 – 2.72 (m, 7H), 2.70 – 2.59 (m, 3H), 2.37 (s, 3H), 2.15 – 1.84 (m, 6H), 1.75 – 1.55 (m, 1H), 1.37 –1.15 (m, 1H), 0.92 – 0.80 (m, 6H).

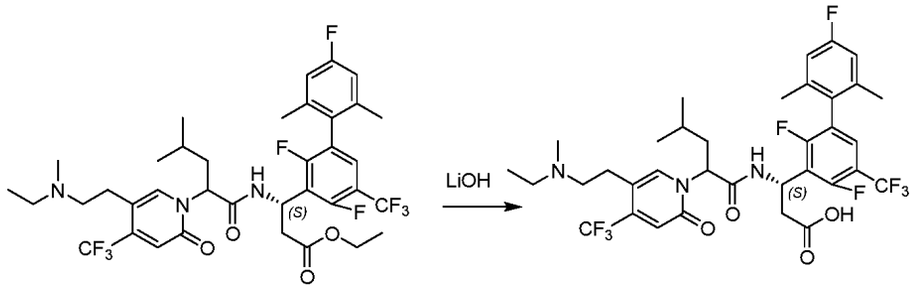
3-91. Preparation of Preparation of (3*S*)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IU-P1 and IU-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (120mg, 0.29 mmol),2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100 mg, 0.29 mmol), TCFH (162.4 mg, 0.58 mmol) and NMI (119.0 mg, 1.45 mmol) in CH_3CN (3 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 20~90%) to provide ethyl (3*S*)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (160.0 mg). Yield 73% (ESI 764.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



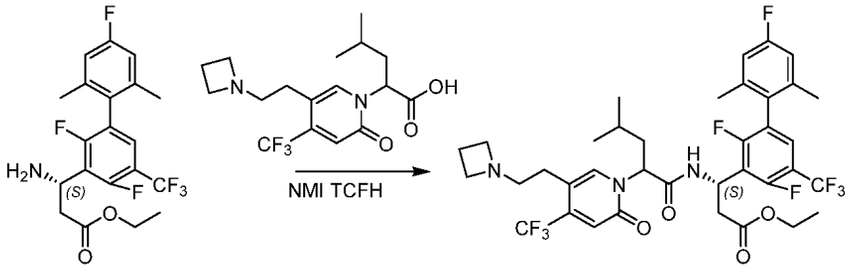
Ethyl (3*S*)-3-(2-(5-(2-(ethyl(methyl)amino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (160.0 mg, 0.21 mmol) was treated with LiOH-H_2O (26.5 mg, 0.63 mmol) in EtOH (3 mL) and water (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-90% MeCN) to give the diastereomeric products **IU-P1** (34.0 mg) and **IU-P2** (32.0 mg) as white solids.

IU-P1 ESI 736.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 6.93 – 6.75 (m, 3H), 5.78 – 5.65 (m, 2H), 3.22 – 3.04 (m, 4H), 3.02 – 2.88 (m, 3H), 2.83 – 2.70 (m, 4H), 2.07 – 1.86 (m, 8H), 1.43 – 1.23 (m, 4H), 0.94 (t, *J* = 6.8 Hz, 6H).

IU-P2 ESI 736.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 6.96 – 6.81 (m, 3H), 5.83 – 5.74 (m, 1H), 5.66 (t, *J* = 7.8 Hz, 1H), 3.27 – 3.09 (m, 4H), 2.97 (t, *J* = 7.4 Hz, 2H), 2.92 – 2.63 (m, 5H), 2.03 (d, *J* = 3.5 Hz, 6H), 1.92 – 1.82 (m, 1H), 1.79 – 1.65 (m, 1H), 1.37 – 1.25 (m, 4H), 0.94 – 0.81 (m, 6H)

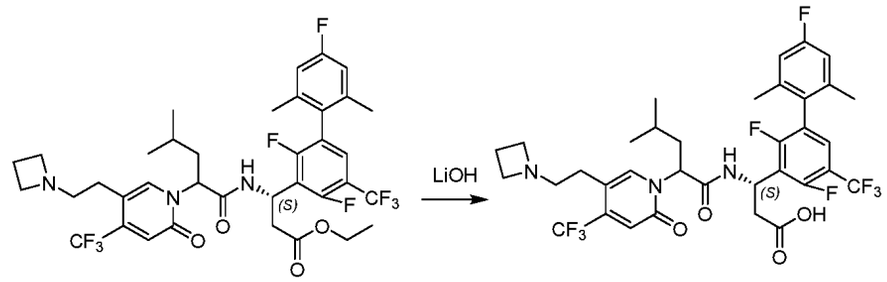
3-92. Preparation of Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IV-P1 and IV-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (120.0 mg, 0.29 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (103.0 mg, 0.29 mmol), TCFH (162.4 mg, 0.58 mmol) and NMI (118.9 mg, 1.45 mmol) in CH_3CN (3 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 20~80%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (180.0 mg). Yield 82.6% (ESI 762.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



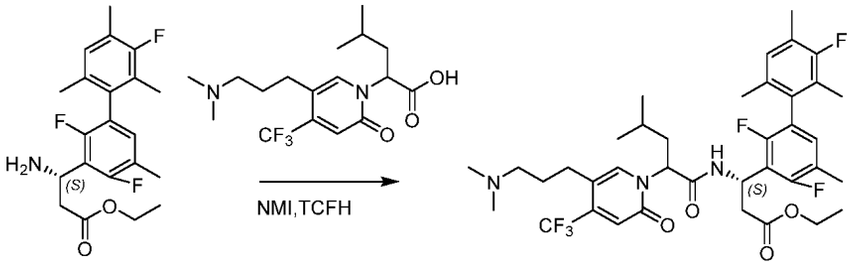
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (180.0 mg, 0.24 mmol) was treated with LiOH-H_2O (30.2 mg, 0.72 mmol) in EtOH (3 mL) and water (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5

with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-90% MeCN) to give the diastereomeric products **IV-P1** (34.0 mg) and **IV-P2** (27.0 mg) as white solids.

IV-P1 ESI 734.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 6.97 – 6.78 (m, 3H), 5.78 – 5.60 (m, 2H), 4.05 (t, *J* = 7.8 Hz, 4H), 3.29 – 3.20 (m, 2H), 2.97 – 2.80 (m, 3H), 2.78 – 2.69 (m, 1H), 2.53 – 2.38 (m, 2H), 2.08 – 1.90 (m, 8H), 1.45 – 1.31 (m, 1H), 0.93 (t, *J* = 6.4 Hz, 6H).
IV-P2 ESI 734.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.00 – 6.86 (m, 3H), 5.95 – 5.85 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.12 (t, *J* = 7.9 Hz, 4H), 3.50 – 3.34 (m, 2H), 2.96 – 2.73 (m, 3H), 2.65 – 2.55 (m, 1H), 2.52 – 2.40 (m, 2H), 2.03 (d, *J* = 1.7 Hz, 6H), 1.96 – 1.85 (m, 1H), 1.78 – 1.65 (m, 1H), 1.40 – 1.25 (m, 1H), 0.95 – 0.82 (m, 6H).

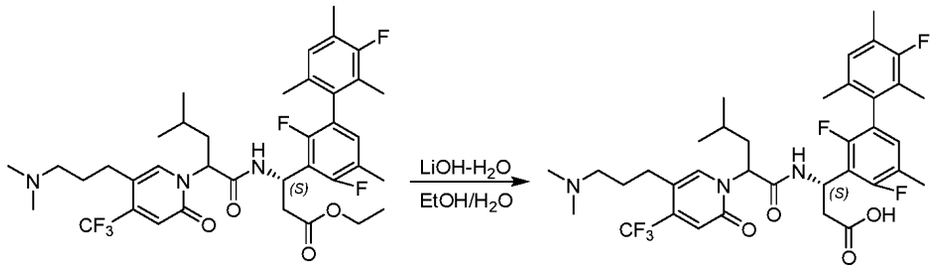
3-93. Preparation of Preparation of (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IW-P1 and IW-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (170 mg, 0.45 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (151 mg, 0.54 mmol), *TCFH* (213.2 mg, 0.76 mmol) and NMI (177 mg, 2.16 mmol) in CH_3CN (3 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 20~95%) to provide ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (210.0 mg). Yield 65% (ESI 724.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid

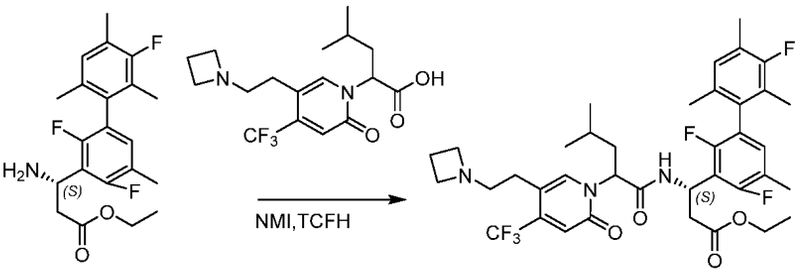


Ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (210.0 mg, 0.29 mmol) was treated with LiOH-H_2O (36.5 mg, 0.87 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (20-85% MeCN) to give the diastereomeric products **IW-P1** (68 mg) and **IW-P2** (52 mg) as white solids.

IW-P1 ESI 696.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 6.98 – 6.80 (m, 3H), 5.83 – 5.69 (m, 2H), 3.09 (t, *J* = 7.9 Hz, 2H), 3.00 – 2.90 (m, 1H), 2.81 (d, *J* = 0.8 Hz, 6H), 2.73 – 2.58 (m, 3H), 2.26 (d, *J* = 1.3 Hz, 6H), 2.15 – 1.78 (m, 10H), 1.43 – 1.30 (m, 1H), 1.00 – 0.90 (m, 6H).
IW-P2 ESI 696.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.02 – 6.79 (m, 3H), 5.89 – 5.79 (m, 1H), 5.57 (t, *J* = 7.6 Hz, 1H), 3.09 – 2.95 (m, 2H), 2.91 – 2.71 (m, 7H), 2.70 – 2.47 (m, 3H), 2.32 – 2.19 (m, 6H), 2.07 – 1.83 (m, 9H), 1.67 – 1.55 (m, 1H), 1.37 – 1.27 (m, 1H), 0.90 – 0.80 (m, 6H).

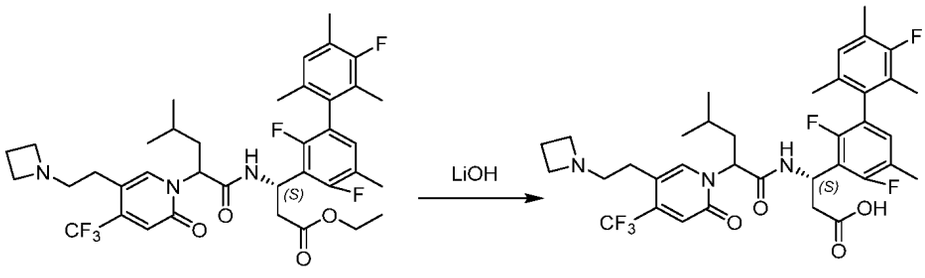
3-94. Preparation of Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds IX-P1 and IX-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (170 mg, 0.45 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (162 mg, 0.45mmol), NMI (0.5 mL) and TCFH (241 mg, 0.86 mmol) in CH_3CN (3 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (50-80% CH3CN) to provideethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (200 mg). Yield 62% (ESI 722.1 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid



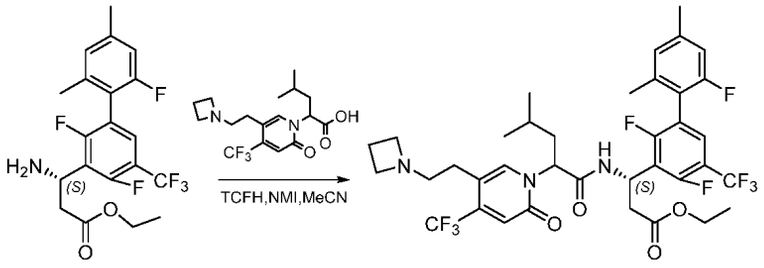
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.28 mmol) was treated with LiOH-H_2O (35 mg, 0.84mmol) in MeOH (3.0 mL) and H_2O (1.0 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (50-80% CH_3CN) to give the diastereomeric products **IX-P1** (42.0 mg) and **IX-P2** (53.0 mg) as white solids.

IX-P1 ESI 694.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.01 – 6.77 (m, 3H), 5.84 – 5.58 (m, 2H), 4.00 (t, *J* = 8.0 Hz, 4H), 3.29 – 3.20 (m, 2H), 2.95 – 2.80 (m, 3H), 2.70 – 2.60 (m, 1H), 2.50 – 2.35 (m, 2H), 2.24 (d, *J* = 3.4 Hz, 6H), 2.04 – 1.80 (m, 8H), 1.45 – 1.33 (m, 1H), 0.93 (t, *J* = 6.1 Hz, 6H).

IX-P2 ESI 694.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 7.00 – 6.90 (m, 3H), 5.97 – 5.85 (m,1H), 5.61 (t, *J* = 7.7 Hz, 1H), 4.10 (t, *J* = 8.0 Hz, 4H), 3.47 – 3.34 (m, 2H), 2.96 – 2.73 (m, 3H), 2.57 – 2.37 (m, 3H), 2.31 – 2.17 (m, 6H), 1.99 – 1.84 (m, 7H), 1.78 – 1.65 (m, 1H), 1.42 – 1.30 (m, 1H), 0.93 – 0.82 (m, 6H).

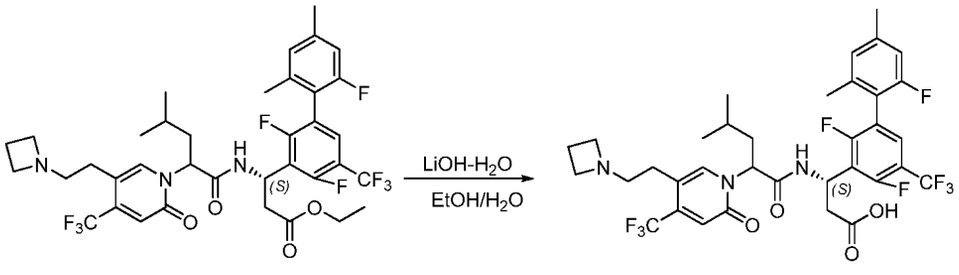
3-95. Preparation of ((3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds IY-P1 and IY-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (115 mg, 0.32 mmol), (3*S*)-ethyl 3-amino-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (120 mg, 0.29 mmol), NMI (71 mg, 0.87 mmol) and TCFH (98 mg, 0.35 mmol) in CH_3CN (4 mL) was stirred at room temperature for 2 hours. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: CH_3CN, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (140 mg). Yield 64 % (ESI 762.3 $[M+H]^+$).

Step 2: ((3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (140 mg, 0.19 mmol) was treated with LiOH-H_2O (32 mg, 0.76 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The

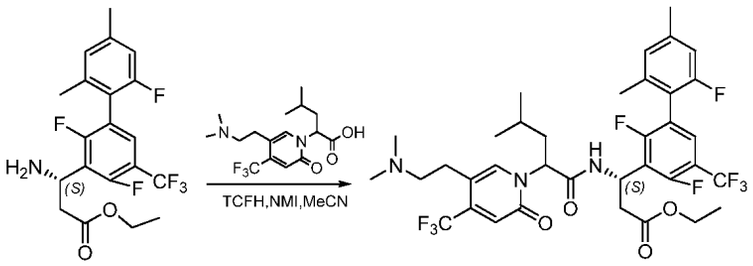
reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **IY-P1** (36 mg) and **IY-P2** (51 mg) as white solids.

IY-P1 ESI 734.2 $(M+H)^+$. ^{1}HNMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.55 – 7.45 (m, 1H), 6.98 (s, 1H), 6.89 – 6.80 (m, 2H), 5.79 – 5.67 (m, 2H),4.12 – 3.97 (m, 4H), 3.35 – 3.12 (m, 2H), 3.00 – 2.66 (m, 4H), 2.52 – 2.27 (m, 5H), 2.16 – 1.88 (m, 5H), 1.44 – 1.30 (m, 1H), 0.98 – 0.90 (m, 6H).

IY-P2 ESI 734.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.01 (s, 1H), 6.99 – 6.85 (m, 2H), 5.97 – 5.82 (m, 1H), 5.66 (t, J = 7.7 Hz, 1H), 4.12 (t, J = 8.0 Hz, 4H), 3.45 – 3.31 (m, 2H), 2.97 – 2.76 (m, 3H), 2.66 – 2.57 (m, 1H), 2.53 – 2.39 (m, 2H), 2.37 (s, 3H), 2.11 (d, J = 5.0 Hz, 3H), 1.97 – 1.86 (m, 1H), 1.78 – 1.67 (m, 1H), 1.40 – 1.27 (m, 1H), 0.95 – 0.81 (m, 6H).

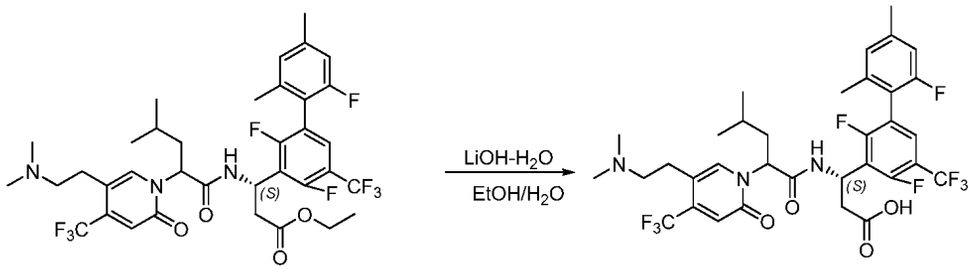
3-96. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds IZ-P1 and IZ-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (110 mg, 0.32 mmol), (3*S*)-ethyl 3-amino-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (120 mg, 0.29 mmol), NMI (71 mg, 0.87 mmol) and TCFH (98 mg, 0.35 mmol) in CH_3CN (4 mL) was stirred at room temperature for 2 hours. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (140 mg). Yield 65 % (ESI 750.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



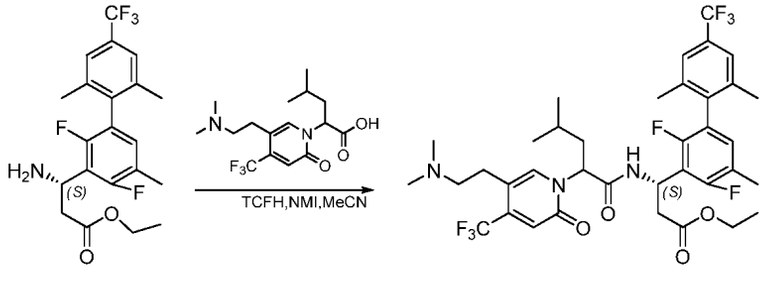
(3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,2',4-trifluoro-4',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (140 mg, 0.19 mmol) was treated with LiOH-H_2O (32 mg, 0.76 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **IZ-P1** (38 mg) and **IZ-P2** (52 mg) as white solids.

IZ-P1 ESI 722.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.56 – 7.36 (m, 1H), 6.97 (s, 1H), 6.89 – 6.80 (m, 2H), 5.79 – 5.64 (m, 2H), 3.18 – 3.03 (m, 2H), 3.02 – 2.87 (m, 3H), 2.81 – 2.69 (m, 7H), 2.35 (s, 3H), 2.12 – 1.90 (m, 5H), 1.48 – 1.31 (m, 1H), 0.99 – 0.87 (m, 6H).

IZ-P2 ESI 722.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.53 (t, J = 7.5 Hz, 1H), 7.00 (s, 1H), 6.94 – 6.83 (m, 2H), 5.87 – 5.77 (m, 1H), 5.73 – 5.63 (m, 1H), 3.27 – 3.06 (m, 2H), 3.01 – 2.92 (m, 2H), 2.91 – 2.73 (m, 7H), 2.73 – 2.60 (m, 1H), 2.36 (s, 3H), 2.11 (d, J = 6.6 Hz, 3H), 1.97 – 1.63 (m, 2H), 1.43 – 1.20 (m, 1H), 0.98 – 0.82 (m, 6H).

3-97. Preparation of (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido) propanoic acid (compounds JA-P1 and JA-P2)

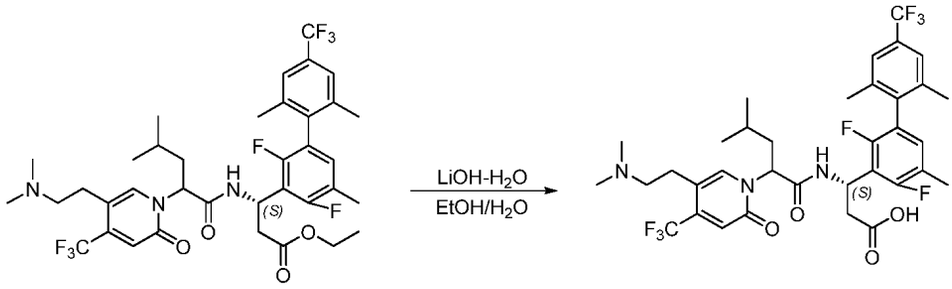
Step 1: (3*S*)-ethyl 3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoate (170 mg, 0.41 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-

1(2*H*)-yl)-4-methylpentanoic acid (140 mg, 0.41 mmol), NMI (100 mg, 1.23 mmol) and TCFH (140 mg, 0.49 mmol) in CH_3CN (6 mL) was stirred at room temperature for 2 hours. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide (3*S*)-ethyl 3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (200 mg). Yield 66 % (ESI 746.1 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



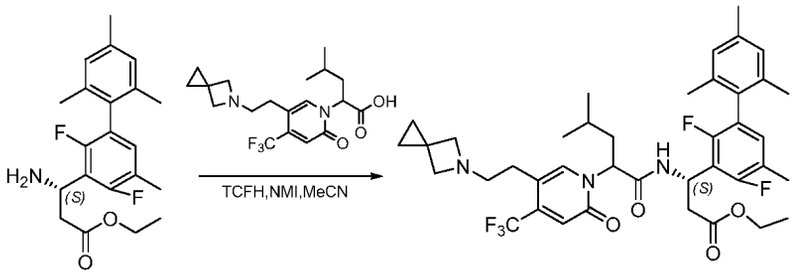
(3*S*)-ethyl 3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (200 mg, 0.27 mmol) was treated with LiOH-H_2O (45 mg, 1.08 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JA-P1** (56 mg) and **JA-P2** (65 mg) as white solids.

JA-P1 ESI 718.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.39 (d, *J* = 2.4 Hz, 2H), 6.92 (t, *J* = 8.1 Hz, 1H), 6.82 (s, 1H), 5.75 – 5.65 (m, 2H), 3.17 – 2.83 (m, 5H), 2.82 – 2.65 (m, 7H), 2.25 (s, 3H), 2.07 (s, 3H), 2.02 – 1.91 (m, 5H), 1.54 – 1.27 (m, 1H), 0.93 (t, J = 6.8 Hz, 6H).

JA-P2 ESI 718.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.42 (s, 2H), 6.98 (t, *J* = 8.1 Hz, 1H), 6.90 (s, 1H), 5.88 – 5.84 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 3.29 – 3.09 (m, 2H), 3.04 – 2.92 (m, 2H), 2.88 – 2.76 (m, 7H), 2.62 – 2.52 (m, 1H), 2.29 (s, 3H), 2.09 (d, *J* = 3.4 Hz, 6H), 1.95 – 1.68 (m, 2H), 1.40 – 1.25 (m, 1H), 0.92 – 0.82 (m, 6H).

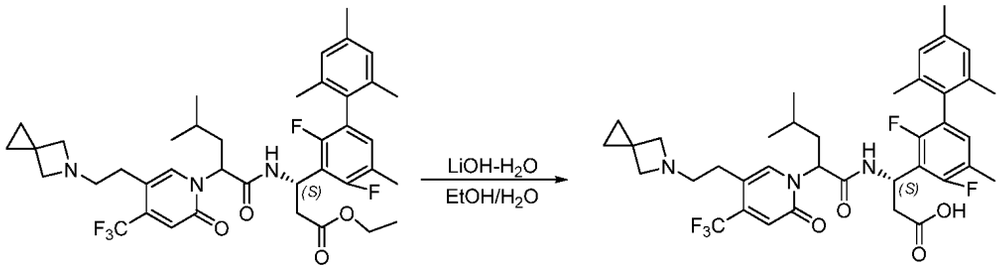
3-98. Preparation of (3*S*)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (compounds JB-P1 and JB-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate



A mixture of (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (160 mg, 0.43 mmol), 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150 mg, 0.39 mmol), NMI (100 mg, 1.17 mmol) and TCFH (130 mg, 0.47 mmol) in CH_3CN (6 mL) was stirred at room temperature for 2 hours. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate as a yellow oil (210 mg). Yield 75 % (ESI 730.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid



(3*S*)-ethyl 3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (210 mg, 0.29 mmol) was treated with LiOH-H_2O (37 mg, 0.87 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JB-P1** (50 mg) and **JB-P2** (55 mg) as white solids.

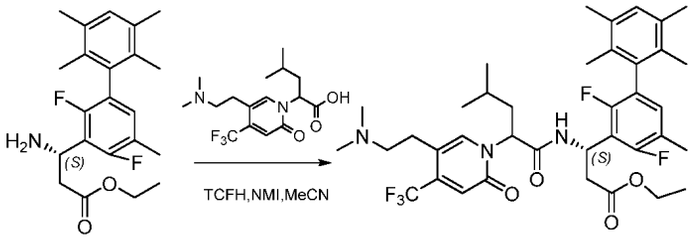
JB-P1 ESI 702.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 6.97 – 6.76 (m, 4H), 5.80 – 5.61 (m, 2H), 4.04 (s, 4H), 3.45 – 3.32 (m, 2H), 3.12 – 2.81 (m, 3H), 2.70 – 2.61 (m, 1H), 2.28 (s,

3H), 2.24 (s, 3H), 2.01 – 1.93 (m, 5H), 1.89 (s, 3H), 1.58 – 1.26 (m, 1H), 0.98 – 0.89 (m, 6H), 0.72 (s, 4H).

JB-P2 ESI 702.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.07 – 6.86 (m, 4H), 5.96 – 5.89(m, 1H), 5.64 (t, *J* = 7.7 Hz, 1H), 4.34 – 4.02 (m, 4H), 3.66 – 3.37 (m, 2H), 3.11 – 2.71 (m, 3H), 2.56 – 2.48 (m, 1H), 2.37 – 2.19 (m, 6H), 2.10 – 1.87 (m, 7H), 1.77 – 1.60 (m, 1H), 1.46 – 1.30 (m, 1H), 1.00 – 0.64 (m, 10H).

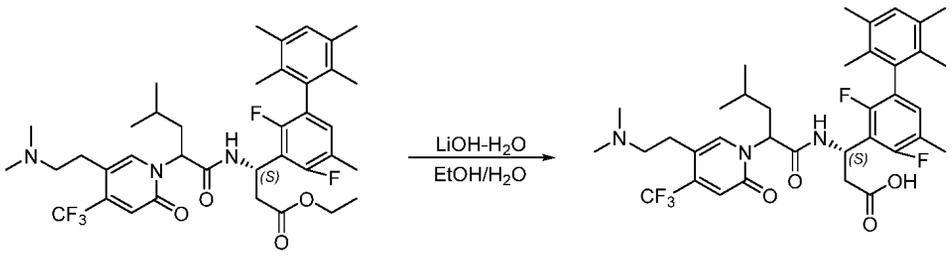
3-99. Preparation of (3*S*)-3-(2,4-difluoro-2',3',5,5',6'-pentamethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds JC-P1 and JC-P2)

Step 1: (3*S*)-ethyl 3-(2,4-difluoro-2',3',5,5',6'-pentamethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',3',5,5',6'-pentamethylbiphenyl-3-yl)propanoate (160 mg, 0.43 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150 mg, 0.43 mmol), NMI (110 mg, 1.29 mmol) and TCFH (150 mg, 0.52 mmol) in CH_3CN (6 mL) was stirred at room temperature for 2 hours. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide (3*S*)-ethyl 3-(2,4-difluoro-2',3',5,5',6'-pentamethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (200 mg). Yield 69 % (ESI 706.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',3',5,5',6'-pentamethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



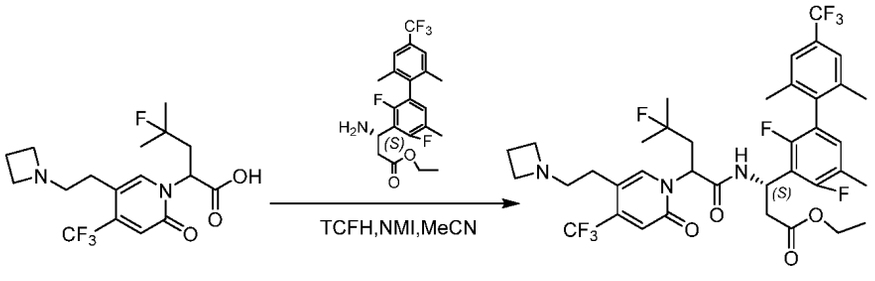
(3*S*)-ethyl 3-(2,4-difluoro-2',3',5,5',6'-pentamethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (200 mg, 0.28 mmol) was treated with LiOH-H_2O (47 mg, 1.12 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JC-P1** (56 mg) and **JC-P2** (64 mg) as white solids.

JC-P1 ESI 678.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 6.97 (s, 1H), 6.88 – 6.79 (m, 2H), 5.84 – 5.63 (m, 2H), 3.18 – 2.89 (m, 5H), 2.79 – 2.65 (m, 7H), 2.32 – 2.17 (m, 9H), 1.98 (t, *J* = 7.6 Hz, 2H), 1.86 (s, 3H), 1.76 (s, 3H), 1.47 – 1.34 (m, 1H), 0.95 (t, *J* = 6.9 Hz, 6H).

JC-P2 ESI 678.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 6.99 (s, 1H), 6.94 – 6.84 (m, 2H), 5.91 – 5.84 (m, 1H), 5.66 (t, *J* = 7.7 Hz, 1H), 3.28 – 3.10 (m, 2H), 3.09 – 2.92 (m, 2H), 2.89 – 2.73 (m, 7H), 2.70 – 2.52 (m, 1H), 2.28 (s, 3H), 2.25 (s, 6H), 1.99 – 1.82 (m, 7H), 1.83 – 1.61 (m, 1H), 1.49 – 1.25 (m, 1H), 0.94– 0.84 (m, 6H).

3-100. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds JD-P1 and JD-P2)

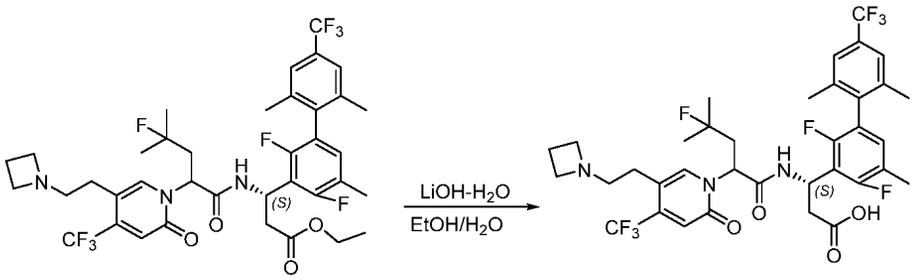
Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoic acid (100 mg, 0.26 mmol), (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-4'-

(trifluoromethyl)biphenyl-3-yl)propanoate (120 mg, 0.29 mmol), NMI (64 mg, 0.78 mmol) and TCFH (90 mg, 0.32 mmol) in CH_3CN (4 mL) was stirred at room temperature for 2 hours. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (80 mg). Yield 39 % (ESI 776.1 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid



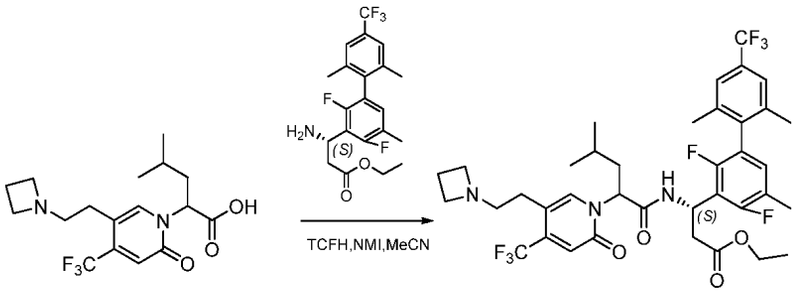
(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoate (80 mg, 0.10 mmol) was treated with LiOH-H_2O (17 mg, 0.40 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JD-P1** (17 mg) and **JD-P2** (15 mg) as white solids.

JD-P1 ESI 748.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.39 (s, 2H), 6.93 (t, J = 8.1 Hz, 1H), 6.81 (s, 1H), 6.08 – 5.62 (m, 2H), 4.03 (t, J = 8.0 Hz, 4H), 3.30 – 3.18 (m, 3H), 2.98 – 2.75 (m, 3H), 2.72 – 2.62 (m, 1H), 2.58 – 2.36 (m, 4H), 2.25 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.45 – 1.28 (m, 6H).

JD-P2 ESI 748.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 7.42 (s, 2H), 6.99 (t, J = 8.2 Hz, 1H), 6.92 (s, 1H), 5.95 – 5.88 (m, 1H), 5.78 (t, J = 6.7 Hz, 1H), 4.11 (t, J = 7.9 Hz, 4H), 3.46 – 3.31 (m, 2H), 3.00 – 2.69 (m, 3H), 2.64 – 2.38 (m, 4H), 2.30 (s, 3H), 2.26 – 2.15 (m, 1H), 2.09 (s, 6H), 1.36 – 1.24 (m, 6H).

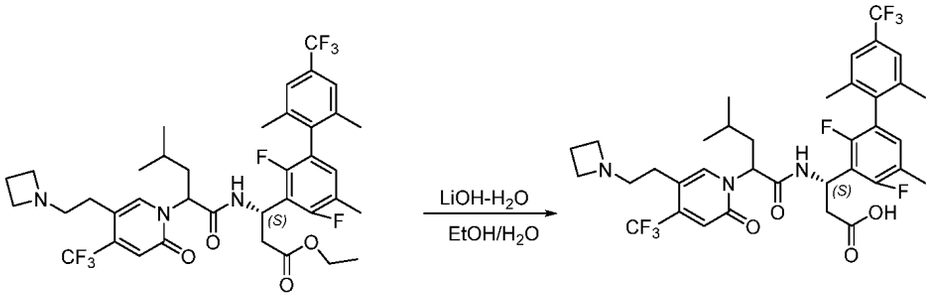
3-101. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds JE-P1 and JE-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (160 mg, 0.44 mmol), (*S*)-ethyl 3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoate (180 mg, 0.44 mmol), NMI (110 mg, 1.32 mmol) and TCFH (150 mg, 0.53 mmol) in CH_3CN (6 mL) was stirred at room temperature for 2 hours. The solvent was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (180 mg). Yield 54 % (ESI758.2 $[M+H]^+$).

Step 2: of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid



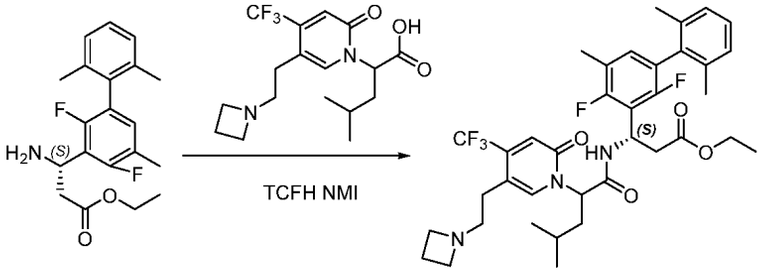
(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoate (180 mg, 0.24 mmol) was treated with LiOH-H_2O (30 mg, 0.72 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JE-P1** (48 mg) and **JE-P2** (55 mg) as white solids.

JE-P1 ESI 730.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.39 (s, 2H), 6.94 (t, *J* = 8.1 Hz, 1H), 6.86 (s, 1H), 5.79 – 5.63 (m, 2H), 4.02 (t, *J* = 8.1 Hz, 4H), 3.35 – 3.20 (m, 2H), 2.98 – 2.80 (m, 3H), 2.72 – 2.63 (m, 1H), 2.49 – 2.37 (m, 2H), 2.26 (s, 3H), 2.08 (s, 3H), 2.05 – 1.93 (m, 5H), 1.50 – 1.28 (m, 1H), 0.93 (t, *J* = 6.1 Hz, 6H).

JE-P2 ESI 730.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 7.42 (s, 2H), 6.99 (t, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 5.96 – 5.88 (m, 1H), 5.61 (t, *J* = 7.7 Hz, 1H), 4.11 (t, *J* = 8.1 Hz, 4H), 3.46 – 3.31 (m, 2H), 2.97 – 2.73 (m, 3H), 2.60 – 2.38 (m, 3H), 2.30 (s, 3H), 2.10 (d, *J* = 2.6 Hz, 6H), 1.99 – 1.89 (m, 1H), 1.80 – 1.66 (m, 1H), 1.51 – 1.22 (m, 1H), 0.92 – 0.83 (m, 6H).

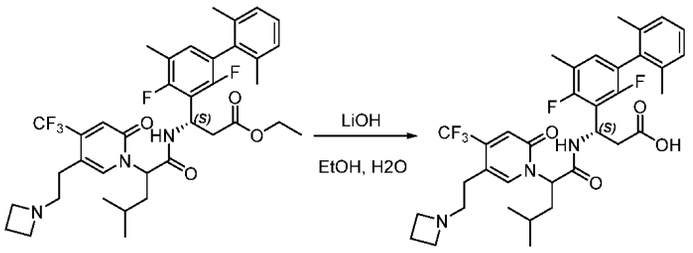
3-102. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JF-P1 and JF-P2)

Step 1: ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (240 mg, 0.6 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (253 mg, 0.66 mmol), TCFH (336 mg, 1.2 mmol) and NMI (246 mg, 3.0 mmol) in CH_3CN (4 mL) was stirred at 60 ºC for 30 min. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (280 mg). Yield 67.7 % (ESI 690.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



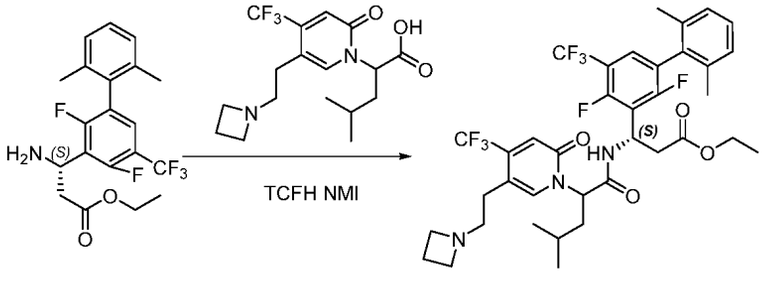
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (280 mg, 0.41 mmol) was treated with LiOH-H_2O (50 mg, 1.2 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 30 min. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (35-58% CH_3CN) to give the diastereomeric products **JF-P1** (74 mg) and **JF-P2** (81 mg) as white solids.

JF-P1 ESI 662.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.17 – 7.03 (m, 3H), 6.94 – 6.85 (m, 2H), 5.78 – 5.71 (m, 1H), 5.67 (t, *J* = 8.1 Hz, 1H), 4.01 (t, *J* = 8.1 Hz, 4H), 2.94 – 2.79 (m, 3H), 2.71 – 2.59 (m, 1H), 2.48 – 2.36 (m, 2H), 2.25 (s, 3H), 2.06 – 1.88 (m, 8H), 1.42 – 1.33 (m, 1H), 0.93 (t, *J* = 6.5 Hz, 6H).

JF-P2 ESI 662.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 7.20 – 7.04 (m, 3H), 6.98 – 6.90 (m, 2H), 5.97 – 5.88 (m, 1H), 5.61 (t, *J* = 7.7 Hz, 1H), 4.12 (s, 4H), 3.47 – 3.33 (m, 2H), 2.93 – 2.74 (m, 3H), 2.59 – 2.40 (m, 3H), 2.29 (s, 3H), 2.01 (d, *J* = 2.4 Hz, 6H), 1.96 – 1.87 (m, 1H), 1.80 – 1.68 (m, 1H), 1.42 – 1.30 (m, 1H), 0.92 – 0.83 (m, 6H).

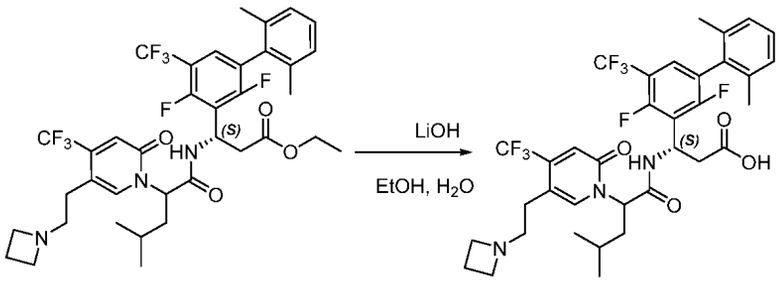
3-103. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JG-P1 and JG-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (240 mg, 0.6 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (230 mg, 0.58 mmol), TCFH (325 mg, 1.16 mmol) and NMI (238 mg, 2.9 mmol) in CH_3CN (4 mL) was stirred at 50°C for 30 mins. The reaction was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (250 mg). Yield 58.0 % (ESI 744.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



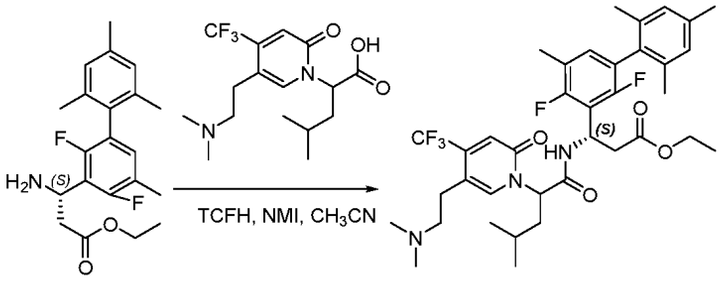
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (250 mg, 0.34 mmol) was treated with LiOH-H_2O (58 mg, 1.37 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (40-61% CH_3CN) to give the diastereomeric products **JG-P1** (72 mg) and **JG-P2** (78 mg) as white solids.

JG-P1 ESI 716.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.15 (m, 1H), 7.12 (d, *J* = 7.7 Hz, 2H), 6.85 (s, 1H), 5.77 – 5.66 (m, 2H), 4.04 (t, *J* = 8.0 Hz, 4H), 3.28 (s, 2H), 2.92 (M, 1H), 2.84 (t, *J* = 6.8 Hz, 2H), 2.76 (s, 1H), 2.46 – 2.38 (m, 2H), 2.05 – 1.95 (m, 5H), 1.95 (d, *J* = 13.7 Hz, 3H), 1.38 (s, 1H), 0.93 (t, *J* = 6.4 Hz, 6H).

JG-P2 ESI 716.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.46 (t, *J* = 7.7 Hz, 1H), 7.25 – 7.19 (m, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 6.91 (s, 1H), 5.91 (M, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 4.12 (t, *J* = 7.8 Hz, 4H), 3.47 – 3.32 (m, 2H), 2.95 – 2.77 (m, 3H), 2.65 – 2.55 (m, 1H), 2.50 – 2.40 (m, 2H), 2.02 (d, *J* = 2.2 Hz, 6H), 1.96 – 1.88 (m, 1H), 1.75 – 1.67 (m, 1H), 1.39 – 1.28 (m, 1H), 0.92 – 0.84 (m, 6H).

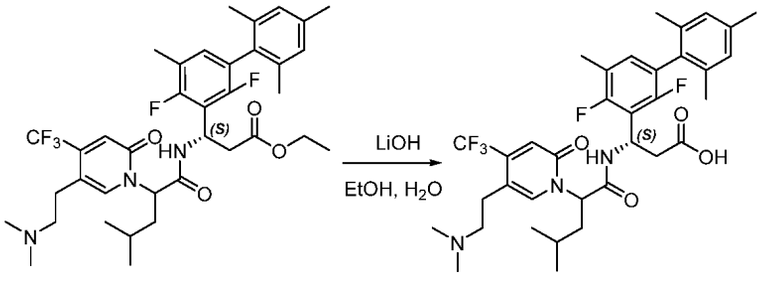
3-104. Preparation of (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds JH-P1 and JH-P2)

Step 1: ethyl (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (*S*)-3-amino-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (220 mg, 0.61 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (250 mg, 0.65 mmol), TCFH (364 mg, 1.3 mmol) and NMI (266 mg, 3.25 mmol) in CH_3CN (4.5 mL) was stirred at 60°C for 30 mins. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~80%) to provide ethyl (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a yellow solid (300 mg). Yield 71.1 % (ESI 692.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



Ethyl (3*S*)-3-(2,4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (300 mg, 0.43 mmol) was treated with LiOH-H_2O (56 mg, 1.34 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 1 hr. The reaction mixture was acidified to pH 5~6 with 1N HCl. The

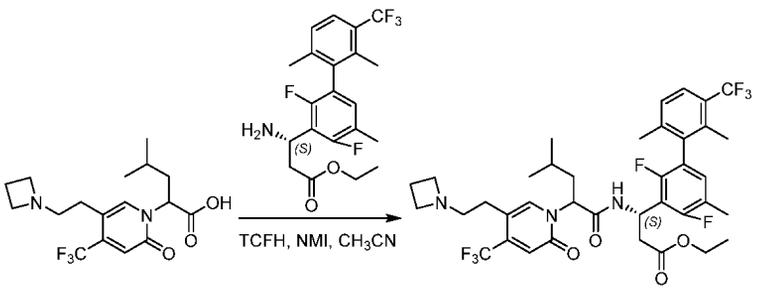
reaction was concentrated in vacuo and the residue purified by prep-HPLC A (35-62% CH_3CN) to give the diastereomeric products **JH-P1** (113 mg) and **JH-P2** (87 mg) as white solids.

JH-P1 ESI 664.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 6.96 – 6.77 (m, 4H), 5.81 – 5.63 (m, 2H), 3.10 (d, *J* = 21.9 Hz, 2H), 2.98 – 2.86 (m, 3H), 2.76 – 2.63 (m, 7H), 2.25 (d, *J* = 19.9 Hz, 6H), 2.01 – 1.92 (m, 5H), 1.87 (s, 3H), 1.44 – 1.35 (m, 1H), 0.93 (t, *J* = 6.8 Hz, 6H).

JH-P2 ESI 664.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (d, *J* = 11.6 Hz, 1H), 7.01 – 6.84 (m, 4H), 5.85 (d, *J* = 8.7 Hz, 1H), 5.63 (s, 1H), 3.25 – 3.09 (m, 2H), 3.05 – 2.91 (m, 2H), 2.77 (s, 7H), 2.55 (d, *J* = 14.8 Hz, 1H), 2.28 (d, *J* = 10.3 Hz, 6H), 1.96 (d, *J* = 3.6 Hz, 6H), 1.93 – 1.85 (m, 1H), 1.80 – 1.67 (m, 1H), 1.39 – 1.27 (m, 1H), 0.93 – 0.81 (m, 6H).

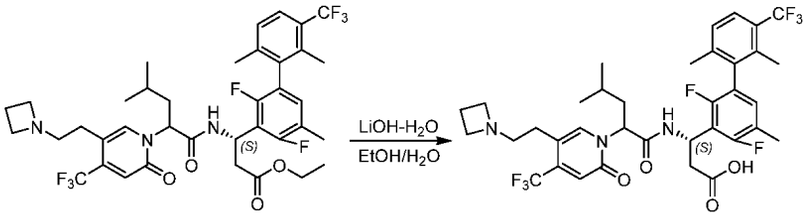
3-105. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JI-P1 and JI-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (174.5 mg, 0.42 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150.0 mg, 0.42 mmol), TCFH (140.3 mg, 0.50 mmol) and NMI (137.9 mg, 1.68 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (160.0 mg). Yield 51% (ESI 758.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid

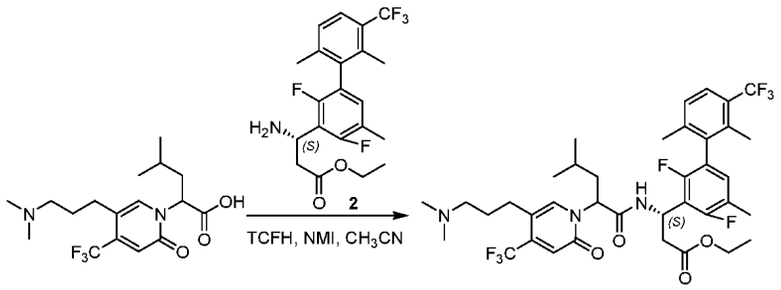


Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (160.0 mg, 0.21 mmol) was treated with LiOH-H_2O (26.4 mg, 0.63 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to PH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **JI-P1** (39.5 mg) and **JI-P2** (53.3 mg) as white solids.

JI-P1 ESI 730.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.80 (d, *J* = 4.4 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 6.92 (t, *J* = 8.2 Hz, 1H), 6.86 (s, 1H), 5.79 – 5.61 (m, 2H), 4.01 (t, *J* = 8.1 Hz, 4H), 3.37 – 3.31 (m, 1H), 3.29 – 3.20 (m, 1H), 2.95 – 2.80 (m, 3H), 2.71 – 2.64 (m, 1H), 2.49 – 2.35 (m, 2H), 2.26 (s, 3H), 2.14 – 1.92 (m, 8H), 1.46 – 1.30 (m, 1H), 0.93 (t, *J* = 6.7 Hz, 6H).
JI-P2 ESI 730.1 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.70 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 6.98 (t, *J* = 8.2 Hz, 1H), 6.92 (s, 1H), 5.94 – 5.88 (m, 1H), 5.64 – 5.58 (m, 1H), 4.10 (t, *J* = 8.0 Hz, 4H), 3.44 – 3.32 (m, 2H), 2.96 – 2.74 (m, 3H), 2.58 – 2.37 (m, 3H), 2.30 (s, 3H), 2.12 (s, 3H), 2.07 (d, *J* = 2.6 Hz, 3H), 2.00 – 1.86 (m, 1H), 1.80 – 1.66 (m, 1H), 1.41 – 1.31 (m, 1H), 0.92 – 0.85 (m, 6H).

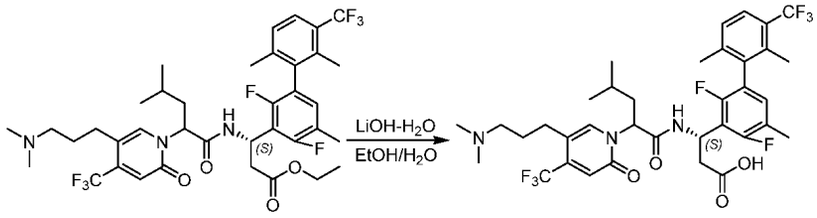
3-106. Preparation of (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds JJ-P1 and JJ-P2)

Step 1: ethyl (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (3*S*)-3-amino-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (114.6 mg, 0.28 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (100.0 mg, 0.28 mmol), TCFH (95.4 mg, 0.34 mmol) and NMI (92.0 mg, 1.12 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. The reaction was concentrated in vacuo and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a light yellow solid (100.0 mg). Yield 48% (ESI 760.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



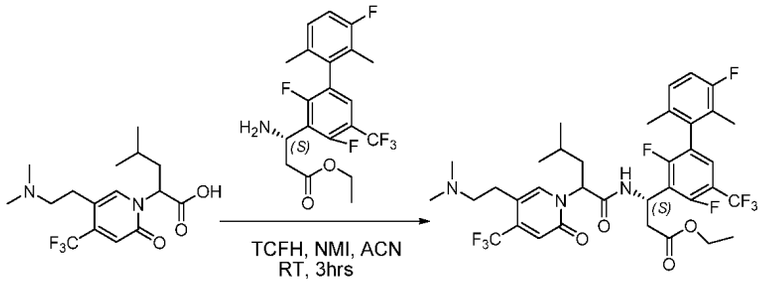
Ethyl (3*S*)-3-(2,4-difluoro-2',5,6'-trimethyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (100.0 mg, 0.13 mmol) was treated with LiOH-H_2O (16.4 mg, 0.39 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **JJ-P1** (6.0 mg) and **JJ-P2** (36.5 mg) as white solids.

JJ-P1 ESI 732.2 $(M+H)^+$ ^1H NMR (400 MHz, MeOD) δ 7.77 (d, *J* = 3.4 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 8.1 Hz, 1H), 6.79 (s, 1H), 5.81 – 5.67 (m, 2H), 3.14 – 3.00 (m, 2H), 2.97 – 2.89 (m, 1H), 2.78 (s, 6H), 2.72 – 2.58 (m, 3H), 2.25 (s, 3H), 2.11 – 1.81 (m, 10H), 1.41 – 1.29 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 6H).

JJ-P2 ESI 732.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 8.1 Hz, 1H), 6.84 (s, 1H), 5.86 – 5.80 (m, 1H), 5.61 – 5.55 (m, 1H), 3.11 – 2.91 (m, 2H), 2.91 – 2.82 (m, 1H), 2.77 (s, 6H), 2.70 – 2.51 (m, 3H), 2.29 (s, 3H), 2.14 – 2.04 (m, 6H), 2.03 – 1.88 (m, 3H), 1.67 – 1.58 (m, 1H), 1.38 – 1.28 (m, 1H), 0.92 – 0.81 (m, 6H).

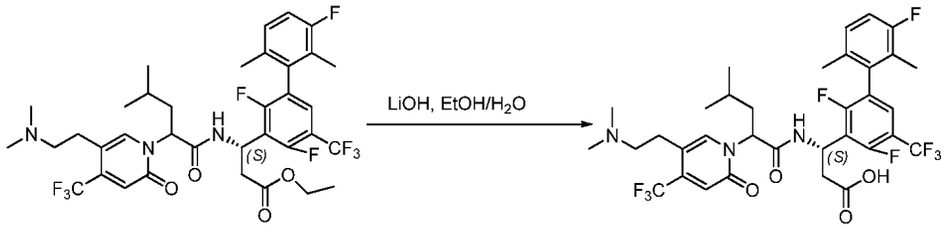
3-107. Preparation of (*3S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds JK-P1 and JK-P2)

Step 1: (*3S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (*3S*)-ethyl 3-amino-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (120 mg, 0.29 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (100 mg, 0.29 mmol), TCFH (157 mg, 0.56 mmol) and NMI (69 mg, 0.84 mmol) in MeCN (5 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 97: 3) to provide (3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a colorless oil (120 mg). Yield 55% (ESI 750.3 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



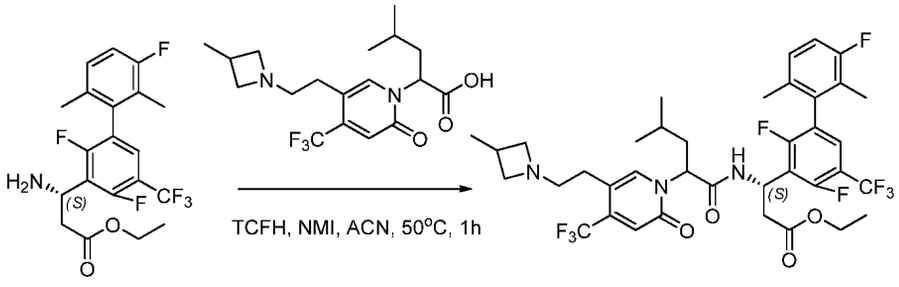
(3*S*)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (100 mg, 0.13 mmol) was treated with LiOH-H_2O (27 mg, 0.65 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 3 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JK-P1** (30.3 mg) and **JK-P2** (23.1 mg) as white solids.

JK-P1 ESI 722.3 $(M+H)^+$. 1H NMR (400 MHz, DMSO) δ 9.26 (d, *J* = 6.4 Hz, 1H), 7.78 (s, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.25 – 7.12 (m, 2H), 6.70 (s, 1H), 5.58-5.55 (m, 1H), 5.46 (d, J = 6.2 Hz, 1H), 3.04 – 2.87 (m, 2H), 2.67 – 2.52 (m, 2H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.18 (s, 6H), 1.96 – 1.73 (m, 8H), 1.35 – 1.27 (m, 1H), 0.85-0.83 (m, 6H).

JK-P2 ESI 722.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.24 – 7.10 (m, 1H), 7.04 (t, *J* = 9.0 Hz, 1H), 6.90 (s, 1H), 5.80-5.78 (m, 1H), 5.66 (t, *J* = 7.8 Hz, 1H), 3.19-3.15 (m, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 2.92 – 2.76 (m, 7H), 2.69-2.66 (m, 1H), 2.00 (d, *J* = 2.4 Hz, 3H), 1.97 – 1.92 (m, 3H), 1.93 – 1.86 (m, 1H), 1.79 – 1.70 (m, 1H), 1.33-1.30 (m, 1H), 0.88 - 0.85(m, 6H).

3-108. Preparation of (3S)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds JL-P1 and JL-P2)

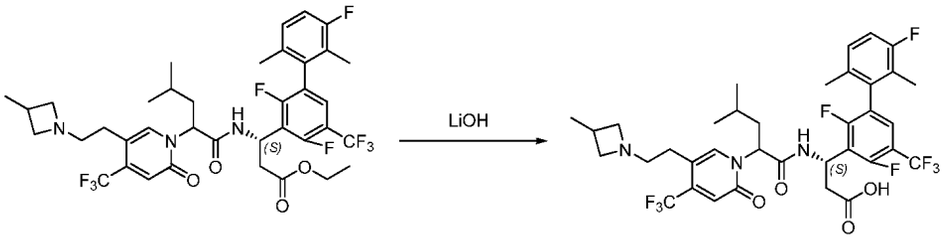
Step 1: (3S)-ethyl 3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (3S)-ethyl 3-amino-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (120 mg, 0.28 mmol), 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid (105 mg, 0.28 mmol), NMI (69 mg, 0.84 mmol) and TCFH (117 mg, 0.42 mmol) in CH_3CN (10 mL) was stirred at 50°C for 1 hour. The solvent was concentrated *in vacuo* and the residue was purified by silica gel column (DCM: MeOH 10:1) to

provide (3S)-ethyl 3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (151 mg). Yield 68.0 % (ESI 776.3 $[M+H]^+$).

Step 2: (3S)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



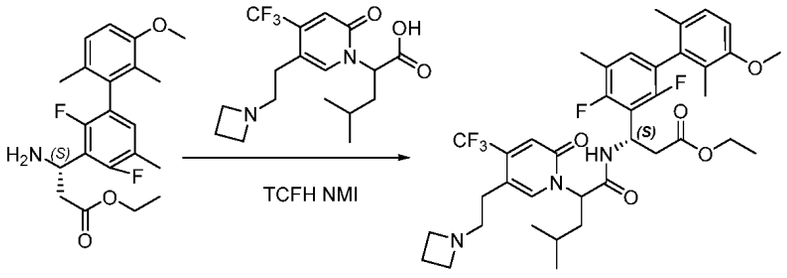
(3S)-ethyl 3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)-3-(2,3',4-trifluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (151 mg, 0.19 mmol) was treated with LiOH-H_2O (24.5 mg, 0.58 mmol) in EtOH (3 mL) and water (1 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (20-70% MeCN) to give the diastereomeric products **JL-P1** (49 mg) and **JL-P2** (51 mg) as white solids.

JL-P1 ESI 748.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 5.9 Hz, 1H), 7.02 (t, J = 8.9 Hz, 1H), 6.84 (s, 1H), 5.77 – 5.65 (m, 2H), 4.13 (t, J = 9.2 Hz, 2H), 3.67 (t, J = 8.8 Hz, 2H), 3.30 – 3.20 (m, 2H), 2.89 – 2.81 (m, 5H), 2.04 – 1.83 (m, 8H), 1.41 – 1.35 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.93 (t, J = 6.0 Hz, 6H).

JL-P2 ESI 748.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.77 (s, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.20 – 7.13 (m, 1H), 7.04 (t, J = 8.9 Hz, 1H), 6.90 (s, 1H), 5.89 – 5.81 (m, 1H), 5.66 (t, J = 7.8 Hz, 1H), 4.13 (t, J = 9.2 Hz, 2H), 3.66 (s, 2H), 3.30 (s, 2H), 2.96 – 2.74 (m, 4H), 2.68 – 2.62 (m, 1H), 2.00 (d, J = 2.2 Hz, 3H), 1.97 – 1.83 (m, 4H), 1.77 – 1.71 (m, 1H), 1.36 – 1.29 (m, 1H), 1.25 (d, J = 6.9 Hz, 3H), 0.90 – 0.85 (m, 6H).

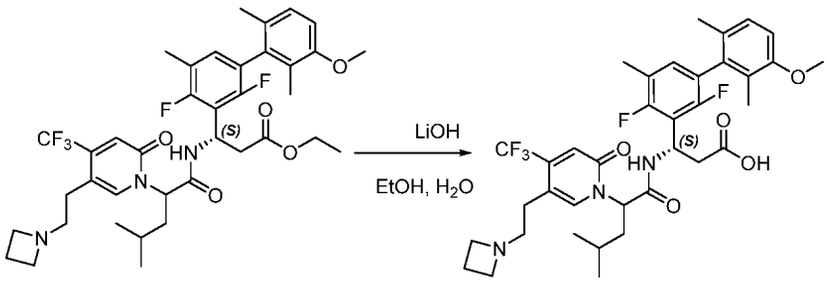
3-109. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JM-P1 and JM-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3S)-3-amino-3-(2,4-difluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (190 mg, 0.5 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (198 mg, 0.55 mmol), TCFH (302 mg, 1.08 mmol) and NMI (220 mg, 2.7 mmol) in CH_3CN (4 mL) was stirred at 25 °C for 1 hr. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~90%) to provide ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (250 mg). Yield 69.4 % (ESI 720.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4-difluoro-3'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (250 mg, 0.35 mmol) was treated with LiOH-H_2O (42 mg, 1 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 30 min. The reaction mixture was acidified to pH 5~6 with 1N HCl. The reaction was concentrated in vacuo and the residue purified by prep-HPLC A (35-65% CH_3CN) to give the diastereomeric products **JM-P1** (68 mg) and **JM-P2** (86 mg) as white solids.

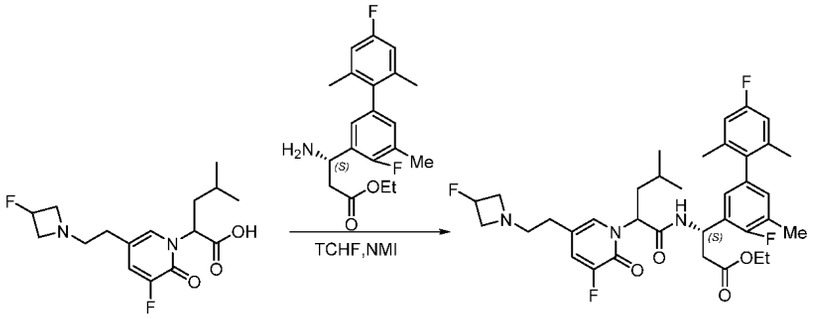
JM-P1 ESI 692.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.79 (s, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.90 – 6.79 (m, 3H), 5.77 – 5.63 (m, 2H), 3.99 (t, J = 8.0 Hz, 4H), 3.81 (s, 3H), 3.30 – 3.23 (m, 2H), 2.94 –

2.81 (m, 3H), 2.70 – 2.61 (m, 1H), 2.46 – 2.35 (m, 2H), 2.24 (s, 3H), 1.97 (t, *J* = 7.6 Hz, 2H), 1.93 – 1.77 (m, 6H), 1.44 – 1.34 (m, 1H), 0.92 (t, *J* = 6.2 Hz, 6H).

JM-P2 ESI 692.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 7.06 (d, *J* = 8.4 Hz, 1H), 6.96 – 6.82 (m, 3H), 5.95 – 5.87 (m, 1H), 5.61 (t, *J* = 7.7 Hz, 1H), 4.12 (t, *J* = 8.1 Hz, 4H), 3.82 (s, 3H), 3.47 – 3.33 (m, 2H), 2.98 – 2.73 (m, 3H), 2.56 – 2.40 (m, 3H), 2.28 (s, 3H), 1.97 – 1.88 (m, 4H), 1.86 (d, *J* = 3.0 Hz, 3H), 1.78 – 1.68 (m, 1H), 1.41 – 1.30 (m, 1H), 0.88 (dd, *J* = 10.5, 6.6 Hz, 6H).

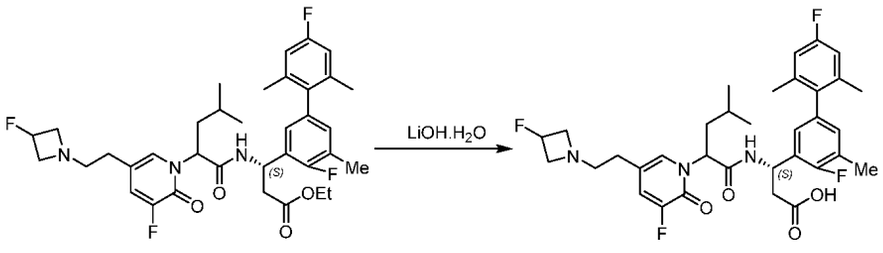
3-110. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (JN-P1 and JN-P2)

Step 1: ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanoic acid (200.0 mg, 0.61 mmol), ethyl (*S*)-3-amino-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (260.0 mg, 0.61 mmol), TCHF (205.0 mg, 0.73 mmol) and NMI (150.0 mg, 1.83 mmol) in CH_3CN (4 mL) was stirred at room temperature for 1.5 hours. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18 / 40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow solid (210.0 mg). Yield 52.5% (ESI 658.3 $[M+H]^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid

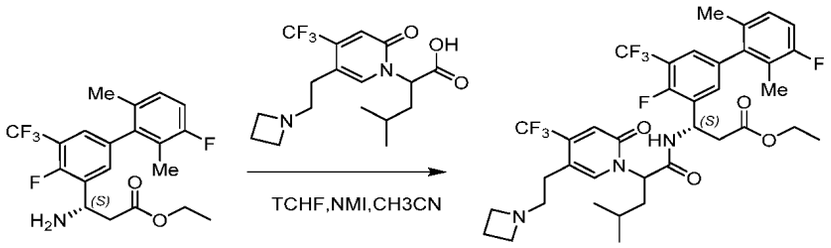


Ethyl (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (210.0 mg, 0.32 mmol) was treated with LiOH-H_2O (150.0 mg, 3.2 mmol) in THF (4 mL) and water (2 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% MeCN) to provide the diastereomeric products **JN-P1** (81 mg) and **JN-P2** (83 mg) as white solids.

JN-P1 ESI 630.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.30 (s, 1H), 7.25 – 7.22 (m, 1H), 6.77 – 6.75 (m, 1H), 6.72 – 6.69 (m, 3H), 5.55 (t, J = 8.0 Hz, 1H), 5.40 – 5.37 (m, 1H), 5.18 – 5.01 (m, 1H), 3.99 – 3.82 (m, 2H), 3.66 – 3.48 (m, 2H), 3.06 – 2.99 (m, 2H), 2.66 – 2.50 (m, 4H), 2.18 (d, J = 1.5 Hz, 3H), 1.89 – 1.81 (m, 5H), 1.78 (s, 3H), 1.34 – 1.27 (m, 1H), 0.85 – 0.78 (m, 6H).
JN-P2 ESI 630.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.27 – 7.23 (m, 2H), 6.80 (d, J = 6.9 Hz, 2H), 6.73 (d, J = 9.6 Hz, 2H), 5.56 – 5.49 (m, 2H), 5.28 – 5.11 (m, 1H), 4.33 – 4.18 (m, 2H), 3.97 – 3.83 (m, 2H), 3.27 – 3.22 (m, 2H), 2.64 – 2.35 (m, 4H), 2.21 (d, J = 1.9 Hz, 3H), 1.89 – 1.82 (m, 7H), 1.69 – 1.62 (m, 1H), 1.31 – 1.21 (m, 1H), 0.83 – 0.78 (m, 6H).

3-111. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid

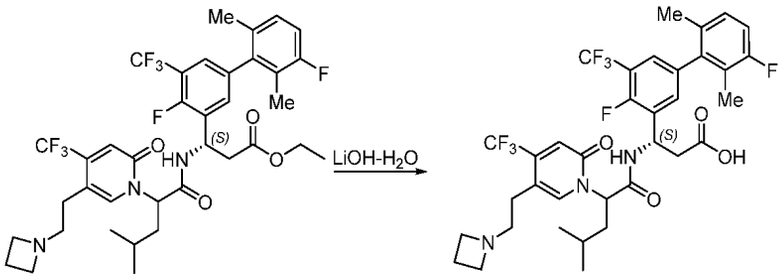
Step 1: ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (230mg, 0.57 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (205 mg, 0.57 mmol), NMI (0.6 mL) and TCFH (241 mg, 0.86 mmol) in CH_3CN (3 mL) was stirred at room temperature for 2.0 hour. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (50-80% CH3CN) to provideethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-

difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a white solid (320 mg). Yield 76% (ESI 744.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



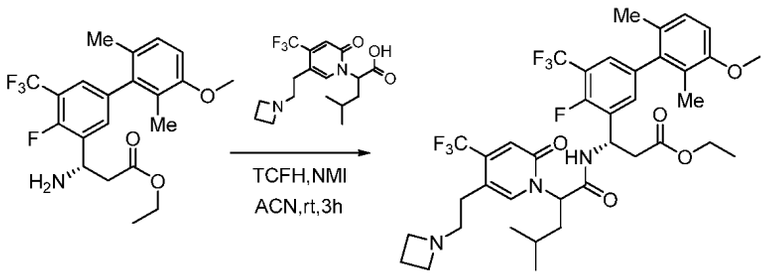
Ethyl (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (320 mg, 0.43 mmol) was treated with LiOH-H_2O (35 mg, 0.84mmol) in MeOH (3.0 mL) and H_2O (1.0 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (50-80% CH_3CN) to provide the diastereomeric products **JO – P1** (100 mg) and **JO – P2** (102 mg) as white solids.

JO-P1 ESI 716.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.42 – 7.29 (m, 2H), 7.18 – 7.03 (m, 1H), 6.98 (t, J = 9.0 Hz, 1H), 6.71 (d, J = 10.0 Hz, 1H), 5.70 – 5.50 (m, 2H), 4.05 (t, J = 8.1 Hz, 4H), 3.30 – 3.25 (m, 1H), 2.87 – 2.65 (m, 4H), 2.50 – 2.38 (m, 2H), 2.08 – 1.86 (m, 5H), 1.83 – 1.68 (m, 3H), 1.47 – 1.33 (m, 1H), 0.93 – 0.85 (m, 6H).

JO-P2 ESI 716.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.48 – 7.38 (m, 2H), 7.19 – 7.09 (m, 1H), 7.00 (t, J = 9.0 Hz, 1H), 6.88 (s, 1H), 5.88 – 5.78 (m, 1H), 5.61 (t, J = 7.5 Hz, 1H), 4.13 (t, J = 8.1 Hz, 4H), 3.49 – 3.32 (m, 2H), 2.97 – 2.73 (m, 2H), 2.70 – 2.40 (m, 4H), 2.05 – 1.85 (m, 7H), 1.73 – 1.60 (m, 1H), 1.44 – 1.26 (m, 1H), 0.87 (d, J = 6.6 Hz, 6H).

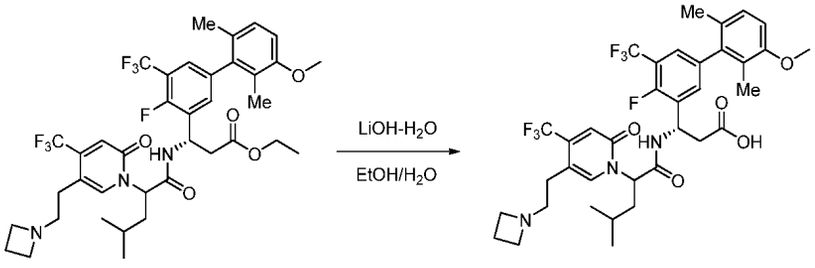
3-112. Preparation of (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds JP-P1 and JP-P2)

Step 1: (3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (S)-ethyl 3-amino-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (200 mg, 0.48 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (173 mg, 0.48 mmol), NMI (120 mg, 1.44 mmol) and TCFH (160 mg, 0.58 mmol) in CH_3CN (8 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide (3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a yellow oil (270 mg). Yield 72 % (ESI 756.2 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



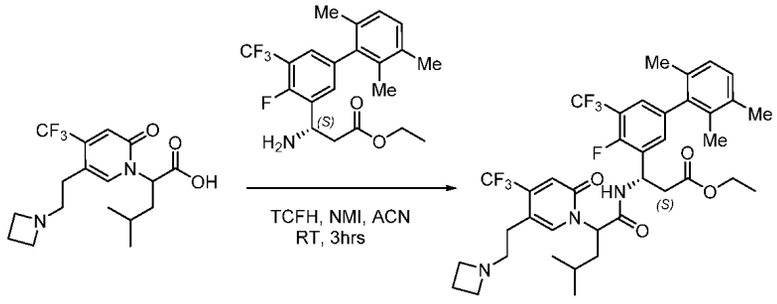
(3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-3'-methoxy-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (270 mg, 0.36 mmol) was treated with LiOH-H_2O (60 mg, 1.44mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JP-P1** (75 mg) and **JP-P2** (85 mg) as white solids.

JP-P1 ESI 727.8 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.36 – 7.25 (m, 2H), 7.05 (t, *J* = 8.7 Hz, 1H), 6.87 – 6.73 (m, 2H), 5.64 – 5.59 (m, 2H), 4.04 (t, *J* = 8.1 Hz, 4H), 3.82 (s, 3H), 3.29 – 3.25 (m, 2H), 2.85 – 2.69 (m, 4H), 2.47 – 2.39 (m, 2H), 2.05 – 1.94 (m, 2H), 1.91 – 1.68 (m, 6H), 1.43 – 1.37 (m, 1H), 0.94 – 0.90 (m, 6H).

JP-P2 ESI 727.8 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.42 – 7.31 (m, 2H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.89 – 6.87 (m, 2H), 5.81 – 5.78 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 4.13 (t, *J* = 8.0 Hz, 4H), 3.83 (s, 3H), 3.44 – 3.32 (m, 2H), 2.94 – 2.42 (m, 6H), 2.00 – 1.84 (m, 7H), 1.68 – 1.61 (m, 1H), 1.41 – 1.34 (m, 1H), 0.87 – 0.85 (m, 6H).

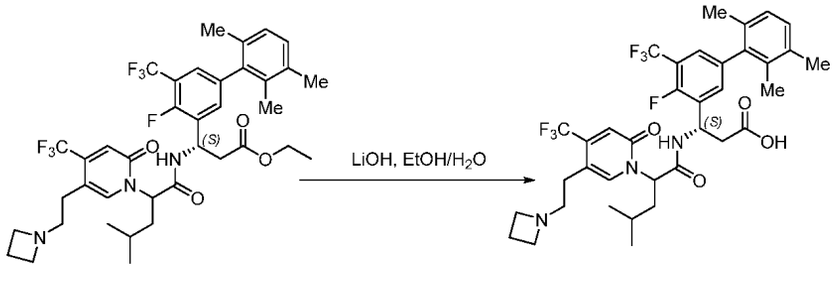
3-113. Preparation of (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds JQ-P1 and JQ-P2)

Step 1: (S)-ethyl 3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (S)-ethyl 3-amino-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (170 mg, 0.43 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (155 mg, 0.43 mmol), TCFH (241 mg, 0.86 mmol) and NMI (106 mg, 1.3 mmol) in MeCN (5mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM : MeOH 10 : 1) to provide (S)-ethyl 3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a colorless oil (200 mg). Yield 63% (ESI 740.3 $(M+H)^+$).

Step 2: (S)-3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



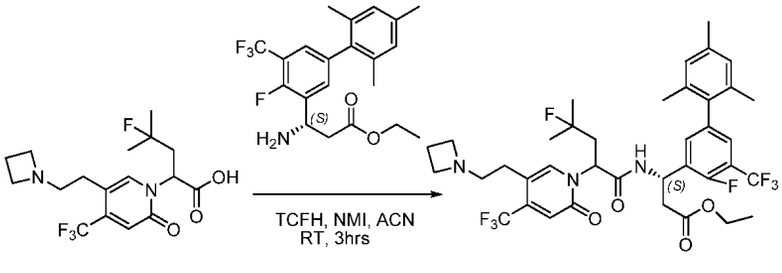
(S)-ethyl 3-((S)-2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (200 mg, 0.27 mmol) was treated with LiOH-H_2O (53 mg, 1.27 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JQ-P1** (62 mg) and **JQ-P2** (87 mg) as white solids.

JQ-P1 ESI 712.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.82 (d, J = 5.2 Hz, 1H), 7.36 (s, 1H), 7.29 – 7.22 (m, 1H), 7.07 (d, J = 7.7 Hz, 1H), 7.03 – 6.92 (m, 1H), 6.75 (d, J = 16.4 Hz, 1H), 5.62-5.60 (m, 2H), 4.05 (t, J = 7.9 Hz, 4H), 3.30 (s, 2H), 2.83 (d, J = 3.3 Hz, 2H), 2.76 – 2.64 (m, 2H), 2.54 – 2.37 (m, 2H), 2.26 (s, 3H), 2.06 – 1.95 (m, 2H), 1.99-1.92 (m, 3H), 1.78 (s, 3H), 1.39 (d, J = 6.4 Hz, 1H), 0.94-0.90 (m, 6H).

JQ-P2 ESI 712.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.41 (d, J = 6.4 Hz, 1H), 7.32 (d, J = 6.3 Hz, 1H), 7.08 (d, J = 7.7 Hz, 1H), 7.01 (d, J = 7.7 Hz, 1H), 6.88 (s, 1H), 5.80 (d, J = 10.3 Hz, 1H), 5.61 (t, J = 7.7 Hz, 1H), 4.13 (t, J = 7.9 Hz, 4H), 3.34-3.29 (m, 2H), 2.91 (d, J = 16.4 Hz, 1H), 2.85 – 2.74 (m, 1H), 2.68-2.64 (m, 1H), 2.58 – 2.38 (m, 3H), 2.28 (s, 3H), 1.98-1.93 (m, 7H), 1.67-1.64 (m, 1H), 1.39-1.37 (m, 1H), 0.87 (s, 6H).

3-114. Preparation of (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (compounds JR-P1 and JR-P2)

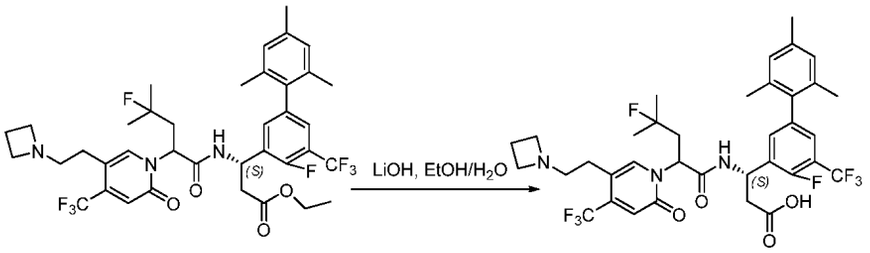
Step 1: (3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate



A mixture of (S)-ethyl 3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (170 mg, 0.43 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanoic acid (163 mg, 0.43 mmol), TCFH (241 mg, 0.86 mmol) and NMI (106 mg, 1.3 mmol) in MeCN (5mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM:MeOH 97: 3) to provide

(3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate as a colorless oil (100 mg). Yield 31% (ESI 758.3 $(M+H)^+$).

Step 2: (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid



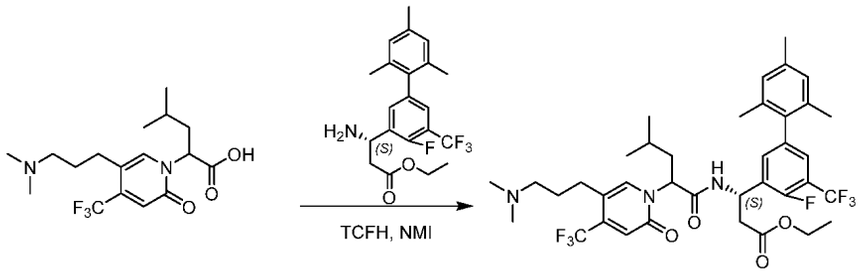
(3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (100 mg, 0.13 mmol) was treated with LiOH-H_2O (27 mg, 0.65 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JR-P1** (36 mg) and **JR-P2** (22 mg) as white solids.

JR-P1 ESI 730.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.26 (d, J = 6.4 Hz, 2H), 6.92 (s, 2H), 6.58 (s, 1H), 5.65 (s, 1H), 5.59 – 5.50 (m, 1H), 4.09 (t, J = 8.1 Hz, 4H), 3.33 (d, J = 11.0 Hz, 2H), 2.90 – 2.40 (m, 8H), 2.30 (s, 3H), 1.99 – 1.90 (m, 3H), 1.84 (d, J = 15.3 Hz, 3H), 1.46 – 1.25 (m, 6H).

JR-P2 ESI 730.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.43 (d, J = 4.9 Hz, 1H), 7.32 (d, J = 6.5 Hz, 1H), 6.94 (s, 2H), 6.88 (s, 1H), 5.78 (t, J = 6.6 Hz, 2H), 4.14 (s, 4H), 3.51 – 3.36 (m, 2H), 2.92 (d, J = 15.8 Hz, 1H), 2.82-2.79 (m, 1H), 2.68 – 2.42 (m, 5H), 2.30 (s, 3H),2.16- 2.13 (m, 1H), 1.95 (d, J = 3.6 Hz, 6H), 1.34-1.31 (m, 6H).

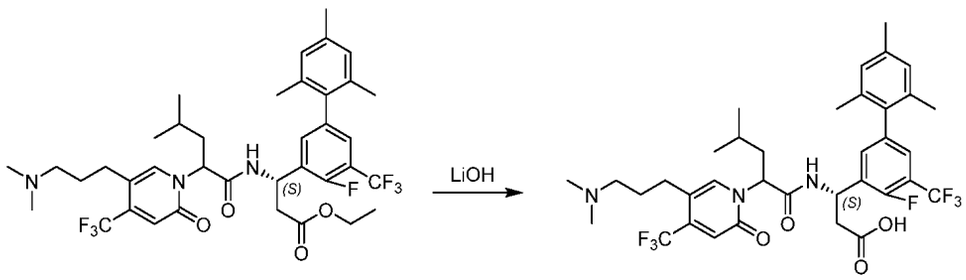
3-115. Preparation of (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JS-P1 and JS-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (290 mg, 0.73 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (240 mg, 0.662 mmol), *N,N,N',N'*-tetramethylchloroformamidinium hexafluorophosphate (278 mg, 0.993 mmol) and 1-methylimidazole (217 mg, 2.65 mmol) in acetonitrile (10 mL) was stirred at room temperature for 2 hours. The mixture was purified by reverse phase HPLC on a C18 / 40g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (370 mg) as a white solid. Yield 75% (ESI 742.2 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



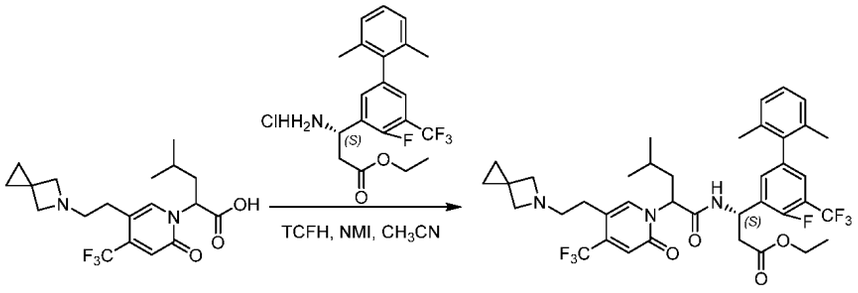
Ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (370 mg, 0.50 mmol) was treated with LiOH-H_2O (84 mg, 2.0 mmol) in MeOH (5 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JS-P1** (123 mg) and **JS-P2** (91 mg) as white solids.

JS-P1 ESI 713.9 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.78 (s, 1H), 7.35 (d, J = 5.0 Hz, 1H), 7.30 – 7.21 (m, 1H), 6.91 (d, J = 13.8 Hz, 2H), 6.68 (s, 1H), 5.70 – 5.66 (m, 1H), 5.59 (t, J = 6.8 Hz, 1H), 3.09 – 3.04 (m, 2H), 2.79 (s, 6H), 2.74-2.63(m, 4H), 2.29 (s, 3H), 2.03 – 1.95 (m, 7H), 1.78 (s, 3H), 1.42 – 1.33 (m, 1H), 0.94 – 0.91(m, 6H).

JS-P2 ESI 713.9 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 7.37 – 7.30(m, 2H), 6.94 (s, 2H), 6.83 (s, 1H), 5.76 – 5.72 (m, 1H), 5.58 (t, J = 7.6 Hz, 1H), 3.05 – 3.00 (m, 2H), 2.79 (s, 6H), 2.74 – 2.49 (m, 4H), 2.30 (s, 3H), 2.03 – 1.91 (m, 9H), 1.67 – 1.60(m, 1H), 1.37 – 1.29 (m, 1H), 0.86 – 0.83 (m, 6H).

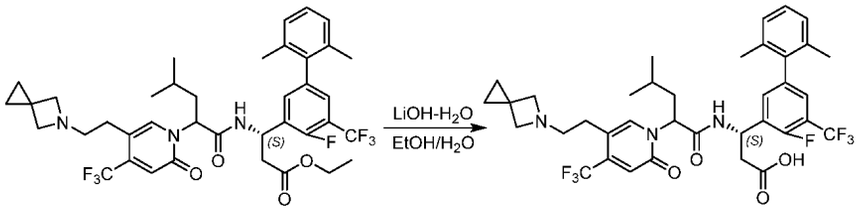
3-116. Preparation of (3*S*)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JT-P1 and JT-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (150 mg, 0.36 mmol), 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (139.0 mg, 0.36 mmol), TCHF (120.6 mg, 0.43 mmol) and NMI (88.7 mg, 1.08 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (100 mg). Yield 37% (ESI 752.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid

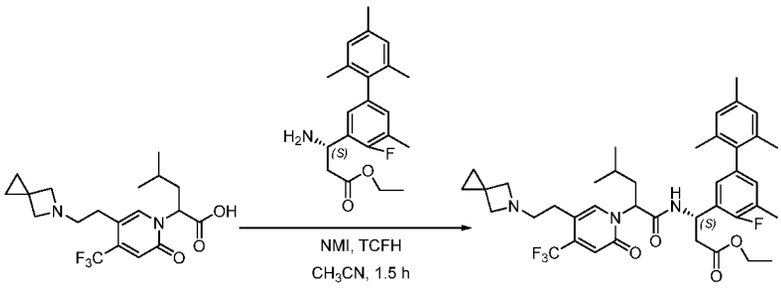


Ethyl (3*S*)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (100.0 mg, 0.13 mmol) was treated with LiOH-H_2O (16.4 mg, 0.39 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 5~6 with 2N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **JT-P1** (29 mg) and **JT-P2** (38 mg) as white solids.

JT-P1 ESI 724.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.40 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 6.3 Hz, 1H), 7.19 – 7.06 (m, 3H), 6.73 (s, 1H), 5.67 – 5.60 (m, 2H), 4.10 (s, 4H), 3.42 – 3.33 (m, 2H), 2.87 (t, J = 7.1 Hz, 2H), 2.72 (d, J = 6.9 Hz, 2H), 2.07 – 1.90 (m, 5H), 1.84 (s, 3H), 1.46-1.34 (m, 1H), 1.00 – 0.88 (m, 6H), 0.75 (s, 4H).
JT-P2 ESI 724.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.46 – 7.43 (m, 1H), 7.37 – 7.34 (m, 1H), 7.21 – 7.10 (m, 3H), 6.88 (s, 1H), 5.81 – 5.76 (m, 1H), 5.63 (t, J = 7.7 Hz, 1H), 4.26 – 4.09 (m, 4H), 3.53 – 3.39 (m, 2H), 3.03 – 2.75 (m, 2H), 2.70 – 2.50 (m, 2H), 2.04 – 1.91 (m, 7H), 1.69 – 1.60 (m, 1H), 1.45 – 1.35 (m, 1H), 0.90 – 0.86 (m, 6H), 0.83 – 0.72 (m, 4H).

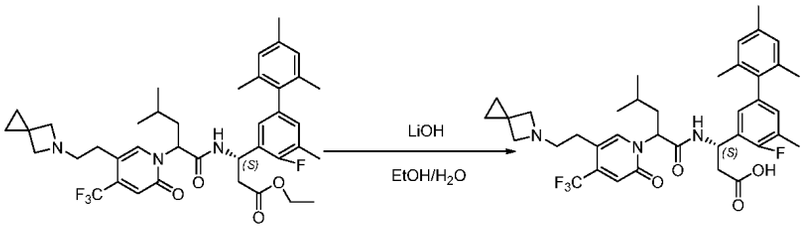
3-117. Preparation of (3S)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (compounds JU-P1 and JU-P2)

Step 1: (3S)-ethyl 3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (150 mg, 0.39 mmol), (S)-ethyl 3-amino-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (133 mg, 0.39 mmol), NMI (160 mg, 1.96 mmol) and TCHF (218 mg, 0.78 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1.5 hours. The solvent was concentrated *in vacuo* and the residue purified by silica gel column (DCM: MeOH 9:1) to provide (3S)-ethyl 3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoateas a colorless oil (180 mg). Yield 65 % (ESI 712.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid



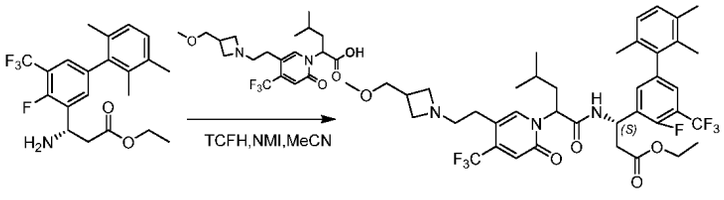
(3S)-ethyl 3-(2-(5-(2-(5-azaspiro[2.3]hexan-5-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (180 mg, 0.25 mmol) was treated with LiOH-H_2O (53 mg, 1.27 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JU-P1** (51 mg) and **JU-P2** (60 mg) as white solids.

JU-P1 ESI 684.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 6.92 – 6.89 (m, 5H), 5.60 (t, J = 7.2 Hz, 1H), 5.75-5.72 (m, 1H), 4.27 (d, J = 8.1 Hz, 4H), 3.55 – 3.40 (m, 2H), 2.98 – 2.53 (m, 4H), 2.28 (s, 3H), 2.30 (s, 3H), 2.08 – 1.93 (m, 7H), 1.99-1.95 (m, 1H), 1.42-1.40 (m, 1H), 1.09 – 0.69 (m, 10H).

JU-P2 ESI 684.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.00 – 6.80 (m, 5H), 5.74-5.70 (m, 1H), 5.60 (t, J = 7.6 Hz, 1H), 4.18 (s, 4H), 3.58 – 3.42 (m, 2H), 2.97 (d, J = 16.0 Hz, 1H), 2.89 – 2.74 (m, 1H), 2.67-2.63 (m, 1H), 2.53-2.50 (m, 1H), 2.29 (d, J = 11.2 Hz, 6H), 2.03-1.97 (m, 7H), 1.65-1.61 (m, 1H), 1.43-1.41 (m, 1H), 0.88 (d, J = 5.6 Hz, 6H), 0.77 (t, J = 10.3 Hz, 4H).

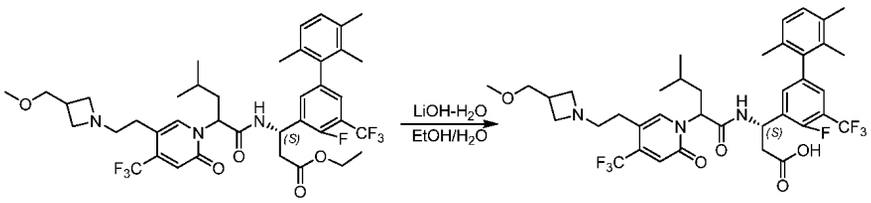
3-118. Preparation of (3S)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds JV-P1 and JV-P2)

Step 1: (3S)-ethyl 3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of (S)-ethyl 3-amino-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoate (240 mg, 0.60 mmol), 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (242 mg, 0.60 mmol), NMI (197 mg, 1.8 mmol) and TCFH (252 mg, 0.9 mmol) in CH_3CN (8 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: CH_3CN, 0~100%) to provide (3S)-ethyl 3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a yellow oil (270 mg). Yield 57 % (ESI 784.0 $[M+H]^+$).

Step 2: (3S)-3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic



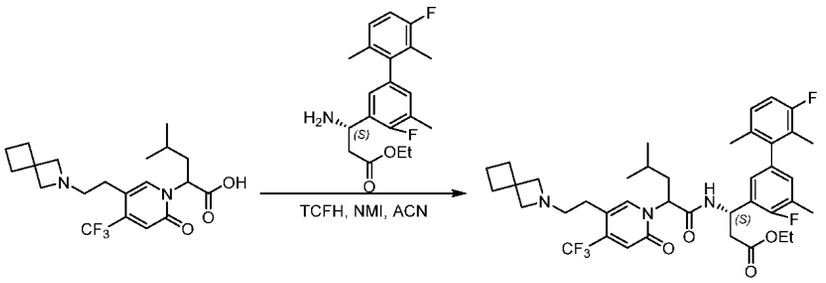
(3S)-ethyl 3-(4-fluoro-2',3',6'-trimethyl-5-(trifluoromethyl)biphenyl-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (270 mg, 0.34 mmol) was treated with LiOH-H_2O (57 mg, 1.36 mmol) in EtOH (3mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **JV-P1** (67 mg) and **JV-P2** (90 mg) as white solids.

JV-P1 ESI 755.9 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.83 (d, J = 5.9 Hz, 1H), 7.38 – 7.24 (m, 2H), 7.08 – 6.95 (m, 2H), 6.74 (d, J = 19.4 Hz, 1H), 5.64 – 5.60 (m, 2H), 4.13 – 4.09 (m, 2H), 3.89 – 3.81 (m, 2H), 3.47 – 3.38 (m, 5H), 3.28 – 3.24 (m, 2H), 3.05 – 2.95 (s, 1H), 2.89 – 2.66 (m, 4H), 2.26 (d, J = 2.9 Hz, 3H), 2.06 – 1.89 (m, 5H), 1.76 – 1.75 (m, 3H), 1.44 – 1.36 (m, 1H), 0.94 – 0.91 (m, 6H).

JV-P2 ESI 755.9 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.42 – 7.31 (m, 2H), 7.09 – 7.00 (m, 2H), 6.88 (s, 1H), 5.81 – 5.78 (m, 1H), 5.61 (t, J = 7.6 Hz, 1H), 4.25 – 4.17 (m, 2H), 3.98 – 3.88 (m, 2H), 3.50 (d, J = 4.4 Hz, 2H), 3.45 – 3.32 (m, 5H), 3.11 – 3.02 (m,1H), 2.94 – 2.74 (m, 2H), 2.68 – 2.51 (m, 2H), 2.28 (s, 3H), 2.00 – 1.89 (m, 7H), 1.69 – 1.61 (m, 1H), 1.42 – 1.33 (m, 1H), 0.88 – 0.86 (m, 6H).

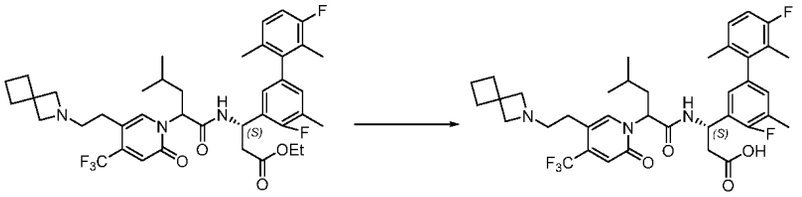
3-119. Preparation of (S)-3-((R)-2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JW-P1 and JW-P2)

Step 1: ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (250.0 mg, 0.63 mmol), ethyl (S)-3-amino-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (218.0 mg, 0.63 mmol), TCHF (210.0 mg, 0.75 mmol) and NMI (155.0 mg, 1.89 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hrs. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: CH3CN, 0~100%) to provide ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyri -din-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (300.0 mg). Yield 66.1% (ESI 730.0 $[M+H]^+$).

Step 2: (S)-3-((R)-2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl) pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



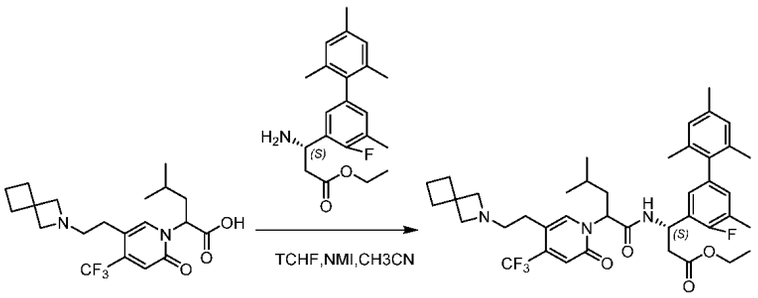
Ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl) pyridine-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphen yl]-3-yl)propanoate (300.0 mg, 0.41 mmol) was treated with LiOH-H_2O (86.0 mg, 2.05 mmol) in EtOH (4 mL) and water (2 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue was purified by Prep HPLC A (30-60% MeCN) to give the diastereomeric products **JW-P1** (64 mg) and **JW-P2** (85 mg) as white solids.

JW-P1 ESI 702.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.10 – 6.99 (m, 1H), 6.96 – 6.81 (m, 3H), 6.76 (d, *J* = 6.0 Hz, 1H), 5.65-5.59 (m, 2H), 4.05 – 3.88 (m, 4H), 3.26 – 3.12 (m, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.68 (d, *J* = 6.6 Hz, 2H), 2.33 – 2.15 (m, 7H), 2.00 – 1.73 (m, 10H), 1.46 – 1.32 (m, 1H), 0.94-0.91 (m, 6H).

JW-P2 ESI 702.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.11 – 7.02 (m, 1H), 6.98 – 6.81 (m, 4H), 5.73 (dd, *J* = 11.0, 3.4 Hz, 1H), 5.60 (t, *J* = 7.2 Hz, 1H), 4.12-4.09 (m, 4H), 3.32-3.3 (m, 2H), 2.88-2.85 (m, 2H), 2.60-2.45 (m, 2H), 2.39 – 2.19 (m, 7H), 2.03 – 1.78 (m, 9H), 1.66 – 1.54 (m, 1H), 1.43-1.38 (m, 1H), 0.90-0.88 (m, 6H).

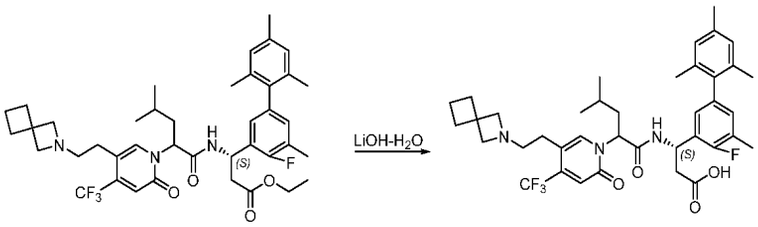
3-120. Preparation of (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JX-P1 and JX-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (250mg, 0.63 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (216 mg, 0.63 mmol), NMI (0.6 mL) and TCFH (213 mg, 0.76 mmol) in CH_3CN (3 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue was purified by prep-HPLC A (50-70% CH3CN) to provide ethyl (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a white solid (280 mg). Yield 62% (ESI 726.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid



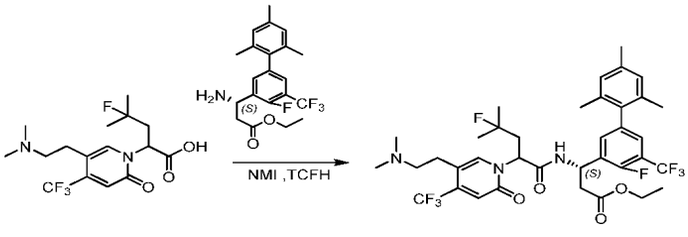
Ethyl (3*S*)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (280 mg, 0.39mmol) was treated with LiOH-H_2O (33 mg, 0.78 mmol) in MeOH (3.0 mL) and H_2O (1.0 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC A (50-80% CH_3CN) to give the diastereomeric products **JX-P1** (57 mg) and **JX-P2** (127 mg) as white solids.

JX-P1 ESI 698.3$(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 6.92 – 6.78 (m, 4H), 6.74 (s, 1H), 5.67 (t, *J* = 8.0 Hz, 1H), 5.59 (t, *J* = 6.8 Hz, 1H), 4.02 – 3.87 (m, 4H), 3.27– 3.15 (m, 2H), 2.82 (t, *J* = 7.0 Hz, 2H), 2.68 (d, *J* = 6.8 Hz, 2H), 2.33 – 2.15 (m, 10H), 2.03 – 1.90 (m, 5H), 1.87 – 1.73 (m, 5H), 1.45 – 1.34 (m, 1H), 0.92 (t, *J* = 6.2 Hz, 6H).

JX-P2 ESI 698.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 6.93 – 6.85 (m, 5H), 5.75 – 5.70 (m, 1H), 5.62 – 5.58 (m, 1H), 4.11 (s, 4H), 3.40 – 3.32 (m, 2H), 2.91 (d, *J* = 16.0 Hz, 1H), 2.83 – 2.75 (m, 1H), 2.62 – 2.53 (m, 1H), 2.51 – 2.43 (m, 1H), 2.38 – 2.20 (m, 10H), 2.03 – 1.79 (m, 9H), 1.63 – 1.57 (m, 1H), 1.45 – 1.38 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 6H).

3-121. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JY-P1 and JY-P2)

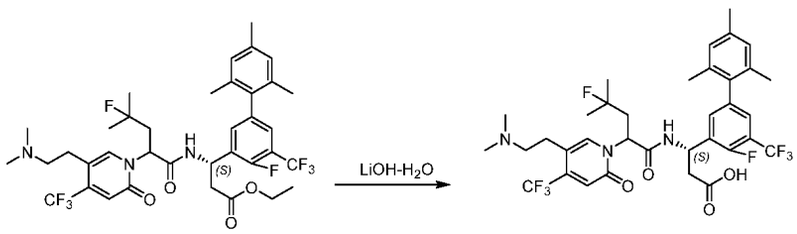
Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanoic acid (270 mg, 0.74 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.74 mmol), NMI (0.5 mL) and TCFH

(294 mg, 1.11 mmol) in CH_3CN (3 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue purified by prep-HPLC A (50-80% CH_3CN) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a white solid (300 mg). Yield 55% (ESI 746.2 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



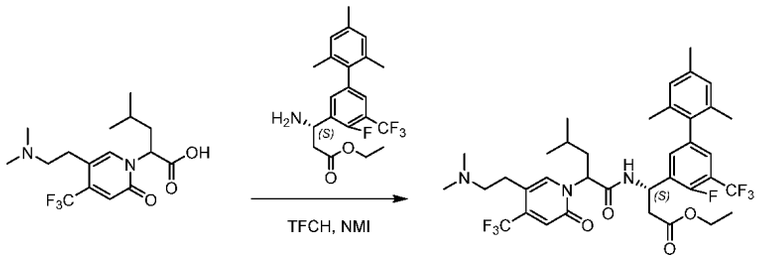
Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-fluoro-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (300 mg, 0.40mmol) was treated with LiOH-H_2O (34 mg, 0.80 mmol) in MeOH (3 mL) and H_2O (1.0 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (50-80% CH_3CN) to give the diastereomeric products **JY-P1** (111 mg) and **JY-P2** (102 mg) as white solids.

JY-P1 ESI 717.9$(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.95 (s, 1H), 7.35 – 7.20 (m, 2H), 6.90 (d, *J* = 13.6 Hz, 2H), 6.59 (s, 1H), 5.79 (s, 1H), 5.59 – 5.50 (m, 1H), 3.19 – 3.06 (m, 2H), 3.00 – 2.88 (m, 2H), 2.82 – 2.57 (m, 8H), 2.55 – 2.42 (m, 2H), 2.29 (s, 3H), 1.93 (s, 3H), 1.75 (s, 3H), 1.43 – 1.25 (m, 6H).

JY-P2 ESI 717.9 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.40 (d, *J* = 6.3 Hz, 1H), 7.31 (d, *J* = 6.4 Hz, 1H), 6.94 (s, 2H), 6.87 (s, 1H), 5.80 – 5.68 (m, 2H), 3.27 – 3.14 (m, 2H), 2.98 (t, *J* = 6.4 Hz, 2H), 2.84 (s, 6H), 2.65 – 2.48 (m, 3H), 2.30 (s, 3H), 2.25 – 2.12 (m, 1H), 1.95 (s, 6H), 1.37 – 1.25 (m, 6H).

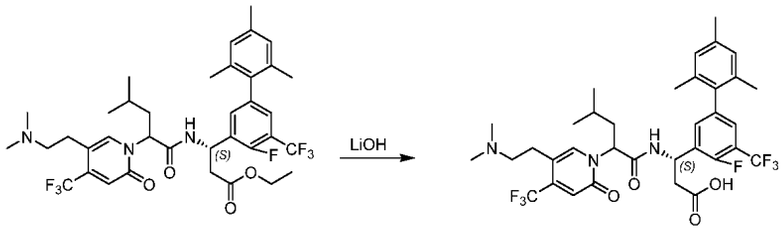
3-122. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds JZ-P1 and JZ-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (301 mg, 0.76 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (240 mg, 0.69 mmol), TCHF (290 mg, 1.04 mmol) and NMI (226 mg, 2.76 mmol) in acetonitrile (10 mL) was stirred at room temperature for 2 hours. The mixture was purified by reverse phase HPLC on a C18 / 40g column (A: water 10 mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (380 mg) as a white solid. Yield 75.6 % (ESI 728.1 $(M+H)^+$).

Step 2: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (380 mg, 0.52 mmol) was treated with LiOH-H_2O (88 mg, 2.1 mmol) in MeOH (5 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to provide the diastereomeric products **JZ-P1** (116 mg) and **JZ-P2** (88 mg) as white solids.

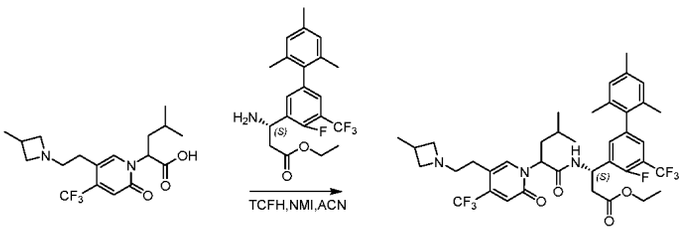
JZ-P1 ESI 699.9 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.33 (d, J = 5.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.68 (s, 1H), 5.66 – 5.54 (m, 2H), 3.13 – 3.05 (m, 2H),

2.95 – 2.91 (m, 2H), 2.77 (s, 6H), 2.73 – 2.70 (m, 2H), 2.29 (s, 3H), 1.99 – 1.94 (m, 5H), 1.74 (s, 3H), 1.46 – 1.38 (m, 1H), 0.95 – 0.91 (m, 6H).

JZ-P2 ESI 699.9 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.38 (d, J = 4.9 Hz, 1H), 7.32 (d, J = 6.4 Hz, 1H), 6.94 (s, 2H), 6.87 (s, 1H), 5.73 – 5.69 (m, 1H), 5.60 (t, J = 7.7 Hz, 1H), 3.18 – 3.28 (m, 2H), 2.98 (t, J = 7.0 Hz, 2H), 2.83 (s, 6H), 2.68 – 2.52 (m, 2H), 2.30 (s, 3H), 2.00 – 1.93 (m, 7H), 1.74 – 1.67 (m, 1H), 1.40 – 1.33 (m, 1H), 0.88 – 0.86 (m, 6H).

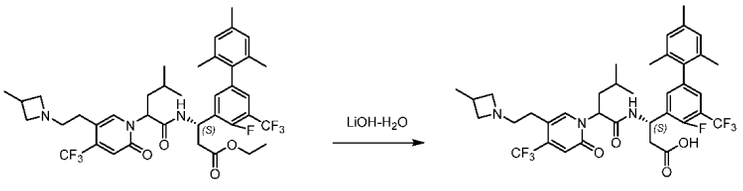
3-123. Preparation of (3*S*)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoic acid (compounds KA-P1 and KA-P2)

Step 1: ethyl (3*S*)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate



A mixture of ethyl ethyl 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanoic acid (190.7 mg, 0.51 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (202.5 mg, 0.51 mmol), TCFH (285.6 mg, 1.02 mmol) and NMI (167.3 mg, 2.04 mmol) in CH_3CN (10 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 4: 1) to provide ethyl (3*S*)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate as a brown solid (250 mg). Yield 65% (ESI 754.3 $(M+H)^+$).

Step 2: (3*S*)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoic acid



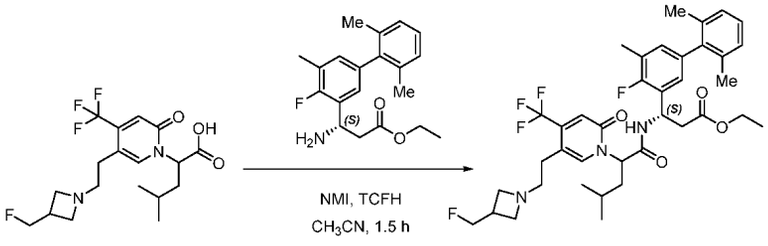
Ethyl (3*S*)-3-(4-fluoro-2',4',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)propanoate (250.0 mg, 0.33 mmol)) was treated with LiOH-H_2O (54.6 mg, 1.3 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **KA-P1** (96 mg) and **KA-P2** (87 mg) as white solids.

KA-P1 ESI 726.3$(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.41 – 7.31 (m, 1H), 7.32 – 7.17 (m, 1H), 6.91 (d, J = 11.7 Hz, 2H), 6.70 (s, 1H), 5.69 – 5.53 (m, 2H), 4.21 – 4.04 (m, 2H), 3.66 (t, J = 8.7 Hz, 2H), 2.98 – 2.79 (m, 3H), 2.77 – 2.63 (m, 2H), 2.29 (s, 3H), 2.06 – 1.89 (m, 5H), 1.78 (d, J = 11.5 Hz, 3H), 1.49 – 1.31 (m, 1H), 1.23 (d, J = 6.9 Hz, 3H), 0.98 – 0.81 (m, 6H).

KA-P2 ESI 726.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.46 – 7.36 (m, 1H), 7.36 – 7.23 (m, 1H), 6.91 (d, J = 27.6 Hz, 3H), 5.83 – 5.73 (m, 1H), 5.61 (t, J = 7.6 Hz, 1H), 4.28 – 4.10 (m, 2H), 3.83 – 3.64 (m, 2H), 3.45 – 3.33 (m, 2H), 3.02 – 2.86 (m, 2H), 2.86 – 2.73 (m, 1H), 2.69 – 2.45 (m, 2H), 2.30 (s, 3H), 2.04 – 1.87 (m, 7H), 1.68 – 1.56 (m, 1H), 1.44 – 1.19 (m, 4H), 0.86 (d, J = 6.6 Hz, 6H).

3-124. Preparation of (S)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-((S)-2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds KB-P1 and KB-P2)

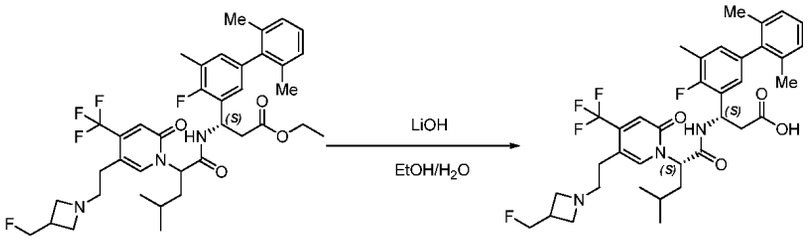
Step 1: (3S)-ethyl 3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (180 mg, 0.46 mmol), (S)-ethyl 3-amino-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (151 mg, 0.46 mmol), NMI (160 mg, 1.96 mmol) and TCFH (252 mg, 0.9 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1.5 hours. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 9:1) to provide (3S)-ethyl 3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-

oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a colorless oil (230 mg). Yield 71 % (ESI 704.3 $[M+H]^+$).

Step 2: 3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-((S)-2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



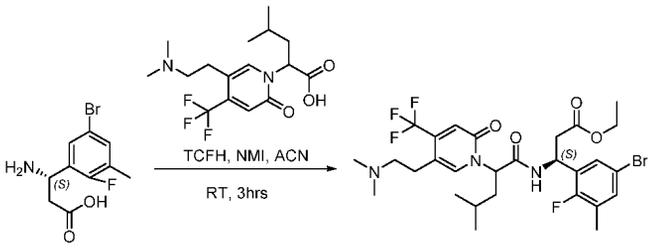
Ethyl 3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-(fluoromethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (230 mg, 0.33 mmol) was treated with LiOH-H_2O (69 mg, 1.64 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to provide diastereomeric products **KB-P1** (50 mg) and **KB-P2** (101 mg) as white solids.

KB-P1 ESI 676.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.07 -7.03 (m, 3H), 6.93 – 6.82 (m, 2H), 6.75 (s, 1H), 5.70 – 5.55 (m, 2H), 4.57 (d, J = 4.4 Hz, 1H), 4.45 (d, J = 4.1 Hz, 1H), 4.03 (t, J = 9.4 Hz, 2H), 3.82 – 3.67 (m, 2H), 3.13-3.10 (m, 3H), 2.80 (t, J = 7.0 Hz, 2H), 2.71 (d, J = 6.3 Hz, 2H), 2.28 (d, J = 1.6 Hz, 3H), 2.02 – 1.90 (m, 5H), 1.84 (s, 3H), 1.41-1.39 (m, 1H), 0.93-0.90 (m, 6H).

KB-P2 ESI 676.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.15 – 7.00 (m, 3H), 7.00 – 6.82 (m, 3H), 5.75 (m, 1H), 5.60 (t, J = 7.6 Hz, 1H), 4.60 (t, J = 7.3 Hz, 1H), 4.49 (t, J = 7.5 Hz, 1H), 4.25-4.22 (m, 2H), 4.04 – 3.84 (m, 2H), 3.45 – 3.32 (m, 2H), 3.25 – 3.11 (m, 1H), 2.92 -2.90 (m, 1H), 2.84 – 2.74 (m, 1H), 2.63-2.60 (m, 1H), 2.50 -2.48 (m, 1H), 2.31 (d, J = 1.8 Hz, 3H), 2.04 – 1.84 (m, 7H), 1.64 -1.60 (m, 1H), 1.41-1.39 (m, 1H), 0.87 (d, J = 6.6 Hz, 6H).

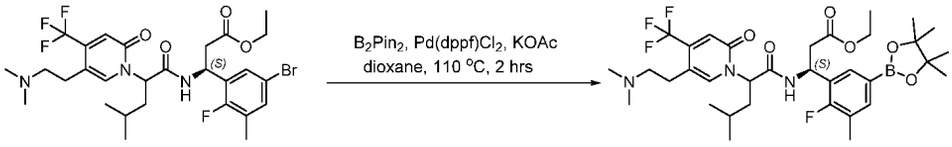
3-125. Preparation of (3S)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds KC-P1 and KC-P2)

Step 1: (S)-ethyl 3-(5-bromo-2-fluoro-3-methylphenyl)-3-((S)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



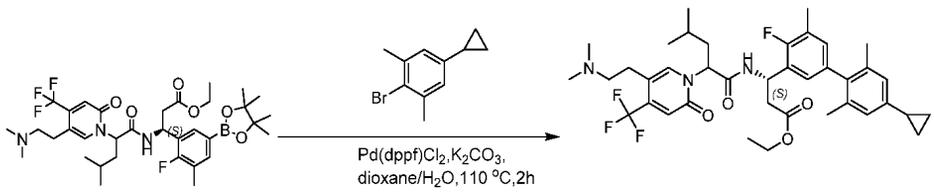
A mixture of (S)-ethyl 3-amino-3-(5-bromo-2-fluoro-3-methylphenyl)propanoate (8.6 g, 28.0 mmol), 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (9.8 g, 28.0 mmol), TCFH (9.4 g, 34.0mmol) and NMI (6.9 g, 84.0 mmol) in MeCN (5mL) was stirred at room temperature for 3 hrs. The solvent was removed *in vacuo* and the residue was purified by silica gel column (DCM:MeOH 97: 3) to provide (S)-ethyl 3-(5-bromo-2-fluoro-3-methylphenyl)-3-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a white solid (12.2 g). Yield 68% (ESI 634.3 $(M+H)^+$).

Step 2: (S)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate



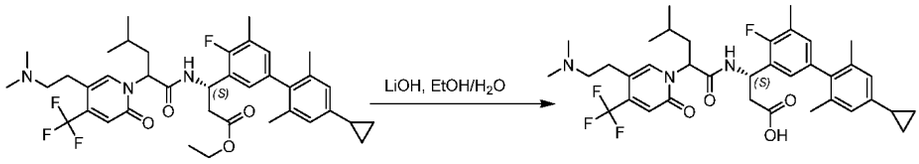
A mixture of (S)-ethyl 3-(5-bromo-2-fluoro-3-methylphenyl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (633 mg, 1.0 mmol) in dioxane (5 mL) was added B_2Pin_2 (508 mg, 2.0 mmol), $Pd(dppf)Cl_2$ (73 mg, 0.1 mmol) and KOAc (294 mg, 3.0 mmol). The mixture was heated to 110°C for 2 hrs under nitrogen atmosphere. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL*3). The combined organic phases were concentrated *in vacuo* and the residue was purified by silica gel column (pet ether: EtOAc 2:1) to provide (S)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (600 mg) as a dark solid. Yield 88 % (ESI 682.1 [M+H]+).

Step 3: (3S)-ethyl 3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



To a mixture of 2-bromo-5-cyclopropyl-1,3-dimethylbenzene (100 mg, 0.45 mmol), (3S)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (300 mg, 0.45 mmol) in dioxane (10 mL) and H_2O (1 mL)was added $Pd(dppf)Cl_2$ (37 mg, 0.05 mmol) and K_2CO_3 (207 mg, 1.5 mmol). The mixture was heated to 110°C for 2 hrs under nitrogen atmosphere. Water (20 mL) was added and the solution was extracted with EtOAc (20 mL x*3). The combined organic phases were concentrated *in vacuo* and the residue purified by silica gel column (pet ether: EtOAc 2:1) to provide (3S)-ethyl 3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (150 mg). Yield 48 % (ESI 700.1 [M+H]+).

Step 4: (3S)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



A mixture of (3S)-ethyl 3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate in EtOH (3 mL) and H_2O (1 mL) was treated with $LiOH-H_2O$ (42 mg, 1.0 mmol) at room temperature for 30 mins. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% MeCN) to give the diastereomeric products **KC-P1** (39 mg) and **KC-P2** (35 mg) as white solids.

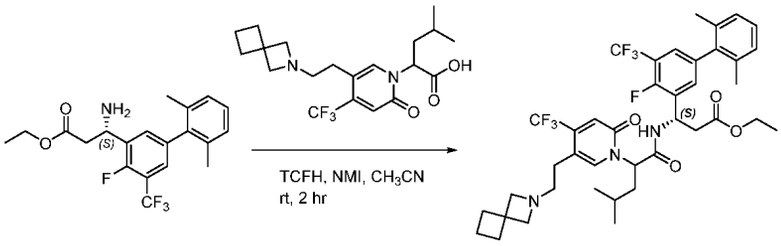
KC-P1 ESI 672.1 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 6.84 (t, J = 5.9 Hz, 2H), 6.78 (s, 1H), 6.74 (d, J = 4.4 Hz, 2H), 5.68 (t, J = 8.1 Hz, 1H), 5.61 – 5.48 (m, 1H), 3.07 (d, J = 7.3 Hz, 2H), 2.94 (d, J = 7.0 Hz, 2H), 2.72 (d, J = 9.8 Hz, 8H), 2.27 (d, J = 1.3 Hz, 3H), 2.02 – 1.92 (m, 5H), 1.85-1.83 (m, 1H), 1.76 (s, 3H), 1.43-1.40 (m, 1H), 1.00 – 0.87 (m, 8H), 0.70 – 0.63 (m, 2H).

KC-P2 ESI 672.1 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.75 (d, J = 12.3 Hz, 1H), 6.79 (t, J = 6.1 Hz, 3H), 6.69 (s, 2H), 5.60 (d, J = 6.9 Hz, 1H), 5.51 (t, J = 7.6 Hz, 1H), 3.18 – 3.04 (m, 2H), 2.89 (t, J = 6.6 Hz, 2H), 2.71 (s, 6H), 2.48-2.45 (m, 2H), 2.21 (s, 3H), 1.87-1.85 (m, 7H), 1.76-1.73 (m, 1H),

1.58 – 1.55 (m, 1H), 1.32 – 1.25 (m, 1H), 0.88 – 0.81 (m, 2H), 0.81 – 0.69 (m, 6H), 0.63 – 0.52 (m, 2H).

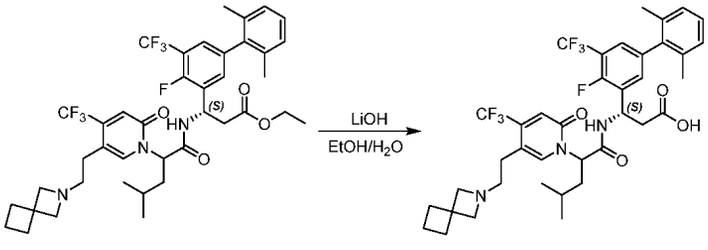
3-126. Preparation of (3S)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (KD-P1 and KD-P2)

Step 1: ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (S)-3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (220 mg, 0.57 mmol), 2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (228 mg, 0.57 mmol), TCFH (319 mg, 1.14 mmol) and NMI (234 mg, 2.85 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO3, B: CH_3OH, 0~80%) to provide ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (290 mg). Yield 66.4 % (ESI 766.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl) pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3S)-3-(2-(5-(2-(2-azaspiro[3.3]heptan-2-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate

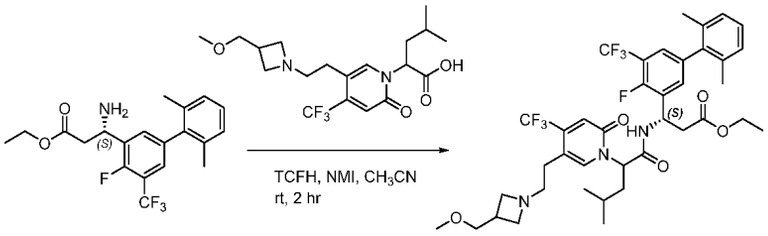
(290 mg, 0.38 mmol) was treated with LiOH-H_2O(48 mg, 1.14 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 30 min. LCMS showed that the reaction was completed. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (35-63% CH_3CN) to give the diastereomeric products **KD-P1** (97 mg) and **KD-P2** (114 mg) as white solids.

KD-P1 ESI 738.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.39 (d, J = 5.1 Hz, 1H), 7.29 (d, J = 4.8 Hz, 1H), 7.20 – 7.04 (m, 3H), 6.73 (s, 1H), 5.68 – 5.59 (m, 2H), 4.01 (s, 4H), 3.29 – 3.16 (m, 2H), 2.83 (t, J = 7.0 Hz, 2H), 2.71 (d, J = 6.9 Hz, 2H), 2.25 (t, J = 7.7 Hz, 4H), 2.03 – 1.93 (m, 5H), 1.88 – 1.78 (m, 5H), 1.43 – 1.34 (m, 1H), 0.93 (t, J = 6.4 Hz, 6H).

KD-P2 ESI 738.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.44 (d, J = 5.5 Hz, 1H), 7.35 (d, J = 6.2 Hz, 1H), 7.23 – 7.08 (m, 3H), 6.87 (s, 1H), 5.82 – 5.73 (m, 1H), 5.62 (t, J = 7.6 Hz, 1H), 4.11 (s, 4H), 3.41 - 3.315 (m, 2H), 2.90 (d, J = 16.4 Hz, 1H), 2.84 – 2.72 (m, 1H), 2.66 – 2.48 (m, 2H), 2.38 – 2.23 (m, 4H), 2.06 – 1.92 (m, 7H), 1.92 – 1.81 (m, 2H), 1.68 – 1.57 (m, 1H), 1.46 – 1.34(m, 1H), 0.93 – 0.84 (m, 6H)

3-127. Preparation of (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (KE-P1 and KE-P2)

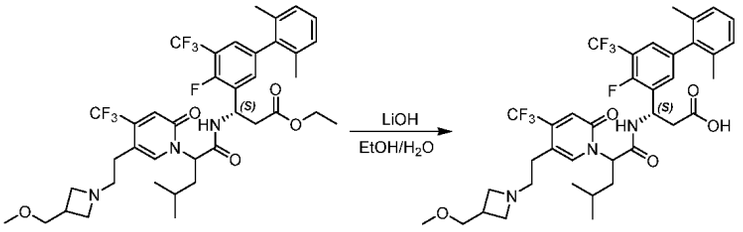
Step 1: ethyl (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of ethyl (S)-3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (200 mg, 0.52 mmol), 2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (210 mg, 0.52 mmol), TCFH (291 mg, 1.04 mmol) and NMI (213 mg, 2.6 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The reaction was concentrated and purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO3, B: CH_3OH, 0~85%) to provide ethyl (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-

(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate as a yellow solid (250 mg). Yield 62.4 % (ESI 770.3 $[M+H]^+$).

Step 2: (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid



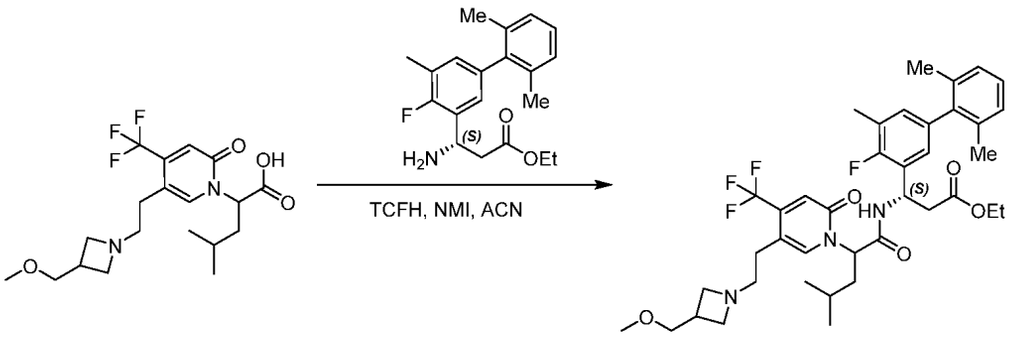
Ethyl (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (250 mg, 0.32 mmol) was treated with LiOH-H_2O (40 mg, 0.96 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 2 hr. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-65% CH_3CN) to give the diastereomeric products **KE-P1** (91 mg) and **KE-P2** (104 mg) as white solids.

KE-P1 ESI 742.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.39 (d, J = 5.0 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.14 – 7.05 (m, 2H), 6.73 (s, 1H), 5.62 (t, J = 6.8 Hz, 2H), 4.19 – 4.04 (m, 2H), 3.95 – 3.81 (m, 2H), 3.46 (d, J = 4.1 Hz, 2H), 3.41 (s, 3H), 3.29 – 3.24 (m, 2H), 3.01 (s, 1H), 2.83 (t, J = 7.0 Hz, 2H), 2.75 – 2.66 (m, 2H), 2.03 – 1.94 (m, 5H), 1.84 (s, 3H), 1.43 – 1.35 (m, 1H), 0.98 – 0.85 (m, 6H).

KE-P2 ESI 742.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.51 – 7.28 (m, 2H), 7.3 – 7.01 (m, 3H), 6.88 (s, 1H), 5.90 – 5.71 (m, 1H), 5.61 (t, J = 7.6 Hz, 1H), 4.31 – 4.11 (m, 2H), 4.07 – 3.80 (m, 2H), 3.53 – 3.47 (m, 2H), 3.43 (s, 3H), 3.40 – 3.31 (m, 2H), 3.12 – 3.00 (m, 1H), 2.96 – 2.86 (m, 1H), 2.84 – 2.73 (m, 1H), 2.70 – 2.61 (m, 1H), 2.59 – 2.48 (m, 1H), 2.04 – 1.91 (m, 7H), 1.71 – 1.60 (m, 1H), 1.43 – 1.32 (m, 1H), 0.87 (d, J = 6.5 Hz, 6H).

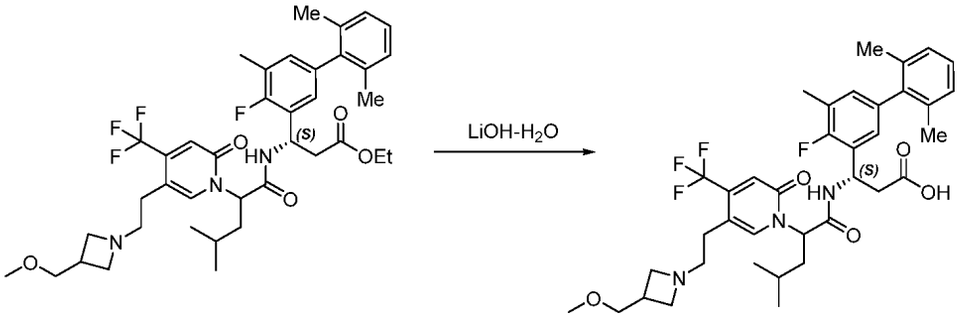
3-128. Preparation of (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (compounds KF-P1 and KF-P2)

Step 1: ethyl (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate



A mixture of (S)-2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (277.0 mg, 0.68 mmol), ethyl (S)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (230.0 mg, 0.70 mmol), TCHF (211.0 mg, 0.84 mmol) and NMI (115.0 mg, 1.4 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1.5 h. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (300 mg). Yield 61.2% (ESI 715.9 $[M+H]^+$).

Step 2: (3S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoicacid



Ethyl (S)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((S)-2-(5-(2-(3-(methoxymethyl)azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoate (300.0 mg, 0.42 mmol) was treated with LiOH-H_2O (88.0 mg, 2.1 mmol) in EtOH (4 mL) and water (2 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue purified by purified by Prep HPLC A (30-80% MeCN) to give the diastereomeric product **KF-P1** (66 mg) and **KF-P2** (113 mg) as white solids.

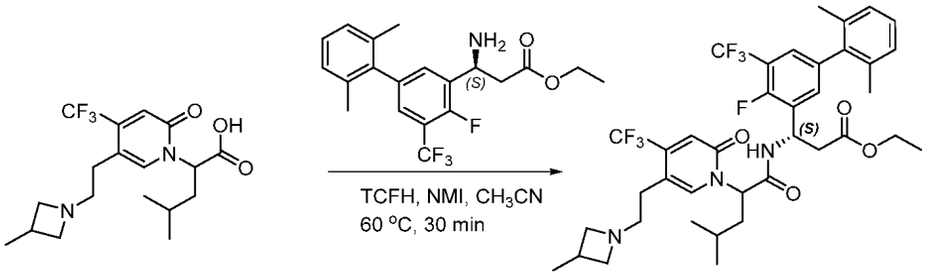
KF-P1 ESI 688.3 $(M+H)^+$ ^1H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.13 – 6.98 (m, 3H), 6.87 (dd, J = 13.1, 6.8 Hz, 2H), 6.77 (s, 1H), 5.68 – 5.52 (m, 2H), 4.08 (t, J = 9.6 Hz, 2H), 3.84-3.77 (m, 2H),

3.49 – 3.37 (m, 5H), 3.26 (t, *J* = 7.2 Hz, 2H), 2.98 (m, 1H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.69 (d, *J* = 6.8 Hz, 2H), 2.28 (s, 3H), 2.03 – 1.90 (m, 5H), 1.85 (s, 3H), 1.45 – 1.33 (m, 1H), 0.94-0.89 (m, 6H).

KF-P2 ESI 688.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.13-7.05 (m, 3H), 6.98 – 6.83 (m, 3H), 5.75 (dd, *J* = 10.9, 3.4 Hz, 1H), 5.59 (t, *J* = 7.6 Hz, 1H), 4.21 (dd, *J* = 17.0, 7.5 Hz, 2H), 3.94 (dd, *J* = 23.0, 13.3 Hz, 2H), 3.50 (d, *J* = 4.7 Hz, 2H), 3.47-3.35 (m, 5H), 3.07-3.05 (m, 1H), 2.91-2.89 (m, 1H), 2.82-2.80 (m, 1H), 2.65-2.60(dd, *J* = 15.5, 3.5 Hz, 1H), 2.49 (dd, *J* = 15.5, 11.0 Hz, 1H), 2.31 (s, 3H), 2.00-1.93 (m, 7H), 1.67-1.60 (m, 1H), 1.43 – 1.33 (m, 1H), 0.88-0.86 (m, 6H).

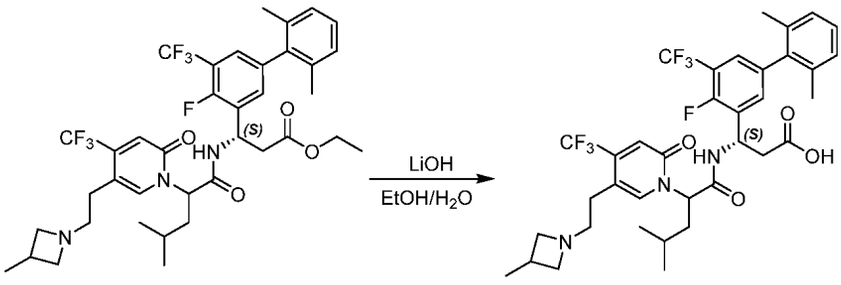
3-129. Preparation of (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoic acid (compounds KG-P1 and KG-P2)

Step 1: ethyl (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate



A mixture of ethyl (S)-3-amino-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (250 mg, 0.65 mmol), 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid (243 mg, 0.65 mmol), TCFH (364 mg, 1.3 mmol) and NMI (267 mg, 3.25 mmol) in CH_3CN (5 mL) was stirred at 60 °C for 1.5 hours. The reaction mixture was purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH4HCO3, B: CH3CN, 0~100%) to provide ethyl (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate as a yellow solid (300 mg). Yield 62.4 % (ESI 739.3 $[M+H]^+$).

Step 2: (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoic acid



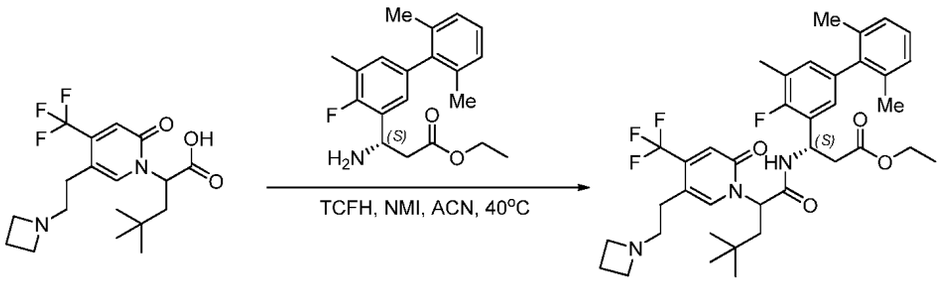
Ethyl (3S)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate(300 mg, 0.41 mmol) was treated with LiOH-H_2O (52 mg, 1.23 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 30 min. LCMS showed that the reaction was completed. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **KG-P1** (88 mg) and **KG-P2** (106 mg) as white solids.

KG-P1 ESI 711.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.39 (d, J = 4.8 Hz, 1H), 7.29 (d, J = 4.9 Hz, 1H), 7.20 – 7.04 (m, 3H), 6.73 (s, 1H), 5.62 (t, J = 6.7 Hz, 2H), 4.14 (t, J = 9.1 Hz, 2H), 3.68 (t, J = 8.4 Hz, 2H), 3.295 – 3.25 (m, 2H), 2.96 – 2.87 (m, 1H), 2.83 (t, J = 6.9 Hz, 2H), 2.75 – 2.66 (m, 2H), 2.03 – 1.92 (m, 5H), 1.85(s, 3H), 1.43 – 1.35 (m, 1H), 1.24 (d, J = 6.8 Hz, 3H), 0.9 – 0.88 (m, 6H).

KG-P2 ESI 711.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.44 (d, J = 6.4 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.33-7.21 (m, 3H), 6.88 (s, 1H), 5.82-5.76 (m, 1H), 5.61 (t, J = 7.6 Hz, 1H), 4.21 (t, J = 9.4 Hz, 2H), 3.76 (t, J = 8.5 Hz, 2H), 3.45 – 3.33 (m, 2H), 3.00 – 2.86 (m, 2H), 2.83 – 2.74 (m, 1H), 2.69-2.47 (m, 2H), 2.04 – 1.90 (m, 7H), 1.69-1.59 (m, 1H), 1.43-1.33 (m, 1H), 1.28 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.6 Hz, 6H).

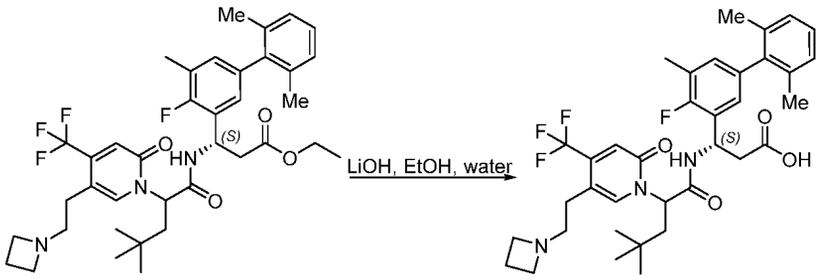
3-130. Preparation of (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (compounds KH-P1 and KH-P2)

Step 1: (3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanoic acid (300 mg, 0.80 mmol), (S)-ethyl 3-amino-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (264 mg, 0.80 mmol), NMI (0.5 mL) and TCFH (336 mg, 1.20 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue purified by prep-HPLC A (30-90% CH_3CN) to provide (3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate as a white solid (250 mg). Yield 45% (ESI 686.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid



(3S)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (250 mg, 0.36 mmol) was treated with $LiOH\text{-}H_2O$ (76 mg, 1.80 mmol) in MeOH (5 mL) and H_2O (0.5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **KH-P1** (72 mg) and **KH-P2** (75 mg) as white solids.

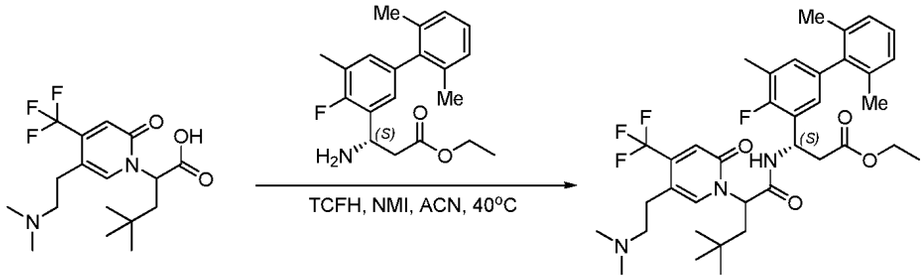
KH-P1 ESI 658.3$(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.92 (s, 1H), 7.17 – 7.00 (m, 3H), 6.86 (d, *J* = 6.9 Hz, 2H), 6.73 (s, 1H), 5.68 (s, 1H), 5.54 (t, *J* = 6.5 Hz, 1H), 4.02 (t, *J* = 8.1 Hz, 4H), 3.27 (t, *J* = 7.1 Hz, 2H), 2.83 (t, *J* = 7.0 Hz, 2H), 2.70 (d, *J* = 6.5 Hz, 2H), 2.49 – 2.36 (m, 2H), 2.29 (d, *J* = 1.7 Hz, 3H), 2.23 – 2.10 (m, 1H), 2.03 – 1.95 (m, 4H), 1.86 (s, 3H), 0.90 (s, 9H).

KH-P2 ESI 658.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.19 – 7.07 (m, 3H), 7.02 – 6.85 (m, 3H), 5.87 – 5.72 (m, 1H), 5.69 – 5.55 (m, 1H), 4.15 (s, 4H), 3.47 – 3.35 (m, 2H), 3.01 – 2.75

(m, 2H), 2.71 – 2.41 (m, 4H), 2.41 – 2.27 (m, 4H), 2.00 (d, *J* = 6.9 Hz, 6H), 1.49 (d, *J* = 13.2 Hz, 1H), 0.88 (s, 9H).

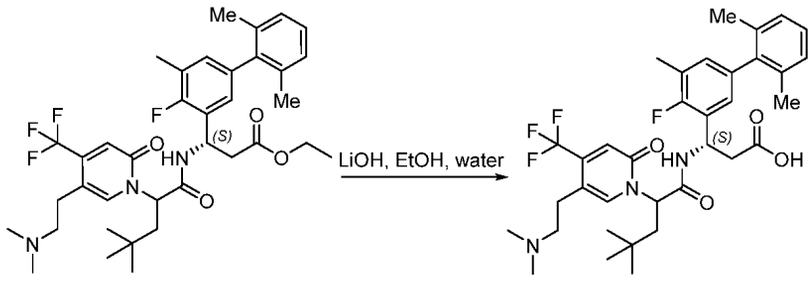
3-131. Preparation of (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (compounds KI-P1 and KI-P2)

Step 1: (3S)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanoic acid (250 mg, 0.69 mmol), (S)-ethyl 3-amino-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (227 mg, 0.69 mmol), NMI (0.5 mL) and TCFH (291 mg, 1.04 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour. The solvent was concentrated *in vacuo* and the residue purified by prep-HPLC A (30-90% CH_3CN) to provide (3S)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate as a white solid (200 mg). Yield 43% (ESI 674.2 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid



(3S)-ethyl 3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4,4-dimethylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (200 mg, 0.30 mmol) was treated with LiOH-H_2O (63 mg, 1.50 mmol) in MeOH (5 mL) and H_2O (0.5 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was

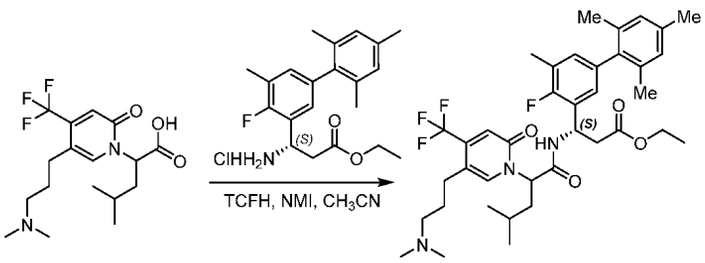
removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to give the diastereomeric products **KI-P1** (67 mg) and **KI-P2** (62 mg) as white solids.

KI-P1 ESI 646.3(M+H)$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.97 (s, 1H), 7.15 – 6.98 (m, 3H), 6.84 (d, *J* = 7.1 Hz, 2H), 6.70 (s, 1H), 5.74 (s, 1H), 5.58 – 5.44 (m, 1H), 3.12 – 2.84 (m, 4H), 2.77 – 2.64 (m, 8H), 2.28 (d, *J* = 1.6 Hz, 3H), 2.20 – 2.11 (m, 1H), 2.02 – 1.90 (m, 4H), 1.79 (s, 3H), 0.91 (s, 9H).

KI-P2 ESI 646.3 (M+H)$^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.19 – 7.04 (m, 3H), 7.00 – 6.85 (m, 3H), 5.73 (d, *J* = 10.3 Hz, 1H), 5.66 – 5.56 (m, 1H), 3.32 – 3.15 (m, 2H), 3.07 – 2.95 (m, 2H), 2.83 (s, 6H), 2.66 – 2.44 (m, 2H), 2.32 (d, *J* = 1.6 Hz, 3H), 2.30 – 2.23 (m, 1H), 1.99 (d, *J* = 4.0 Hz, 6H), 1.65 – 1.51 (m, 1H), 0.86 (d, *J* = 1.7 Hz, 9H).

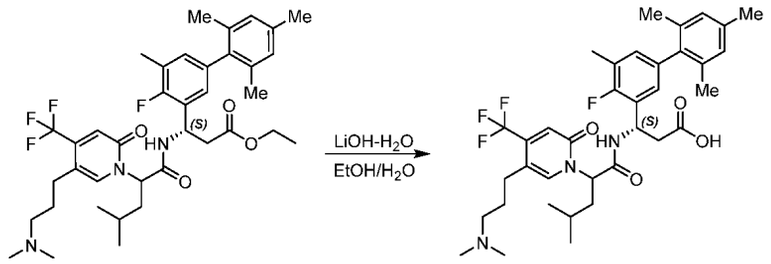
3-132. Preparation of (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds KJ-P1 and KJ-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (239.3 mg, 0.63 mmol), 2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (230.0 mg, 0.63 mmol), TCHF (213.2 mg, 0.76 mmol) and NMI (206.9 mg, 2.52 mmol) in CH_3CN (5 mL) was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (270.0 mg). Yield 62% (ESI 688.3 [M+H]$^+$).

Step 2: (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid

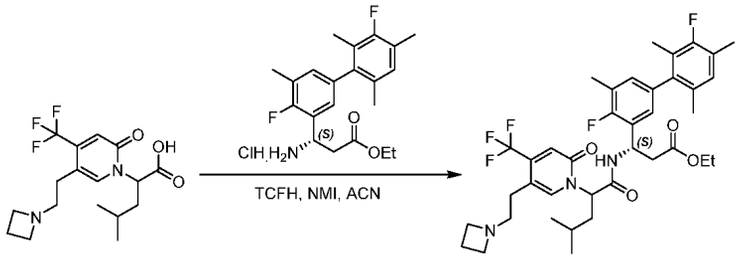


Ethyl (3*S*)-3-(2-(5-(3-(dimethylamino)propyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (270.0 mg, 0.39 mmol) was treated with LiOH-H_2O (49.1 mg, 1.17 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to PH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **KJ-P1** (84 mg) and **KJ-P2** (74 mg) as white solids.

KJ-P1 ESI 660.0 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.80 (s, 1H), 6.95 – 6.78 (m, 4H), 6.72 (s, 1H), 5.75 – 5.69 (m, 1H), 5.58 (t, J = 6.8 Hz, 1H), 3.12 – 2.97 (m, 2H), 2.78 (s, 6H), 2.72 – 2.62 (m, 4H), 2.33 – 2.23 (m, 6H), 2.05 – 1.88 (m, 7H), 1.80 (s, 3H), 1.43 – 1.34 (m, 1H), 0.96 – 0.92 (m, 6H).
KJ-P2 ESI 660.0 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 6.93 – 6.86 (m, 4H), 6.84 (s, 1H), 5.77 – 5.72 (m, 1H), 5.60 – 5.53 (m, 1H), 3.09 – 2.94 (m, 2H), 2.79 (s, 6H), 2.73 – 2.45 (m, 4H), 2.36 – 2.26 (m, 6H), 2.10 – 1.85 (m, 9H), 1.65 – 1.54 (m, 1H), 1.42 – 1.30 (m, 1H), 0.87 – 0.81 (m, 6H).

3-133. Preparation of (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds KK-P1 and KK-P2)

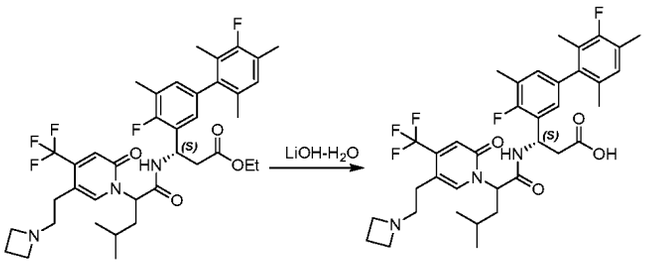
Step 1: ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (230.0 mg, 0.64 mmol), ethyl (S)-3-amino-3-(3',4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate hydrochloride (230.0 mg, 0.64 mmol), TCHF (214.0 mg,

0.76 mmol) and NMI (105.0 mg, 1.28 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The solvent was concentrated *in vacuo* and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provideethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (220 mg). Yield 50.1% (ESI 704.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid

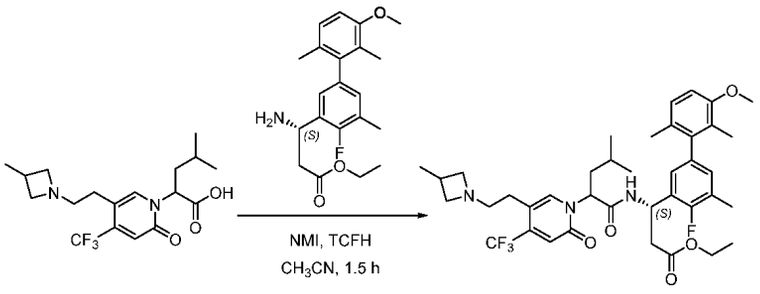


Ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(3',4-difluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (220.0 mg, 0.31 mmol) was treated with LiOH-H_2O (66.0 mg, 1.55 mmol) in EtOH (4 mL) and water (2 mL) at 30 °C for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue purified by Prep HPLC A (30-80% MeCN) to give the diastereomeric products **KK-P1** (85 mg) and **KK-P2** (84 mg) as white solids.

KK-P1 ESI 676.1 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 6.94-6.76 (m, 3H), 6.77 (d, J = 9.2 Hz, 1H), 5.68 – 5.54 (m, 2H), 4.07-4.02 (s, 4H), 3.28 (d, J = 6.7 Hz, 2H), 2.85 (t, J = 6.9 Hz, 2H), 2.71-2.68 (m,, 2H), 2.43 (m, 2H), 2.30 (s, 3H), 2.25 (s, 3H), 2.00 (t, J = 7.5 Hz, 2H), 1.95 – 1.88 (m, 3H), 1.80 (d, J = 16.8 Hz, 3H), 1.42-4.41 (m, 1H), 0.96-0.92 (m, 6H).
KK-P2 ESI 676.1 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.62 (s, 1H), 6.84-6.78 (m, 4H), 5.64 (dd, J = 10.8, 3.3 Hz, 1H), 5.49 (t, J = 7.6 Hz, 1H), 4.04-3.99 (m, 4H), 3.31-3.21 (m, 2H), 2.84-2.69 (m, 2H), 2.55-2.50 (m, 1H), 2.44 – 2.29 (m, 3H), 2.22 (d, J = 1.7 Hz, 3H), 2.14 (d, J = 1.6 Hz, 3H), 1.91-1.78 (m, 7H), 1.60 – 1.49 (m, 1H), 1.37 – 1.22 (m, 1H), 0.80 – 0.73 (m, 6H).

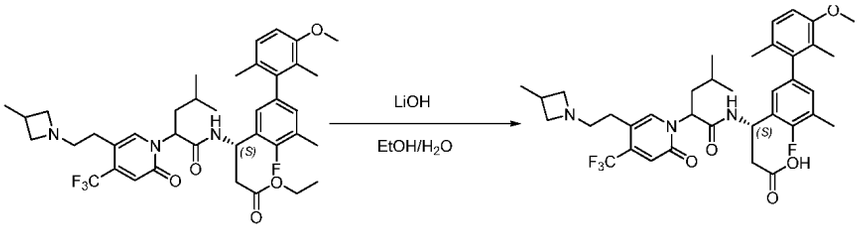
3-134. Preparation of (3S)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoic acid (compounds KL-P1 and KL-P2)

Step 1: (3S)-ethyl 3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate



A mixture of 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid (170 mg, 0.45 mmol), (S)-ethyl 3-amino-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate (163 mg, 0.45 mmol), NMI (160 mg, 1.96 mmol) and TCFH (252 mg, 0.9 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1.5 hours. The solvent was concentrated *in vacuo* and the residue purified by silica gel column (DCM: MeOH 9:1) to provide (3S)-ethyl 3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate as a yellow solid (220 mg). Yield 68 % (ESI 716.3 $[M+H]^+$).

Step 2: (3S)-3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoic acid



(3S)-ethyl 3-(4-fluoro-3'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate (220 mg, 0.31 mmol) was treated with LiOH-H_2O (64 mg, 1.53 mmol) in EtOH (3 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-80% CH_3CN) to give the diastereomeric products **KL-P1** (73 mg) and **KL-P2** (100 mg) as white solids.

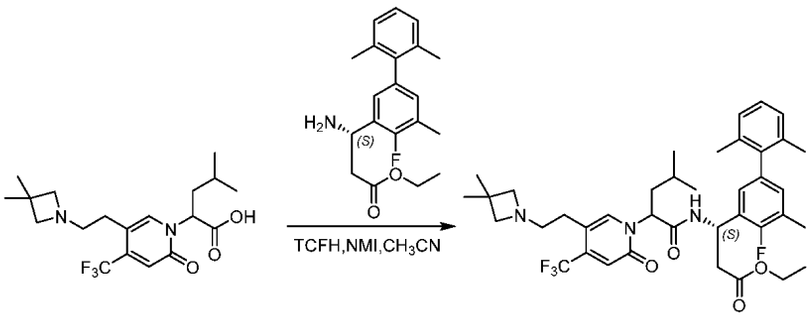
KL-P1 ESI 688.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.92 – 6.67 (m, 4H), 5.73 – 5.51 (m, 2H), 4.18 – 4.00 (m, 2H), 3.82 (s, 3H), 3.70 – 3.55 (m, 2H), 3.31 – 3.22 (m, 2H), 3.01 – 2.79 (m, 3H), 2.70 (d, J = 6.0 Hz, 2H), 2.32 (d, J = 25.7 Hz, 3H), 1.98 (t, J = 7.5 Hz, 2H), 1.82-1.80 (m, 6H), 1.49 – 1.37 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.94-0.90 (m, 6H).

KL-P2 ESI 688.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.05 (d, J = 8.3 Hz, 1H), 7.00 – 6.84 (m, 3H), 6.83 (d, J = 8.4 Hz, 1H), 5.76-5.75 (m, 1H), 5.60 (t, J = 7.5 Hz, 1H), 4.21 (t, J = 9.3

Hz, 2H), 3.83 (d, J = 1.0 Hz, 3H), 3.80 – 3.67 (m, 2H), 3.46 – 3.35 (m, 2H), 3.04 – 2.86 (m, 2H), 2.85 – 2.74 (m, 1H), 2.71 – 2.59 (m, 1H), 2.50-2.48 (m, 1H), 2.33 (d, J = 1.7 Hz, 3H), 2.06 – 1.95 (m, 1H), 1.93 (d, J = 6.5 Hz, 3H), 1.85 (d, J = 5.3 Hz, 3H), 1.68 – 1.56 (m, 1H), 1.42-1.40 (m, 1H), 1.29 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.6 Hz, 6H).

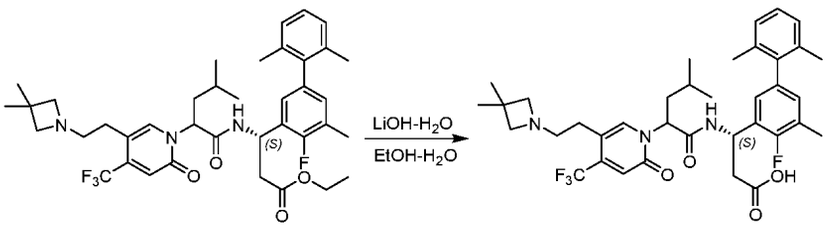
3-135. Preparation of (3*S*)-3-(2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds KM-P1 and KM-P2)

Step 1: ethyl (3*S*)-3-(2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (216.6 mg, 0.59 mmol), 2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (230.0 mg, 0.59 mmol), TCHF (199.2 mg, 0.71 mmol) and NMI (145.3 mg, 1.77 mmol) in CH_3CN (5 mL) was stirred at 40 °C for 1 hour. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate as a light yellow solid (270.0 mg). Yield 65% (ESI 700.3 $[M+H]^+$).

Step 2: (3*S*)-3-(2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid



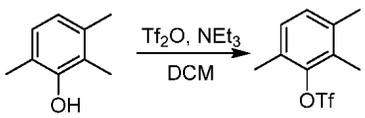
Ethyl (3*S*)-3-(2-(5-(2-(3,3-dimethylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (270.0 mg, 0.39

mmol) was treated with LiOH-H_2O (49.1 mg, 1.17 mmol) in EtOH (2 mL) and H_2O (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-80% MeCN) to give the diastereomeric products **KM-P1** (83 mg) and **KM-P2** (96 mg) as white solids.

KM-P1 ESI 672.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.15 – 7.02 (m, 3H), 6.94 – 6.84 (m, 2H), 6.78 (s, 1H), 5.72 – 5.61 (m, 2H), 3.84 – 3.71 (m, 4H), 3.32 – 3.20 (m, 2H), 2.85 (t, J = 7.1 Hz, 2H), 2.78 – 2.66 (m, 2H), 2.29 (d, J = 1.4 Hz, 3H), 2.04 – 1.94 (m, 5H), 1.85 (s, 3H), 1.45 – 1.38 (m, 1H), 1.34 (s, 6H), 0.94 (t, J = 6.6 Hz, 6H).
KM-P2 ESI 672.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.17 – 7.05 (m, 3H), 6.98 – 6.87 (m, 3H), 5.80 – 5.75 (m, 1H), 5.62 (t, J = 7.6 Hz, 1H), 3.91 (s, 4H), 3.42 (t, J = 5.9 Hz, 2H), 3.00 – 2.74 (m, 2H), 2.66 – 2.46 (m, 2H), 2.33 (d, J = 1.7 Hz, 3H), 2.05 – 1.94 (m, 7H), 1.66 – 1.58 (m, 1H), 1.47 – 1.35 (m, 7H), 0.89 (d, J = 6.6 Hz, 6H).

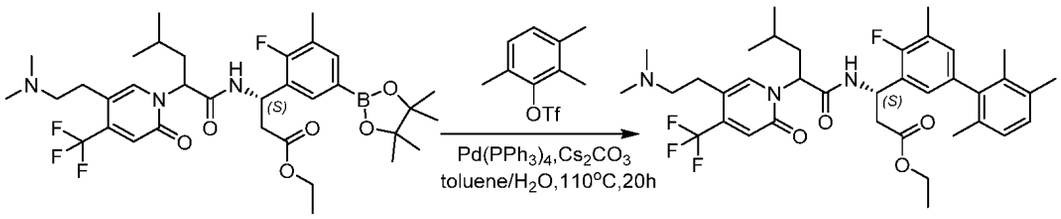
3-136. Preparation of (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds KN-P1 and KN-P2)

Step 1: 2,3,6-trimethylphenyl trifluoromethanesulfonate



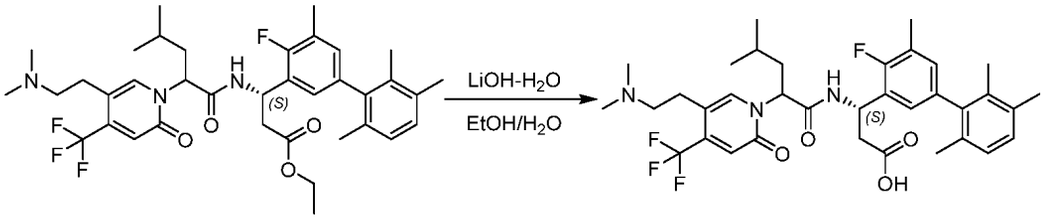
A mixture of 2,3,6-trimethylphenol (5.0 g, 36.7 mmol) and triethylamine (11.1 g, 110.1 mmol) in DCM (100 mL) was cooled at 0 °C. Trifluoromethanesulfonic anhydride (15.5 g, 55.1 mmol) was added dropwise to the reaction mixture and the mixture was stirred at 0 °C for 3 hours. The mixture was quenched with a NH_4Cl aqueous solution (50 mL). The organic layer was washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (pet ether) to provide **2**,3,6-trimethylphenyl trifluoromethanesulfonate as a colourless oil (8.0 g). Yield 81 % (no Mass) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (dd, J = 19.3, 7.8 Hz, 2H), 2.35 (s, 3H), 2.27 (d, J = 5.2 Hz, 6H).

Step 2: ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2-fluoro-3-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propanoate (250.0 mg, 0.37 mmol), 2,3,6-trimethylphenyl trifluoromethanesulfonate (119.1 mg, 0.44 mmol), Cs_2CO_3 (361.6 mg, 1.11 mmol) and $Pd(PPh_3)_4$ (42.7 mg, 0.037 mmol) in toluene (6 mL) and H_2O (0.6 mL) was stirred at 110 °C under a nitrogen atmosphere for 20 hours. LCMS showed that the reaction was completed. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (EtOAc) to provide ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate a light yellow oil (110 mg). Yield 45 % (ESI 674.3 $(M+H)^+$)

Step 3: (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',3',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (110.0 mg, 0.16 mmol) was treated with $LiOH-H_2O$ (35.6 mg, 0.80 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 1 hour. The reaction mixture was acidified to pH 4~5 with 2N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-80% MeCN) to provide the diastereomeric products **KN-P1** (47 mg) and **KN-P2** (39 mg) as white solids.

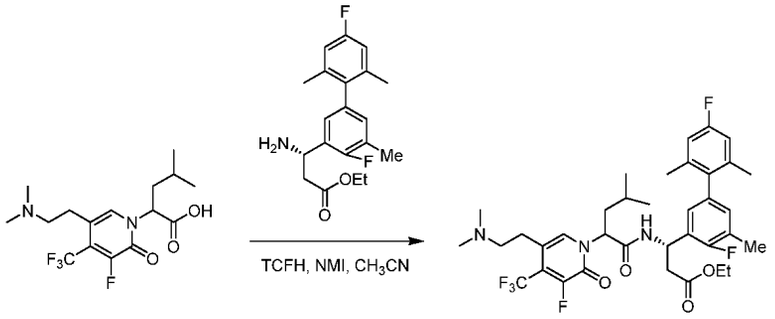
KN-P1 ESI 646.3 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.91 (d, J = 8.6 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 6.97 – 6.72 (m, 4H), 5.71 – 5.66 (m, 1H), 5.58 – 5.54 (m, 1H), 3.16 – 3.00 (m, 2H), 2.96 – 2.91 (m, 2H), 2.79 – 2.64 (m, 8H), 2.32 – 2.21 (m, 6H), 1.99 – 1.88 (m, 2H), 1.92 (d, J = 12.7 Hz, 3H), 1.74 (d, J = 9.6 Hz, 3H), 1.47 – 1.39 (m, 1H), 0.96 – 0.91(m, 6H).

KN-P2 ESI 646.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.03 (d, J = 7.7 Hz, 1H), 6.97 (d, J = 7.7 Hz, 1H), 6.94 – 6.85 (m, 3H), 5.74 – 5.70 (m, 1H), 5.62 (t, J = 7.7 Hz, 1H), 3.28 – 3.16 (m, 2H), 3.03 – 2.95 (m, 2H), 2.82 (d, J = 4.2 Hz, 6H), 2.67 – 2.61 (m, 1H), 2.56 – 2.49 (m, 1H), 2.32 (d,

J = 1.5 Hz, 3H), 2.27 (s, 3H), 2.03 – 1.84 (m, 7H), 1.74 – 1.65 (m 1H), 1.42 – 1.35 (m, 1H), 0.92 – 0.82 (m, 6H).

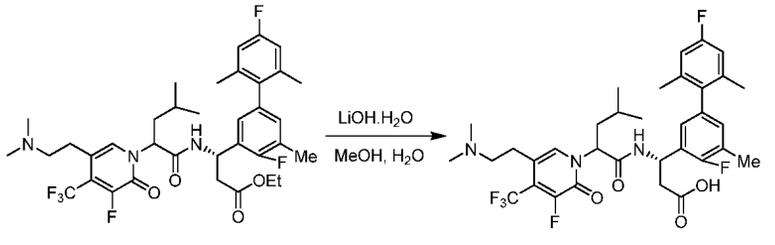
3-137. Preparation of (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds KO-P1 and KO-P2)

Step 1: (3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate



A mixture of 2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (150 mg, 0.41 mmol), (*S*)-ethyl 3-amino-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoate (142 mg, 0.41 mmol), TCFH (230 mg, 0.82 mmol) and NMI (67 mg, 0.82 mmol) in CH_3CN (6 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 10: 1) to provide (3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate as a yellow oil (120 mg). Yield 42% (ESI 696.1 $(M+H)^+$).

Step 2: (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid



(3*S*)-ethyl 3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoate (120 mg, 0.17 mmol)) was treated with LiOH-H_2O (36 mg, 0.85 mmol) in MeOH (4 mL) and H_2O (1 mL) at room

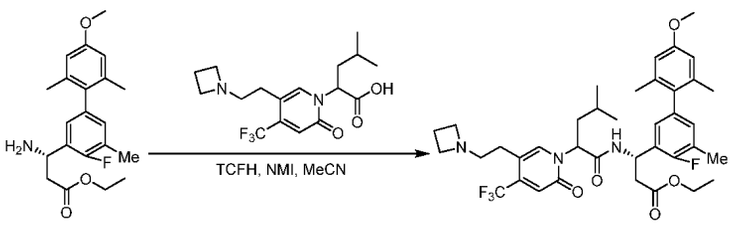
temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% MeCN) to provide the diastereomeric products **KO-P1** (42 mg) and **KO-P2** (47 mg) as white solids.

KO-P1 ESI 668.2(M+H)$^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.71 (s, 1H), 6.88 – 6.79 (m, 4H), 5.68 (t, *J* = 8.0 Hz, 1H), 5.55 (t, *J* = 6.8 Hz, 1H), 3.09 (d, *J* = 7.2 Hz, 2H), 3.00 (d, *J* = 7.9 Hz, 2H), 2.81 – 2.68 (m, 8H), 2.29 (s, 3H), 1.98 (d, *J* = 10.1 Hz, 5H), 1.83 (s, 3H), 1.48 – 1.41 (m, 1H), 0.96 – 0.92 (m, , 6H).

KO-P2 ESI 668.2 (M+H)$^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.66 (s, 1H), 6.93 (t, *J* = 7.5 Hz, 2H), 6.84 (d, *J* = 9.6 Hz, 2H), 5.74 – 5.70 (m, 1H), 5.63 (t, *J* = 7.6 Hz, 1H), 3.29 – 3.15 (m, 2H), 3.06 – 3.00 (m, 2H), 2.83 (d, *J* = 7.9 Hz, 6H), 2.67 – 2.59 (m, 1H), 2.55 – 2.49 (m, 1H), 2.32 (d, *J* = 1.2 Hz, 3H), 2.08 – 1.96 (m, 7H), 1.76 – 1.66 (m, 1H), 1.42 – 1.37 (m, 1H), 0.90 – 0.85 (m, 6H).

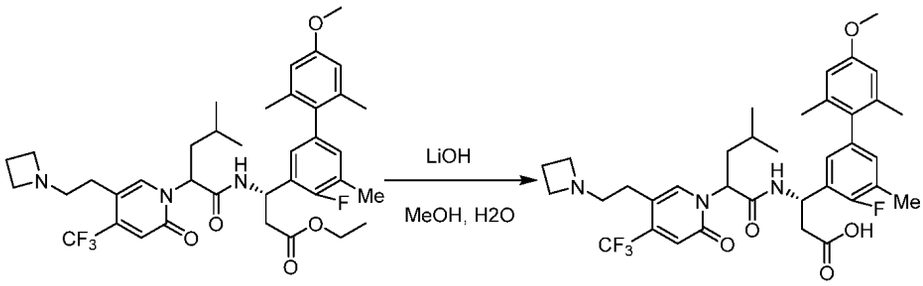
3-138. Preparation of (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (compounds KP-P1 and KP-P2)

Step 1: (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate



A mixture of (*S*)-ethyl 3-amino-3-(4-fluoro-4'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate (170 mg, 0.47 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanoic acid (169 mg, 0.47 mmol), TCFH (263 mg, 0.94 mmol) and NMI (241 mg, 2.94 mmol) in CH_3CN (6 mL) was stirred at room temperature for 1 hour. The solvent was removed *in vacuo* and the residue purified by silica gel column (DCM: MeOH 10: 1) to provide (3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate as a yellow oil (140 mg). Yield 42% (ESI 702.2 (M+H)$^+$).

Step 2: (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid



(3*S*)-ethyl 3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethylbiphenyl-3-yl)propanoate (140 mg, 0.2 mmol)) was treated with LiOH-H_2O (42 mg, 1 mmol) in MeOH (4 mL) and H_2O (1 mL) at room temperature for 2 hours. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% MeCN) to provide the diastereomeric products **KP-P1** (48 mg) and **KP-P2** (47 mg) as white solids.

KP-P1 ESI 674.2$(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 6.89 – 6.85 (m, 2H), 6.80 (s, 1H), 6.64 (d, J = 6.8 Hz, 2H), 5.67 – 5.57 (m, 2H), 4.05 – 4.00 (m, 4H), 3.79 (s, 3H), 3.29 (d, J = 6.6 Hz, 2H), 2.86 (t, J = 6.9 Hz, 2H), 2.77 – 2.65 (m, 2H), 2.53 – 2.38 (m, 2H), 2.29 (d, J = 1.3 Hz, 3H), 2.06 – 1.92 (m, 5H), 1.86 (s, 3H), 1.51 – 1.29 (m, 1H), 0.96 – 0.92 (m, 6H).

KP-P2 ESI 674.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 6.95 – 6.90 (m, 3H), 6.67 (s, 2H), 5.79 – 5.75 (m, 1H), 5.61 (t, J = 7.6 Hz, 1H), 4.14 (t, J = 8.0 Hz, 4H), 3.80 (s, 3H), 3.46 – 3.41(m, 1H), 3.39 – 3.34 (m, 1H), 2.96 – 2.92 (m, 1H), 2.84 – 2.81 (m, 1H), 2.67 – 2.63(m, 1H), 2.55 – 2.44 (m, 3H), 2.32 (d, J = 1.4 Hz, 3H), 2.05 – 1.93 (m, 7H), 1.71 – 1.61 (m, 1H), 1.45 – 1.38 (m, 1H), 0.90 – 0.88 (m, 6H).

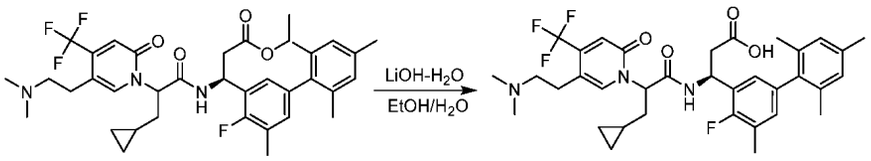
3-139. Preparation of (3*S*)-3-(3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (compounds KQ-P1 and KQ-P2)

Step 1: ethyl (3*S*)-3-(3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate

A mixture of ethyl (*S*)-3-amino-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (162.4 mg, 0.47 mmol), 3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanoic acid (150.0 mg, 0.43 mmol), TCHF (144.8 mg, 0.52 mmol) and NMI (105.9 mg, 1.29 mmol) in CH_3CN (5 mL) was stirred at room temperature for 1 hour.

The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO_3, B: MeOH, 0~100%) to provide ethyl (3*S*)-3-(3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (120.0 mg). Yield 41.2% (ESI 672.3 $[M+H]^+$).

Step 2: (3*S*)-3-(3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid



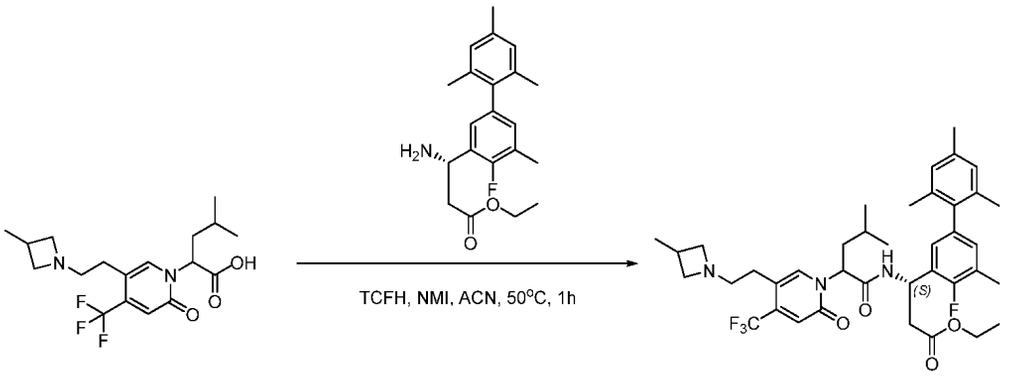
Ethyl (3*S*)-3-(3-cyclopropyl-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)propanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoate (100.0 mg, 0.15 mmol) was treated with LiOH-H_2O (18.9 mg, 0.45 mmol) in EtOH (2 mL) and water (0.5 mL) at room temperature for 0.5 hour. The reaction mixture was acidified to pH 6~7 with 2N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-80% MeCN) to provide the diastereomeric products **KQ-P1** (22 mg) and **KQ-P2** (20 mg) as white solids.

KQ-P1 ESI 644.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 6.78 – 6.61 (m, 4H), 6.55 (s, 1H), 5.49 – 5.37 (m, 2H), 2.94 – 2.88 (m, 2H), 2.82 – 2.69 (m, 2H), 2.66 – 2.44 (m, 8H), 2.19 – 2.03 (m, 6H), 1.92 – 1.85 (m, 1H), 1.82 – 1.71 (m, 4H), 1.60 (s, 3H), 0.56 – 0.38 (m, 1H), 0.34 – 0.19 (m, 2H), 0.07 – -0.17 (m, 2H).

KQ-P2 ESI 644.2 $(M+H)^+$ ^{1}H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 6.98 – 6.79 (m, 5H), 5.70 (dd, J = 10.3, 4.1 Hz, 1H), 5.57 (t, J = 7.4 Hz, 1H), 3.27 – 3.15 (m, 2H), 2.96 (t, J = 6.9 Hz, 2H), 2.79 (s, 6H), 2.69 – 2.42 (m, 2H), 2.34 – 2.20 (m, 6H), 2.14 – 1.99 (m, 1H), 1.92 (d, J = 10.7 Hz, 6H), 1.67 – 1.49 (m, 1H), 0.55 (dd, J = 13.0, 6.4 Hz, 1H), 0.57 – 0.53 (m, 2H), 0.08 – -0.16 (m, 2H).

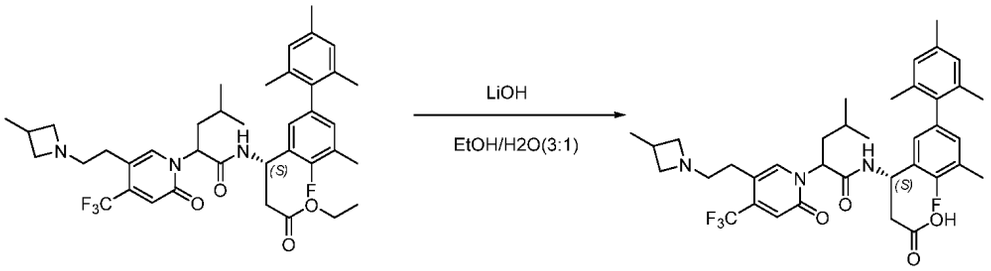
3-140. Preparation of (3S)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoic acid (compounds KR-P1 and KR-P2)

Step 1: (3S)-ethyl 3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl) pentanamido)propanoate



A mixture of 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid (240 mg, 0.58 mmol), (S)-ethyl 3-amino-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoate (200 mg, 0.58 mmol), NMI (142 mg, 1.74 mmol) and TCFH (243 mg, 0.87 mmol) in CH_3CN (10 mL) was stirred at 50°C for 1 hour. The solvent was concentrated *in vacuo* and the residue purified by silica gel column (DCM: MeOH 15:1) to provide (3S)-ethyl 3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate as a yellow oil (310 mg). Yield 75.7 % (ESI 700.3 $[M+H]^+$).

Step 2: (3S)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl) pentanamido) propanoic acid



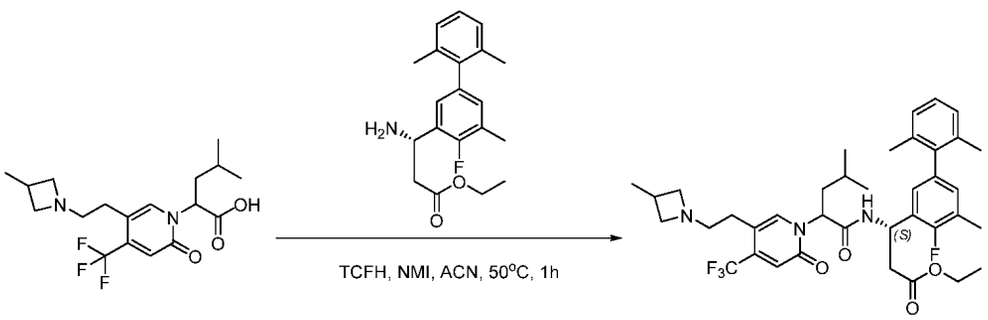
(3S)-ethyl 3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl) pentanamido)propanoate (310 mg, 0.44 mmol) was treated with LiOH-H_2O (56 mg, 1.33 mmol) in EtOH (2 mL) and H_2O (1 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-70% CH_3CN) to provide the diastereomeric products **KR-P1** (60 mg) and **KR-P2** (118 mg) as white solids.

KR-P1 ESI 672.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 6.86 – 6.82 (m, 4H), 6.75 (s, 1H), 5.66 – 5.64 (m, 1H), 5.61 – 5.53 (m, 1H), 4.14 – 4.01 (m, 2H), 3.63 – 3.59 (m, 2H), 3.30 – 3.20 (m, 2H), 2.89 – 2.82 (m, 3H), 2.73 – 2.64 (m, 2H), 2.29 (s, 6H), 2.01 – 1.90 (m, 5H), 1.81 (s, 3H), 1.49 – 1.36 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.94 (t, J = 7.2 Hz, 6H).

KR-P2 ESI 672.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 6.98 – 6.83 (m, 5H), 5.78 – 5.76 (m, 1H), 5.61 – 5.59 (m, 1H), 4.24 – 4.21 (m, 2H), 3.75 – 3.70 (m, 2H), 3.47 – 3.33 (m, 2H), 3.01 – 2.85 (m, 2H), 2.88 – 2.73 (m, 1H), 2.65 – 2 .61 (m, 1H), 2.58 – 2.44 (m, 1H), 2.33 – 2.22 (m, 6H), 2.01 – 1.86 (m, 7H), 1.60 – 1.55 (m, 1H), 1.45 – 1.34 (m, 1H), 1.29 (d, J = 6.9 Hz, 3H), 0.85 – 0.80 (m, 6H).

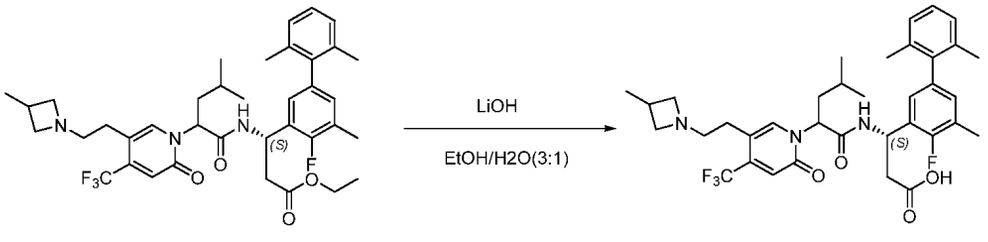
3-141. Preparation of (3S)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoic acid (compounds KS-P1 and KS-P2)

Step 1: (3S)-ethyl 3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate



A mixture of 4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanoic acid (250 mg, 0.61 mmol), ethyl (*S*)-3-amino-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoate (201 mg, 0.61 mmol), NMI (150 mg, 1.83 mmol) and TCFH (256 mg, 0.91 mmol) in CH_3CN (10 mL) was stirred at 50°C for 1 hour. The solvent was concentrated *in vacuo* and the residue purified by silica gel column (DCM: MeOH 10:1) to providet (3S)-ethyl 3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate as a yellow oil (320 mg). Yield 76.6 % (ESI 686.2 $[M+H]^+$).

Step 2: (3S)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoic acid



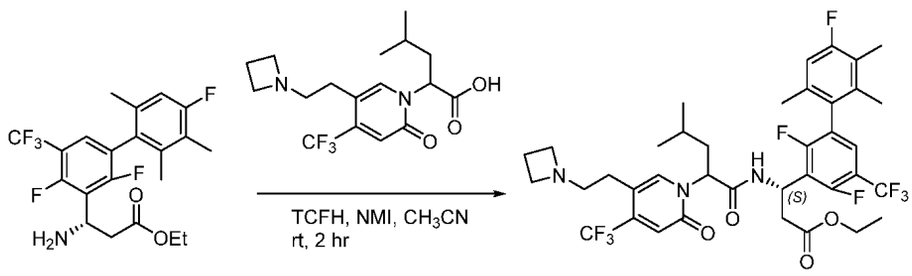
(3S)-ethyl 3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(4-methyl-2-(5-(2-(3-methylazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)propanoate (320 mg, 0.47 mmol) was treated with LiOH-H_2O (59 mg, 1.41 mmol) in EtOH (2 mL) and H_2O (1 mL) at room temperature for 30 mins. The reaction mixture was acidified to pH 4~5 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-60% CH_3CN) to provide the diastereomeric products **KS-P1** (75 mg) and **KS-P2** (132 mg) as white solids.

KS-P1 ESI 658.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.15 – 6.99 (m, 3H), 6.94 – 6.81 (m, 3H), 6.76 (s, 1H), 5.61 – 5.63 (m, 2H), 4.07 –4.09 (m, 2H), 3.60 – 3.62 (m, 2H), 3.22 – 3.24 (m, 2H), 2.94 – 2.76 (m, 3H), 2.72 – 2.62 (m, 2H), 2.28 – 2.29 (m, 2H), 2.03 – 1.93 (m, 5H), 1.85 (s, 3H), 1.41 – 1.42 (m, 1H), 1.24 (d, J = 6.9 Hz, 3H), 0.97 – 0.88 (m, 6H).

KS-P2 ESI 658.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.76 (s, 1H), 7.11 – 7.09 (m, 3H), 6.98 – 6.81 (m, 3H), 5.77– 5.75 (m, 1H), 5.61 (t, J = 7.6 Hz, 1H), 4.21 – 4.18 (m, 2H), 3.75 – 3.72 (m, 2H), 3.44 – 3.34 (m, 2H), 3.05 – 2.85 (m, 2H), 2.85 – 2.71 (m, 1H), 2.65 – 2.63 (m, 1H), 2.52 – 2.50 (m, 1H), 2.33 (d, J = 1.4 Hz, 3H), 2.03 – 1.90 (m, 7H), 1.65 – 1.59 (m, 1H), 1.43 – 1.38 (m, 1H), 1.29 (d, J = 6.9 Hz, 3H), 0.89 – 0.82 (m, 6H).

3-142. Preparation of (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid (compounds KT-P1 and KT-P2)

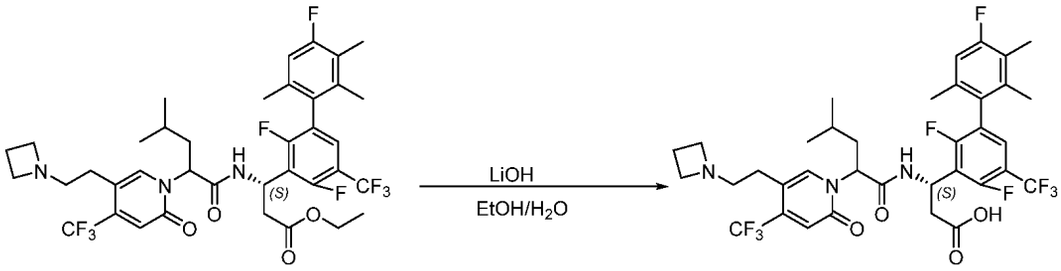
Step 1: ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate



A mixture of ethyl (3S)-3-amino-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (140 mg, 0.32 mmol), 2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanoic acid (116 mg, 0.32 mmol), TCFH (179

mg, 0.64 mmol) and NMI (131 mg, 1.6 mmol) in CH_3CN (5 mL) was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue purified by reverse phase HPLC on a C18/40g column (A: water 10mM NH_4HCO3, B: CH_3OH, 0~85%) to provide ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate as a yellow solid (140 mg). Yield 56.4 % (ESI 776.3 $[M+H]^+$).

Step 2: (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoic acid



Ethyl (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2,4,4'-trifluoro-2',3',6'-trimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)propanoate (140 mg, 0.18 mmol) was treated with LiOH-H_2O (22 mg, 0.54 mmol) in EtOH (4 mL) and H_2O (1 mL) at room temperature for 2 hrs. The reaction mixture was acidified to pH 5~6 with 1N HCl. The solvent was removed *in vacuo* and the residue purified by prep-HPLC A (30-65% CH_3CN) to provide the diastereomeric products **KT-P1** (24 mg) and **KT-P2** (30 mg) as white solids.

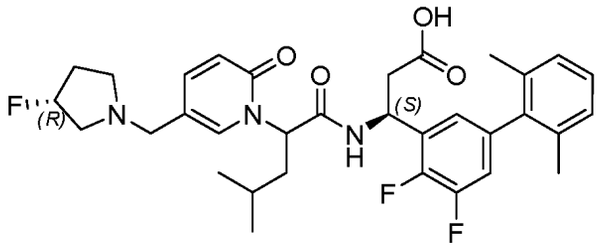
KT-P1 ESI 748.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.39 (m, J = 7.5 Hz, 1H), 6.99 – 6.80 (m, 2H), 5.71 (m, J = 9.2, 5.9 Hz, 2H), 4.12 (m, J = 8.1 Hz, 4H), 3.42 – 3.30 (m, 2H), 2.99 – 2.71 (m, 4H), 2.52 – 2.35 (m, 2H), 2.18 (s, 3H), 2.09 – 1.93 (m, 5H), 1.86 (s, 3H), 1.45 – 1.32 (m, 1H), 0.94 (m, J = 6.9 Hz, 6H).

KT-P2 ESI 748.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.44 (m, J = 7.6 Hz, 1H), 7.00 – 6.77 (m, 2H), 5.90 (d, J = 8.1 Hz, 1H), 5.63 (m, J = 7.7 Hz, 1H), 4.12 (m, J = 8.1 Hz, 4H), 3.39 (m, J = 19.1, 13.7 Hz, 2H), 2.86 (m, J = 14.4, 13.3 Hz, 3H), 2.60 (m, J = 15.6, 4.2 Hz, 1H), 2.45 (m, J = 8.1 Hz, 2H), 2.20 (s, 3H), 1.94 (m, J = 21.4, 9.3, 4.8 Hz, 7H), 1.72 (m, J = 14.4, 7.3 Hz, 1H), 1.33 (m, J = 13.4, 6.7 Hz, 1H), 0.88 (m, J = 10.6, 6.6 Hz, 6H).

Example 4: Characterization of examplary compounds of the invention

The following compounds were synthesized using procedures similar to the ones used in example 3.

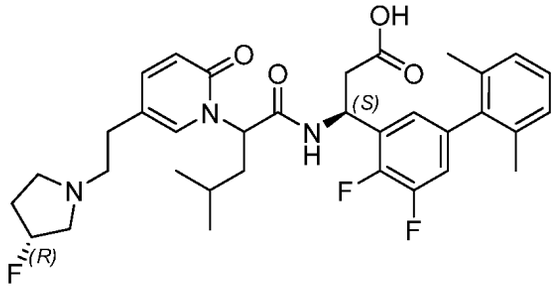
4-1. (3*S*)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(((*R*)-3-fluoropyrrolidin-1-yl)methyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BB-P1 and BB-P2)



BB-P1 ESI 598.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.74 (d, *J* = 2.1 Hz, 1H), 7.53 – 7.42 (m, 1H), 7.16 – 7.00 (m, 3H), 6.93 – 6.80 (m, 2H), 6.42 (d, *J* = 9.3 Hz, 1H), 5.71 (t, *J* = 8.1 Hz, 1H), 5.55 (t, *J* = 7.1 Hz, 1H), 5.34 – 5.13 (m, 1H), 3.80 – 3.61 (m, 2H), 3.17 – 2.93 (m, 3H), 2.83 – 2.63 (m, 3H), 2.33 – 2.16 (m, 1H), 2.16 – 2.02 (m, 1H), 1.98 (s, 3H), 1.92 (t, *J* = 7.6 Hz, 2H), 1.83 (s, 3H), 1.47 – 1.33 (m, 1H), 0.99 – 0.87 (m, 6H).

BB-P2 ESI 598.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.69 (d, *J* = 2.2 Hz, 1H), 7.62 – 7.51 (m, 1H), 7.16 – 7.01 (m, 3H), 6.99 – 6.84 (m, 2H), 6.54 (d, *J* = 9.3 Hz, 1H), 5.80 – 5.69 (m, 1H), 5.51 – 5.45 (m, 1H), 5.33 (d, *J* = 54.4 Hz, 1H), 4.18 (d, *J* = 13.2 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.55 – 3.31 (m, 4H), 2.73 – 2.64 (m, 1H), 2.58 – 2.46 (m, 1H), 2.42 – 2.18 (m, 2H), 2.03 – 1.86 (m, 7H), 1.58 – 1.36 (m, 2H), 0.84 (s, 6H).

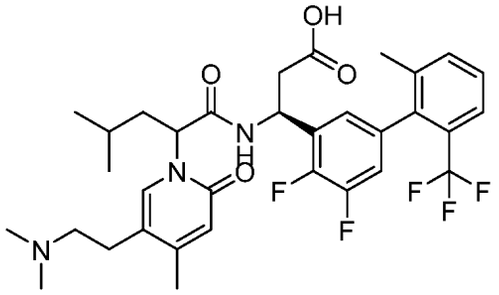
4-2. (3*S*)-3-(4,5-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BC-P1 and BC-P2)



BC-P1 ESI 612.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.63 (s, 1H), 7.45 (d, *J* = 9.3 Hz, 1H), 7.22 – 7.04 (m, 3H), 6.98 – 6.87 (m, 1H), 6.80 (d, *J* = 5.1 Hz, 1H), 6.43 (d, *J* = 9.3 Hz, 1H), 5.68 – 5.57 (m, 1H), 5.50 (d, *J* = 5.7 Hz, 1H), 5.29 (d, *J* = 53.5 Hz, 1H), 3.48 – 3.33 (m, 1H), 3.31 – 3.02 (m, 5H), 2.83 – 2.57 (m, 4H), 2.42 – 2.10 (m, 2H), 2.05 – 1.81 (m, 8H), 1.51 – 1.35 (m, 1H), 0.98 – 0.79 (m, 6H).

BC-P2 ESI 612.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.61 (s, 1H), 7.47 (d, *J* = 9.3 Hz, 1H), 7.19 – 7.00 (m, 3H), 6.97 – 6.90 (m, 1H), 6.86 (d, *J* = 4.7 Hz, 1H), 6.51 (d, *J* = 9.2 Hz, 1H), 5.66 – 5.52 (m, 2H), 5.36 (s, 1H), 3.66 – 3.32 (m, 5H), 3.16 (s, 1H), 2.83 (s, 2H), 2.63 – – 2.42 (m, 2H), 2.30 (d, *J* = 29.3 Hz, 2H), 2.05 – 1.85 (m, 8H), 1.45 – 1.30 (m, 1H), 0.88 (t, *J* = 6.1 Hz, 6H).

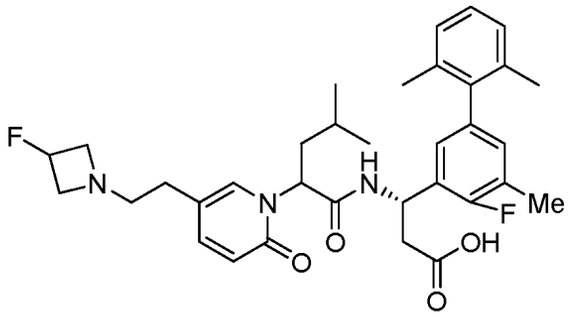
4-3. (3*S*)-3-(4,5-difluoro-2'-methyl-6'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BD-P1 and BD-P2)



BD-P1 ESI 636.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.65 – 7.46 (m, 4H), 7.03 – 6.87 (m, 2H), 6.30 (d, *J* = 21.6 Hz, 1H), 5.55-5.52 (m, 2H), 3.18 – 3.02 (m, 2H), 2.88-2.84 (m, 2H), 2.78 (s, 3H)), 2.75(S,3H), 2.67-2.64 (m, 2H), 2.25 (s, 3H), 2.06 (s, 2H), 1.97 – 1.85 (m, 3H), 1.45 – 1.35 (m, 1H), 0.94-0.90 (m, 6H).

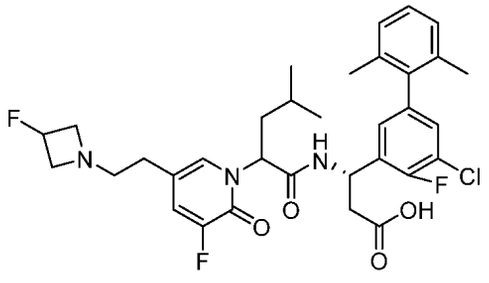
BD-P2 ESI 636.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.67 – 7.44 (m, 4H), 7.08 – 6.91 (m, 2H), 6.42 (d, *J* = 20.9 Hz, 1H), 5.70 – 5.51 (m, 2H), 3.32 – 3.23 (m, 1H), 3.20-3.18 (m, 1H), 2.99 – 2.74 (m, 8H), 2.64-2.59 (m, 1H), 2.52-2.47 (m, 1H), 2.28-2.26 (d, J = 10.0 Hz, 3H), 2.07-2.06 (d, *J* = 6.6 Hz, 3H), 2.00 – 1.88 (m, 1H), 1.81 – 1.65 (m, 1H), 1.43 – 1.32 (m, 1H), 0.90-0.87 (m, 6H).

4-4. (3*S*)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BE-P1 and BE-P2)



BE-P1 ESI 594.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.52 (d, *J* = 2.1 Hz, 1H), 7.47 – 7.39 (m, 1H), 7.19 – 7.02 (m, 3H), 6.89 (d, *J* = 5.6 Hz, 1H), 6.83 – 6.73 (m, 1H), 6.48 (d, *J* = 9.3 Hz, 1H), 5.69 – 5.57 (m, 1H), 5.54 – 5.43 (m, 1H), 5.33 – 5.09 (m, 1H), 4.20 – 4.06 (m, 1H), 4.03 – 3.87 (m, 1H), 3.78 – 3.63 (m, 2H), 3.27 – 3.06 (m, 2H), 2.77 – 2.53 (m, 4H), 2.31 (d, *J* = 1.3 Hz, 3H), 2.03 – 1.85 (m, 8H), 1.58 – 1.34 (m, 1H), 1.03 – 0.84 (m, 6H).
BE-P2 ESI 594.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.57 – 7.41 (m, 2H), 7.23 – 7.05 (m, 3H), 6.92 (d, *J* = 6.9 Hz, 2H), 6.56 (d, *J* = 9.3 Hz, 1H), 5.67 – 5.57 (m, 2H), 5.46 – 5.17 (m, 1H), 4.50 – 4.24 (m, 2H), 4.08 – 3.89 (m, 2H), 3.42 – 3.35 (m, 2H), 2.86 – 2.60 (m, 3H), 2.57 – 2.45 (m, 1H), 2.33 (s, 3H), 2.05 – 1.91 (m, 7H), 1.86 – 1.71 (m, 1H), 1.48 – 1.32 (m, 1H), 0.91 (t, *J* = 6.3 Hz, 6H).

4-5. (3*S*)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BD2-P1 and BD2-P2)

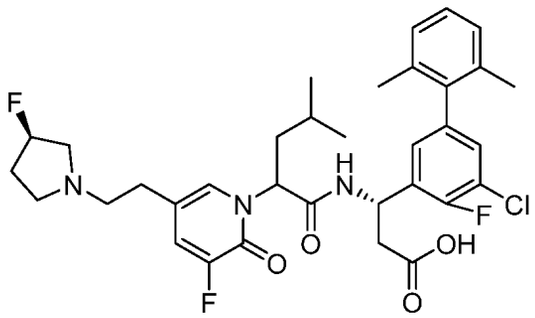


BD2-P1 ESI 632.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.69 – 7.28 (m, 2H), 7.23 – 7.05 (m, 4H), 6.97 (dd, *J* = 6.3, 1.9 Hz, 1H), 5.69 (dd, *J* = 9.4, 6.8 Hz, 1H), 5.52 (t, *J* = 6.4 Hz, 1H), 5.25 (dt, *J* = 57.2, 4.2 Hz, 1H), 4.15 (dt, *J* = 44.5, 9.1 Hz, 2H), 3.96 – 3.70 (m, 2H), 3.23

(dt, *J* = 11.3, 5.6 Hz, 2H), 2.94 – 2.45 (m, 4H), 2.13 – 1.80 (m, 8H), 1.59 – 1.25 (m, 1H), 1.15 – 0.78 (m, 6H).

BD2-P2 ESI 632.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.54 – 7.27 (m, 2H), 7.14 (dt, *J* = 12.8, 6.1 Hz, 5H), 5.87 – 5.52 (m, 2H), 5.30 (dt, *J* = 57.3, 4.4 Hz, 1H), 4.43 – 4.14 (m, 2H), 4.06 – 3.75 (m, 2H), 3.33 – 3.25 (m, 2H), 2.87 – 2.40 (m, 4H), 2.17 – 1.85 (m, 7H), 1.88 – 1.67 (m, 1H), 1.50 – 1.22 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H).

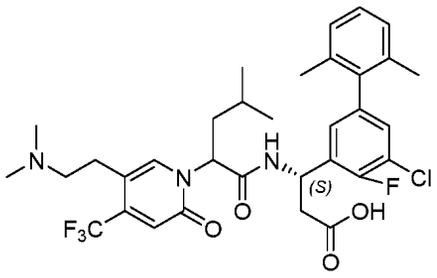
4-6. (3*S*)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BE2-P1 and BE2-P2)



BE2-P1 ESI 646.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.51 (s, 1H), 7.37 (d, *J* = 10.2 Hz, 1H), 7.16 – 7.08 (m, 4H), 6.98 – 6.97 (m, 1H), 5.71 – 5.67 (m, 1H), 5.52 – 5.49 (m, 1H), 5.35 – 5.21 (m, 1H), 3.41 – 3.12 (m, 6H), 2.81 – 2.69 (m, 4H), 2.37 – 2.20 (m, 2H), 2.05 – 1.88 (m, 8H), 1.44 – 1.40 (m, 1H), 0.96 – 0.92 (m, 6H).

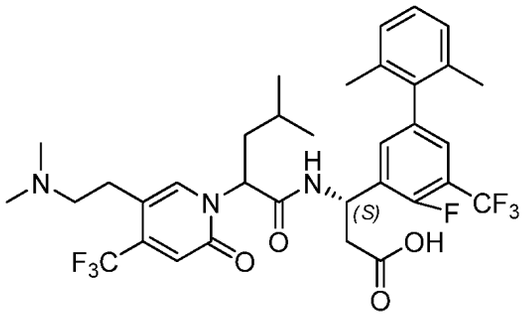
BE2-P2 ESI 646.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.51 (s, 1H), 7.40 (d, *J* = 10.2 Hz, 1H), 7.18 – 7.06 (m, 5H), 5.70 – 5.58 (m, 2H), 5.41 – 5.27 (m, 1H), 3.67 – 3.21 (m, 6H), 2.88 – 2.83 (m, 2H), 2.60 – 2.53 (m, 2H), 2.39 – 2.27 (m, 2H), 1.97 – 1.83 (m, 7H), 1.83 – 1.76 (m, 1H), 1.40 – 1.35 (m, 1H), 0.91 – 0.89 (m, 6H).

4-7. (3*S*)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BF-P1 and BF-P2)



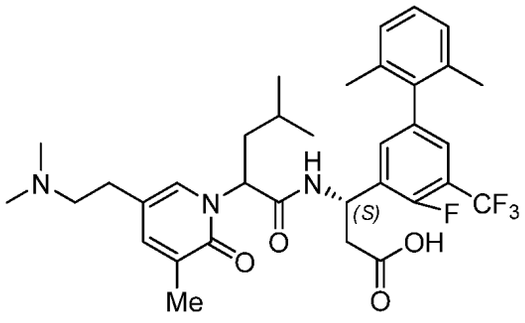
BF-P1 ESI 652.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.11– 7.03 (m, 5H), 6.75 (s, 1H), 5.82 – 5.62 (m, 1H), 5.62 – 5.46 (m, 1H), 3.21 – 2.89 (m, 4H), 2.83 (s, 6H), 2.77 – 2.72 (m, 2H), 2.05 – 1.89 (m, 5H), 1.83 (s, 3H), 1.46 – 1.40 (m, 1H), 0.98 – 0.93 (m, 6H).
BF-P2 ESI 652.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.24 – 7.04 (m, 5H), 6.89 (s, 1H), 5.75 – 5.70 (m, 1H), 5.66 – 5.62 (m, 1H), 3.29 – 3.21 (m, 2H), 3.09 – 2.98(m, 2H), 2.84 (d, J = 5.9 Hz, 6H), 2.68 – 2.53 (m, 2H), 2.03 – 1.86 (m, 7H), 1.76 – 1.69 (m, 1H), 1.42 – 1.33 (m, 1H), 0.88 – 0.86 (m, 6H).

4-8. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (diastereomeric compounds BG-P1 and BG-P2)



BG-P1 ESI 686.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.39 (d, J = 4.8 Hz, 1H), 7.31 (d, J = 6.3 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 7.1 Hz, 1H), 7.09 (d, J = 7.4 Hz, 1H), 6.73 (s, 1H), 5.73 – 5.64 (m, 1H), 5.62 – 5.59 (m, 1H), 3.17 – 3.12 (m, 2H), 2.97 (d, J = 8.4 Hz, 2H), 2.80 (d, J = 11.1 Hz, 6H), 2.76 – 2.73 (m, 2H), 2.11 – 1.89 (m, 5H), 1.82 (s, 3H), 1.47 – 1.41 (m, 1H), 0.98 – 0.93 (m, 6H).
BG-P2 ESI 686.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.44 (d, J = 5.4 Hz, 1H), 7.38 (d, J = 6.6 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.14 (d, J = 7.3 Hz, 2H), 6.90 (s, 1H), 5.76 – 5.72(m, 1H), 5.64 (t, J = 7.7 Hz, 1H), 3.25 (d, J = 8.1 Hz, 2H), 3.00 (t, J = 7.0 Hz, 2H), 2.85 (s, 6H), 2.71 – 2.66 (m, 1H), 2.61 – 2.54 (m, 1H), 2.02 (d, J = 2.4 Hz, 6H), 1.99 – 1.94 (m, 1H), 1.78 – 1.68 (m, 1H), 1.46 – 1.30 (m, 1H), 0.91 – 0.89 (m, 6H).

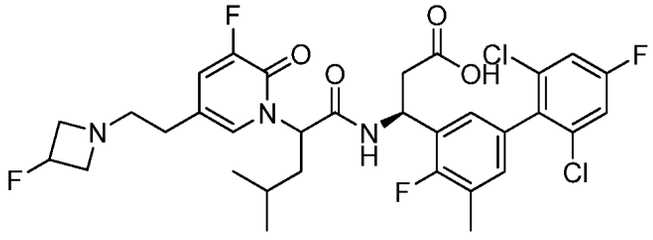
4-9. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',6'-dimethyl-5-(trifluoromethyl)biphenyl-3-yl)propanoic acid (diastereomeric compounds BH-P1 and BH-P2)



BH-P1 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.42 (s, 1H), 7.32 (d, *J* = 4.9 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.17 – 7.10 (m, 2H), 5.52 (s, 1H), 5.45 (t, *J* = 5.3 Hz, 1H), 3.37 (d, *J* = 7.6 Hz, 1H), 3.32 – 3.29 (m, 1H), 3.27 – 3.17 (m, 1H), 2.82 (t, *J* = 6.5 Hz, 2H), 2.74 (s, 6H), 2.71 – 2.66 (m, 1H), 2.56 – 2.51 (m, 1H), 2.03 (d, *J* = 14.9 Hz, 1H), 1.97 (d, *J* = 7.2 Hz, 6H), 1.94 (s, 3H), 1.44 – 1.39 (m, 1H), 0.95 – 0.90 (m, 6H).

BH-P2 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.44 (d, *J* = 4.8 Hz, 1H), 7.38 (d, *J* = 6.5 Hz, 1H), 7.22 – 7.18 (m, 1H), 7.14 (d, *J* = 7.2 Hz, 2H), 6.90 (s, 1H), 5.76 – 5.72 (m, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 3.35 (s, 3H), 3.25 (s, 2H), 3.00 (t, *J* = 7.1 Hz, 2H), 2.86 (s, 6H), 2.70 – 2.54 (m, 2H), 2.02 (d, *J* = 2.4 Hz, 6H), 1.99 – 1.92 (m, 1H), 1.77 – 1.72 (m, 1H), 1.46 – 1.30 (m, 1H), 0.91 – 0.89 (m, 6H).

4-10. (3*S*)-3-(2',6'-dichloro-4,4'-difluoro-5-methylbiphenyl-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BI-P1 and BI-P2)

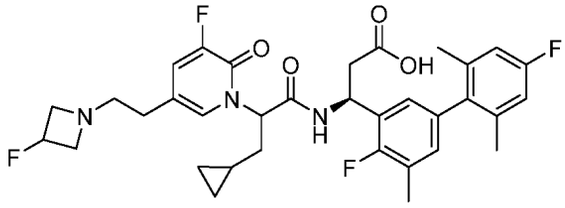


GI-P1 ESI 670.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.42 (s, 1H), 7.40 – 7.32 (m, 3H), 7.01 (d, *J* = 6.7 Hz, 1H), 6.96 (d, *J* = 6.6 Hz, 1H), 5.70 (t, *J* = 8.1 Hz, 1H), 5.59 – 5.46 (m, 1H), 5.32 – 5.08 (m, 1H), 4.18 – 3.92 (m, 2H), 3.82 – 3.57 (m, 2H), 3.22 – 3.03 (m, 2H), 2.79

– 2.53 (m, 4H), 2.31 (d, *J* = 1.3 Hz, 3H), 1.97 (t, *J* = 7.6 Hz, 2H), 1.51 – 1.33 (m, 1H), 1.01 – 0.86 (m, 6H).

GI-P2 ESI 670.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.45 – 7.31 (m, 4H), 7.14 – 6.99 (m, 2H), 5.75 – 5.61 (m, 2H), 5.42 – 5.18 (m, 1H), 4.44 – 4.21 (m, 2H), 4.11 – 3.85 (m, 2H), 3.36 – 3.34 (m, 2H), 2.80 – 2.44 (m, 4H), 2.34 (d, *J* = 1.3 Hz, 3H), 2.03 – 1.90 (m, 1H), 1.83 – 1.70 (m, 1H), 1.47 – 1.30 (m, 1H), 0.99 – 0.86 (m, 6H).

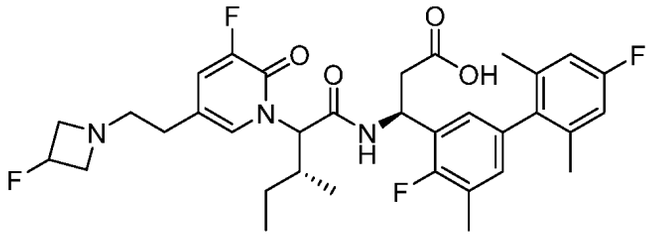
4-11. (3*S*)-3-(3-cyclopropyl-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)propanamido)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds BJ-P1 and BJ-P2)



BJ-P1 ESI 628.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.37 (s, 1H), 7.26 (d, *J* = 10.2 Hz, 1H), 6.91 – 6.64 (m, 4H), 5.55 (t, *J* = 7.6 Hz, 1H), 5.48 – 5.40 (m, 1H), 5.13 (d, *J* = 57.3 Hz, 1H), 3.98 (d, *J* = 16.3 Hz, 2H), 3.63 (s, 2H), 3.03 (d, *J* = 6.5 Hz, 2H), 2.74 – 2.59 (m, 2H), 2.59 – 2.50 (m, 3H), 1.99 – 1.85 (m, 5H), 1.81 (d, *J* = 9.0 Hz, 3H), 0.56 (d, *J* = 7.3 Hz, 1H), 0.36 (d, *J* = 8.0 Hz, 2H), 0.13 – -0.07 (m, 2H).

BJ-P2 ESI 628.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.50 – 7.28 (m, 2H), 7.03 – 6.71 (m, 4H), 5.75 – 5.55 (m, 2H), 5.30 (d, *J* = 57.3 Hz, 1H), 4.47 – 4.17 (m, 2H), 4.12 – 3.75 (m, 2H), 3.44 – 3.32 (m, 2H), 2.82 – 2.46 (m, 4H), 2.32 (s, 3H), 2.18 – 1.91 (m, 7H), 1.77 – 1.60 (m, 1H), 0.58 (s, 1H), 0.42 – 0.23 (m, 2H), 0.15 – -0.07 (m, 2H).

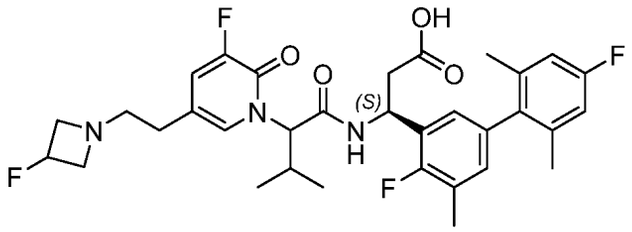
4-12. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-((3*R*)-2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylpentanamido)propanoic acid (diastereomeric compounds BK-P1 and BK-P2)



BK-P1 ESI 630.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.31-7.28 (m, 1H), 6.86-6.76 (m, 4H), 5.66 – 5.55 (m, 1H), 5.35-5.33 (d, *J* = 11.2 Hz, 1H), 5.23.5.09 (m, 1H), 3.85-3.80 (m, 2H), 3.52-3.49 (m, 2H), 2.91-2.88 (t, *J* = 6.7 Hz, 2H), 2.80 – 2.78 (m, 2H), 2.55-2.52 (t, *J* = 7.1 Hz, 2H), 2.28 (d, J = 1.5 Hz, 4H), 1.98 (s, 3H), 1.75 (s, 3H), 1.69-1.68 (m, 1H), 1.30-1.26 (m, 1H), 1.03-0.99 (t, *J* = 7.4 Hz, 3H), 0.75-0.74 (d, *J* = 6.6 Hz, 3H).

BK-P2 ESI 630.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.46 (s, 1H), 7.36-7.34 (d, *J* = 10.3 Hz, 1H), 7.00-6.93 (dd, *J* = 20.7, 6.6 Hz, 2H), 6.86-6.84 (d, *J* = 9.6 Hz, 2H), 5.75-5.72 (dd, *J* = 10.3, 4.1 Hz, 1H), 5.39 – 5.23 (m, 2H), 4.47 – 4.22 (m, 2H), 4.09 – 3.85 (m, 2H), 3.30-3.28 (m, 2H), 2.75-2.72 (m, 2H), 2.67 – 2.47 (m, 2H), 2.41 – 2.20 (m, 4H), 2.02 (s, 6H), 1.17-1.10 (m, 1H), 1.08 – 0.88 (m, 4H), 0.85-0.81 (t, *J* = 7.2 Hz, 3H).

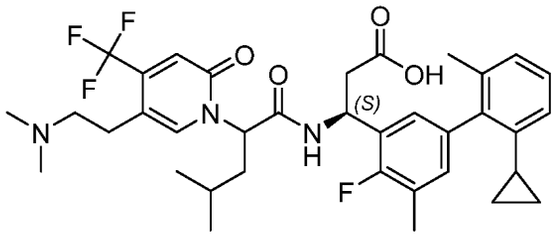
4-13. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-3-methylbutanamido)propanoic acid (diastereomeric compounds BL-P1 and BL-P2)



BL-P1 ESI 616.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.29 (d, *J* = 10.9 Hz, 1H), 6.94 – 6.65 (m, 4H), 5.62 (s, 1H), 5.26 (d, *J* = 11.1 Hz, 1H), 5.07 (s, 1H), 3.75 (s, 2H), 3.15 (s, 1H), 2.78 (s, 5H), 2.48 (d, *J* = 31.1 Hz, 3H), 2.28 (s, 3H), 1.98 (s, 3H), 1.74 (s, 3H), 1.14 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H).

BL-P2 ESI 616.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.44 (s, 1H), 7.40 – 7.28 (m, 1H), 7.02 – 6.72 (m, 4H), 5.88 – 5.62 (m, 1H), 5.38 (s, 2H), 5.24 (d, *J* = 11.0 Hz, 2H), 4.32 (s, 2H), 3.97 (s, 2H), 2.74 (d, *J* = 5.1 Hz, 2H), 2.66 – 2.39 (m, 3H), 2.33 (d, *J* = 1.6 Hz, 3H), 2.01 (d, *J* = 3.3 Hz, 6H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.75 (d, *J* = 6.7 Hz, 3H).

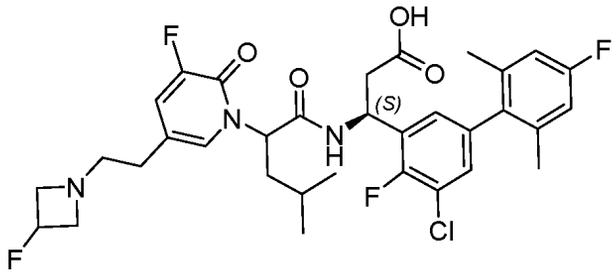
4-14. (3*S*)-3-(2'-cyclopropyl-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BM-P1 and BM-P2)



BM-P1 ESI 658.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.91 (d, *J* = 5.9 Hz, 1H), 7.13 (t, *J* = 7.7 Hz, 1H), 7.07 – 6.87 (m, 3H), 6.76 (d, *J* = 11.4 Hz, 2H), 5.83 – 5.64 (m, 1H), 5.57 (t, *J* = 5.9 Hz, 1H), 3.18 – 2.98 (m, 2H), 2.94 (d, *J* = 7.1 Hz, 2H), 2.82 (d, *J* = 4.7 Hz, 1H), 2.80 – 2.48 (m, 8H), 2.32 (d, *J* = 17.2 Hz, 3H), 2.12 – 1.89 (m, 3H), 1.81 (s, 1H), 1.57 – 1.26 (m, 2H), 1.02 – 0.83 (m, 6H), 0.75 – 0.61 (m, 1H), 0.60 – 0.22 (m, 3H).

BM-P2 ESI 658.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (d, *J* = 11.7 Hz, 1H), 7.28 – 6.65 (m, 6H), 5.82 – 5.43 (m, 2H), 3.30 – 3.09 (m, 2H), 2.99 (t, *J* = 6.9 Hz, 2H), 2.80 (d, *J* = 2.6 Hz, 6H), 2.70 – 2.42 (m, 2H), 2.33 (d, *J* = 1.6 Hz, 3H), 2.10 – 1.90 (m, 4H), 1.80 – 1.60 (m, 1H), 1.55 – 1.28 (m, 2H), 1.00 – 0.80 (m, 6H), 0.79 – 0.45 (m, 4H).

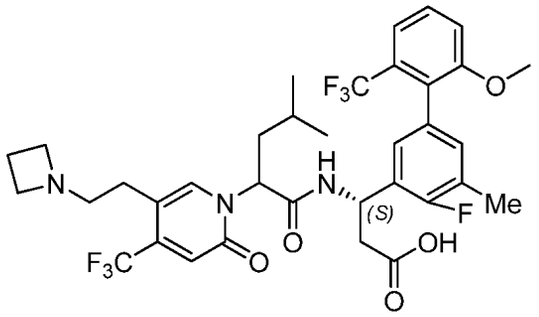
4-15. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BN-P1 and BN-P2)



BN-P1 ESI 650.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.38 (s, 1H), 7.34 – 7.27 (m, 1H), 7.12 – 7.06 (m, 1H), 6.96 – 6.88 (m, 1H), 6.81 (d, *J* = 9.6 Hz, 2H), 5.65 – 5.52 (m, 1H), 5.45 (t, *J* = 6.3 Hz, 1H), 5.18 (d, *J* = 57.7 Hz, 1H), 4.14 – 3.88 (m, 2H), 3.72 (s, 2H), 3.10 (s, 2H), 2.78 – 2.52 (m, 4H), 2.02 – 1.75 (m, 8H), 1.46 – 1.28 (m, 1H), 0.98 – 0.76 (m, 6H).

BN-P2 ESI 650.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.19 – 7.09 (m, 1H), 7.06 – 6.94 (m, 1H), 6.83 (d, *J* = 9.6 Hz, 2H), 5.70 – 5.51 (m, 2H), 5.27 (d, *J* = 57.4 Hz, 1H), 4.32 (s, 2H), 4.00 (s, 2H), 2.76 – 2.35 (m, 4H), 1.96 (d, *J* = 13.7 Hz, 6H), 1.94 – 1.85 (m, 1H), 1.80 – 1.67 (m, 1H), 1.39 – 1.24 (m, 1H), 0.96 – 0.63 (m, 6H).

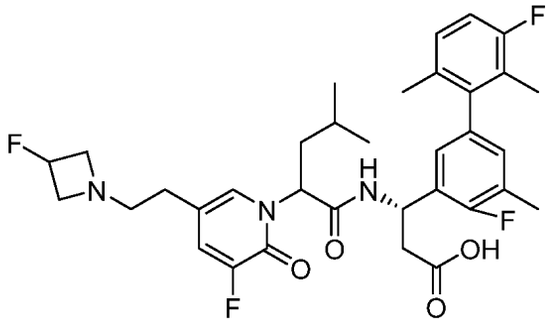
4-16. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2'-methoxy-5-methyl-6'-(trifluoromethyl)biphenyl-3-yl)propanoic acid (diastereomeric compounds BO-P1 and BO-P2)



BO-P1 ESI 714.2 $(M+H)^+$. 1H NMR (500 MHz, MeOD) δ 7.83 (d, *J* = 6.8 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.41 – 7.25 (m, 2H), 7.04 – 6.96 (m, 1H), 6.93 (t, *J* = 7.0 Hz, 1H), 6.82 (d, *J* = 10.1 Hz, 1H), 5.74 – 5.60 (m, 2H), 4.09 – 3.89 (m, 4H), 3.72 (d, *J* = 21.5 Hz, 3H), 3.32 – 3.19 (m, 2H), 2.94 – 2.81 (m, 2H), 2.77 – 2.62 (m, 2H), 2.50 – 2.34 (m, 2H), 2.29 (s, 3H), 2.06 – 1.89 (m, 2H), 1.53 – 1.32 (m, 1H), 0.96-0.92 (m, 6H).

BO-P2 ESI 714.1 $(M+H)^+$. ^{1}H NMR (500 MHz, MeOD) δ 7.71 (d, *J* = 4.3 Hz, 1H), 7.54 (t, *J* = 8.2 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.97 (d, *J* = 6.6 Hz, 1H), 6.91 (d, *J* = 4.9 Hz, 1H), 5.85 – 5.72 (m, 1H), 5.63 – 5.59 (m, 1H), 4.14 (s, 4H), 3.75 (d, *J* = 2.7 Hz, 3H), 3.40 (d, *J* = 25.2 Hz, 2H), 2.94 (d, *J* = 16.0 Hz, 1H), 2.82 (d, *J* = 9.4 Hz, 1H), 2.70 – 2.57 (m, 1H), 2.54 – 2.42 (m, 3H), 2.32 (s, 3H), 2.08 – 1.91 (m, 1H), 1.70 – 1.57 (m, 1H), 1.46 – 1.41 (m, 1H), 0.91 (t, *J* = 4.9 Hz, 6H).

4-17. (3*S*)-3-(3',4-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds BP-P1 and BP-P2)

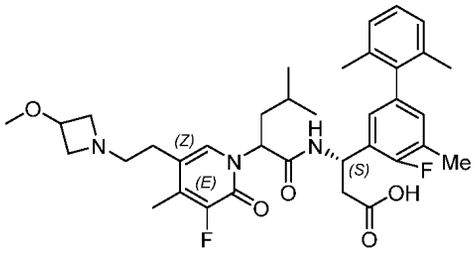


BP-P1 ESI 630.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.42 (s, 1H), 7.34 (d, *J* = 10.6 Hz, 1H), 7.15 – 7.02 (m, 1H), 7.01 – 6.76 (m, 3H), 5.67 (t, *J* = 7.6 Hz, 1H), 5.51 (s, 1H), 5.20 (d, *J* = 57.8 Hz, 1H), 4.00 (d, *J* = 43.3 Hz, 2H), 3.76 – 3.45 (m, 2H), 3.09 (d, *J* = 5.7 Hz, 2H),

2.84 – 2.50 (m, 4H), 2.31 (s, 3H), 2.02 – 1.64 (m, 8H), 1.48 – 1.18 (m, 1H), 1.06 – 0.77 (m, 6H).

BP-P2 ESI 630.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.37 (d, *J* = 10.7 Hz, 2H), 7.16 – 7.03 (m, 1H), 6.95 (t, *J* = 8.9 Hz, 3H), 5.75 – 5.52 (m, 2H), 5.30 (d, *J* = 57.4 Hz, 1H), 4.30 (d, *J* = 18.4 Hz, 2H), 3.97 (s, 2H), 3.31 – 3.14 (m, 2H), 2.84 – 2.42 (m, 4H), 2.34 (d, *J* = 1.3 Hz, 3H), 2.03 – 1.84 (m, 7H), 1.83 – 1.66 (m, 1H), 1.50 – 1.21 (m, 1H), 0.99 – 0.75 (m, 6H).

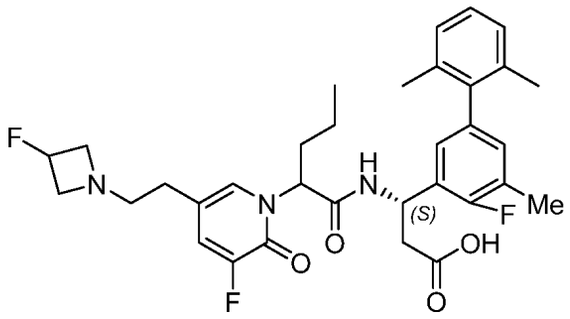
4-18. (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (compounds BQ-P1 and BQ-P2)



BQ-P1 ESI 638.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.39 (s, 1H), 7.16 – 7.04 (m, 3H), 6.88 (t, *J* = 7.3 Hz, 2H), 5.64-5.53 (m, 2H), 4.24-4.08 (m, 3H), 3.73-3.61 (m, 2H), 3.30-3.26 (m, 5H), 2.83 – 2.67 (m, 4H), 2.31 (s, 3H), 2.24 (t, *J* = 6.7 Hz, 3H), 2.02 – 1.92 (m, 8H), 1.40-1.35 (m, 1H), 0.96-0.90 (m, 6H).

BQ-P2 ESI 638.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.20 (s, 1H), 7.04-6.94 (m, 3H), 6.84-6.80 (t, *J* = 7.6 Hz, 2H), 5.61 – 5.42 (m, 2H), 4.37 – 4.09 (m, 3H), 3.83-3.70 (m, 2H), 3.38-3.22(m,5H), 2.83-2.32(m,4H), 2.22 (d, *J* = 1.6 Hz, 3H), 2.10 (d, *J* = 2.8 Hz, 3H), 1.96 – 1.80 (m, 7H), 1.63 – 1.52 (m, 1H), 1.32 – 1.19 (m, 1H), 0.79-0.78 (m, 6H).

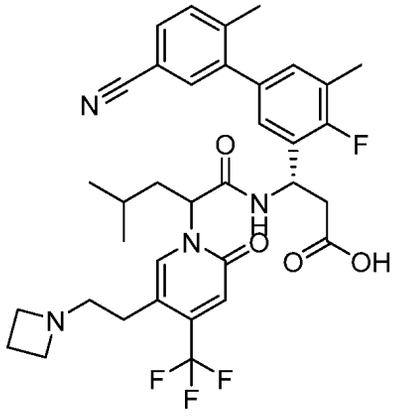
4-19. (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pentanamido)propanoic acid (diastereomeric compounds BR-P1 and BR-P2)



BR-P1 ESI 598.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.49 – 7.23 (m, 2H), 7.19 – 7.00 (m, 3H), 6.96 – 6.66 (m, 2H), 5.74 – 5.44 (m, 2H), 5.19 (d, *J* = 57.3 Hz, 1H), 3.94 (s, 2H), 3.77 – 3.41 (m, 2H), 3.18 – 3.00 (m, 2H), 2.87 – 2.47 (m, 4H), 2.38 – 2.22 (m, 3H), 2.22 – 2.06 (m, 1H), 2.06 – 1.73 (m7H), 1.44 – 1.20 (m, 2H), 1.06 – 0.78 (m, 3H).

BR-P2 ESI 598.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.44 – 7.29 (m, 2H), 7.18 – 7.01 (m, 3H), 6.99 – 6.79 (m, 2H), 5.73 – 5.49 (m, 2H), 5.24 (d, *J* = 57.6 Hz, 1H), 4.11 (s, 2H), 3.73 (d, *J* = 9.2 Hz, 2H), 3.14 (d, *J* = 6.1 Hz, 2H), 2.75 – 2.48 (m, 4H), 2.33 (d, *J* = 1.7 Hz, 3H), 2.16 – 2.04 (m, 1H), 2.02 (t, *J* = 8.9 Hz, 6H), 1.91 – 1.76 (m, 1H), 1.35 – 1.12 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H).

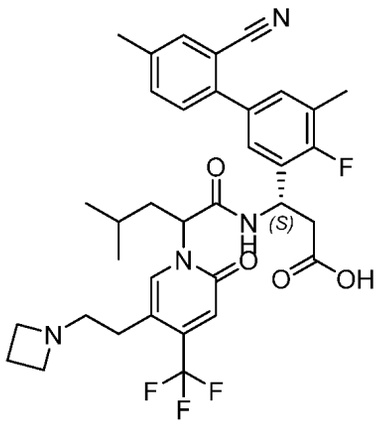
4-20. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5'-cyano-4-fluoro-2',5-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds BS-P1 and BS-P2)



BS-P1 ESI 655.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.69 – 7.57 (m, 1H), 7.54 (s, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.17 – 7.01 (m, 2H), 6.82 (s, 1H), 5.75 – 5.43 (m, 2H), 4.04 (t, *J* = 8.1 Hz, 4H), 3.15 (s, 2H), 2.85 (t, *J* = 6.9 Hz, 2H), 2.78 – 2.61 (m, 2H), 2.52 – 2.37 (m, 2H), 2.31 (d, *J* = 7.7 Hz, 6H), 2.11 – 1.90 (m, 2H), 1.42 (d, *J* = 7.2 Hz, 1H), 0.96 (t, *J* = 6.4 Hz, 6H).

BS-P2 ESI 655.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.68 – 7.60 (m, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 6.7 Hz, 2H), 6.93 (s, 1H), 5.83 – 5.71 (m, 1H), 5.64 (t, *J* = 7.7 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 4H), 3.42 (d, *J* = 15.1 Hz, 2H), 3.01 – 2.75 (m, 2H), 2.70 – 2.42 (m, 4H), 2.41 – 2.26 (m, 6H), 2.10 – 1.93 (m, 1H), 1.79 – 1.63 (m, 1H), 1.55 – 1.29 (m, 1H), 0.93 (t, *J* = 6.4 Hz, 6H).

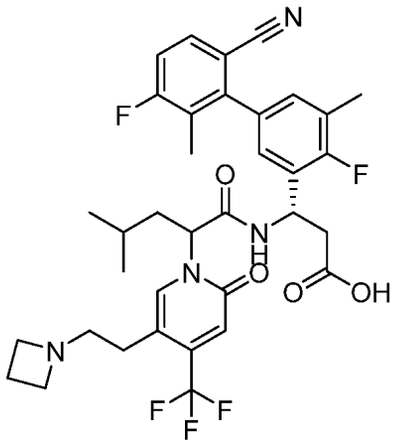
4-21. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-cyano-4-fluoro-4',5-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds BT-P1 and BT-P2)



BT-P1 ESI 655.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.60 (s, 1H), 7.47 (s, 1H), 7.36 – 7.30 (s, 3H), 6.74 (s, 1H), 5.78 – 5.59 (m, 2H), 3.84 – 3.80 (m, 4H), 3.15 – 3.10 (m, 2H), 2.75 – 2.72 (m, 4H), 2.43 (s, 3H), 2.34 – 2.30 (m, 5H), 2.06 – 2.01 (m, 2H), 1.40 – 1.37 (m, 1H), 0.99 – 0.96 (m, 6H).

BT-P2 ESI 655.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.66 (s, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.51 – 7.34 (m, 3H), 6.92 (s, 1H), 5.75 – 5.69 (m, 2H), 4.05 – 4.01 (m, 4H), 2.95 – 2.55 (m, 5H), 2.46 – 2.37 (m, 9H), 2.06 – 1.96 (m, 1H), 1.85 – 1.75 (m, 1H), 1.49 – 1.37 (m, 1H),), 0.94 – 0.92 (m, 6H).

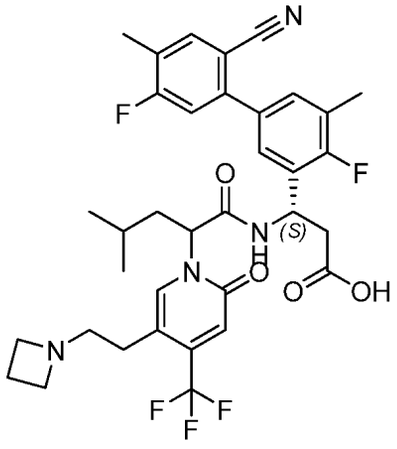
4-22. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(6'-cyano-3',4-difluoro-2',5-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds BU-P1 and BU-P2)



BU-P1 ESI 673.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.71-7.62 (m, 1H), 7.31-7.27 (t, *J* = 8.8 Hz, 1H), 7.14-7.10 (m, 2H), 6.80-6.75 (d, *J* = 22.1 Hz, 1H), 5.76-5.62 (m, 2H), 4.02-3.97 (m, 4H), 3.32-3.15 (m, 2H), 2.95 – 2.60 (m, 4H), 2.51 – 2.25 (m, 5H), 2.11 – 1.93 (m, 5H), 1.45-1.44 (m, 1H), 0.97-0.96 (m, 6H).

BU-P2 ESI 673.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.81 – 7.66 (m, 2H), 7.37 – 7.08 (m, 3H), 6.92 (s, 1H), 5.85 – 5.56 (m, 2H), 4.16-4.10 (m, 4H), 3.43-3.42 (m, 2H), 3.02 – 2.75 (m, 2H), 2.66 (d, *J* = 12.1 Hz, 1H), 2.62 – 2.30 (m, 6H), 2.18 – 1.95 (m, 4H), 1.80 – 1.64 (m, 1H), 1.45-1.38 (m, 1H), 0.92-0.91 (m, 6H).

4-23. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-cyano-4,5'-difluoro-4',5-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds BV-P1 and BV-P2)

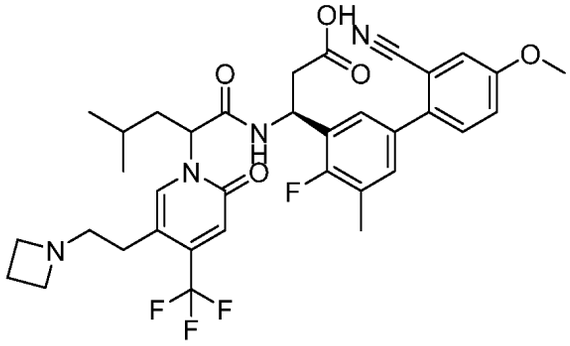


BV-P1 ESI 673.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.96 (s, 1H), 7.73 – 7.46 (m, 2H), 7.31 (d, *J* = 4.5 Hz, 1H), 7.07 – 6.69 (m, 1H), 5.75 (s, 1H), 5.62 (t, *J* = 6.8 Hz, 1H), 3.96 (s,

4H), 3.27 – 3.11 (m, 2H), 2.92 – 2.58 (m, 4H), 2.45 – 2.21 (m, 8H), 2.12 – 1.91 (m, 2H), 1.41 (s, 1H), 1.04 – 0.88 (m, 6H).

BV-P2 ESI 673.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.72 (s, 1H), 7.47 – 7.38 (m, 2H), 7.32 (d, *J* = 10.2 Hz, 1H), 6.93 (s, 1H), 5.78 – 5.65 (m, 2H), 4.13 (t, *J* = 8.0 Hz, 4H), 3.48 – 3.35 (m, 2H), 2.99 – 2.75 (m, 2H), 2.70 – 2.42 (m, 4H), 2.37 (s, 6H), 2.11 – 1.93 (m, 1H), 1.85 – 1.71 (m, 1H), 1.51 – 1.30 (m, 1H), 1.05 – 0.85 (m, 6H).

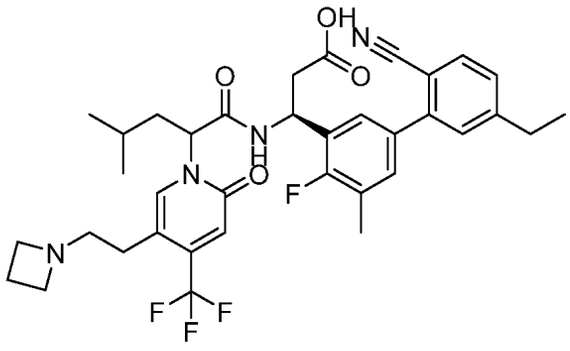
4-24. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-cyano-4-fluoro-4'-methoxy-5-methyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds BW-P1 and BW-P2)



BW-P1 ESI 671.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.93 (s, 1H), 7.44 (s, 1H), 7.26 (s, 2H), 7.15 (d, *J* = 52.3 Hz, 2H), 6.75 (s, 1H), 5.80 – 5.70 (m, 1H), 5.68 – 5.60 (m, 1H), 3.95 (d, *J* = 7.9 Hz, 4H), 3.90 (d, *J* = 10.4 Hz, 3H), 3.24 (m, 2H), 2.81 (m, 1H), 2.75 (m, 3H), 2.46 – 2.35 (m, 2H), 2.31 (s, 3H), 2.04 (m, 2H), 1.48 – 1.38 (m, 2H), 0.98 (m, 6H).

BW-P2 ESI 671.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.72 (s, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.38 (ddm, 2H), 7.35 – 7.29 (m, 2H), 6.93 (s, 1H), 5.75 (m, 1H), 5.70 (t, *J* = 7.7 Hz, 1H), 4.11 (m, 4H), 3.91 (s, 3H), 3.39 (m, 2H), 2.94 (d, *J* = 16.7 Hz, 1H), 2.86 – 2.77 (m, 1H), 2.66 (m, 1H), 2.55 (m, 1H), 2.50 – 2.41 (m, 2H), 2.37 (s, 3H), 2.02 (m, 1H), 1.83 – 1.74 (m, 1H), 1.41 (m, 2H), 0.93 (m, 6H).

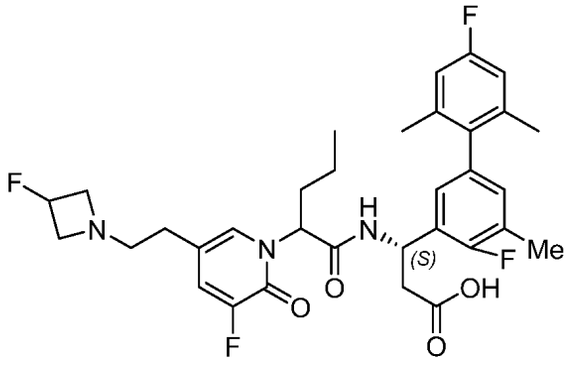
4-25. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-cyano-5'-ethyl-4-fluoro-5-methyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds BX-P1 and BX-P2)



BX-P1 ESI 669.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.96 – 7.83 (m, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.46 – 7.16 (m, 4H), 6.76 (s, 1H), 5.82 – 5.48 (m, 2H), 4.07 – 3.90 (m, 4H), 3.31 – 3.14 (m, 2H), 2.88 – 2.66 (m, 6H), 2.49 – 2.30 (m, 5H), 2.13 – 1.99 (m, 2H), 1.52 – 1.21 (m, 4H), 0.97 (d, *J* = 6.6 Hz, 6H).

BX-P2 ESI 669.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 – 7.66 (m, 2H), 7.47 – 7.28 (m, 4H), 6.93 (s, 1H), 5.73 (t, *J* = 7.7 Hz, 2H), 4.16 (t, *J* = 8.0 Hz, 4H), 3.53 – 3.34 (m, 2H), 3.04 – 2.30 (m, 11H), 2.10 – 1.93 (m, 1H), 1.89 – 1.77 (m, 1H), 1.46 – 1.23 (m, 4H), 1.01 – 0.83 (m, 6H).

4-26. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)pentanamido)propanoic acid (diastereomeric compounds BY-P1 and BY-P2)

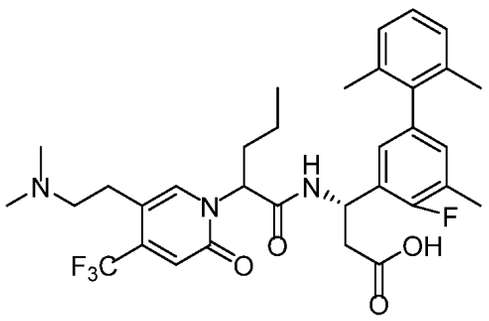


BY-P1 ESI 616.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.43 (s, 1H), 7.38 – 7.27 (m, 1H), 6.91 – 6.68 (m, 4H), 5.67 – 5.44 (m, 2H), 5.21 (d, *J* = 57.3 Hz, 1H), 4.02 (d, *J* = 35.4 Hz, 2H), 3.83 – 3.54 (m, 2H), 3.20 – 2.99 (m, 2H), 2.82 – 2.53 (m, 4H), 2.29 (d, *J* = 1.6 Hz, 3H), 2.24 – 2.08 (m, 1H), 2.05 – 1.92 (m, 4H), 1.88 (s, 3H), 1.42 – 1.21 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H).

BY-P2 ESI 616.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.44 – 7.28 (m, 2H), 7.01 – 6.76 (m, 4H), 5.69 – 5.49 (m, 2H), 5.29 (d, *J* = 57.4 Hz, 1H), 4.38 – 4.13 (m, 2H), 4.02 – 3.74 (m,

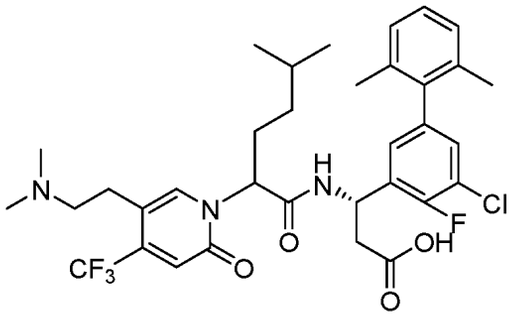
2H), 3.37 – 3.20 (m, 2H), 2.81 – 2.43 (m, 4H), 2.33 (d, *J* = 1.7 Hz, 3H), 2.16 – 2.04 (m, 1H), 2.01 (s, 6H), 1.90 – 1.77 (m, 1H), 1.35 – 1.09 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H).

4-27. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)pentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds BZ-P1 and BZ-P2)



BZ-P1 ESI 618.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.90 (s, 1H), 7.11 – 7.02 (m, 3H), 6.90 – 6.86 (m, 2H), 6.74 (s, 1H), 5.59 – 5.56 (m, 2H), 3.18 – 3.14 (m, 2H), 2.99 (d, *J* = 22.6 Hz, 2H), 2.81 (s, 6H), 2.76 – 2.73 (m, 2H), 2.29 (s, 3H), 2.19 – 2.12 (m, 1H), 2.02 – 1.95 (m, 4H), 1.80 (s, 3H), 1.37 – 1.30 (m, 2H), 0.96 (t, *J* = 7.3 Hz, 3H).
BZ-P2 ESI 618.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.86 (s, 1H), 7.14 – 7.65 (m, 3H), 6.95 – 6.89 (m, 3H), 5.73 (d, *J* = 7.3 Hz, 1H), 5.53 (t, *J* = 7.6 Hz, 1H), 3.33 – 3.20 (m, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.82 (s, 6H), 2.68 – 2.62 (m, 1H), 2.56 – 2.51 (m, 1H), 2.32 (s, 3H), 2.07 – 2.00 (m, 7H), 1.82 – 1.72 (m, 1H), 1.23 (s, 2H), 0.89 (d, *J* = 3.5 Hz, 3H).

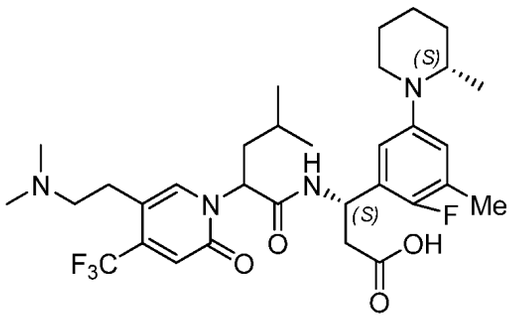
4-28. (3*S*)-3-(5-chloro-4-fluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-5-methylhexanamido)propanoic acid (diastereomeric compounds CA-P1 and CA-P2)



CA-P1 ESI 666.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.09 – 7.06 (m, 2H), 7.04 (s, 1H), 7.02 (s, 1H), 6.69 (s, 1H), 5.53 (t, *J* = 7.2 Hz, 1H), 5.49 – 5.45 (m, 1H), 3.16 – 3.04 (m, 2H), 2.94 (t, *J* = 8.0 Hz, 2H), 2.76 (s, 6H), 2.73 – 2.71 (m, 2H), 2.23 – 2.14 (m, 1H), 1.99 (s, 3H), 1.97 – 1.91 (m, 1H), 1.79 (s, 3H), 1.63 – 1.51 (m, 1H), 1.27 – 1.18 (m, 1H), 1.13 – 1.04 (m, 1H), 0.88 (d, *J* = 3.2 Hz, 3H), 0.86 (d, *J* = 3.6 Hz, 3H).

CA-P2 ESI 666.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.17 – 7.13 (m, 2H), 7.10 – 7.08 (m, 3H), 6.88 (s, 1H), 5.71 – 5.68 (m, 1H), 5.46 (t, *J* = 7.4 Hz, 1H), 3.28 – 3.15 (m, 2H), 2.98 (t, *J* = 7.0 Hz, 2H), 2.81 (s, 6H), 2.68 – 2.63 (m, 1H), 2.58 – 2.52 (m, 1H), 2.16 – 2.05 (m, 1H), 2.01 (s, 3H), 2.00 (s, 3H), 1.83 – 1.74 (m, 1H), 1.56 – 1.46 (m, 1H), 1.16 – 0.99 (m, 2H), 0.82 (d, *J* = 5.2 Hz, 3H), 0.80 (d, *J* = 4.8 Hz, 3H).

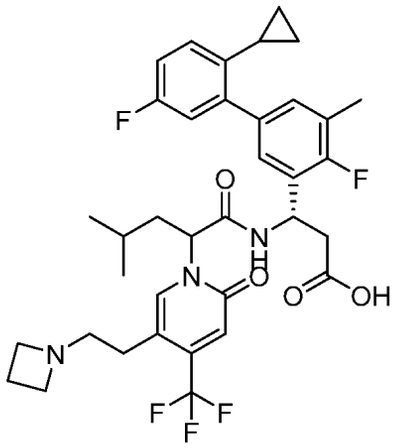
4-29. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2-fluoro-3-methyl-5-((*S*)-2-methylpiperidin-1-yl)phenyl)propanoic acid (diastereomeric compounds CB-P1 and CB-P2)



CB-P1 ESI 625.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.92 (s, 1H), 6.91 – 6.74 (m, 3H), 5.74 (t, *J* = 8.0 Hz, 1H), 5.49 (t, *J* = 7.0 Hz, 1H), 3.49 – 3.38 (m, 1H), 3.13 – 2.82 (m, 6H), 2.77 – 2.62 (m, 8H), 2.21 (s, 3H), 2.01 (t, *J* = 7.6 Hz, 2H), 1.91 – 1.36 (m, 7H), 0.98 (d, *J* = 6.5 Hz, 6H), 0.79 (d, *J* = 6.4 Hz, 3H).

CB-P2 ESI 625.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.01 – 6.78 (m, 3H), 5.74 – 5.55 (m, 2H), 3.59 – 3.44 (m, 1H), 3.30 – 3.14 (m, 2H), 3.08 – 2.90 (m, 4H), 2.82 (s, 6H), 2.62 – 2.42 (m, 2H), 2.25 (d, *J* = 1.7 Hz, 3H), 2.04 – 1.35 (m, 9H), 0.99 – 0.86 (m, 9H).

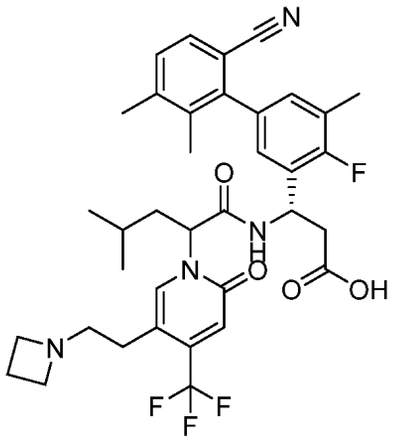
4-30. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-cyclopropyl-4,5'-difluoro-5-methyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds CC-P1 and CC-P2)



CC-P1 ESI 674.4 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.87 (s, 1H), 7.23 – 7.17 (m, 2H), 7.03 – 6.98 (m, 2H), 6.89 – 6.82 (m, 2H), 5.73 – 5.56 (m, 2H), 4.09 (t, *J* = 8.1 Hz, 4H), 3.35 – 3.32 (m, 2H), 2.87 – 2.84 (m, 2H), 2.76 – 2.75 (m, 2H), 2.48 – 2.43 (m, 2H), 2.31 (d, *J* = 1.6 Hz, 3H), 2.05 – 1.97 (m, 2H), 1.81 – 1.74 (m, 1H), 1.16 – 1.39 (m, 1H), 0.97 – 0.91 (m, 6H), 0.79 – 0.74 (m, 2H), 0.57 – 0.53 (m, 2H).

CC-P2 ESI 674.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.27 – 7.21 (m, 2H), 7.05 – 6.91 (m, 4H), 5.77 – 5.74 (m, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 4.14 (t, *J* = 8.1 Hz, 4H), 3.42 – 3.32 (m, 2H), 2.96 – 2.81 (m, 2H), 2.67 – 2.45 (m, 4H), 2.35 (t, *J* = 8.8 Hz, 3H), 2.03 – 1.96 (m, 1H), 1.83 – 1.66 (m, 2H), 1.42 – 1.38 (m, 1H), 0.92 – 0.89 (m, 6H), 0.84 – 0.79 (m, 2H), 0.63 – 0.59 (m, 2H).

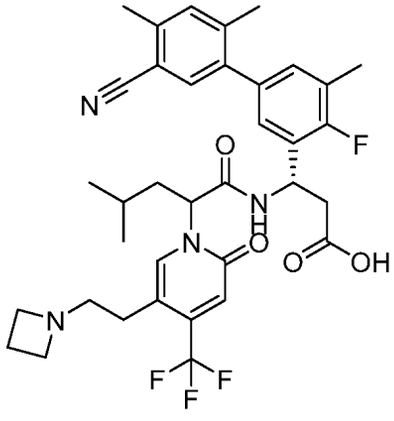
4-31. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(6'-cyano-4-fluoro-2',3',5-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds CD-P1 and CD-P2)



CD-P1 ESI 669.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (d, *J* = 8.9 Hz, 1H), 7.61 – 7.27 (m, 2H), 7.16 – 6.95 (m, 2H), 6.77 (d, *J* = 35.8 Hz, 1H), 5.80 – 5.43 (m, 2H), 4.11 – 3.86 (m, 4H), 3.31 – 3.15 (m, 2H), 2.94 – 2.60 (m, 4H), 2.51 – 2.24 (m, 8H), 2.15 – 1.89 (m, 5H), 1.56 – 1.38 (m, 1H), 1.09 – 0.83 (m, 6H).

CD-P2 ESI 669.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (d, *J* = 6.8 Hz, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.22 – 7.05 (m, 2H), 6.91 (s, 1H), 5.90 – 5.53 (m, 2H), 4.32 – 3.89 (m, 4H), 3.54 – 3.33 (m, 2H), 3.11 – 2.29 (m, 12H), 2.07 – 1.92 (m, 4H), 1.83 – 1.64 (m, 1H), 1.52 – 1.30 (m, 1H), 0.97 – 0.81 (m, 6H).

4-32. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5'-cyano-4-fluoro-2',4',5-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds CE-P1 and CE-P2)

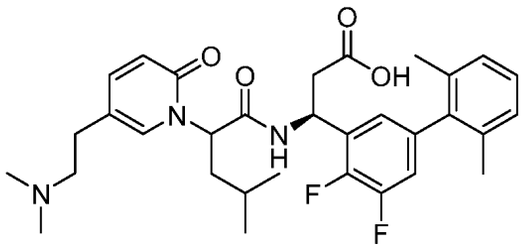


CE-P1 ESI 669.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.26 (d, J = 40.1 Hz, 2H), 6.96 (t, *J* = 7.5 Hz, 2H), 6.65 (s, 1H), 5.74 – 5.22 (m, 2H), 3.92 (t, *J* = 8.1 Hz, 4H), 3.21

– 3.09 (m, 2H), 2.66 (dt, *J* = 11.9, 7.1 Hz, 4H), 2.49 – 2.19 (m, 5H), 2.15 (d, *J* = 20.6 Hz, 6H), 1.90 (m, *J* = 13.4, 6.1 Hz, 2H), 1.47 – 1.10 (m, 1H), 0.83 (t, *J* = 6.2 Hz, 6H).

CE-P2 ESI 669.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.42 (d, *J* = 42.0 Hz, 2H), 7.13 (d, *J* = 6.4 Hz, 2H), 6.92 (s, 1H), 5.92 – 5.45 (m, 2H), 4.14 (t, *J* = 8.0 Hz, 4H), 3.40 (d, *J* = 16.8 Hz, 2H), 2.92 (s, 2H), 2.75 – 2.55 (m, 1H), 2.52 – 2.41 (m, 6H), 2.40 – 2.18 (m, 6H), 2.12 – 1.88 (m, 1H), 1.82 – 1.53 (m, 1H), 1.53 – 1.20 (m, 1H), 0.92 (t, *J* = 6.6 Hz, 6H).

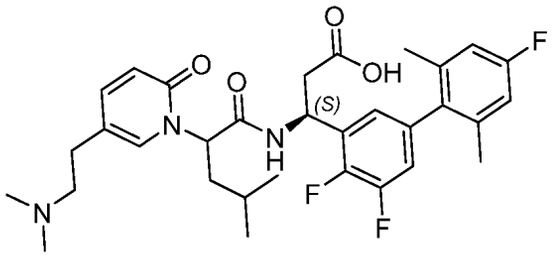
4-33. (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CF-P1 and CF-P2)



CF-P1 ESI 568.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.64 (d, *J* = 2.0 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 6.8 Hz, 2H), 6.99 – 6.90 (m, 1H), 6.78 (d, *J* = 5.9 Hz, 1H), 6.52 (d, *J* = 9.3 Hz, 1H), 5.61 – 5.56 (m, 1H), 5.42 (t, *J* = 5.6 Hz, 1H), 3.32 – 3.19 (s, 1H), 3.24 – 3.10 (m, 1H), 2.88 – 2.80 (m, 2H), 2.73 (s, 6H), 2.70 – 2.64 (m, 1H), 2.59 – 2.53 (m, 1H), 2.06 – 1.89 (m, 8H), 1.50 – 1.36 (m, 1H), 0.97 – 0.90 (m, 6H).

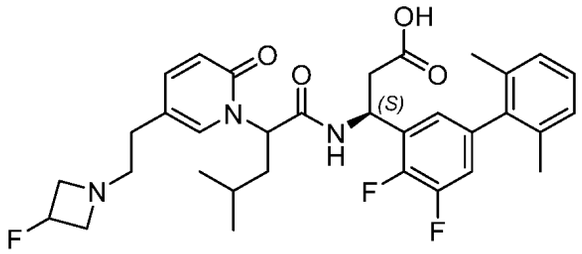
CF-P2 ESI 568.2 $(M+H)^+$. 1H NMR (500 MHz, MeOD) δ ^1H NMR (500 MHz, MeOD) δ 7.65 (d, *J* = 2.1 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.22 – 7.13 (m, 1H), 7.14 – 7.07 (m, 2H), 7.01 – 6.90 (m, 1H), 6.88 (d, *J* = 5.8 Hz, 1H), 6.54 (d, *J* = 9.3 Hz, 1H), 5.66 – 5.52 (m, 2H), 3.38 – 3.34 (m, 1H), 3.28 – 3.21 (m, 1H), 2.98 – 2.86 (m, 1H), 2.86 – 2.73 (m, 7H), 2.64 – 2.59 (m, 1H), 2.51 – 2.44 (m, 1H), 2.08 – 1.91 (m, 7H), 1.92 – 1.81 (m, 1H), 1.49 – 1.35 (m, 1H), 0.93 – 0.88 (m, 6H).

4-34. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds CG-P1 and CG-P2)



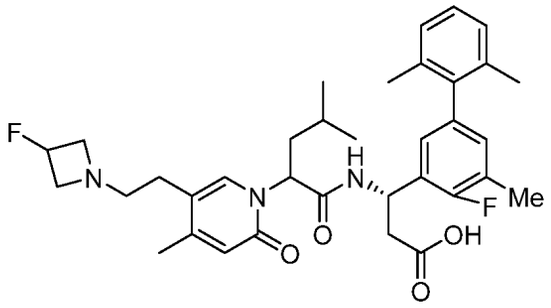
CG-P1 ESI 586.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.65 (s, 1H), 7.57 – 7.48 (m, 1H), 6.99 – 6.90 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 5.8 Hz, 1H), 6.52 (d, *J* = 9.4 Hz, 1H), 5.56 (s, 1H), 5.42 (t, *J* = 5.6 Hz, 1H), 3.32 – 3.27 (m, 1H), 3.23 – 3.16 (m, 1H), 2.93 – 2.80 (m, 2H), 2.75 (s, 6H), 2.70 – 2.62 (m, 1H), 2.59 – 2.52 (m, 1H), 2.10 – 1.91 (m, 8H), 1.44 (s, 1H), 0.98 – 0.87 (m, 6H).
CG-P2 ESI 586.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.65 (d, *J* = 2.1 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.01 – 6.94 (m, 1H), 6.90 – 6.81 (m, 3H), 6.55 (d, *J* = 9.3 Hz, 1H), 5.64 – 5.54 (m, 2H), 3.45 – 3.36 (m, 1H), 3.31 – 3.24 (m, 1H), 2.99 – 2.90 (m, 1H), 2.90 – 2.78 (m, 7H), 2.64 – 2.55 (m, 1H), 2.51 – 2.41 (m, 1H), 2.07 – 1.95 (m, 7H), 1.92 – 1.83 (m, 1H), 1.46 – 1.36 (m, 1H), 0.96 – 0.86 (m, 6H).

4-35. (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CH-P1 and CH-P2)



CH-P1 ESI 598.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.54 (d, *J* = 1.9 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.21 – 7.14 (m, 1H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.99 – 6.90 (m, 1H), 6.81 (d, *J* = 5.9 Hz, 1H), 6.47 (d, *J* = 9.3 Hz, 1H), 5.62 (t, *J* = 8.1 Hz, 1H), 5.51 (t, *J* = 6.1 Hz, 1H), 5.31 – 5.14 (m, 1H), 4.17 – 3.96 (m, 2H), 3.82 – 3.67 (m, 2H), 3.21 – 3.11 (m, 2H), 2.78 – 2.58 (m, 4H), 2.03 – 1.89 (m, 8H), 1.47 – 1.40 (m, 1H), 0.97 – 0.88 (m, 6H).
CH-P2 ESI 598.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.53 (d, *J* = 2.0 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 2H), 7.03 – 6.94 (m, 1H), 6.92 (d, *J* = 5.9 Hz, 1H), 6.55 (d, *J* = 9.3 Hz, 1H), 5.68 – 5.60 (m, 2H), 5.41 – 5.22 (m, 1H), 4.47 – 4.27 (m, 2H), 4.09 – 3.94 (m, 2H), 3.37 (s, 2H), 2.79 – 2.62 (m, 3H), 2.60 – 2.50 (m, 1H), 2.03 (d, *J* = 2.2 Hz, 6H), 1.98 – 1.91 (m, 1H), 1.84 – 1.76 (m, 1H), 1.47 – 1.37 (m, 1H), 0.91 (t, *J* = 6.1 Hz, 6H).

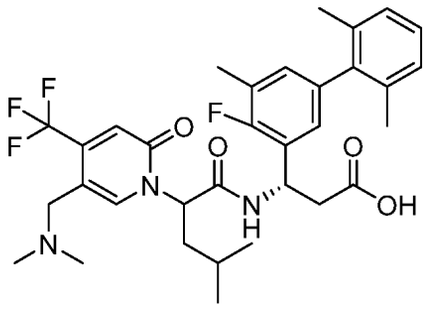
4-36. (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CI-P1 and CI-P2)



CI-P1 ESI 608.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 8.45 (s, 0.47HCOOH), 7.54 (s, 1H), 7.15 – 7.05 (m, 3H), 6.89 – 6.81 (m, 2H), 6.30 (s, 1H), 5.68 – 5.48 (m, 2H), 5.40 – 5.14 (m, 1H), 4.35 – 4.13 (m, 2H), 4.06 – 3.86 (m, 2H), 3.26 – 3.20 (m, 2H), 2.88 – 2.65 (m, 4H), 2.29 (s, 3H), 2.23 (s, 3H), 2.01 – 1.89 (m, 5H), 1.85 (s, 3H), 1.48 – 1.38 (m, 1H), 0.98 – 0.91 (m, 6H).

CI-P2 ESI 608.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 8.45 (s, 0.23HCOOH), 7.46 (s, 1H), 7.20 – 7.02 (m, 3H), 6.93 (d, J = 5.0 Hz, 2H), 6.44 (s, 1H), 5.75 – 5.54 (m, 2H), 5.34 (d, J = 57.3 Hz, 1H), 4.48 – 4.35 (m, 2H), 4.16 – 3.96 (m, 2H), 3.42 – 3.34 (m, 2H), 2.90 – 2.82 (m, 1H), 2.74 – 2.63(m, 2H), 2.60 – 2.52 (m, 1H), 2.33 (s, 3H), 2.25 (s, 3H), 2.07 – 1.85 (m, 7H), 1.82 – 1.70 (m, 1H), 1.44 – 1.34 (m, 1H), 0.91 – 0.87 (m, 6H).

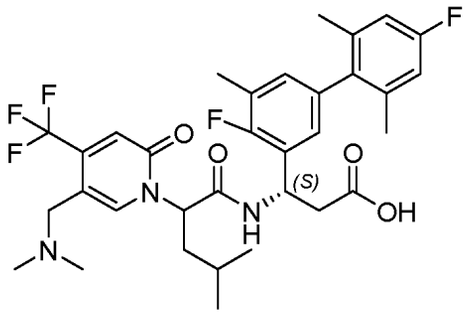
4-37. (3*S*)-3-(2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds CJ-P1 and CJ-P2)



CJ-P1 ESI 618.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.07 (s, 1H), 7.15 – 7.00 (m, 3H), 6.94 – 6.83 (m, 2H), 6.77 (s, 1H), 5.75 (t, J = 8.1 Hz, 1H), 5.63 – 5.52 (m, 1H), 3.83 – 3.59 (m, 2H), 2.82 – 2.72 (m, 2H), 2.52 (s, 6H), 2.29 (d, J = 1.3 Hz, 3H), 2.05 – 1.95 (m, 5H), 1.80 (s, 3H), 1.49 – 1.37 (m, 1H), 1.01 – 0.91 (m, 6H).

CJ-P2 ESI 618.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.09 (s, 1H), 7.18 – 7.00 (m, 3H), 7.00 – 6.84 (m, 3H), 5.81 – 5.70 (m, 1H), 5.63 – 5.46 (m, 1H), 4.10 (d, *J* = 14.4 Hz, 1H), 3.87 (d, *J* = 14.4 Hz, 1H), 2.79 – 2.55 (m, 8H), 2.34 (d, *J* = 1.5 Hz, 3H), 2.05 – 1.93 (m, 7H), 1.71 – 1.61 (m, 1H), 1.48 – 1.39 (m, 1H), 0.93 – 0.82 (m, 6H).

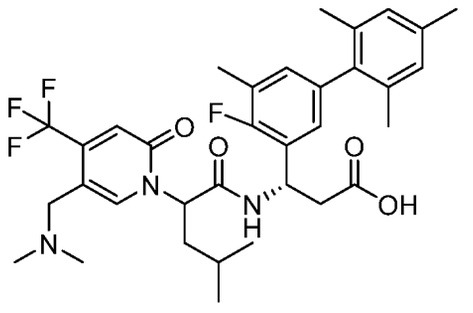
4-38. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CK-P1 and CK-P2)



CK-P1 ESI 636.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.06 (s, 1H), 6.95 – 6.72 (m, 5H), 5.75 (t, *J* = 8.1 Hz, 1H), 5.62 – 5.56 (m, 1H), 3.79 – 3.65 (m, 2H), 2.86 – 2.65 (m, 2H), 2.52 (s, 6H), 2.29 (s, 3H), 2.04 – 1.93 (m, 5H), 1.81 (s, 3H), 1.50 – 1.38 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 6H).

CK-P2 ESI 636.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.08 (s, 1H), 6.95 – 6.88 (m, 3H), 6.85 (d, *J* = 9.6 Hz, 2H), 5.76 – 5.70 (m, 1H), 5.55 (t, *J* = 7.5 Hz, 1H), 4.08 (d, *J* = 14.4 Hz, 1H), 3.85 (d, *J* = 14.4 Hz, 1H), 2.79 – 2.52 (m, 8H), 2.34 (s, 3H), 2.03 – 1.93 (m, 7H), 1.70 – 1.61 (m, 1H), 1.50 – 1.38 (m, 1H), 0.95 – 0.80 (m, 6H).

4-39. (3*S*)-3-(2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds CL-P1 and CL-P2)

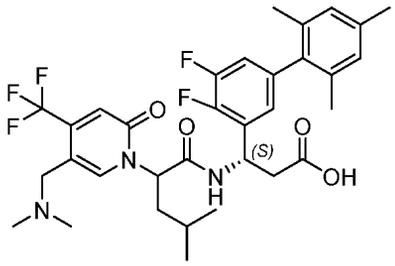


CL-P1 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.05 (s, 1H), 6.92 – 6.82 (m, 4H), 6.76 (s, 1H), 5.75 (t, *J* = 8.1 Hz, 1H), 5.63 – 5.50 (m, 1H), 3.78 – 3.62 (m, 2H), 2.88 – 2.65 (m, 2H), 2.50 (s,

6H), 2.29 (d, *J* = 3.7 Hz, 6H), 2.03 – 1.89 (m, 5H), 1.76 (s, 3H), 1.52 – 1.36 (m, 1H), 0.96 (t, *J* = 7.2 Hz, 6H).

CL-P2 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.09 (s, 1H), 6.95 – 6.83 (m, 5H), 5.81 – 5.68 (m, 1H), 5.54 (t, *J* = 7.4 Hz, 1H), 4.09 (d, *J* = 14.4 Hz, 1H), 3.85 (d, *J* = 14.3 Hz, 1H), 2.81 – 2.52 (m, 8H), 2.32 (d, *J* = 9.8 Hz, 6H), 1.97 (t, *J* = 9.1 Hz, 7H), 1.71 – 1.58 (m, 1H), 1.50 – 1.34 (m, 1H), 0.88 (d, *J* = 6.4 Hz, 6H).

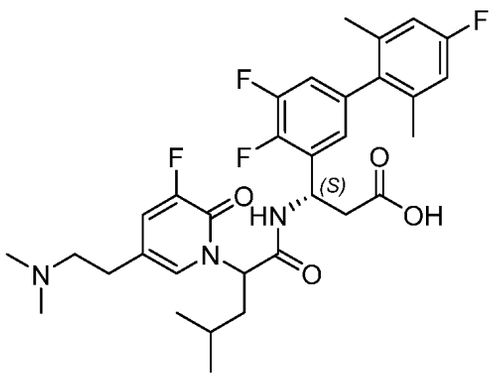
4-40. (3S)-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CM-P1 and CM-P2)



CM-P1 ESI 636.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.99 (s, 1H), 6.92 – 6.84 (m, 4H), 6.72 (s, 1H), 5.82 – 5.68 (m, 1H), 5.61 – 5.55 (m, 1H), 3.61 – 3.48 (m, 2H), 2.83 – 2.65 (m, 2H), 2.38 (s, 6H), 2.30 (s, 3H), 2.03 – 1.92 (m, 5H), 1.73 (s, 3H), 1.49 – 1.37 (m, 1H), 0.99 – 0.93 (m, 6H).

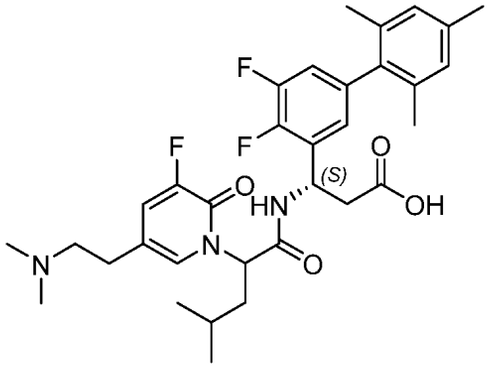
CM-P2 ESI 636.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.08 (s, 1H), 7.02 – 6.84 (m, 5H), 5.77 – 5.72 (m, 1H), 5.59 – 5.52 (m, 1H), 4.08 (d, *J* = 14.4 Hz, 1H), 3.85 (d, *J* = 14.4 Hz, 1H), 2.79 – 2.75 (m, 1H), 2.70 – 2.54 (m, 7H), 2.31 (s, 3H), 2.02 – 1.87 (m, 7H), 1.74 – 1.57 (m, 1H), 1.49 – 1.37 (m, 1H), 0.91 – 0.86 (m, 6H).

4-41. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds CN-P1 and CN-P2)



CN-P1 ESI 604.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.44 (s, 1H), 7.34 – 7.30 (m, 1H), 6.96 – 6.75 (m, 4H), 5.76 – 5.71 (m, 1H), 5.60 – 5.48 (m, 1H), 2.76 – 2.55 (m, 6H), 2.39 (s, 6H), 2.07 – 1.90 (m, 5H), 1.84 (s, 3H), 1.49 – 1.33 (m, 1H), 0.98 – 0.92 (m, 6H).
CN-P2 ESI 604.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.46 – 7.10 (m, 1H), 7.04 – 6.93 (m, 1H), 6.91 – 6.84 (m, 3H), 5.67 – 5.57 (m, 2H), 3.47 – 3.37 (m, 1H), 3.31 – 3.21 (m, 1H), 3.02 – 2.91 (m, 1H), 2.90 – 2.79 (m, 7H), 2.64 – 2.57 (m, 1H), 2.50 – 2.42 (m, 1H), 2.07 – 1.92 (m, 7H), 1.90 – 1.78 (m, 1H), 1.47 – 1.31 (m, 1H), 0.94 – 0.89 (m, 6H).

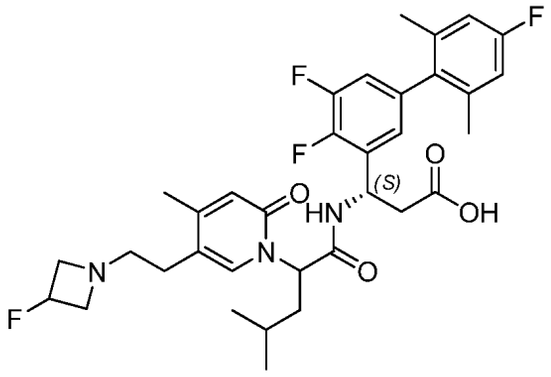
4-42. (3S)-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propa -noic acid (diastereomeric compounds CO-P1 and CO-P2)



CO-P1 ESI 600.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.49-7.44 (m, 2H), 6.92 (t, J = 8.2 Hz, 3H), 6.76 (d, J = 6.0 Hz, 1H), 5.65-5.61 (m, 1H), 5.40 (t, J = 5.6 Hz, 1H), 3.19-3.15 (m, 2H), 2.90-2.84 (m, 3H), 2.75 – 2.63 (m, 7H), 2.57-2.52 (m, 1H), 2.31 (s, 3H), 2.03 – 1.87 (m, 9H), 1.46-1.40 (m, 1H), 0.98-0.91 (m, 6H).

CO-P2 ESI 600.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.37-7.29 (m, 2H), 6.87 – 6.71 (m, 4H), 5.57 – 5.42 (m, 2H), 3.34 – 3.24 (m, 1H), 3.18 – 3.07 (m, 1H), 2.87-2.81 (m, 1H), 2.73-2.70 (m, 7H), 2.50-2.45 (m, 1H), 2.36-2.30 (m, 1H), 2.19 (s, 3H), 1.96 – 1.80 (m, 7H), 1.74 – 1.63 (m, 1H), 1.30-1.25 (m, 1H), 0.81-0.79 (m, 6H).

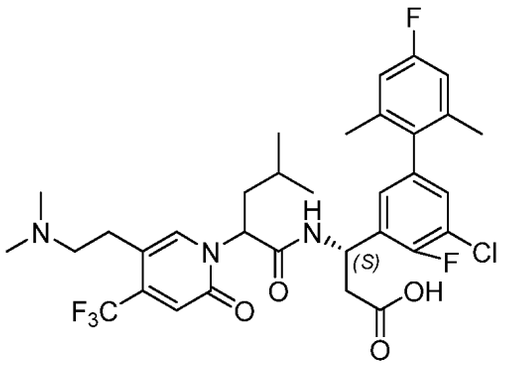
4-43. (3*S*)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4',5-trifluoro-2',6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds CP-P1 and CP-P2)



CP-P1 ESI 630.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.49 (s, 1H), 6.99 – 6.89 (m, 1H), 6.89 – 6.76 (m, 3H), 6.29 (s, 1H), 5.66 – 5.50 (m, 2H), 5.40 – 5.10 (m, 1H), 4.14 – 3.90 (m, 2H), 3.86 – 3.55 (m, 2H), 3.03 (s, 2H), 2.86 – 2.53 (m, 4H), 2.23 (s, 3H), 2.06 – 1.90 (m, 5H), 1.86 (s, 3H), 1.49 – 1.32 (m, 1H), 1.02 – 0.84 (m, 6H).

CP-P2 ESI 630.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.49 (s, 1H), 7.09 – 6.86 (m, 4H), 6.44 (s, 1H), 5.72 – 5.55 (m, 2H), 5.30 (d, J = 57.8 Hz, 1H), 4.28 (s, 2H), 3.93 (s, 2H), 3.19 (s, 2H), 2.87 – 2.50 (m, 4H), 2.25 (s, 3H), 2.04 (s, 6H), 1.93 – 1.73 (m, 2H), 1.47 – 1.28 (m, 1H), 0.91 – 0.85 (m, 6H).

4-44. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CQ-P1 and CQ-P2)

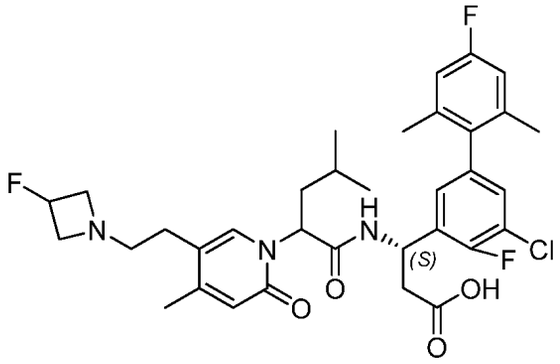


CQ-P1 ESI 670.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.13 – 7.11 (m, 1H), 7.04 – 7.02 (m, 1H), 6.88 – 6.81 (m, 2H), 6.74 (s, 1H), 5.69 – 5.65 (m, 1H), 5.57 – 5.53 (m, 1H), 3.16 – 3.10 (m, 2H), 2.97 – 2.94 (m, 2H), 2.80 (s, 6H), 2.74 – 2.71 (m, 2H), 2.02 – 1.98 (m, 5H), 1.84 (s, 3H), 1.47 – 1.40 (m, 1H), 0.98 – 0.93 (m, 6H).

CQ-P2 ESI 670.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.20 – 7.18 (m, 1H), 7.07 (d, J = 6.1 Hz, 1H), 6.88 (d, J = 11.2 Hz, 3H), 5.73 – 5.67 (m, 1H), 5.63 (t, J = 7.6 Hz, 1H), 3.30 – 3.18

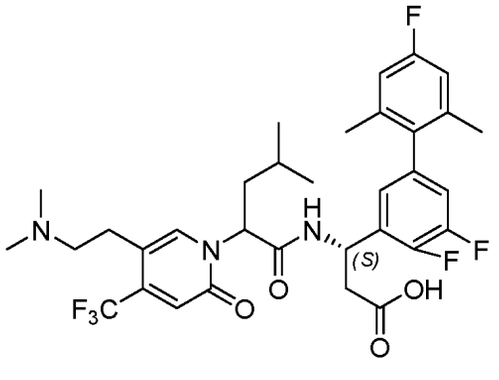
(m, 2H), 3.01 (t, *J* = 6.9 Hz, 2H), 2.85 (s, 6H), 2.69 – 2.60 (m, 1H), 2.58 – 2.52 (m, 1H), 2.03 – 1.95 (m, 7H), 1.77 – 1.70 (m, 1H), 1.41 – 1.36 (m, 1H), 0.91 – 0.89 (m, 6H).

4-45. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CR-P1 and CR-P2)



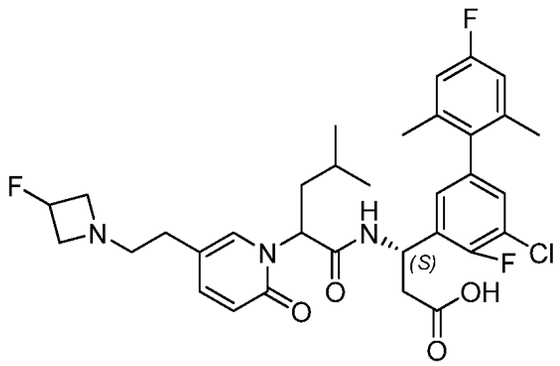
CR-P1 ESI 646.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.15 – 7.13 (m, 1H), 6.99 – 6.97 (m, 1H), 6.88 – 6.85 (m, 2H), 6.29 (s, 1H), 5.64 – 5.49 (m, 2H), 5.32 – 5.18 (m, 1H), 4.11 – 4.07 (m, 2H), 3.85 – 3.72 (m, 2H), 3.10 (t, *J* = 6.9 Hz, 2H), 2.82 – 2.62 (m, 4H), 2.24 (s, 3H), 2.09 – 1.90 (m, 5H), 1.89 (d, *J* = 8.2 Hz, 3H), 1.43 – 1.38 (m, 1H), 0.96 – 0.92 (m, 6H).
CR-P2 ESI 646.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.45 (s, 1H), 7.21 – 7.18 (m, 1H), 7.08 – 7.06 (m, 1H), 6.89 (d, *J* = 9.6 Hz, 2H), 6.43 (s, 1H), 5.73 – 5.53 (m, 2H), 5.43 – 5.25 (m, 1H), 4.44 – 4.41 (m, 2H), 4.16 – 4.01 (m, 2H), 3.39– 3.36 (m, 2H), 2.91 – 2.87 (m, 1H), 2.73 – 2.62 (m, 2H), 2.52 – 2.49 (m, 1H), 2.25 (s, 3H), 2.03 (s, 6H), 1.98 – 1.88 (m, 1H), 1.81 – 1.72 (m, 1H), 1.44 – 1.33 (m, 1H), 0.91 – 0.89 (m, 6H).

4-46. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4',5-trifluoro-2',6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds CS-P1 and CS-P2)



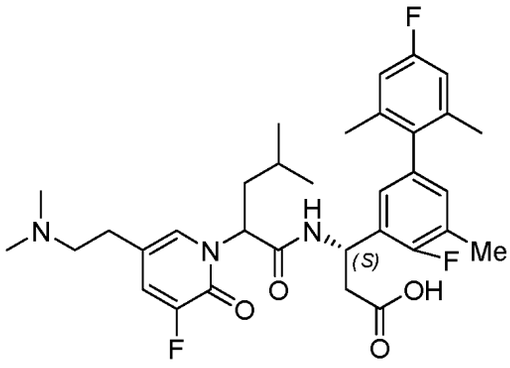
CS-P1 ESI 654.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 6.98 – 6.78 (m, 4H), 6.75 (s, 1H), 5.69 – 5.65 (m, 1H), 5.59 – 5.56 (m, 1H), 3.15– 3.06 (m, 2H), 2.95 (d, *J* = 6.2 Hz, 2H), 2.77 (s, 6H), 2.74 – 2.71 (m, 2H), 2.13 – 1.91 (m, 5H), 1.85 (s, 3H), 1.50 – 1.40 (m, 1H), 0.98 – 0.94 (m, 6H).
CS-P2 ESI 654.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.05 – 6.96 (m, 1H), 6.95 – 6.83 (m, 4H), 5.73 – 5.69 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 3.28 – 3.14 (m, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.82 (s, 6H), 2.69 – 2.64 (m, 1H), 2.62 – 2.52 (m, 1H), 2.03 (d, *J* = 2.1 Hz, 6H), 1.99 – 1.94 (m, 1H), 1.77 – 1.72 (m, , 1H), 1.45 – 1.31 (m, 1H), 0.91 – 0.89 (m, 6H).

4-47. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CT-P1 and CT-P2)



CT-P1 ESI 632.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.59 (s, 1H), 7.46 – 7.43 (m, 1H), 7.15 – 7.13 (m, 1H), 7.00 – 6.92 (m, 1H), 6.87 (d, *J* = 9.6 Hz, 2H), 6.45 (d, *J* = 9.3 Hz, 1H), 5.68 – 5.57 (m, 1H), 5.51 (t, *J* = 6.2 Hz, 1H), 5.38 – 5.16 (m, 1H), 4.25 – 4.04 (m, 2H), 3.96 – 3.76 (m, 2H), 3.25 – 3.13 (m, 2H), 2.83 – 2.58 (m, 4H), 2.08 – 1.92 (m, 5H), 1.88 (s, 3H), 1.47 – 1.40 (m, 1H), 0.97 – 0.92 (m, 6H).
CT-P2 ESI 632.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.20 – 7.18 (m, 1H), 7.04 (d, *J* = 4.5 Hz, 1H), 6.88 (d, *J* = 9.6 Hz, 2H), 6.56 (d, *J* = 9.1 Hz, 1H), 5.71 – 5.57 (m, 2H), 5.34 (d, *J* = 59.0 Hz, 1H), 4.40 (s, 2H), 4.08 (s, 2H), 3.42 (s, 1H), 2.70 (d, *J* = 52.7 Hz, 3H), 2.52 (s, 1H), 2.03 (d, *J* = 3.5 Hz, 6H), 1.99 – 1.93 (m, 2H), 1.88 – 1.76 (m, 1H), 1.49 – 1.31 (m, 1H), 0.91 (t, *J* = 6.7 Hz, 6H).

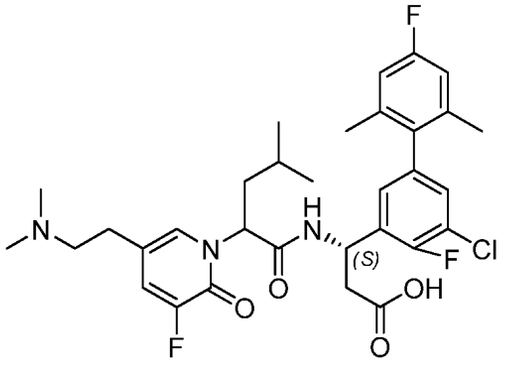
4-48. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CU-P1 and CU-P2)



CU-P1 ESI 600.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.47 – 7.44 (m, 1H), 6.91 – 6.81 (m, 3H), 6.78 (d, *J* = 6.8 Hz, 1H), 5.64 – 5.60 (m, 1H), 5.40 (t, *J* = 5.6 Hz, 1H), 3.36 (d, *J* = 6.1 Hz, 1H), 3.24 – 3.12 (m, 1H), 2.97 – 2.77 (m, 2H), 2.73 (s, 6H), 2.70 – 2.61 (m, 1H), 2.57 – 2.52 (m, 1H), 2.30 (d, *J* = 1.6 Hz, 3H), 2.12 – 1.96 (m, 5H), 1.95 (s, 3H), 1.52 – 1.37 (m, 1H), 0.97 – 0.91 (m, 6H).

CU-P2 ESI 600.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.45 – 7.42 (m, 1H), 6.89 (t, *J* = 6.1 Hz, 2H), 6.84 (d, *J* = 9.6 Hz, 2H), 5.66 – 5.62 (m, 1H), 5.59 – 5.56 (m, 1H), 3.47 – 3.36 (m, 1H), 3.30 – 3.25 (m, 1H), 3.00 – 2.94 (m, 1H), 2.90 – 2.77 (m, 7H), 2.61 – 2.56 (m, 1H), 2.46 – 2.40 (m, 1H), 2.32 (d, *J* = 1.8 Hz, 3H), 2.09 – 1.94 (m, 7H), 1.87 – 1.79 (m, 1H), 1.48 – 1.37 (m, 1H), 0.93 – 0.90 (m, 6H).

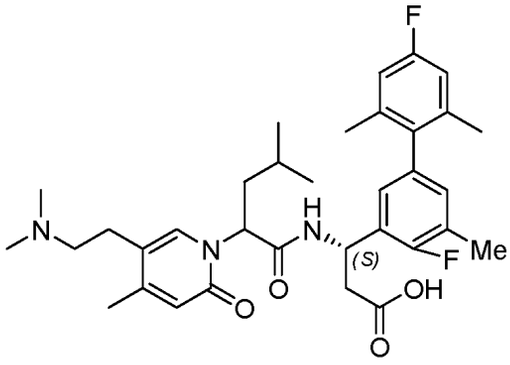
4-49. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CV-P1 and CV-P2)



CV-P1 ESI 620.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.53 (s, 1H), 7.46 – 7.43 (m , 1H), 7.15 – 7.12 (m, 1H), 6.95 – 6.93 (m, 1H), 6.87 (d, *J* = 9.6 Hz, 2H), 5.65 – 5.61 (m, 1H), 5.42 (t, *J* = 5.8 Hz, 1H), 3.31 – 3.26 (m, 1H), 3.20 – 3.15 (m, 1H), 2.96 – 2.81 (m, 2H), 2.75 (s, 6H), 2.70 – 2.65 (m, 1H), 2.59 – 2.54 (m, 1H), 2.19 – 1.78 (m, 8H), 1.46 – 1.40 (m, 1H), 0.97 – 0.91 (m, 6H).

CV-P2 ESI 620.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.45 – 7.42 (m, 1H), 7.18 – 7.16 (m, 1H), 7.04– 7.02 (m, 1H), 6.88 (d, *J* = 9.6 Hz, 2H), 5.67 – 5.63 (m, 1H), 5.59 – 5.56 (m, 1H), 3.46 – 3.36 (m, 1H), 3.29 – 3.22 (m, 1H), 2.98 – 2.92 (m, 1H), 2.86 – 2.84 (m, 1H), 2.82 (s, 6H), 2.62 – 2.58 (m, 1H), 2.51 – 2.41 (m, 1H), 2.03 (d, *J* = 1.5 Hz, 6H), 1.97 (t, *J* = 7.1 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.41 – 1.36 (m, 1H), 0.97 – 0.74 (m, 6H).

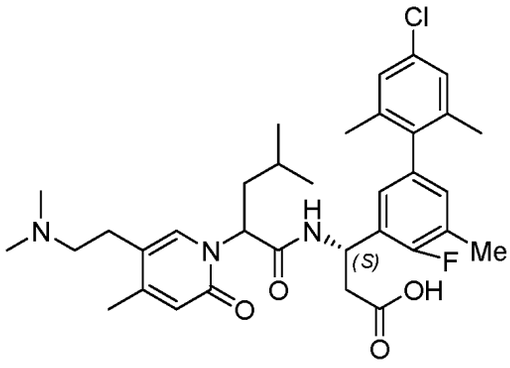
4-50. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CW-P1 and CW-P2)



CW-P1 ESI 596.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.59 (s, 1H), 6.83 (t, *J* = 7.2 Hz, 4H), 6.32 (s, 1H), 5.70 – 5.56 (m, 1H), 5.54 – 5.47 (m, 1H), 3.21 – 3.06 (m, 2H), 2.95 – 2.83 (m, 2H), 2.79 (s, 6H), 2.73 – 2.55 (m, 2H), 2.35 – 2.20 (m, 6H), 2.07 – 1.91 (m, 5H), 1.85 (s, 3H), 1.50 – 1.29 (m, 1H), 1.02 – 0.83 (m, 6H).

CW-P2 ESI 596.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.57 (s, 1H), 6.99 – 6.78 (m, 4H), 6.43 (s, 1H), 5.71 – 5.53 (m, 2H), 3.28 – 3.06 (m, 2H), 2.97 – 2.85 (m, 2H), 2.81 (s, 6H), 2.66 – 2.56 (m, 1H), 2.56 – 2.40 (m, 1H), 2.36 – 2.24 (m, 6H), 2.05 – 1.89 (m, 7H), 1.86 – 1.72 (m, 1H), 1.43 – 1.28 (m, 1H), 0.89 (t, *J* = 5.2 Hz, 6H).

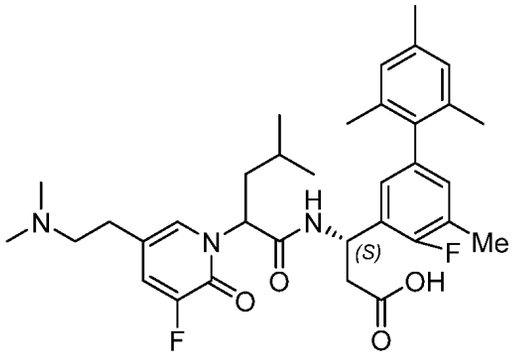
4-51. (3*S*)-3-(4'-chloro-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CX-P1 and CX-P2)



CX-P1 ESI 612.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.58 (s, 1H), 7.11 (d, *J* = 2.5 Hz, 2H), 6.92 – 6.76 (m, 2H), 6.32 (s, 1H), 5.61 – 5.41 (m, 2H), 3.25 – 3.05 (m, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.78 (s, 6H), 2.71 – 2.54 (m, 2H), 2.28 (d, *J* = 13.0 Hz, 6H), 2.05 – 1.92 (m, 5H), 1.88 (s, 3H), 1.48 – 1.32 (m, 1H), 1.04 – 0.85 (m, 6H).

CX-P2 ESI 612.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.55 (s, 1H), 7.13 (s, 2H), 6.93 – 6.84 (m, 2H), 6.42 (s, 1H), 5.70 – 5.54 (m, 2H), 3.24 – 3.11 (m, 2H), 2.99 – 2.76 (m, 8H), 2.64 – 2.42 (m, 2H), 2.36 – 2.20 (m, 6H), 2.03 – 1.90 (m, 7H), 1.83 – 1.72 (m, 1H), 1.47 – 1.28 (m, 1H), 0.90 (t, *J* = 6.2 Hz, 6H).

4-52. (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds CY-P1 and CY-P2)

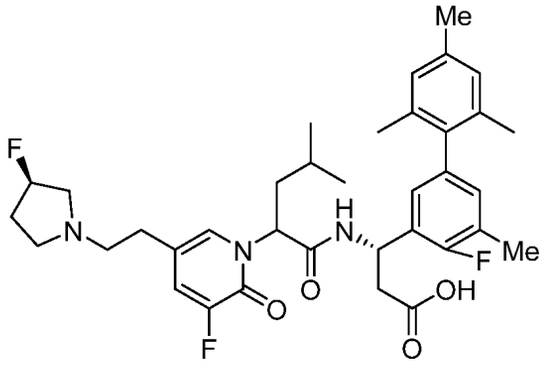


CY-P1 ESI 596.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.37 (m, 2H), 6.96 – 6.64 (m, 4H), 5.76 – 5.58 (m, 1H), 5.39 (t, *J* = 5.5 Hz, 1H), 3.42 – 3.25 (m, 1H), 3.23 – 3.06 (m, 1H), 2.96 – 2.76 (m, 2H), 2.73 – 2.46 (m, 8H), 2.41 – 2.22 (m, 6H), 2.05 – 1.88 (m, 8H), 1.44 (m, *J* = 13.7, 6.7 Hz, 1H), 0.93 (m, *J* = 17.3, 6.6 Hz, 6H).

CY-P2 ESI 596.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.51 (s, 1H), 7.42 (m, *J* = 10.3, 2.1 Hz, 1H), 6.89 (m, *J* = 7.0, 4.6 Hz, 4H), 5.62 (m, *J* = 14.0, 9.4, 5.4 Hz, 2H), 3.43 – 3.30 (m, 1H), 3.23 (s, 1H), 2.93 (m, *J* = 9.6, 4.9 Hz, 1H), 2.87 – 2.75 (m, 7H), 2.59 (m, *J* = 14.9, 4.0 Hz, 1H), 2.44 (m, *J* =

14.8, 10.1 Hz, 1H), 2.34 – 2.22 (m, 6H), 2.05 – 1.91 (m, 7H), 1.84 – 1.72 (m, 1H), 1.46 – 1.22 (m, 1H), 0.91 (m, *J* = 6.6, 3.1 Hz, 6H).

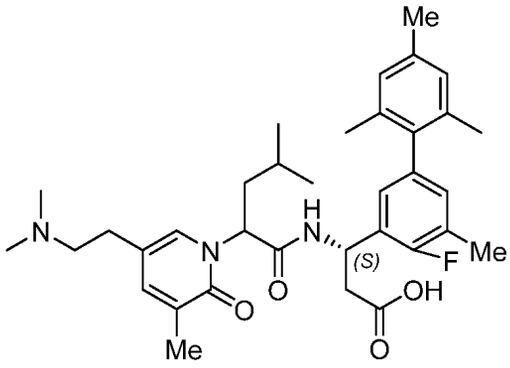
4-53. (3S)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds CZ-P1 and CZ-P2)



CZ-P1 ESI 640.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.41 – 7.31 (m, 1H), 6.91 (s, 2H), 6.85 (d, *J* = 7.0 Hz, 1H), 6.79 (d, *J* = 6.7 Hz, 1H), 5.70 (s, 1H), 5.49 (s, 1H), 5.24 (d, *J* = 53.7 Hz, 1H), 3.26 – 3.00 (m, 5H), 2.88 – 2.56 (m, 4H), 2.41 – 2.13 (m, 9H), 2.07 – 1.90 (m, 5H), 1.85 (s, 3H), 1.53 – 1.26 (m, 1H), 1.05 – 0.80 (m, 6H).

CZ-P2 ESI 640.2 $(M+H)^+$. 1H NMR (500 MHz, MeOD) δ 7.49 (s, 1H), 7.47 – 7.36 (m, 1H), 6.90 (d, J = 8.8 Hz, 4H), 5.67 (t, J = 7.7 Hz, 1H), 5.61 – 5.52 (m, 1H), 5.33 (d, J = 54.6 Hz, 1H), 3.73 – 3.38 (m, 5H), 3.28 (s, 1H), 2.97 – 2.76 (m, 2H), 2.65 – 2.43 (m, 2H), 2.41 – 2.19 (m, 6H), 2.07 – 1.88 (m, 7H), 1.84 – 1.73 (m, 1H), 1.51 – 1.20 (m, 1H), 0.91 (d, J = 6.5 Hz, 6H).

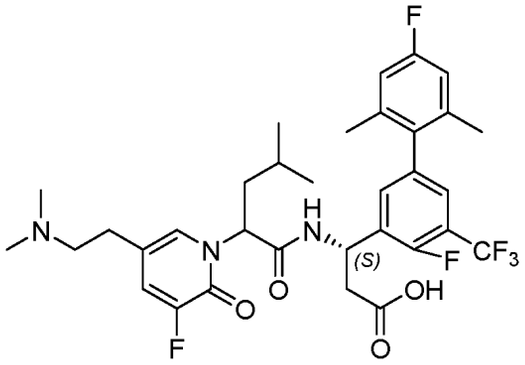
4-54. (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds DA-P1 and DA-P2)



DA-P1 ESI 592.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.35(S, 1H), 7.32(S, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 5.5 Hz, 1H), 6.59 (d, *J* = 6.7 Hz, 1H), 5.48-5.46 (m, 1H), 5.23 (t, *J* = 5.1 Hz, 1H), 3.08 – 2.98 (m, 1H), 2.68-2.67 (m, 2H), 2.56 (s, 6H), 2.51-2.35 (m, 3H), 2.25 – 2.11 (m, 6H), 1.97 – 1.74 (m, 11H), 1.36 – 1.24 (m, 1H), 0.88 – 0.76 (m, 6H).

DA-P2 ESI 592.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.40 (s, 1H), 7.29 (s, 1H), 6.78-6.74 (m, 3H), 6.67 (d, *J* = 7.0 Hz, 1H), 5.52-5.48 (m, 1H), 5.42-5.39 (m, 1H), 3.33-3.27 (m, 1H), 3.20-3.14 (m, 1H), 2.85 – 2.61 (m, 8H), 2.49-2.44 (m, 1H), 2.33-2.27 (m, 1H), 2.18 (s, 6H), 1.97 – 1.67 (m, 11H), 1.38 – 1.24 (m, 1H), 0.82-0.77 (m, 6H).

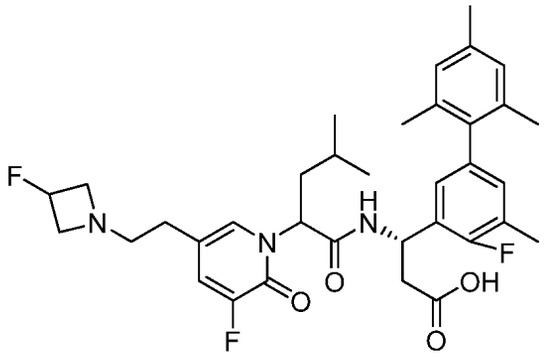
4-55. (3S)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DB-P1 and DB-P2)



DB-P1 ESI 654.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.55 (s, 1H), 7.50 – 7.37 (m, 1H), 7.40 – 7.25 (m, 2H), 6.89 (d, J = 9.6 Hz, 2H), 5.73 – 5.55 (m, 1H), 5.47 (t, J = 5.9 Hz, 1H), 3.27 – 3.13 (m, 1H), 2.98 – 2.82 (m, 3H), 2.78 (s, 6H), 2.73 – 2.64 (m, 1H), 2.63 – 2.50 (m, 1H), 2.13 – 1.97 (m, 5H), 1.93 (s, 3H), 1.42 (s, 1H), 1.11 – 0.79 (m, 6H).

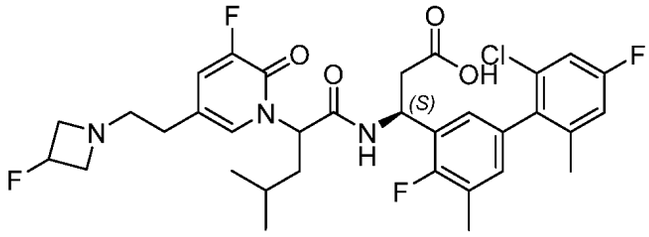
DB-P2 ESI 654.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.51 (s, 1H), 7.48 – 7.41 (m, 1H), 7.38 (t, J = 6.0 Hz, 2H), 6.90 (d, J = 9.6 Hz, 2H), 5.76 – 5.43 (m, 2H), 3.42 (d, J = 10.1 Hz, 1H), 3.28 (d, J = 12.8 Hz, 1H), 2.96 (d, J = 9.5 Hz, 1H), 2.85 (d, J = 7.2 Hz, 6H), 2.74 – 2.54 (m, 1H), 2.55 – 2.34 (m, 1H), 2.15 – 1.93 (m, 6H), 1.93 – 1.72 (m, 1H), 1.52 – 1.27 (m, 1H), 0.92 (t, J = 6.5 Hz, 6H).

4-56. (3S)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DC-P1 and DC-P2)



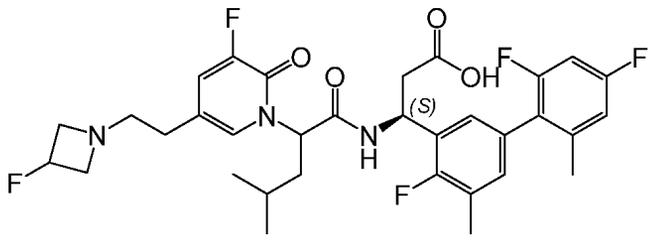
DC-P1 ESI 626.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.45 – 7.33 (m, 2H), 6.96 – 6.85 (m, 3H), 6.83 – 6.75 (m, 1H), 5.69 (t, *J* = 8.1 Hz, 1H), 5.52 – 5.45 (m, 1H), 5.30 – 5.10 (m, 1H), 4.23 – 4.09 (m, 1H), 4.02 – 3.89 (m, 1H), 3.78 – 3.62 (m, 2H), 3.26 – 3.16 (m, 2H), 2.78 – 2.56 (m, 4H), 2.36 – 2.25 (m, 6H), 2.00 – 1.92 (m, 5H), 1.88 (s, 3H), 1.48 – 1.39 (m, 1H), 0.98 – 0.86 (m, 6H).
DC-P2 ESI 626.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.45 – 7.35 (m, 2H), 6.97 – 6.86 (m, 4H), 5.76 – 5.62 (m, 2H), 5.42 – 5.20 (m, 1H), 4.49 – 4.28 (m, 2H), 4.12 – 3.95 (m, 2H), 3.44 – 3.36 (m, 2H), 2.78 – 2.63 (m, 2H), 2.67 – 2.52 (m, 1H), 2.61 – 2.52 (m, 1H), 2.37 – 2.25 (m, 6H), 2.01 – 1.91 (m, 7H), 1.85 – 1.69 (m, 1H), 1.43 –1.36(m, 1H), 0.96 – 0.85 (m, 6H).

4-57. (3*S*)-3-(2'-chloro-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DD-P1 and DD-P2)



DD-P1 ESI 650.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) *δ* 7.43 – 7.34 (m, 2H), 7.17 – 7.13 (m, 1H), 7.06 – 7.01 (m, 1H), 6.89 – 6.85 (m, 1H), 5.72 – 5.67 (m, 1H), 5.54 – 5.49 (m, 1H), 5.32 – 5.09 (m, 1H), 4.15 – 3.65 (m, 4H), 3.19 – 3.10 (m, 2H), 2.78 – 2.60 (m, 4H), 2.31 (s, 3H), 2.08 – 1.92 (m, 5H), 1.49 – 1.39 (m, 1H), 0.97– 0.93 (m, 6H).
DD-P2 ESI 650.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.39 – 7.36 (m, 2H), 7.15 (d, *J* = 8.5 Hz, 1H), 7.08 – 6.96 (m, 3H), 5.73 – 5.61 (m, 2H), 5.41 – 5.22 (m, 1H), 4.48 – 4.28 (m, 2H), 4.11 – 3.94 (m, 2H), 3.42 – 3.33 (m, 2H), 2.80 – 2.47 (m, 4H), 2.34 (d, *J* = 1.8 Hz, 3H), 2.09 (d, *J* = 2.7 Hz, 3H), 2.03 – 1.90 (m, 1H), 1.83 – 1.72 (m, 1H), 1.44 – 1.30 (m, 1H), 0.94 – 0.89 (m, 6H).

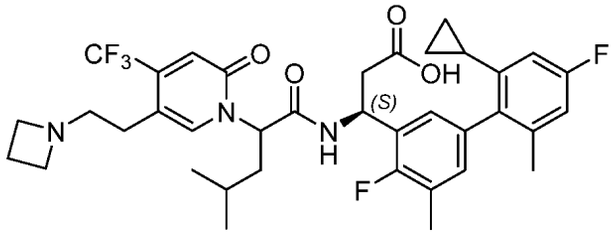
4-58. (3*S*)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2',4,4'-trifluoro-5,6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds DE-P1 and DE-P2)



DE-P1 ESI 634.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.43 (s, 1H), 7.36 (d, *J* = 10.3 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.85 (t, *J* = 9.2 Hz, 1H), 5.69 (t, *J* = 8.1 Hz, 1H), 5.53 – 5.50 (m, 1H), 5.30 – 5.08 (m, 1H), 4.09 – 3.99 (m, 2H), 3.77 – 3.63 (m, 2H), 3.15 – 3.12 (m, 2H), 2.79 – 2.69 (m, 2H), 2.66 – 2.62 (m, 2H), 2.31 (s, 3H), 2.09 (s, 3H), 1.97 (t, *J* = 7.6 Hz, 2H), 1.51 – 1.37 (m, 1H), 0.98 – 0.93 (m, 6H).

DE-P2 ESI 634.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.43 – 7.32 (m, 2H), 7.06 (d, *J* = 6.7 Hz, 2H), 6.93 (d, *J* = 9.3 Hz, 1H), 6.88 – 6.83 (m, 1H), 5.74 – 5.59 (m, 2H), 5.39 – 5.24 (m, 1H), 4.42 – 4.32 (m, 2H), 4.10 – 3.88 (m, 2H), 3.40 – 3.37 (m, 2H), 2.81 – 2.71 (m, 2H), 2.65 – 2.60 (m, 1H), 2.55 – 2.48 (m, 1H), 2.34 (d, *J* = 1.6 Hz, 3H), 2.16 (s, 3H), 2.03 – 1.93 (m, 1H), 1.86 – 1.75 (m, 1H), 1.45 – 1.33 (m, 1H), 0.93– 0.91(m, 6H).

4-59. (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2'-cyclopropyl-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds DF-P1 and DF-P2)

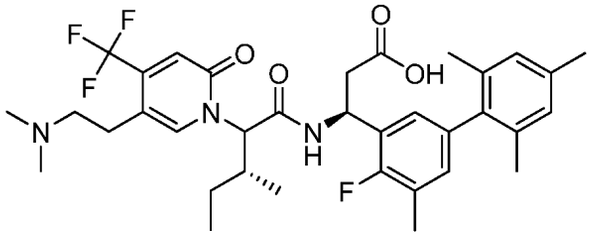


DF-P1 ESI 688.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 6.95 (dd, *J* = 19.9, 7.2 Hz, 2H), 6.86 – 6.64 (m, 2H), 6.55 – 6.23 (m, 1H), 5.75 – 5.49 (m, 2H), 3.85 (t, *J* = 7.7 Hz, 4H), 3.33 (m, *J* = 3.2, 1.6 Hz, 2H), 3.13 (m, *J* = 6.8 Hz, 2H), 2.90 – 2.58 (m, 2H), 2.51 – 2.21 (m, 5H), 2.01 (d, *J* = 5.3 Hz, 4H), 1.87 (s, 1H), 1.40 (s, 2H), 1.07 – 0.85 (m, 6H), 0.75 (m, *J* = 8.6, 3.5 Hz, 1H), 0.66 – 0.43 (m, 3H).

DF-P2 ESI 688.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.74 (d, *J* = 11.5 Hz, 1H), 6.94 (m, *J* = 46.9, 28.6, 8.1 Hz, 4H), 6.50 (d, *J* = 10.4 Hz, 1H), 5.78 (m, *J* = 11.0, 3.1 Hz, 1H), 5.62 (m, *J* = 7.3 Hz,

1H), 4.13 (m, *J* = 8.0 Hz, 4H), 3.50 – 3.32 (m, 2H), 2.94 (d, *J* = 16.3 Hz, 1H), 2.81 (d, *J* = 7.7 Hz, 2H), 2.68 – 2.61 (m, 1H), 2.57 – 2.42 (m, 3H), 2.34 (d, *J* = 1.1 Hz, 3H), 2.05 – 1.79 (m, 4H), 1.65 (m, *J* = 13.9, 7.1 Hz, 1H), 1.50 – 1.30 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.74 (m, *J* = 14.0, 7.3 Hz, 2H), 0.60 (m, *J* = 6.4, 5.0 Hz, 2H).

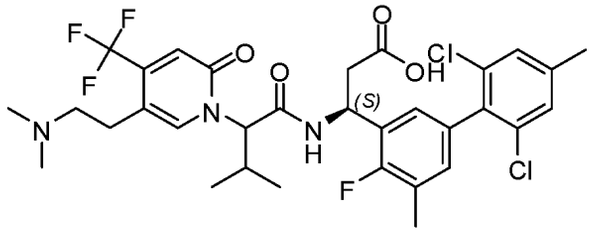
4-60. (3*S*)-3-((3*R*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds DG-P1 and DG-P2)



DG-P1 ESI 646.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.94 (s, 1H), 6.89 (s, 1H), 6.82 – 6.75 (m, 3H), 6.66 (s, 1H), 5.65 – 5.53 (m, 1H), 5.33 (d, *J* = 11.3 Hz, 1H), 3.05 – 2.83 (m, 5H), 2.82 – 2.62 (m, 6H), 2.40 – 2.18 (m, 8H), 2.03 – 1.88 (m, 3H), 1.78 – 1.67 (m, 1H), 1.63 (s, 3H), 1.38 – 1.21 (m, 1H), 1.07 – 0.96 (m, 3H), 0.75 (d, *J* = 6.5 Hz, 3H).

DG-P2 ESI 646.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.92 (s, 1H), 6.91 – 6.72 (m, 5H), 5.69 – 5.52 (m, 1H), 5.21 (d, *J* = 10.9 Hz, 1H), 3.14 – 2.79 (m, 3H), 2.68 (s, 6H), 2.55 – 2.36 (m, 2H), 2.22 – 2.06 (m, H), 1.84 (d, *J* = 3.6 Hz, 4H), 1.32 – 0.99 (m, 3H), 0.93 – 0.61 (m, 7H).

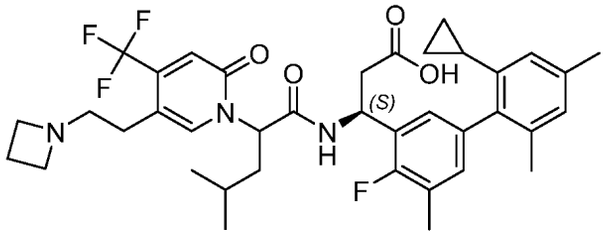
4-61. (3S)-3-(2',6'-dichloro-4-fluoro-4',5-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylbutanamido)propanoic acid (diastereomeric compounds DH-P1 and DH-P2)



DH-P1 ESI 672.1 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ: 7.91 (s, 1H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.14 (d, *J* = 5.2 Hz, 1H), 6.90 (t, *J* = 6.0 Hz, 2H), 6.67 (d, *J* = 5.6 Hz, 1H), 5.64 – 5.60 (m, 1H), 5.29 (d, *J* = 11.2 Hz, 1H), 2.97 – 2.85 (m, 4H), 2.78 – 2.61 (m, 8H), 2.46 – 2.40 (m, 1H), 2.36 (s, 3H), 2.27 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H).

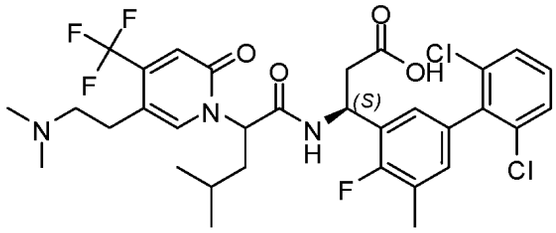
DH-P2 ESI 672.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ: 8.01 (s, 1H), 7.30 (s, 2H), 7.09 – 7.07 (m, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.90 (s, 1H), 5.78 – 5.74 (m, 1H), 5.23 (d, *J* = 11.2 Hz, 1H), 3.27 – 3.20 (m, 1H), 3.17 – 3.11 (m, 1H), 3.09 – 3.01 (m, 1H), 2.99 – 2.93 (m, 1H), 2.78 (s, 6H), 2.61 – 2.50 (m, 2H), 2.47 – 2.37 (m, 4H), 2.31 (d, *J* = 1.2 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H).

4-62. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds DI-P1 and DI-P2)



DI-P1 ESI 684.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 6.97 – 6.78 (m, 4H), 6.58 (s, 1H), 5.69 – 5.59 (m, 2H), 3.97 – 3.94 (m, 4H), 3.26 – 3.21 (m, 2H), 2.86 – 2.81 (m, 2H), 2.72 – 2.68 (m, 2H), 2.46 – 2.38 (m, 2H), 2.29 (d, *J* = 4.9 Hz, 6H), 2.03 – 1.97 (m, 3H), 1.85 (s, 2H), 1.48 – 1.31 (m, 2H), 0.98 – 0.91 (m, 6H), 0.67 (d, *J* = 8.4 Hz, 1H), 0.59 – 0.44 (m, 3H).
DI-P2 ESI 684.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.73 (d, *J* = 10.5 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.91 (s, 1H), 6.90 (s, 1H), 6.59 (s, 1H), 5.78 – 5.75 (m, 1H), 5.64 – 5.59 (m, 1H), 4.14 – 4.10 (m, 4H), 3.47 – 3.38 (m, 2H), 2.97 – 2.92 (m, 1H), 2.85 – 2.75 (m, 1H), 2.69 – 2.60 (m, 1H), 2.55 – 2.45 (m, 3H), 2.34 (s, 3H), 2.29 (s, 3H), 2.05 – 1.96 (m, 4H), 1.71 – 1.61 (m, 1H), 1.49 – 1.39 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.70 – 0.66 (m, 2H), 0.58 – 0.55 (m, 2H).

4-63. (3S)-3-(2',6'-dichloro-4-fluoro-5-methylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DJ-P1 and DJ-P2)

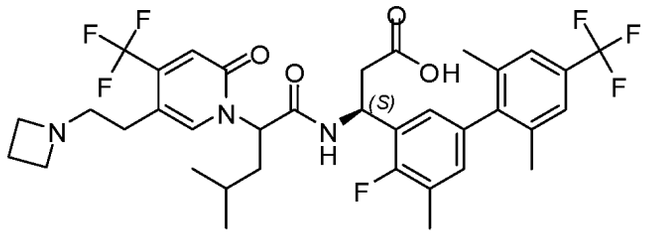


DJ-P1 ESI 672.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ: 7.89 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.75 (s, 1H), 5.72 – 5.68 (m, 1H), 5.60 – 5.56 (m, 1H), 3.10 – 3.01 (m, 2H), 2.94 – 2.92 (m, 2H), 2.74 – 2.65 (m, 8H), 2.27 (d, *J* =

1.2 Hz, 3H), 2.01 – 1.93 (m, 2H), 1.47 – 1.41 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H).

DJ-P2 ESI 672.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ: 7.91 – 5.88 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.08 – 7.02 (m, 2H), 6.89 (s, 1H), 5.78 – 5.74 (m, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 3.27 – 3.15 (m, 2H), 3.06 – 2.95 (m, 2H), 2.80 (s, 6H), 2.65 – 2.60 (m, 1H), 2.55 – 2.49 (m, 1H), 2.32 (s, 3H), 1.99 – 1.92 (m, 1H), 1.71 – 1.64 (m, 1H), 1.41 – 1.34 (m, 1H), 0.86 – 0.84 (m, 6H).

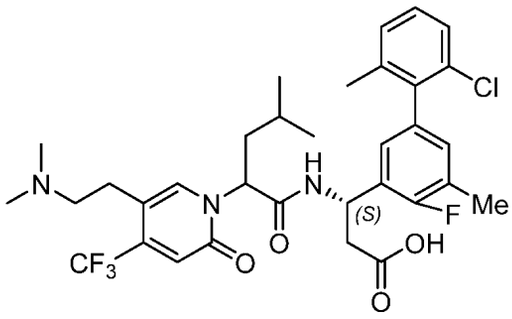
4-64. (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid (diastereomeric compounds DK-P1 and DK-P2)



DK-P1 ESI 712.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ: 7.88 (s, 1H), 7.39 (s, 1H), 7.35 (s, 1H), 6.91 (t, *J* = 6.2 Hz, 2H), 6.70 (s, 1H), 5.66 – 5.57 (m, 2H), 4.04 (t, *J* = 8.2 Hz, 4H), 3.29 (t, *J* = 7.4 Hz, 2H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.78 – 2.67 (m, 2H), 2.48 – 2.40 (m, 2H), 2.30 (d, *J* = 1.2 Hz, 3H), 2.08 (s, 3H), 2.03 – 1.99 (m, 2H), 1.91 (s, 3H), 1.47 – 1.40 (m, 1H),), 0.95 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H).

DK-P2 ESI 712.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ: 7.74 (s, 1H), 7.41 (s, 2H), 6.98 (s, 1H), 6.96 (s, 1H), 6.90 (s, 1H), 5.79 – 5.76 (m, 1H), 5.60 (t, *J* = 8.0 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 4H), 3.48 – 3.42 (m, 1H), 3.38 – 3.33 (m, 1H), 2.98 – 2.91 (m, 1H), 2.84 – 2.77 (m, 1H), 2.69 – 2.64 (m, 1H), 2.55 – 2.45 (m, 3H), 2.35 (d, *J* = 1.6 Hz, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.03 – 1.96 (m, 1H), 1.69 – 1.62 (m, 1H), 1.46 – 1.36 (m, 1H), 0.89 (d, *J* = 1.6 Hz, 3H), 0.87 (d, *J* = 2.0 Hz, 3H).

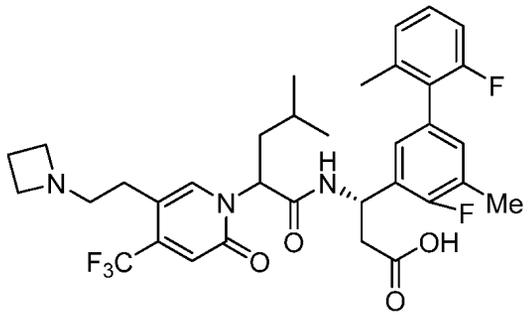
4-65. (3S)-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DL-P1 and DL-P2)



DL-P1 ESI 652.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (d, J = 4.5 Hz, 1H), 7.37 – 7.09 (m, 3H), 6.93 (m, J = 10.9, 4.9 Hz, 2H), 6.75 (d, J = 6.5 Hz, 1H), 5.68 (m, J = 30.2, 23.4 Hz, 2H), 3.00 (d, J = 50.0 Hz, 4H), 2.73 (d, J = 14.3 Hz, 8H), 2.30 (s, 3H), 2.13 – 1.83 (m, 5H), 1.45 (d, J = 6.4 Hz, 1H), 0.96 (m, J = 12.9, 6.6, 2.5 Hz, 6H).

DL-P2 ESI 652.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.34 – 7.09 (m, 3H), 7.11 – 6.51 (m, 3H), 5.69 (m, J = 21.6, 10.6, 4.3 Hz, 2H), 3.15 (s, 2H), 2.98 (s, 2H), 2.88 – 2.53 (m, 8H), 2.34 (s, 3H), 2.08 (d, J = 5.6 Hz, 3H), 1.98 – 1.81 (m, 1H), 1.78 (s, 1H), 1.40 (s, 1H), 0.89 (m, J = 6.4, 4.6 Hz, 6H).

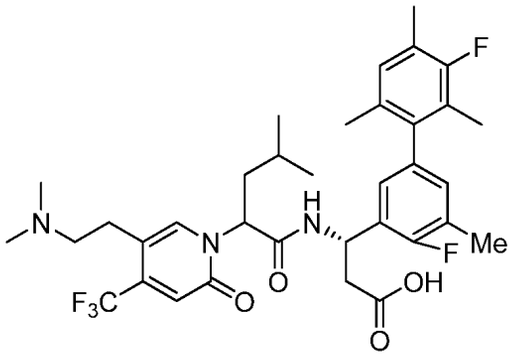
4-66. (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2',4-difluoro-5,6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds DM-P1 and DM-P2)



DM-P1 ESI 648.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.30 – 7.23 (m, 1H), 7.16 – 7.09 (m, 1H), 7.06 –6.92 (m, 3H), 6.81 (s, 1H), 5.71 – 5.60 (m, 2H), 4.01 (t, J = 8.1 Hz, 4H), 3.29 (s, 2H), 2.86 (t, J = 6.8 Hz, 2H), 2.72 (d, J = 6.6 Hz, 2H), 2.46 – 2.36 (m, 2H), 2.36 – 2.31 (m, 3H), 2.10 (s, 3H), 2.00 (t, J = 7.6 Hz, 2H), 1.51 – 1.42 (m, 1H), 0.98 – 0.93 (m, 6H).

DM-P2 ESI 648.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.31 –7.19 (m, 1H), 7.15 – 7.04 (m, 3H), 6.99 (t, J = 8.8 Hz, 1H), 6.92 (s, 1H), 5.81 –5.75 (m, 1H), 5.64 (t, J = 7.6 Hz, 1H), 4.14 (t, J = 8.0 Hz, 4H), 3.49 – 3.35 (m, 2H), 2.94 (d, J = 15.7 Hz, 1H), 2.87 – 2.75 (m, 1H), 2.69 –2.56 (m, 1H), 2.57 – 2.43 (m, 3H), 2.35 (d, J = 1.5 Hz, 3H), 2.17 (d, J = 8.1 Hz, 3H), 2.04 – 1.95 (m, 1H), 1.72 – 1.62 (m, 1H), 1.46 –1.32 (m, 1H), 0.97 –0.91 (m, 6H).

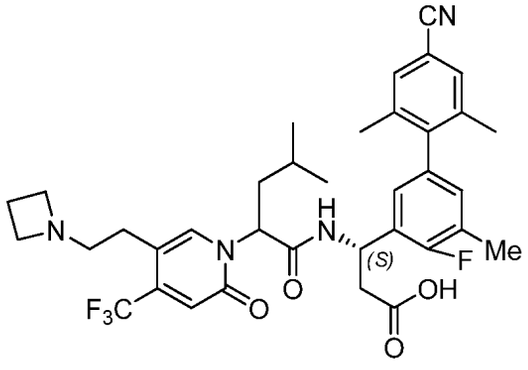
4-67. (3*S*)-3-(3',4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DN-P1 and DN-P2)



DN-P1 ESI 664.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.01 – 6.79 (m, 4H), 5.78 – 5.58 (m, 2H), 3.29 – 3.07 (m, 2H), 3.04 – 2.89 (m, 2H), 2.81 (s, 6H), 2.70 – 2.42 (m, 2H), 2.33 (s, 3H), 2.26 (s, 3H), 2.13 – 1.83 (m, 7H), 1.81 – 1.60 (m, 1H), 1.52 – 1.30 (m, 1H), 1.02 – 0.81 (m, 6H).

DN-P2 ESI 664.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 6.99 – 6.68 (m, 4H), 5.82 – 5.50 (m, 2H), 3.19 – 2.89 (m, 4H), 2.83 – 2.54 (m, 8H), 2.38 – 2.22 (m, 6H), 2.13 – 1.80 (m, 5H), 1.72 (d, J = 14.7 Hz, 3H), 1.51 – 1.36 (m, 1H), 1.06 – 0.84 (m, 6H).

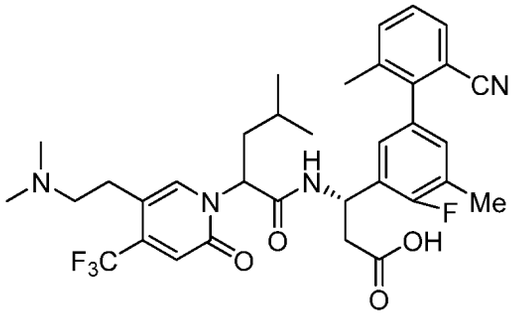
4-68. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyano-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds DO-P1 and DO-P2)



DO-P1 ESI 669.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.47 (d, J = 10.3 Hz, 2H), 6.91 (d, J = 6.7 Hz, 2H), 6.75 (s, 1H), 5.59 (d, J = 7.7 Hz, 2H), 4.06 (t, J = 8.1 Hz, 4H), 3.31 – 3.27 (m, 2H), 2.98 – 2.85 (m, 2H), 2.79 – 2.64 (m, 2H), 2.58 – 2.39 (m, 2H), 2.31 (s, 3H), 2.14 – 1.88 (m, 8H), 1.54 – 1.27 (m, 1H), 1.10 – 0.80 (m, 6H).

DO-P2 ESI 669.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.50 (s, 2H), 7.06 – 6.84 (m, 3H), 5.90 – 5.71 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 4.10 (s, 4H), 3.36 (s, 2H), 3.09 – 2.74 (m, 2H), 2.74 – 2.60 (m, 1H), 2.55 – 2.39 (m, 3H), 2.35 (s, 3H), 2.13 – 1.89 (m, 7H), 1.75 – 1.62 (m, 1H), 1.50 – 1.35 (m, 1H), 0.98 – 0.81 (m, 6H).

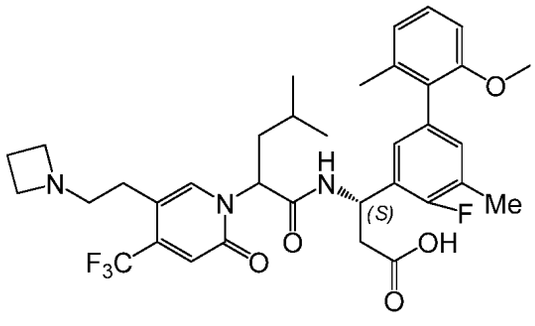
4-69. (3S)-3-(2'-cyano-4-fluoro-5,6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DP-P1 and DP-P2)



DP-P1 ESI 643.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.59 (s, 2H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.06 (s, 2H), 6.71 (d, *J* = 26.7 Hz, 1H), 5.73 (s, 1H), 5.60 (d, *J* = 7.3 Hz, 1H), 3.10 (s, 2H), 2.93 (d, *J* = 8.3 Hz, 2H), 2.80 – 2.69 (m, 8H), 2.32 (s, 3H), 2.19 (s, 2H), 2.00 (s, 3H), 1.49 – 1.42 (m, 1H), 1.00 – 0.92 (m, 6H).

DP-P1 ESI 643.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.66 – 7.52 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 6.4 Hz, 2H), 6.90 (s, 1H), 5.77 – 5.59 (m, 2H), 3.23 (s, 2H), 3.01 (s, 2H), 2.83 (s, 6H), 2.69 – 2.53 (m, 1H), 2.58 – 2.49 (m, 1H), 2.37 (d, *J* = 1.6 Hz, 3H), 2.19 (s, 3H), 2.05 – 1.96 (m, 1H), 1.81 (s, 1H), 1.42 – 1.36 (m, 1H), 0.99 – 0.91 (m, 6H).

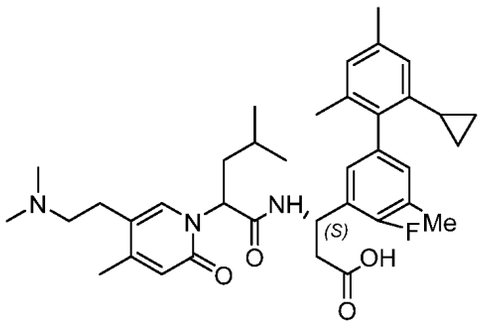
4-70. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2'-methoxy-5,6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds DQ-P1 and DQ-P2)



DQ-P1 ESI 660.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.99 – 6.82 (m, 5H), 5.70 – 5.62 (m, 2H), 4.01 – 3.96 (m, 4H), 3.66 (s, 3H), 3.30 – 3.27 (m, 2H), 2.88 – 2.85 (m, 2H), 2.71 (d, *J* = 7.4 Hz, 2H), 2.45 – 2.39 (m, 2H), 2.29 (s, 3H), 2.02 – 1.93 (m, 5H), 1.45 – 1.38 (m, 1H), 0.97 – 0.93 (m, 6H).

DQ-P2 ESI 660.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.00 – 6.87 (m, 5H), 5.79 – 5.75 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 4.13 (t, *J* = 7.9 Hz, 4H), 3.68 (s, 3H), 3.49 – 3.35 (m, 2H), 2.97– 2.91 (d, *J* = 16.1 Hz, 1H), 2.85 – 2.77 (m, 1H), 2.66 – 2.62(m, 1H), 2.56 – 2.42 (m, 3H), 2.32 (d, *J* = 1.7 Hz, 3H), 2.04 (s, 3H), 2.02 – 1.97 (m, 1H), 1.72 – 1.60 (m, 1H), 1.49 – 1.36 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 6H).

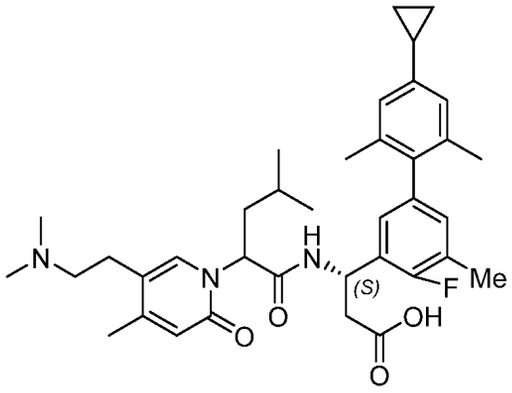
4-71. (3*S*)-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DR-P1 and DR-P2)



DR-P1 ESI 618.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 1.8 Hz,1), 6.91 – 6.84 (m, 3H), 6.57 (d, *J* = 11.0 Hz, 1H), 6.38 (d, *J* = 8.9 Hz, 1H), 5.59 (d, *J* = 5.8 Hz, 1H), 5.46 (t, *J* = 5.9 Hz, 1H), 3.22 – 3.06 (m, 2H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.74 (s, 6H), 2.71 – 2.56 (m, 2H), 2.27 (d, *J* = 13.3 Hz, 9H), 2.04 – 1.87 (m, 5H), 1.48 – 1.38 (m, 2H), 0.95 – 0.89 (m, 6H), 0.72 – 0.67 (m, 1H), 0.63 – 0.55 (m, 1H), 0.53 – 0.48 (m, 2H).

DR-P2 ESI 618.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.54 (d, *J* = 10.5 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.89 (s, 1H), 6.59 (s, 1H), 6.44 (d, *J* = 5.1 Hz, 1H), 5.65 –5.56 (m, 2H), 3.34 – 3.26 (m, 2H), 3.20 – 3.13 (m, 2H), 2.94 – 2.88 (m, 2H), 2.81 (d, *J* = 2.0 Hz, 6H), 2.64 – 2.57 (m, 1H), 2.48 – 2.41 (m, 1H), 2.32 – 2.246 (m, 9H), 1.99 – 1.92 (m, 4H), 1.81 – 1.74 (m, 1H), 1.49 – 1.33 (m, 1H), 0.92 – 0.85 (m, 6H), 0.68 – 0.63 (m, 2H), 0.58 – 0.51 (m, 2H).

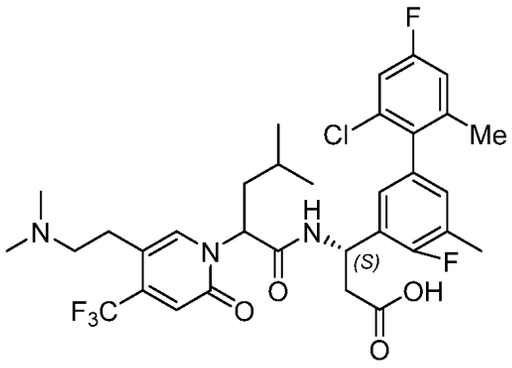
4-72. (3S)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DS-P1 and DS-P2)



DS-P1 ESI 618.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.46 (s, 1H), 6.84 – 6.65 (m, 3H), 6.45 (d, J = 11.2 Hz, 1H), 6.27 (d, J = 8.7 Hz, 1H), 5.48-5.46 (m, 1H), 5.33 (d, J = 5.6 Hz, 1H), 3.15-2.95 (m, 2H), 2.78-2.74 (m, 3H), 2.60 (d, J = 25.4 Hz, 6H), 2.58 – 2.40 (m, 2H), 2.17 (s, 6H), 2.13(s, 3H), 1.95 – 1.73 (m, 5H), 1.34-1.28 (m, 2H), 0.86 – 0.73 (m, 6H), 0.62 – 0.32 (m, 4H).

DS-P2 ESI 618.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.43(s, 1H), 7.40(s, 1H), 6.84 (t, J = 6.2 Hz, 2H), 6.77 (s, 1H), 6.47 (s, 1H), 6.32 (d, J = 5.5 Hz, 1H), 5.52-5.44 (m, 2H), 3.09-3.06 (m, 1H), 2.88 – 2.67 (m, 8H), 2.51-2.45 (m, 1H), 2.37-2.29 (m, 1H), 2.24 – 2.09 (m, 9H), 1.85-1.81 (m, 4H), 1.70 – 1.59 (m, 1H), 1.39 – 1.16 (m, 2H), 0.78-0.76 (m, 6H), 0.54 (t, J = 7.6 Hz, 2H), 0.45 (d, J = 4.5 Hz, 2H).

4-73. (3*S*)-3-(2'-chloro-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DT-P1 and DT-P2)

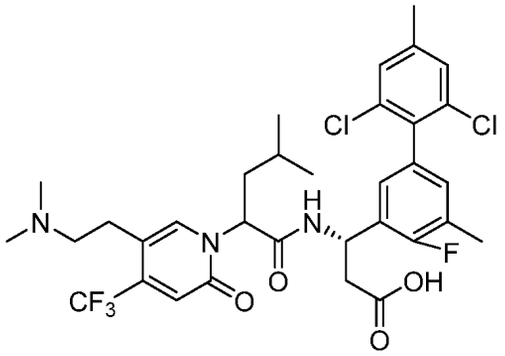


DT-P1 ESI 670.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.90 (d, J = 3.1 Hz, 1H), 7.14 – 6.92 (m, 4H), 6.76 (d, J = 5.6 Hz, 1H), 5.72 – 5.65 (m, 1H), 5.60 – 5.56 (m, 1H), 3.10 – 2.87 (m, 4H), 2.76 – 2.66 (m, 8H), 2.30 (s, 3H), 2.09 – 1.91 (m, 5H), 1.47 – 1.41 (m, 1H), 1.00 – 0.92 (m, 6H).

DT-P2 ESI 670.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.16 – 7.12 (m, 1H), 7.07 – 6.95 (m, 3H), 6.91 (d, J = 2.7 Hz, 1H), 5.74 – 5.59(m, 2H), 3.32 – 3.21 (m, 2H), 3.03 – 2.99 (m, 2H),

2.84 (d, *J* = 2.9 Hz, 6H), 2.67 – 2.49 (m, 2H), 2.34 (d, *J* = 1.6 Hz, 3H), 2.03 – 1.90 (m, 1H), 1.76 – 1.67 (m, 1H), 1.46 – 1.37 (m, 1H), 0.92 – 0.89 (m, 6H).

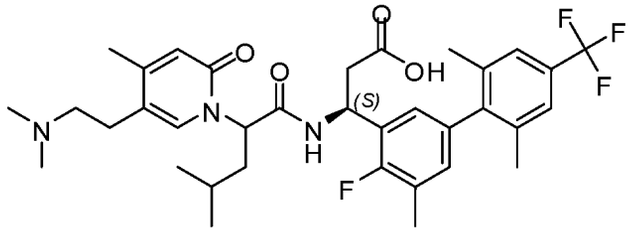
4-74. (3*S*)-3-(2',6'-dichloro-4-fluoro-4',5-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DU-P1 and DU-P2)



DU-P1 ESI 686.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.31 (s, 1H), 7.23 (s, 1H), 7.02 – 6.91 (m, 2H), 6.76 (s, 1H), 5.76 – 5.66 (m, 1H), 5.63 – 5.53 (m, 1H), 3.15 – 3.04 (m, 2H), 2.94 (t, *J* = 11.0 Hz, 2H), 2.80 – 2.66 (m, 8H), 2.38 (s, 3H), 2.29 (d, *J* = 1.3 Hz, 3H), 2.04 – 1.92 (m, 2H), 1.51 – 1.42 (m, 1H), 1.01 – 0.90 (m, 6H).

DU-P2 ESI 686.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.32 (s, 2H), 7.09 – 6.99 (m, 2H), 6.91 (s, 1H), 5.79 – 5.71 (m, 1H), 5.65 (t, *J* = 7.7 Hz, 1H), 3.30 – 3.15 (m, 2H), 3.00 (t, *J* = 6.8 Hz, 2H), 2.81 (s, 6H), 2.67 – 2.50 (m, 2H), 2.39 (s, 3H), 2.33 (d, *J* = 1.5 Hz, 3H), 2.02 – 1.92 (m, 1H), 1.73 – 1.65 (m, 1H), 1.44 – 1.36 (m, 1H), 0.91 – 0.85 (m, 6H).

4-75. (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid (diastereomeric compounds DV-P1 and DV-P2)

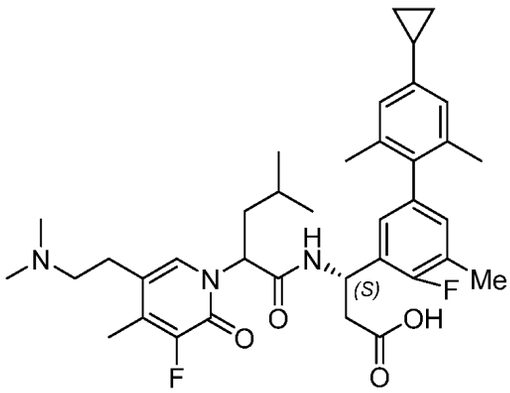


DV-P1 ESI 646.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ: 7.59 (s, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.84 (d, *J* = 6.4 Hz, 1H), 6.28 (s, 1H), 5.55 (t, *J* = 5.6 Hz, 1H), 5.49 (t, *J* = 6.0 Hz, 1H), 3.16 – 3.08 (m, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.78 (s, 6H), 2.73 – 2.68 (m, 1H), 2.65 –

2.60 (m, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.08 (s, 3H), 2.01 – 1.90 (m, 5H), 1.45 – 1.38 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H).

DV-P2 ESI 646.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ: 7.55 (s, 1H), 7.41 (s, 2H), 6.95 – 6.93 (m, 1H), 6.90 (d, *J* = 6.4 Hz, 1H), 6.41 (s, 1H), 5.63 – 5.60 (m, 1H), 5.58 – 5.56 (m, 1H), 3.38 – 3.36 (m, 1H), 3.25 – 3.19 (m, 1H), 2.95 – 2.90 (m, 2H), 2.85 (s, 6H), 2.64 – 2.59 (m, 1H), 2.50 – 2.44 (m, 1H), 2.34 (d, *J* = 1.6 Hz, 3H), 2.26 (s, 3H), 2.08 (s, 6H), 2.00 – 1.93 (m, 1H), 1.83 – 1.76 (m, 1H), 1.42 – 1.35 (m, 1H), 0.89 (t, *J* = 6.4 Hz, 6H).

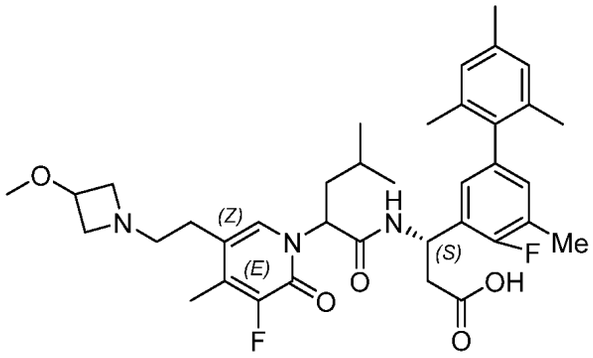
4.76. (3S)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DW-P1 and DW-P2)



DW-P1 ESI 636.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.47 (s, 1H), 6.94 – 6.78 (m, 3H), 6.57 (d, *J* = 12.7 Hz, 1H), 5.74 – 5.57 (m, 1H), 5.46 (t, *J* = 5.9 Hz, 1H), 3.25-3.10(m, 2H), 2.92 (t, *J* = 6.9 Hz, 2H), 2.75 (s, 6H), 2.70 – 2.52 (m, 2H), 2.30-2.25 (m, 9H), 1.99-1.88 (m, 5H), 1.46-1.39 (m, 2H), 0.97 – 0.86 (m, 6H), 0.72 – 0.43 (m, 4H).

DW-P2 ESI 636.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.42 (d, *J* = 11.3 Hz, 1H), 6.97 (t, *J* = 8.2 Hz, 2H), 6.89 (s, 1H), 6.59 (s, 1H), 5.72 – 5.52 (m, 2H), 3.32-3.22 (m, 2H), 2.98-2.90 (m, 2H), 2.85 (s, 6H), 2.67 – 2.38 (m, 2H), 2.32-2.25 (m, 9H), 2.00-1.98 (m, 4H), 1.83 – 1.67 (m, 1H), 1.51 – 1.26 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.70 – 0.48 (m, 4H).

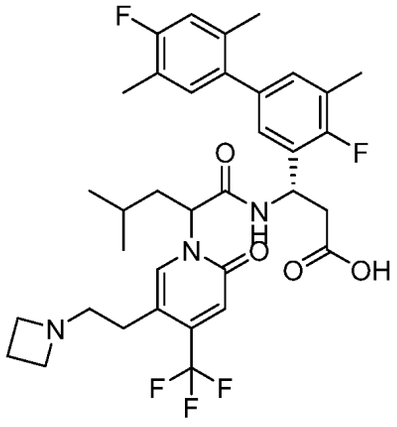
4-77. (3S)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds DX-P1 and DX-P2)



DX-P1 ESI 652.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.26 (s, 1H), 6.84 – 6.68 (m, 4H), 5.54 – 5.45 (m, 1H), 5.41 (t, *J* = 6.3 Hz, 1H), 4.14-3.93 (m, 3H), 3.64 – 3.54 (m, 1H), 3.52-3.50 (m, 1H), 3.25-3.16(m, 5H), 2.74-2.55 (m, 4H), 2.18(s, 6H),2.12 (d, *J* = 4.0 Hz , 3H), 1.88 – 1.74 (m, 8H), 1.29-1.25 (m, 1H), 0.83-0.78 (m, 6H).

DX-P2 ESI 652.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.20 (s, 1H), 6.85 – 6.72 (m, 4H), 5.61 – 5.43 (m, 2H), 4.36 – 4.08 (m, 3H), 3.84 – 3.61 (m, 2H), 3.32-3.22(m, 5H), 2.82-2.78 (m, 1H), 2.64-2.56 (m, 1H), 2.51-2.47 (m, 1H), 2.39-2.32 (m, 1H), 2.23 – 2.13 (m, 6H), 2.10 (d, *J* = 2.7 Hz, 3H), 1.90 – 1.73 (m, 8H), 1.68 – 1.51 (m, 1H), 1.32 – 1.20 (m, 1H), 0.79-0.74 (m, 6H).

4-78. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',5,5'-trimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds DY-P1 and DY-P2)

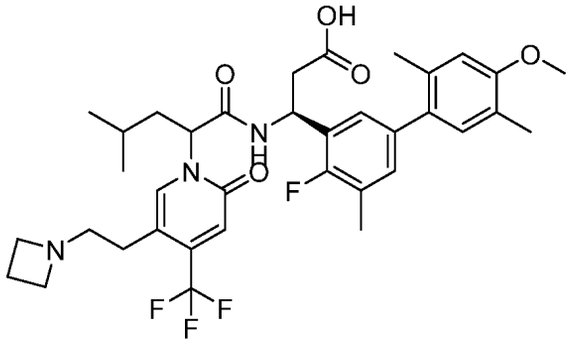


DY-P1 ESI 662.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.03-7.00 (m, 3H), 6.93 (d, *J* = 10.6 Hz, 1H), 6.81 (s, 1H), 5.70 – 5.63 (m, 1H), 5.59 (t, *J* = 6.7 Hz, 1H), 4.02 (t, *J* = 8.2 Hz, 4H), 3.30 (s, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 2.71 (d, *J* = 6.8 Hz, 2H), 2.42 -2.39(m, 2H), 2.30 (d, *J* = 1.4 Hz, 3H), 2.25 (s, 3H), 2.15 (s, 3H), 2.02 -2.19(m, 2H), 1.48 – 1.39 (m, 1H), 0.96-0.90 (m, 6H).

DY-P2 ESI 662.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.09-7.06 (m, 2H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.99 – 6.88 (m, 2H), 5.75-5.70 (m, 1H), 5.64 (t, *J* = 7.7 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 4H), 3.42-3.40 (m, 2H), 2.95 (d, *J* = 16.2 Hz, 1H), 2.82 -2.80(m, 1H), 2.64-2.60 (m, 1H), 2.55 – 2.43

(m, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H), 2.04 – 1.97 (m, 1H), 1.71-1.68 (m, 1H), 1.43-1.38 (m, 1H), 0.92 (t, *J* = 6.3 Hz, 6H).

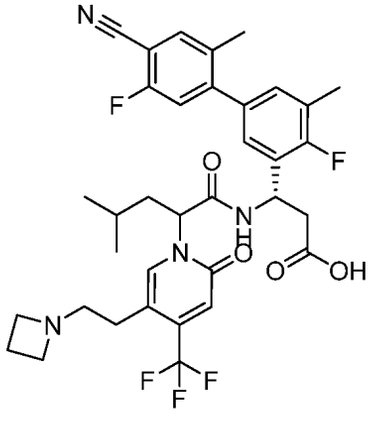
4-79. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,5'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds DZ-P1 and DZ-P2)



DZ-P1 ESI 674.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.03 (t, *J* = 7.3 Hz, 2H), 6.90 (s, 1H), 6.83 (s, 1H), 6.78 (s, 1H), 5.67 (t, *J* = 8.0 Hz, 1H), 5.59 (t, *J* = 6.7 Hz, 1H), 3.99 (t, *J* = 8.2 Hz, 4H), 3.86 (s, 3H), 3.29 (d, *J* = 3.5 Hz, 2H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.71 (d, *J* = 6.7 Hz, 2H), 2.44 – 2.34 (m, 2H), 2.29 (d, *J* = 1.6 Hz, 3H), 2.18 (s, 6H), 2.02 (t, *J* = 7.5 Hz, 2H), 1.46 – 1.39 (m, 1H), 0.96 (t, *J* = 6.2 Hz, 6H).

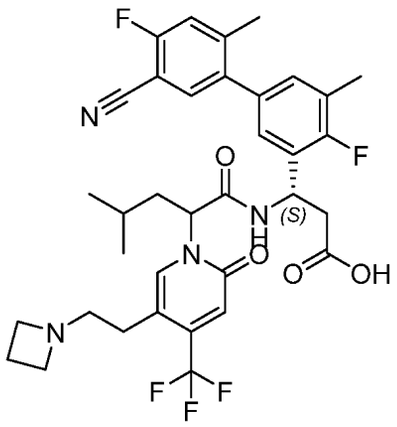
DZ-P2 ESI 674.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.14 – 7.03 (m, 2H), 6.93 (s, 2H), 6.80 (s, 1H), 5.80 – 5.71 (m, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 4.14 (t, *J* = 8.0 Hz, 4H), 3.86 (s, 3H), 3.50 – 3.36 (m, 2H), 2.95 (d, *J* = 15.7 Hz, 1H), 2.87 – 2.78 (m, 1H), 2.67 – 2.60 (m, 1H), 2.57 – 2.42 (m, 3H), 2.33 (d, *J* = 1.6 Hz, 3H), 2.20 (d, *J* = 19.2 Hz, 6H), 2.05 – 1.96 (m, 1H), 1.73 – 1.65 (m, 1H), 1.47 – 1.37 (m, 1H), 0.92 (t, *J* = 6.7 Hz, 6H).

4-80. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyano-4,5'-difluoro-2',5-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds EA-P1 and EA-P2)



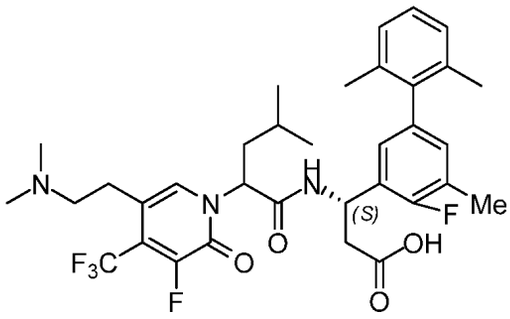
EA-P1 ESI 673.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.86 (s, 1H), 7.67 (d, *J* = 6.6 Hz, 1H), 7.24 – 7.07 (m, 3H), 6.79 (d, *J* = 7.4 Hz, 1H), 5.78 – 5.50 (m, 2H), 4.10 (t, *J* = 8.1 Hz, 4H), 3.41 – 3.34 (m, 2H), 2.92 – 2.65 (m, 4H), 2.61 – 2.40 (m, 2H), 2.32 (s, 3H), 2.23 (s, 3H), 2.15 – 1.86 (m, 2H), 1.54 – 1.38 (m, 1H), 0.97 (t, *J* = 6.6 Hz, 6H).
EA-P2 ESI 673.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.75 – 7.59 (m, 2H), 7.25 – 7.16 (m, 3H), 6.93 (s, 1H), 5.80 – 5.55 (m, 2H), 4.16 (t, *J* = 7.9 Hz, 4H), 3.50 – 3.37 (m, 2H), 3.04 – 2.77 (m, 2H), 2.72 – 2.43 (m, 4H), 2.36 (s, 3H), 2.28 (s, 3H), 2.06 – 1.96 (m, 1H), 1.83 – 1.64 (m, 1H), 1.53 – 1.29 (m, 1H), 0.97 – 0.89 (m, 6H).

4-81. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5'-cyano-4,4'-difluoro-2',5-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds EB-P1 and EB-P2)



EB-P1 ESI 673.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.55 (d, *J* = 6.7 Hz, 1H), 7.32 (d, *J* = 10.3 Hz, 1H), 7.10 (d, *J* = 6.4 Hz, 2H), 6.81 (s, 1H), 5.65 – 5.55 (m, 2H), 4.03 (t, *J* = 8.0 Hz, 4H), 3.32 – 3.26 (m, 2H), 2.84 (t, *J* = 7.0 Hz, 2H), 2.78 – 2.67 (m, 2H), 2.51 – 2.36 (m, 2H), 2.36 – 2.25 (m, 6H), 2.14 – 1.92 (m, 2H), 1.52 – 1.36 (m, 1H), 0.97 (t, *J* = 6.1 Hz, 6H).
EB-P2 ESI 673.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.57 (d, *J* = 6.7 Hz, 1H), 7.34 (d, *J* = 10.2 Hz, 1H), 7.14 (d, *J* = 6.7 Hz, 2H), 6.93 (s, 1H), 5.76 – 5.71 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.13 (t, *J* = 7.9 Hz, 4H), 3.49 – 3.35 (m, 2H), 3.00 – 2.87 (m, 1H), 2.88 – 2.75 (m, 1H), 2.68 – 2.60 (m, 1H), 2.57 – 2.42 (m, 3H), 2.39 – 2.28 (m, 6H), 2.05 – 1.95 (m, 1H), 1.79 – 1.63 (m, 1H), 1.48 – 1.37 (m, 1H), 0.92 (t, *J* = 6.6 Hz, 6H).

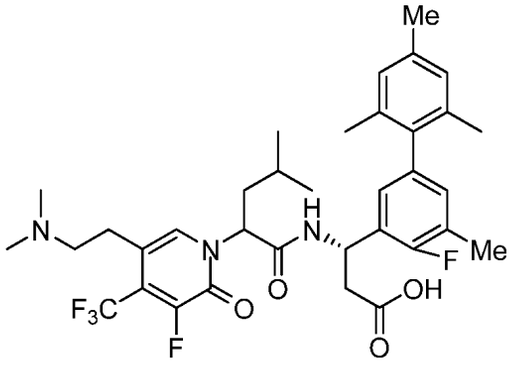
4-82. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds EC-P1 and EC-P2)



EC-P1 ESI 650.2 (M+H)+. 1H NMR (500 MHz, MeOD) δ 7.70 (s, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.89-6.85 (m, 2H), 5.69 (t, *J* = 8.0 Hz, 1H), 5.61 – 5.54 (m, 1H), 3.09-3.02 (m, 2H), 2.99 (d, *J* = 7.3 Hz, 2H), 2.74-2.70 (m, 8H), 2.30 (s, 3H), 2.05 – 1.94 (m, 5H), 1.86 (s, 3H), 1.44 (m, 1H), 0.94-0.90 (m, 6H).

EC-P2 ESI 650.2 (M+H)+. 1H NMR (500 MHz, MeOD) δ 7.62 (s, 1H), 7.18 – 7.07 (m, 3H), 6.94 (t, *J* = 6.8 Hz, 2H), 5.73-5.70 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 3.31 – 3.18 (m, 2H), 3.11 – 2.95 (m, 2H), 2.84 (s, 6H), 2.65-2.60 (m, 1H), 2.52 -2.48(m, 1H), 2.35-2.32 (m, 3H), 2.08 – 1.94 (m, 7H), 1.74 – 1.64 (m, 1H), 1.42-1.39 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 6H).

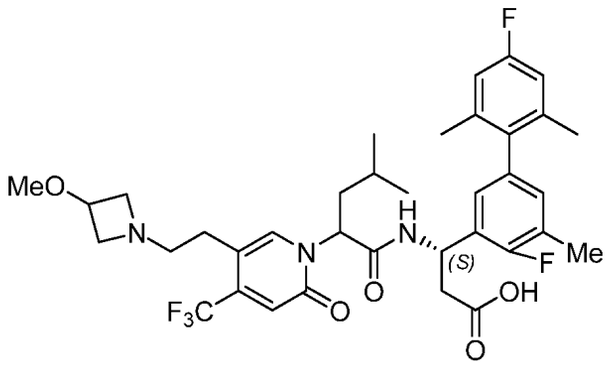
4-83. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds ED-P1 and ED-P2)



ED-P1 ESI 664.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 6.96 – 6.77 (m, 4H), 5.72 – 5.66 (m, 1H), 5.56 (s, 1H), 3.09 – 2.90 (m, 4H), 2.71 (d, *J* = 4.8 Hz, 8H), 2.29 (s, 6H), 2.08 – 1.91 (m, 5H), 1.82 (s, 3H), 1.44 (s, 1H), 0.95-0.90 (m, 6H).

ED-P2 ESI 664.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.62 (d, *J* = 12.1 Hz, 1H), 6.97 – 6.85 (m, 4H), 5.72-5.69 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.22 (qd, J = 13.0, 6.1 Hz, 2H), 3.13 – 2.89 (m, 2H), 2.82 (s, 6H), 2.64-2.60 (m, 1H), 2.49-2.45(m, 1H), 2.36 – 2.23 (m, 6H), 2.04 – 1.90 (m, 7H), 1.74 – 1.64 (m, 1H), 1.41-1.38 (m, 1H), 0.90-0.86 (m, 6H).

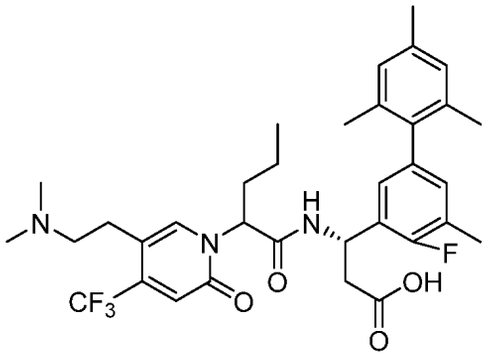
4-84. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EE-P1 and EE-P2)



EE-P1 ESI 692.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 6.96 – 6.68 (m, 5H), 5.75 – 5.48 (m, 2H), 4.26 – 4.01 (m, 3H), 3.74 – 3.52 (m, 2H), 3.31 (s, 3H), 3.14 (t, *J* = 6.8 Hz, 2H), 2.87 – 2.63 (m, 4H), 2.30 (s, 3H), 2.05 – 1.92 (m, 5H), 1.85 (s, 3H), 1.54 – 1.36 (m, 1H), 1.07 – 0.87 (m, 6H).

EE-P2 ESI 692.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.04 – 6.78 (m, 5H), 5.80 – 5.70 (m, 1H), 5.62 (t, *J* = 7.7 Hz, 1H), 4.49 – 4.21 (m, 3H), 4.01 – 3.74 (m, 2H), 3.46 – 3.35 (m, 5H), 3.03 – 2.77 (m, 2H), 2.68 – 2.44 (m, 2H), 2.34 (d, *J* = 1.7 Hz, 3H), 2.12 – 1.90 (m, 7H), 1.74 – 1.57 (m, 1H), 1.53 – 1.32 (m, 1H), 0.99 – 0.83 (m, 6H).

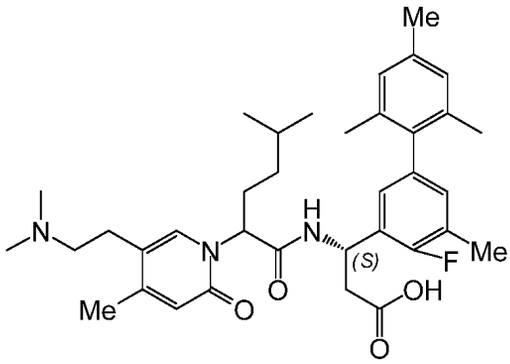
4-85. (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds EF-P1 and EF-P2)



EF-P1 ESI 632.2$(M+H)^+$. 1H NMR (500 MHz, MeOD) δ 7.88 (s, 1H), 6.92 – 6.79 (m, 4H), 6.74 (s, 1H), 5.66 – 5.45 (m, 2H), 3.11 – 2.85 (m, 5H), 2.78 – 2.68 (m, 7H), 2.32 – 2.22 (m, 6H), 2.18 – 2.08 (m, 1H), 2.06 – 1.92 (m, 4H), 1.78 (s, 3H), 1.41 – 1.24 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).

EF-P2 ESI 632.2 $(M+H)^+$. 1H NMR (500 MHz, MeOD) δ 7.82 (s, 1H), 6.90 (d, J = 7.1 Hz, 5H), 5.79 – 5.64 (m, 1H), 5.52 (t, J = 7.6 Hz, 1H), 3.30 – 3.15 (m, 2H), 3.00 (t, J = 6.6 Hz, 2H), 2.83 (s, 6H), 2.69 – 2.59 (m, 1H), 2.58 – 2.44 (m, 1H), 2.31 (d, J = 9.7 Hz, 6H), 2.13 – 2.01 (m, 1H), 1.97 (s, 6H), 1.91 – 1.73 (m, 1H), 1.39 – 1.02 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

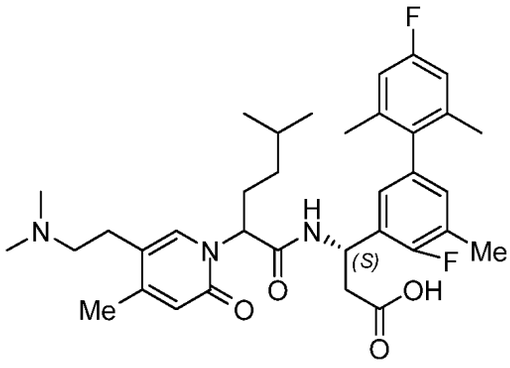
4-86. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds EF2-P1 and EF2-P2)



EF2-P1 ESI 606.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.57 (s, 1H), 6.90 (s, 2H), 6.85 – 6.80 (m, 2H), 6.34 (s, 1H), 5.48 (t, *J* = 6.0 Hz, 1H), 5.42 – 5.37 (s, 1H), 3.24 – 3.02 (m, 2H), 2.89 – 2.85 (m, 2H), 2.76 (s, 6H), 2.71 – 2.60 (m, 2H), 2.30 (d, *J* = 4.9 Hz, 6H), 2.25 (s, 3H), 2.22 – 2.14 (m, 1H), 1.95 (s, 4H), 1.87 (s, 3H), 1.60 – 1.53 (m, 1H), 1.25 – 1.14 (m, 1H), 1.12 – 1.00 (m, 1H), 0.89 – 0.87 (m, 6H).

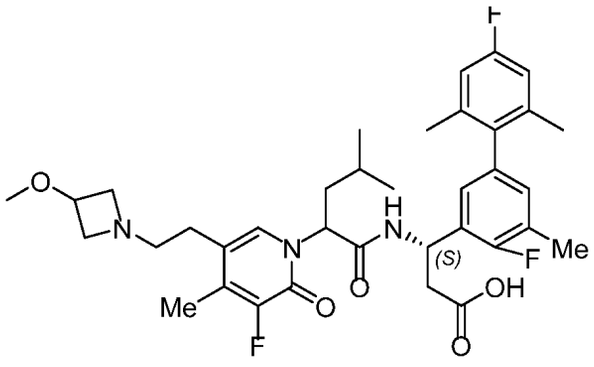
EF2-P2 ESI 606.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 6.98 – 6.78 (m, 4H), 6.44 (s, 1H), 5.66 – 5.63 (m, 1H), 5.42 (t, *J* = 7.7 Hz, 1H), 3.31 – 3.28 (m, 1H), 3.26 – 3.14 (m, 1H), 2.99 – 2.88 (m, 2H), 2.84 (s, 6H), 2.64 – 2.59 (m, 1H), 2.50 – 2.43 (m, 1H), 2.39 – 2.28 (m, 6H), 2.27 (s, 3H), 2.16 – 2.07 (m, 1H), 1.96 (s, 6H), 1.89 – 1.74 (m, 1H), 1.57 – 1.50 (m, 1H), 1.15 – 1.11 (m, 1H), 1.08 – 0.97 (m, 1H), 0.85 (t, *J* = 6.5 Hz, 6H).

4-87. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)propanoic acid (diastereomeric compounds EG-P1 and EG-P2)



EG-P1 ESI 610.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.58 (s, 1H), 6.84 (t, *J* = 9.1 Hz, 4H), 6.32 (s, 1H), 5.50 (t, *J* = 6.2 Hz, 1H), 5.44 – 5.33 (m, 1H), 3.24 – 3.06 (m, 2H), 2.90 – 2.84 (m, 2H), 2.78 (s, 6H), 2.73 – 2.62 (m, 2H), 2.28 (d, *J* = 14.1 Hz, 6H), 2.22 – 2.11 (m, 1H), 2.00 – 1.96 (m, 4H), 1.89 (s, 3H), 1.60 – 1.54 (m, 1H), 1.29 – 1.15 (m, 1H), 1.10 – 1.03 (m, 1H), 0.89 – 0.87 (m, 6H).
EG-P2 ESI 610.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 6.90 (d, *J* = 6.9 Hz, 2H), 6.84 (d, *J* = 9.6 Hz, 2H), 6.44 (s, 1H), 5.66 – 5.62(m, 1H), 5.43 (t, *J* = 7.6 Hz, 1H), 3.38 – 3.35 (m, 1H), 3.24 – 3.20 (m, 1H), 3.00 – 2.89 (m, 2H), 2.85 (s, 6H), 2.64 – 2.59 (m, 1H), 2.50 – 2.44 (m, 1H), 2.33 (d, *J* = 4 Hz, 3H), 2.28 (s, 3H), 2.17 – 2.07 (m, 1H), 2.01 (s, 6H), 1.87 – 1.77 (m, 1H), 1.57 – 1.51 (m, 1H), 1.20 – 1.09 (m, 1H), 1.08 – 0.97 (m, 1H), 0.85 (t, *J* = 6.4 Hz, 6H).

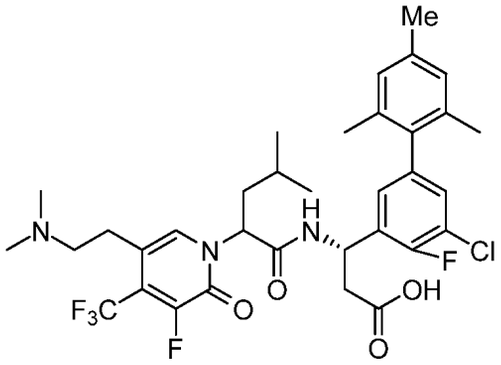
4-88. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EH-P1 and EH-P2)



EH-P1 ESI 656.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.40 (s, 1H), 6.95 – 6.72 (m, 4H), 5.71 – 5.47 (m, 2H), 4.27 – 4.16 (m, 2H), 4.16 – 4.07 (m, 1H), 3.81 – 3.69 (m, 1H), 3.70 – 3.58 (m, 1H), 3.30 (s, 3H), 3.25 (t, *J* = 6.8 Hz, 2H), 2.88 – 2.63 (m, 4H), 2.37 – 2.16 (m, 6H), 2.06 – 1.82 (m, 8H), 1.49 – 1.28 (m, 1H), 0.97 – 0.90 (m, 6H).
EH-P2 ESI 656.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.33 (s, 1H), 6.96 – 6.89 (m, 2H), 6.84 (d, *J* = 9.7 Hz, 2H), 5.72 – 5.58 (m, 2H), 4.39 – 4.14 (m, 3H), 3.85 – 3.65 (m, 2H), 3.31 – 3.20 (m, 5H),

2.93 – 2.78 (m, 1H), 2.77 – 2.55 (m, 2H), 2.54 – 2.45 (m, 1H), 2.33 (d, *J* = 1.7 Hz, 3H), 2.22 (d, *J* = 2.7 Hz, 3H), 2.06 – 1.86 (m, 7H), 1.81 – 1.66 (m, 1H), 1.344 – 1.32 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 6H).

4-89. (3*S*)-3-(5-chloro-4-fluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EI-P1 and EI-P2)

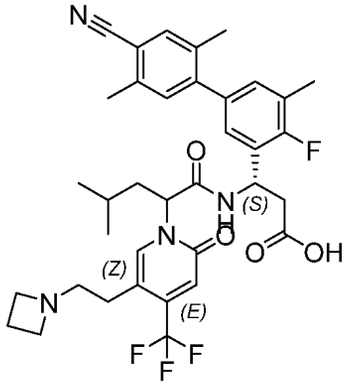


EI-P1 ESI 684.2 $(M+H)^+$. 1H NMR (500 MHz, MeOD) δ 7.65 (s, 1H), 7.13 (d, *J* = 6.3 Hz, 1H), 7.08 (d, *J* = 6.1 Hz, 1H), 6.93 (s, 2H), 5.66 (d, *J* = 5.4 Hz, 2H), 3.13 – 2.89 (m, 4H), 2.70 (s, 6H), 2.67 – 2.62 (m, 1H), 2.62 – 2.53 (m, 1H), 2.30 (s, 3H), 1.98 (d, *J* = 6.9 Hz, 7H), 1.74 -1.70(m, 1H), 1.40 – 1.33 (m, 1H), 0.89 (d, *J* = 5.6 Hz, 6H).

EI-P2 ESI 684.2 $(M+H)^+$.

1H NMR (500 MHz, MeOD) δ 7.67 (s, 1H), 7.10 (d, *J* = 6.9 Hz, 1H), 7.02 (d, *J* = 6.1 Hz, 1H), 6.91 (d, *J* = 13.0 Hz, 2H), 5.68 (t, *J* = 8.1 Hz, 1H), 5.55 (t, *J* = 7.0 Hz, 1H), 3.08 (s, 2H), 2.98 (d, *J* = 7.7 Hz, 2H), 2.73 (d, *J* = 9.7 Hz, 8H), 2.30 (s, 3H), 2.04 – 1.93 (m, 5H), 1.83 (s, 3H), 1.44-1.40 (m, 1H), 0.96 -0.92(m, 6H).

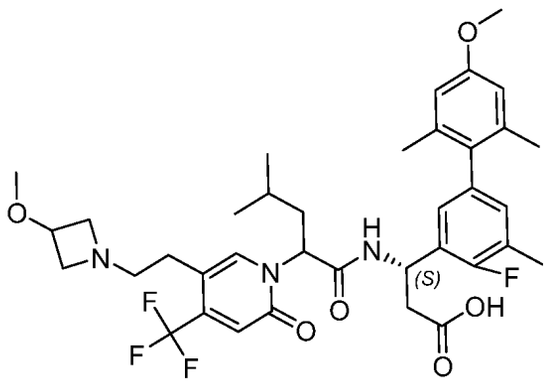
4-90. (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4'-cyano-4-fluoro-2',5,5'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds EJ-P1 and EJ-P2)



EJ-P1 ESI 669.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.45 (s, 1H), 7.10 (s, 1H), 7.06 – 6.92 (m, 2H), 6.65 (s, 1H), 5.57 – 5.40 (m, 2H), 3.92 (t, *J* = 8.1 Hz, 4H), 2.73-2.70 (m, 2H), 2.60 (d, *J* = 7.6 Hz, 2H), 2.40 (s, 3H), 23.0-2.33(m, 2H), 2.36-2.30 (m, 2H), 2.19 (s, 3H), 2.09 (s, 3H), 1.94-1.88 (m, 2H), 1.35 – 1.21 (m, 1H), 0.86-0.83 (m, 6H).

EJ-P2 ESI 669.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.61 (s, 1H), 7.47 (s, 1H), 7.13 (s, 1H), 7.10 – 6.98 (m, 2H), 6.80 (s, 1H), 5.65-5.62 (m, 1H), 5.52 (t, *J* = 7.7 Hz, 1H), 4.04 (t, *J* = 8.1 Hz, 4H), 3.40 – 3.25 (m, 2H), 2.86 – 2.64 (m, 2H), 2.54-2.49 (m, 1H), 2.45 – 2.30 (m, 6H), 2.23 (d, *J* = 1.5 Hz, 3H), 2.14 (s, 3H), 1.95 – 1.81 (m, 1H), 1.63 – 1.52 (m, 1H), 1.31-1.26 (m, 1H), 0.84-0.78 (m, 6H).

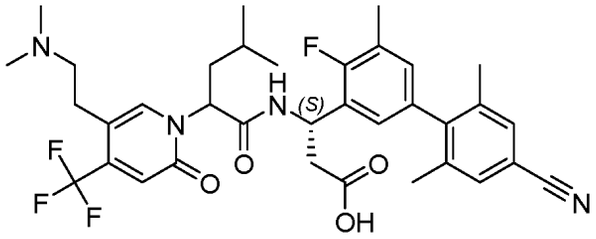
4-91. (3*S*)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EK-P1 and EK-P2)



EK-P1 ESI 704.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 6.86 (t, *J* = 6.2 Hz, 2H), 6.77 (s, 1H), 6.65 (s, 1H), 6.62 (s, 1H), 5.67 (t, *J* = 8.0 Hz, 1H), 5.61 – 5.56 (m, 1H), 4.25 – 4.09 (m, 3H), 3.79 (s, 3H), 3.71 – 3.61 (m, 2H), 3.31(s, 3H), 3.17 (t, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.9 Hz, 2H), 2.76 – 2.69 (m, 2H), 2.28 (s, 3H), 2.04 – 1.97 (m, 5H), 1.82 (s, 3H), 1.48 – 1.41 (m, 1H), 0.98 – 0.93 (m, 6H).

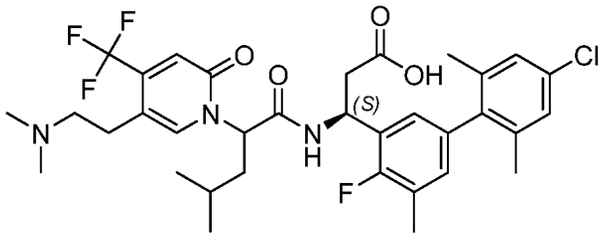
EK-P2 ESI 704.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 6.96 – 6.90 (m, 3H), 6.67 (s, 2H), 5.76 – 5.72(m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.44 – 4.26 (m, 3H), 3.98 – 3.92 (m, 1H), 3.88 – 3.83 (m, 1H), 3.80 (s, 3H), 3.42 – 3.35 (m, 5H), 2.97 – 2.80 (m, 2H), 2.67 – 2.62 (m, 1H), 2.56 – 2.50 (m, 1H), 2.33 (d, *J* = 1.6 Hz, 3H), 2.04 – 1.94 (m, 7H), 1.73 – 1.64 (m, 1H), 1.47 – 1.39 (m, 1H), 0.92 – 0.89 (m, 6H).

4-92. (3*S*)-3-(4'-cyano-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EL-P1 and EL-P2)



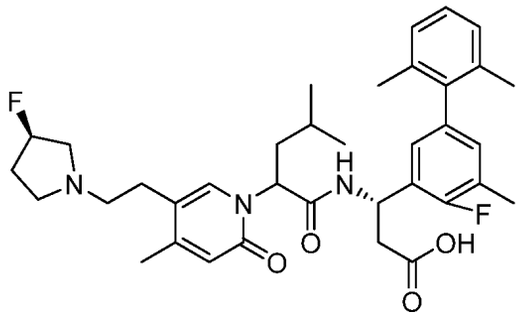
EL-P1 ESI 657.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.45 (d, *J* = 21.6 Hz, 2H), 6.88 (d, *J* = 5.6 Hz, 2H), 6.71 (s, 1H), 5.72 – 5.47 (m, 2H), 3.08 – 2.85 (m, 4H), 2.79 – 2.57 (m, 8H), 2.30 (d, *J* = 1.4 Hz, 3H), 2.11 – 1.93 (m, 5H), 1.88 (s, 3H), 1.50 – 1.37 (m, 1H), 1.06 – 0.86 (m, 6H).
EL-P2 ESI 657.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.49 (s, 2H), 7.02 – 6.74 (m, 3H), 5.75 – 5.53 (m, 2H), 3.25 – 3.06 (m, 2H), 2.98 (t, *J* = 6.9 Hz, 2H), 2.78 (s, 6H), 2.70 – 2.48 (m, 2H), 2.34 (d, *J* = 1.4 Hz, 3H), 2.14 – 1.86 (m, 7H), 1.79 – 1.62 (m, 1H), 1.46 – 1.31 (m, 1H), 0.95 – 0.82 (m, 6H).

4-93. (3*S*)-3-(4'-chloro-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EM-P1 and EM-P2)



EM-P1 ESI 666.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.08 (d, *J* = 24.1 Hz, 2H), 6.91 – 6.80 (m, 2H), 6.72 (s, 1H), 5.68 (t, *J* = 8.0 Hz, 1H), 5.59 – 5.48 (m, 1H), 3.18 – 3.02 (m, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.82 – 2.63 (m, 8H), 2.29 (s, 3H), 2.04 – 1.91 (m, 5H), 1.79 (s, 3H), 1.58 – 1.30 (m, 1H), 1.04 – 0.86 (m, 6H).
EM-P2 ESI 666.3 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.13 (s, 2H), 6.94 – 6.83 (m, 3H), 5.81 – 5.68 (m, 1H), 5.62 (t, *J* = 7.7 Hz, 1H), 3.30 – 3.16 (m, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.83 (s, 6H), 2.72 – 2.45 (m, 2H), 2.33 (d, *J* = 1.1 Hz, 3H), 1.98 (d, 7H), 1.75 – 1.63 (m, 1H), 1.51 – 1.33 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 6H).

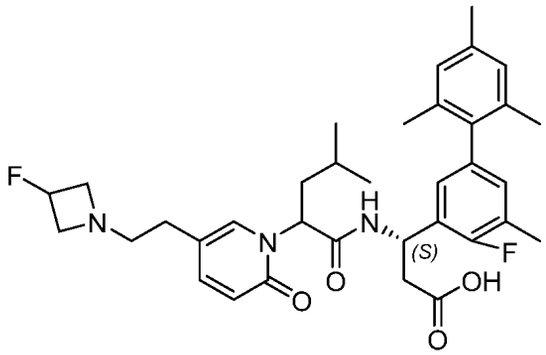
4-94. ((3*S*)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EN-P1 and EN-P2)



EN-P1 ESI 622.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.54 (s, 1H), 7.16 – 7.02 (m, 3H), 6.87 – 6.78 (m, 2H), 6.27 (s, 1H), 5.73 – 5.50 (m, 2H), 5.34 – 5.15 (m, 1H), 3.31 – 3.23 (m, 1H), 3.22 – 3.00 (m, 2H), 2.94 – 2.80 (m, 3H), 2.78 – 2.59 (m, 4H), 2.36 – 2.09 (m, 8H), 2.01 – 1.91 (m, 5H), 1.83 (s, 3H), 1.50 – 1.37 (m, 1H), 0.97 – 0.89 (m, 6H).

EN-P2 ESI 622.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.56 (s, 1H), 7.22 – 7.02 (m, 3H), 6.91 (d, J = 6.8 Hz, 2H), 6.42 (s, 1H), 5.65 – 5.57 (m, 2H), 5.41 – 5.24 (m, 1H), 3.62 – 3.35 (m, 3H), 3.31 – 3.09 (m, 3H), 2.94 – 2.74 (m, 2H), 2.68 – 2.49 (m, 2H), 2.39 – 2.22 (m, 8H), 2.10 – 1.89 (m, 7H), 1.82 – 1.70 (m, 1H), 1.49 – 1.31 (m, 1H), 0.95 – 0.85 (m, 6H).

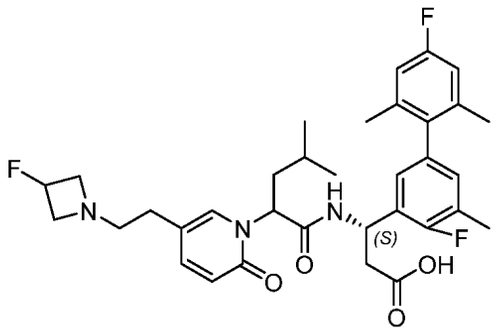
4-95. (3*S*)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EO-P1 and EO-P2)



EO-P1 ESI 608.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.39 (d, J = 9.0 Hz, 1H), 6.96 – 6.79 (m, 3H), 6.73 (s, 1H), 6.43 (d, J = 9.5 Hz, 1H), 5.74 – 5.46 (m, 2H), 5.14 (d, J = 57.6 Hz, 1H), 3.77 (s, 2H), 3.50 (s, 2H), 2.88 (s, 2H), 2.79 – 2.60 (m, 2H), 2.51 (s, 2H), 2.29 (d, J = 14.1 Hz, 6H), 1.96 (d, J = 12.7 Hz, 5H), 1.80 (s, 3H), 1.42 (s, 1H), 1.03 – 0.79 (m, 6H).

EO-P2 ESI 608.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.60 – 7.40 (m, 2H), 6.90 (d, J = 7.8 Hz, 4H), 6.57 (d, J = 9.2 Hz, 1H), 5.70 – 5.57 (m, 2H), 5.32 (d, J = 57.4 Hz, 1H), 4.51 – 4.26 (m, 2H), 4.14 – 3.87 (m, 2H), 3.39 (d, J = 5.3 Hz, 2H), 2.85 – 2.44 (m, 4H), 2.35 – 2.17 (m, 6H), 2.04 – 1.86 (m, 7H), 1.86 – 1.73 (m, 1H), 1.48 – 1.33 (m, 1H), 0.90 (t, J = 6.3 Hz, 6H).

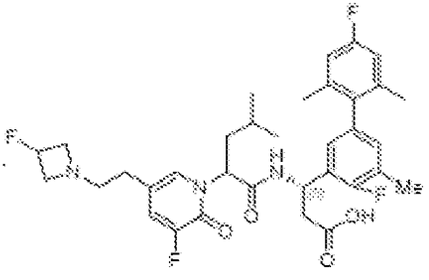
4-96. (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EP-P1 and EP-P2)



EP-P1 ESI 612.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 7.43 (dd, *J* = 9.2, 2.3 Hz, 1H), 6.87-6.82 (m, 3H), 6.76 (d, *J* = 6.7 Hz, 1H), 6.46 (d, *J* = 9.3 Hz, 1H), 5.63 (d, *J* = 7.9 Hz, 1H), 5.54 – 5.43 (m, 1H), 5.20 (d, *J* = 57.2 Hz, 1H), 4.09-3.88 (m, 2H), 3.71-3.55 (m, 2H), 3.10-3.02 (m, 2H), 2.80 – 2.53 (m, 4H), 2.29 (s, 3H), 2.03 – 1.92 (m, 5H), 1.87 (s, 3H), 1.50 – 1.36 (m, 1H), 0.97-0.92 (m, 6H).

EP-P2 ESI 612.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.41 (s, 1H), 7.38-7.35 (m, 1H), 6.79 (t, *J* = 6.1 Hz, 2H), 6.73 (d, *J* = 9.7 Hz, 2H), 6.45 (d, *J* = 9.3 Hz, 1H), 5.53-5.48 (m, 2H), 5.20 (d, *J* = 57.2 Hz, 1H), 4.39 – 4.14 (m, 2H), 3.99-3.87 (m, 2H), 3.32 – 3.25 (m, 2H), 2.67 – 2.48 (m, 3H), 2.40-2.34 (m, 1H), 2.21 (d, *J* = 1.7 Hz, 3H), 1.90 – 1.81 (m, 7H), 1.72 – 1.64 (m, 1H), 1.33 – 1.22 (m, 1H), 0.79 (t, *J* = 6.6 Hz, 6H).

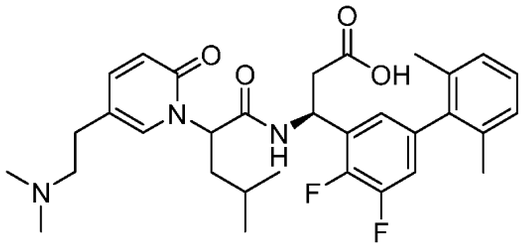
4-97. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EQ-P1 and EQ-P2)



EQ-P1 ESI 630.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.30 (s, 1H), 7.25 – 7.22 (m, 1H), 6.77 – 6.75 (m, 1H), 6.72 – 6.69 (m, 3H), 5.55 (t, *J* = 8.0 Hz, 1H), 5.40 – 5.37 (m, 1H), 5.18 – 5.01 (m, 1H), 3.99 – 3.82 (m, 2H), 3.66 – 3.48 (m, 2H), 3.06 – 2.99 (m, 2H), 2.66 – 2.50 (m, 4H), 2.18 (d, *J* = 1.5 Hz, 3H), 1.89 – 1.81 (m, 5H), 1.78 (s, 3H), 1.34 – 1.27 (m, 1H), 0.85 – 0.78 (m, 6H).

EQ-P2 ESI 630.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.27 – 7.23 (m, 2H), 6.80 (d, *J* = 6.9 Hz, 2H), 6.73 (d, *J* = 9.6 Hz, 2H), 5.56 – 5.49 (m, 2H), 5.28 – 5.11 (m, 1H), 4.33 – 4.18 (m, 2H), 3.97 – 3.83 (m, 2H), 3.27 – 3.22 (m, 2H), 2.64 – 2.35 (m, 4H), 2.21 (d, *J* = 1.9 Hz, 3H), 1.89 – 1.82 (m, 7H), 1.69 – 1.62 (m, 1H), 1.31 – 1.21 (m, 1H), 0.83 – 0.78 (m, 6H).

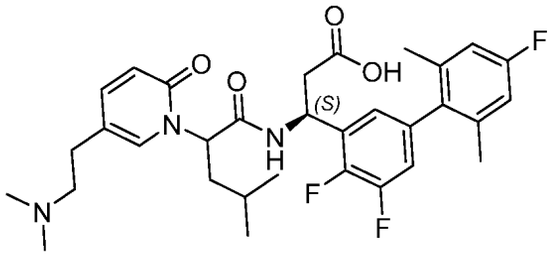
4-98. (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds ER-P1 and ER-P2)



ER-P1 ESI 568.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.64 (d, *J* = 2.0 Hz, 1H), 7.54 – 7.51 (m, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 6.8 Hz, 2H), 6.99 – 6.90 (m, 1H), 6.78 (d, *J* = 5.9 Hz, 1H), 6.52 (d, *J* = 9.3 Hz, 1H), 5.61 – 5.56 (m, 1H), 5.42 (t, *J* = 5.6 Hz, 1H), 3.32 – 3.19 (s, 1H), 3.24 – 3.10 (m, 1H), 2.88 – 2.80 (m, 2H), 2.73 (s, 6H), 2.70 – 2.64 (m, 1H), 2.59 – 2.53 (m, 1H), 2.06 – 1.89 (m, 8H), 1.50 – 1.36 (m, 1H), 0.97 – 0.90 (m, 6H).

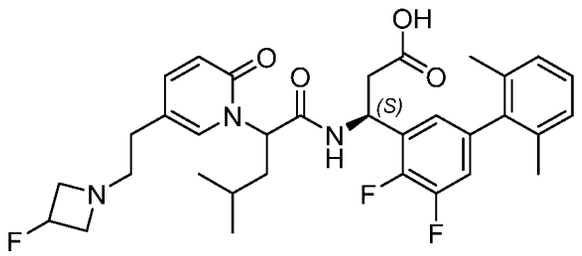
ER-P2 ESI 568.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ ^1H NMR (500 MHz, MeOD) δ 7.65 (d, *J* = 2.1 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.22 – 7.13 (m, 1H), 7.14 – 7.07 (m, 2H), 7.01 – 6.90 (m, 1H), 6.88 (d, *J* = 5.8 Hz, 1H), 6.54 (d, *J* = 9.3 Hz, 1H), 5.66 – 5.52 (m, 2H), 3.38 – 3.34 (m, 1H), 3.28 – 3.21 (m, 1H), 2.98 – 2.86 (m, 1H), 2.86 – 2.73 (m, 7H), 2.64 – 2.59 (m, 1H), 2.51 – 2.44 (m, 1H), 2.08 – 1.91 (m, 7H), 1.92 – 1.81 (m, 1H), 1.49 – 1.35 (m, 1H), 0.93 – 0.88 (m, 6H).

4-99. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds ES-P1 and ES-P2)



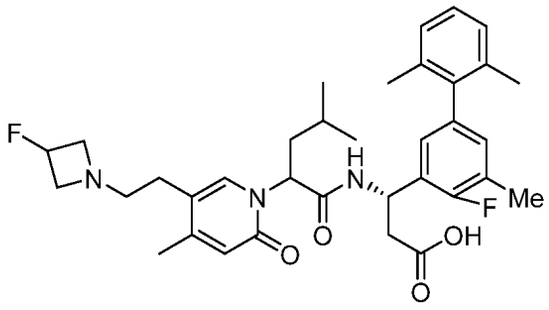
ES-P1 ESI 586.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.65 (s, 1H), 7.57 – 7.48 (m, 1H), 6.99 – 6.90 (m, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 5.8 Hz, 1H), 6.52 (d, *J* = 9.4 Hz, 1H), 5.56 (s, 1H), 5.42 (t, *J* = 5.6 Hz, 1H), 3.32 – 3.27 (m, 1H), 3.23 – 3.16 (m, 1H), 2.93 – 2.80 (m, 2H), 2.75 (s, 6H), 2.70 – 2.62 (m, 1H), 2.59 – 2.52 (m, 1H), 2.10 – 1.91 (m, 8H), 1.44 (s, 1H), 0.98 – 0.87 (m, 6H).
ES-P2 ESI 586.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.65 (d, *J* = 2.1 Hz, 1H), 7.56 – 7.50 (m, 1H), 7.01 – 6.94 (m, 1H), 6.90 – 6.81 (m, 3H), 6.55 (d, *J* = 9.3 Hz, 1H), 5.64 – 5.54 (m, 2H), 3.45 – 3.36 (m, 1H), 3.31 – 3.24 (m, 1H), 2.99 – 2.90 (m, 1H), 2.90 – 2.78 (m, 7H), 2.64 – 2.55 (m, 1H), 2.51 – 2.41 (m, 1H), 2.07 – 1.95 (m, 7H), 1.92 – 1.83 (m, 1H), 1.46 – 1.36 (m, 1H), 0.96 – 0.86 (m, 6H).

4-100. (3*S*)-3-(4,5-difluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds ET-P1 and ET-P2)



ET-P1 ESI 598.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.54 (d, *J* = 1.9 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.21 – 7.14 (m, 1H), 7.11 (d, *J* = 7.3 Hz, 2H), 6.99 – 6.90 (m, 1H), 6.81 (d, *J* = 5.9 Hz, 1H), 6.47 (d, *J* = 9.3 Hz, 1H), 5.62 (t, *J* = 8.1 Hz, 1H), 5.51 (t, *J* = 6.1 Hz, 1H), 5.31 – 5.14 (m, 1H), 4.17 – 3.96 (m, 2H), 3.82 – 3.67 (m, 2H), 3.21 – 3.11 (m, 2H), 2.78 – 2.58 (m, 4H), 2.03 – 1.89 (m, 8H), 1.47 – 1.40 (m, 1H), 0.97 – 0.88 (m, 6H).
ET-P2 ESI 598.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.53 (d, *J* = 2.0 Hz, 1H), 7.49 – 7.42 (m, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.7 Hz, 2H), 7.03 – 6.94 (m, 1H), 6.92 (d, *J* = 5.9 Hz, 1H), 6.55 (d, *J* = 9.3 Hz, 1H), 5.68 – 5.60 (m, 2H), 5.41 – 5.22 (m, 1H), 4.47 – 4.27 (m, 2H), 4.09 – 3.94 (m, 2H), 3.37 (s, 2H), 2.79 – 2.62 (m, 3H), 2.60 – 2.50 (m, 1H), 2.03 (d, *J* = 2.2 Hz, 6H), 1.98 – 1.91 (m, 1H), 1.84 – 1.76 (m, 1H), 1.47 – 1.37 (m, 1H), 0.91 (t, *J* = 6.1 Hz, 6H).

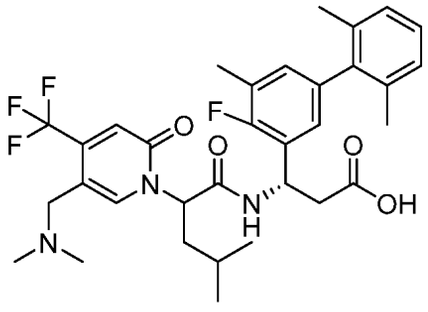
4-101. (3*S*)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EU-P1 and EU-P2)



EU-P1 ESI 608.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 8.45 (s, 0.47HCOOH), 7.54 (s, 1H), 7.15 – 7.05 (m, 3H), 6.89 – 6.81 (m, 2H), 6.30 (s, 1H), 5.68 – 5.48 (m, 2H), 5.40 – 5.14 (m, 1H), 4.35 – 4.13 (m, 2H), 4.06 – 3.86 (m, 2H), 3.26 – 3.20 (m, 2H), 2.88 – 2.65 (m, 4H), 2.29 (s, 3H), 2.23 (s, 3H), 2.01 – 1.89 (m, 5H), 1.85 (s, 3H), 1.48 – 1.38 (m, 1H), 0.98 – 0.91 (m, 6H).

EU-P2 ESI 608.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 8.45 (s, 0.23HCOOH), 7.46 (s, 1H), 7.20 – 7.02 (m, 3H), 6.93 (d, J = 5.0 Hz, 2H), 6.44 (s, 1H), 5.75 – 5.54 (m, 2H), 5.34 (d, J = 57.3 Hz, 1H), 4.48 – 4.35 (m, 2H), 4.16 – 3.96 (m, 2H), 3.42 – 3.34 (m, 2H), 2.90 – 2.82 (m, 1H), 2.74 – 2.63(m, 2H), 2.60 – 2.52 (m, 1H), 2.33 (s, 3H), 2.25 (s, 3H), 2.07 – 1.85 (m, 7H), 1.82 – 1.70 (m, 1H), 1.44 – 1.34 (m, 1H), 0.91 – 0.87 (m, 6H).

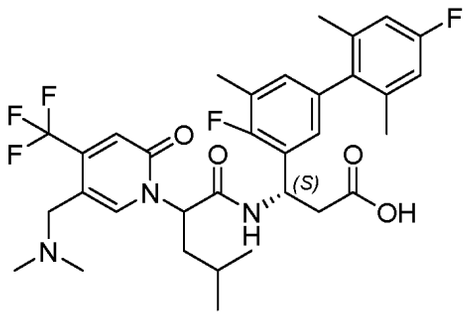
4-102. (3*S*)-3-(2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds EV-P1 and EV-P2)



EV-P1 ESI 618.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.07 (s, 1H), 7.15 – 7.00 (m, 3H), 6.94 – 6.83 (m, 2H), 6.77 (s, 1H), 5.75 (t, J = 8.1 Hz, 1H), 5.63 – 5.52 (m, 1H), 3.83 – 3.59 (m, 2H), 2.82 – 2.72 (m, 2H), 2.52 (s, 6H), 2.29 (d, J = 1.3 Hz, 3H), 2.05 – 1.95 (m, 5H), 1.80 (s, 3H), 1.49 – 1.37 (m, 1H), 1.01 – 0.91 (m, 6H).

EV-P2 ESI 618.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.09 (s, 1H), 7.18 – 7.00 (m, 3H), 7.00 – 6.84 (m, 3H), 5.81 – 5.70 (m, 1H), 5.63 – 5.46 (m, 1H), 4.10 (d, J = 14.4 Hz, 1H), 3.87 (d, J = 14.4 Hz, 1H), 2.79 – 2.55 (m, 8H), 2.34 (d, J = 1.5 Hz, 3H), 2.05 – 1.93 (m, 7H), 1.71 – 1.61 (m, 1H), 1.48 – 1.39 (m, 1H), 0.93 – 0.82 (m, 6H).

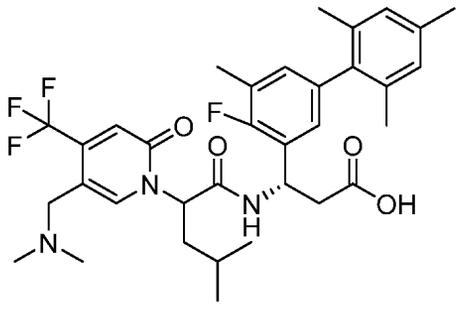
4-103. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EW-P1 and EW-P2)



EW-P1 ESI 636.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.06 (s, 1H), 6.95 – 6.72 (m, 5H), 5.75 (t, *J* = 8.1 Hz, 1H), 5.62 – 5.56 (m, 1H), 3.79 – 3.65 (m, 2H), 2.86 – 2.65 (m, 2H), 2.52 (s, 6H), 2.29 (s, 3H), 2.04 – 1.93 (m, 5H), 1.81 (s, 3H), 1.50 – 1.38 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 6H).

EW-P2 ESI 636.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.08 (s, 1H), 6.95 – 6.88 (m, 3H), 6.85 (d, *J* = 9.6 Hz, 2H), 5.76 – 5.70 (m, 1H), 5.55 (t, *J* = 7.5 Hz, 1H), 4.08 (d, *J* = 14.4 Hz, 1H), 3.85 (d, *J* = 14.4 Hz, 1H), 2.79 – 2.52 (m, 8H), 2.34 (s, 3H), 2.03 – 1.93 (m, 7H), 1.70 – 1.61 (m, 1H), 1.50 – 1.38 (m, 1H), 0.95 – 0.80 (m, 6H).

4-104. (3*S*)-3-(2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds EX-P1 and EX-P2)

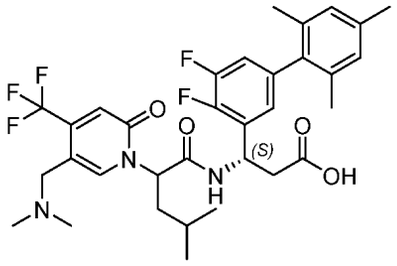


EX-P1 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.05 (s, 1H), 6.92 – 6.82 (m, 4H), 6.76 (s, 1H), 5.75 (t, *J* = 8.1 Hz, 1H), 5.63 – 5.50 (m, 1H), 3.78 – 3.62 (m, 2H), 2.88 – 2.65 (m, 2H), 2.50 (s, 6H), 2.29 (d, *J* = 3.7 Hz, 6H), 2.03 – 1.89 (m, 5H), 1.76 (s, 3H), 1.52 – 1.36 (m, 1H), 0.96 (t, *J* = 7.2 Hz, 6H).

EX-P2 ESI 632.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 8.09 (s, 1H), 6.95 – 6.83 (m, 5H), 5.81 – 5.68 (m, 1H), 5.54 (t, *J* = 7.4 Hz, 1H), 4.09 (d, *J* = 14.4 Hz, 1H), 3.85 (d, *J* = 14.3 Hz, 1H), 2.81 – 2.52 (m,

8H), 2.32 (d, *J* = 9.8 Hz, 6H), 1.97 (t, *J* = 9.1 Hz, 7H), 1.71 – 1.58 (m, 1H), 1.50 – 1.34 (m, 1H), 0.88 (d, *J* = 6.4 Hz, 6H).

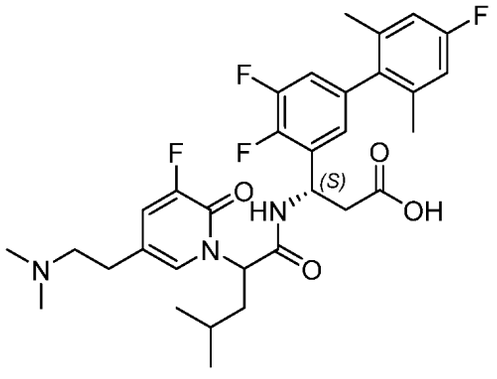
4-105. (3S)-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-((dimethylamino)methyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds EY-P1 and EY-P2)



EY-P1 ESI 636.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.99 (s, 1H), 6.92 – 6.84 (m, 4H), 6.72 (s, 1H), 5.82 – 5.68 (m, 1H), 5.61 – 5.55 (m, 1H), 3.61 – 3.48 (m, 2H), 2.83 – 2.65 (m, 2H), 2.38 (s, 6H), 2.30 (s, 3H), 2.03 – 1.92 (m, 5H), 1.73 (s, 3H), 1.49 – 1.37 (m, 1H), 0.99 – 0.93 (m, 6H).

EY-P2 ESI 636.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 8.08 (s, 1H), 7.02 – 6.84 (m, 5H), 5.77 – 5.72 (m, 1H), 5.59 – 5.52 (m, 1H), 4.08 (d, *J* = 14.4 Hz, 1H), 3.85 (d, *J* = 14.4 Hz, 1H), 2.79 – 2.75 (m, 1H), 2.70 – 2.54 (m, 7H), 2.31 (s, 3H), 2.02 – 1.87 (m, 7H), 1.74 – 1.57 (m, 1H), 1.49 – 1.37 (m, 1H), 0.91 – 0.86 (m, 6H).

4-106. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4',5-trifluoro-2',6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds EZ-P1 and EZ-P2)

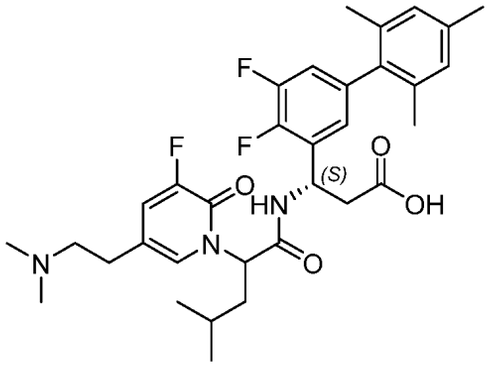


EZ-P1 ESI 604.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.44 (s, 1H), 7.34 – 7.30 (m, 1H), 6.96 – 6.75 (m, 4H), 5.76 – 5.71 (m, 1H), 5.60 – 5.48 (m, 1H), 2.76 – 2.55 (m, 6H), 2.39 (s, 6H), 2.07 – 1.90 (m, 5H), 1.84 (s, 3H), 1.49 – 1.33 (m, 1H), 0.98 – 0.92 (m, 6H).

EZ-P2 ESI 604.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.46 – 7.10 (m, 1H), 7.04 – 6.93 (m, 1H), 6.91 – 6.84 (m, 3H), 5.67 – 5.57 (m, 2H), 3.47 – 3.37 (m, 1H), 3.31 – 3.21 (m, 1H), 3.02 –

2.91 (m, 1H), 2.90 – 2.79 (m, 7H), 2.64 – 2.57 (m, 1H), 2.50 – 2.42 (m, 1H), 2.07 – 1.92 (m, 7H), 1.90 – 1.78 (m, 1H), 1.47 – 1.31 (m, 1H), 0.94 – 0.89 (m, 6H).

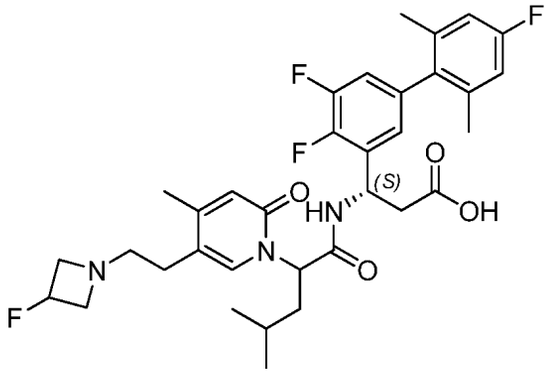
4-107. (3S)-3-(4,5-difluoro-2',4',6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propa -noic acid (diastereomeric compounds FA-P1 and FA-P2)



FA-P1 ESI 600.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.49-7.44 (m, 2H), 6.92 (t, *J* = 8.2 Hz, 3H), 6.76 (d, *J* = 6.0 Hz, 1H), 5.65-5.61 (m, 1H), 5.40 (t, *J* = 5.6 Hz, 1H), 3.19-3.15 (m, 2H), 2.90-2.84 (m, 3H), 2.75 – 2.63 (m, 7H), 2.57-2.52 (m, 1H), 2.31 (s, 3H), 2.03 – 1.87 (m, 9H), 1.46-1.40 (m, 1H), 0.98-0.91 (m, 6H).

FA-P2 ESI 600.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.37-7.29 (m, 2H), 6.87 – 6.71 (m, 4H), 5.57 – 5.42 (m, 2H), 3.34 – 3.24 (m, 1H), 3.18 – 3.07 (m, 1H), 2.87-2.81 (m, 1H), 2.73-2.70 (m, 7H), 2.50-2.45 (m, 1H), 2.36-2.30 (m, 1H), 2.19 (s, 3H), 1.96 – 1.80 (m, 7H), 1.74 – 1.63 (m, 1H), 1.30-1.25 (m, 1H), 0.81-0.79 (m, 6H).

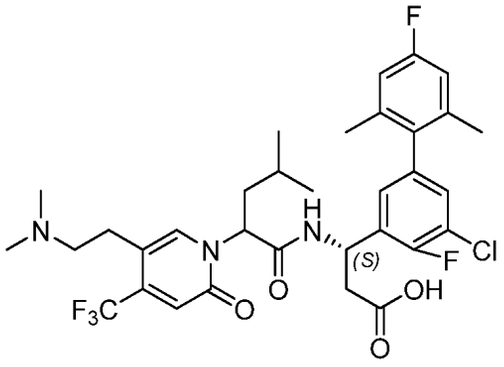
4-108. (3*S*)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4',5-trifluoro-2',6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds FB-P1 and FB-P2)



FB-P1 ESI 630.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.49 (s, 1H), 6.99 – 6.89 (m, 1H), 6.89 – 6.76 (m, 3H), 6.29 (s, 1H), 5.66 – 5.50 (m, 2H), 5.40 – 5.10 (m, 1H), 4.14 – 3.90 (m, 2H), 3.86 – 3.55 (m, 2H), 3.03 (s, 2H), 2.86 – 2.53 (m, 4H), 2.23 (s, 3H), 2.06 – 1.90 (m, 5H), 1.86 (s, 3H), 1.49 – 1.32 (m, 1H), 1.02 – 0.84 (m, 6H).

FB-P2 ESI 630.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.49 (s, 1H), 7.09 – 6.86 (m, 4H), 6.44 (s, 1H), 5.72 – 5.55 (m, 2H), 5.30 (d, J = 57.8 Hz, 1H), 4.28 (s, 2H), 3.93 (s, 2H), 3.19 (s, 2H), 2.87 – 2.50 (m, 4H), 2.25 (s, 3H), 2.04 (s, 6H), 1.93 – 1.73 (m, 2H), 1.47 – 1.28 (m, 1H), 0.91 – 0.85 (m, 6H).

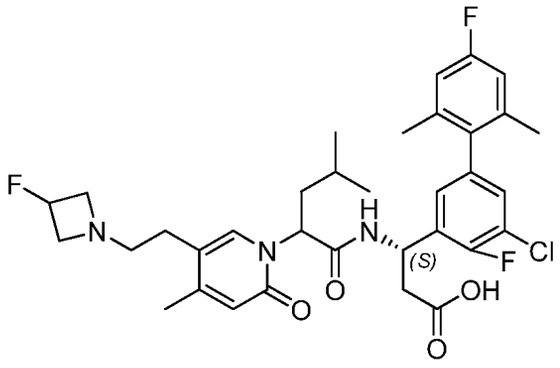
4-109. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FC-P1 and FC-P2)



FC-P1 ESI 670.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.13 – 7.11 (m, 1H), 7.04 – 7.02 (m, 1H), 6.88 – 6.81 (m, 2H), 6.74 (s, 1H), 5.69 – 5.65 (m, 1H), 5.57 – 5.53 (m, 1H), 3.16 – 3.10 (m, 2H), 2.97 – 2.94 (m, 2H), 2.80 (s, 6H), 2.74 – 2.71 (m, 2H), 2.02 – 1.98 (m, 5H), 1.84 (s, 3H), 1.47 – 1.40 (m, 1H), 0.98 – 0.93 (m, 6H).

FC-P2 ESI 670.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.20 – 7.18 (m, 1H), 7.07 (d, J = 6.1 Hz, 1H), 6.88 (d, J = 11.2 Hz, 3H), 5.73 – 5.67 (m, 1H), 5.63 (t, J = 7.6 Hz, 1H), 3.30 – 3.18 (m, 2H), 3.01 (t, J = 6.9 Hz, 2H), 2.85 (s, 6H), 2.69 – 2.60 (m, 1H), 2.58 – 2.52 (m, 1H), 2.03 – 1.95 (m, 7H), 1.77 – 1.70 (m, 1H), 1.41 – 1.36 (m, 1H), 0.91 – 0.89 (m, 6H).

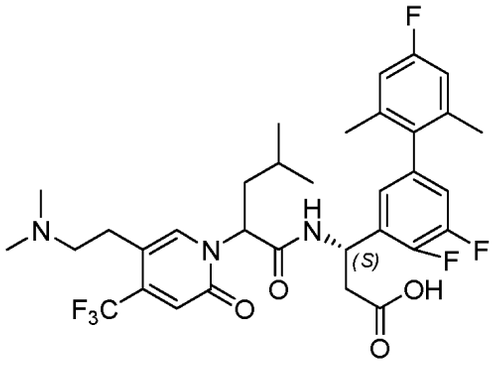
4-110. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FD-P1 and FD-P2)



FD-P1 ESI 646.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.15 – 7.13 (m, 1H), 6.99 – 6.97 (m, 1H), 6.88 – 6.85 (m, 2H), 6.29 (s, 1H), 5.64 – 5.49 (m, 2H), 5.32 – 5.18 (m, 1H), 4.11 – 4.07 (m, 2H), 3.85 – 3.72 (m, 2H), 3.10 (t, *J* = 6.9 Hz, 2H), 2.82 – 2.62 (m, 4H), 2.24 (s, 3H), 2.09 – 1.90 (m, 5H), 1.89 (d, *J* = 8.2 Hz, 3H), 1.43 – 1.38 (m, 1H), 0.96 – 0.92 (m, 6H).

FD-P2 ESI 646.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.45 (s, 1H), 7.21 – 7.18 (m, 1H), 7.08 – 7.06 (m, 1H), 6.89 (d, *J* = 9.6 Hz, 2H), 6.43 (s, 1H), 5.73 – 5.53 (m, 2H), 5.43 – 5.25 (m, 1H), 4.44 – 4.41 (m, 2H), 4.16 – 4.01 (m, 2H), 3.39– 3.36 (m, 2H), 2.91 – 2.87 (m, 1H), 2.73 – 2.62 (m, 2H), 2.52 – 2.49 (m, 1H), 2.25 (s, 3H), 2.03 (s, 6H), 1.98 – 1.88 (m, 1H), 1.81 – 1.72 (m, 1H), 1.44 – 1.33 (m, 1H), 0.91 – 0.89 (m, 6H).

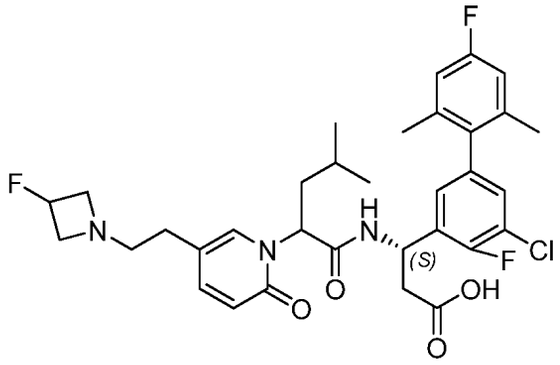
4-111. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4,4',5-trifluoro-2',6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds FE-P1 and FE-P2)



FE-P1 ESI 654.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 6.98 – 6.78 (m, 4H), 6.75 (s, 1H), 5.69 – 5.65 (m, 1H), 5.59 – 5.56 (m, 1H), 3.15– 3.06 (m, 2H), 2.95 (d, *J* = 6.2 Hz, 2H), 2.77 (s, 6H), 2.74 – 2.71 (m, 2H), 2.13 – 1.91 (m, 5H), 1.85 (s, 3H), 1.50 – 1.40 (m, 1H), 0.98 – 0.94 (m, 6H).

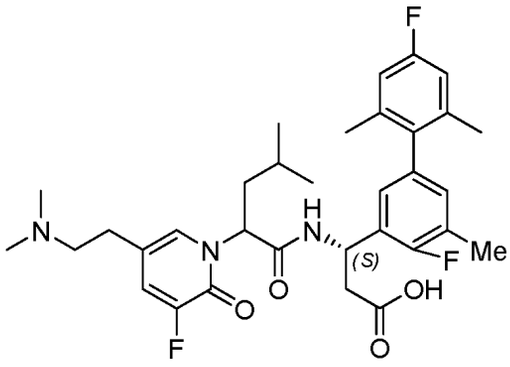
FE-P2 ESI 654.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.86 (s, 1H), 7.05 – 6.96 (m, 1H), 6.95 – 6.83 (m, 4H), 5.73 – 5.69 (m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 3.28 – 3.14 (m, 2H), 2.99 (t, *J* = 7.0 Hz, 2H), 2.82 (s, 6H), 2.69 – 2.64 (m, 1H), 2.62 – 2.52 (m, 1H), 2.03 (d, *J* = 2.1 Hz, 6H), 1.99 – 1.94 (m, 1H), 1.77 – 1.72 (m, , 1H), 1.45 – 1.31 (m, 1H), 0.91 – 0.89 (m, 6H).

4-112. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FF-P1 and FF-P2)



FF-P1 ESI 632.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.59 (s, 1H), 7.46 – 7.43 (m, 1H), 7.15 – 7.13 (m, 1H), 7.00 – 6.92 (m, 1H), 6.87 (d, *J* = 9.6 Hz, 2H), 6.45 (d, *J* = 9.3 Hz, 1H), 5.68 – 5.57 (m, 1H), 5.51 (t, *J* = 6.2 Hz, 1H), 5.38 – 5.16 (m, 1H), 4.25 – 4.04 (m, 2H), 3.96 – 3.76 (m, 2H), 3.25 – 3.13 (m, 2H), 2.83 – 2.58 (m, 4H), 2.08 – 1.92 (m, 5H), 1.88 (s, 3H), 1.47 – 1.40 (m, 1H), 0.97 – 0.92 (m, 6H).
FF-P2 ESI 632.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.20 – 7.18 (m, 1H), 7.04 (d, *J* = 4.5 Hz, 1H), 6.88 (d, *J* = 9.6 Hz, 2H), 6.56 (d, *J* = 9.1 Hz, 1H), 5.71 – 5.57 (m, 2H), 5.34 (d, *J* = 59.0 Hz, 1H), 4.40 (s, 2H), 4.08 (s, 2H), 3.42 (s, 1H), 2.70 (d, *J* = 52.7 Hz, 3H), 2.52 (s, 1H), 2.03 (d, *J* = 3.5 Hz, 6H), 1.99 – 1.93 (m, 2H), 1.88 – 1.76 (m, 1H), 1.49 – 1.31 (m, 1H), 0.91 (t, *J* = 6.7 Hz, 6H).

4-113. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FG-P1 and FG-P2)

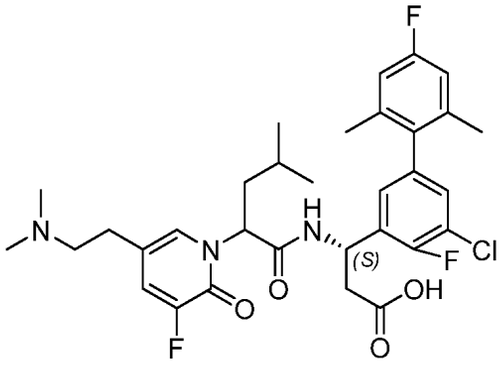


FG-P1 ESI 600.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.47 – 7.44 (m, 1H), 6.91 – 6.81 (m, 3H), 6.78 (d, *J* = 6.8 Hz, 1H), 5.64 – 5.60 (m, 1H), 5.40 (t, *J* = 5.6 Hz, 1H), 3.36 (d, *J* = 6.1 Hz,

1H), 3.24 – 3.12 (m, 1H), 2.97 – 2.77 (m, 2H), 2.73 (s, 6H), 2.70 – 2.61 (m, 1H), 2.57 – 2.52 (m, 1H), 2.30 (d, *J* = 1.6 Hz, 3H), 2.12 – 1.96 (m, 5H), 1.95 (s, 3H), 1.52 – 1.37 (m, 1H), 0.97 – 0.91 (m, 6H).

FG-P2 ESI 600.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.45 – 7.42 (m, 1H), 6.89 (t, *J* = 6.1 Hz, 2H), 6.84 (d, *J* = 9.6 Hz, 2H), 5.66 – 5.62 (m, 1H), 5.59 – 5.56 (m, 1H), 3.47 – 3.36 (m, 1H), 3.30 – 3.25 (m, 1H), 3.00 – 2.94 (m, 1H), 2.90 – 2.77 (m, 7H), 2.61 – 2.56 (m, 1H), 2.46 – 2.40 (m, 1H), 2.32 (d, *J* = 1.8 Hz, 3H), 2.09 – 1.94 (m, 7H), 1.87 – 1.79 (m, 1H), 1.48 – 1.37 (m, 1H), 0.93 – 0.90 (m, 6H).

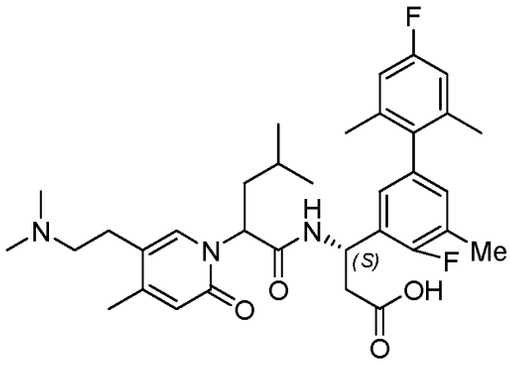
4-114. (3*S*)-3-(5-chloro-4,4'-difluoro-2',6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FH-P1 and FH-P2)



FH-P1 ESI 620.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.53 (s, 1H), 7.46 – 7.43 (m , 1H), 7.15 – 7.12 (m, 1H), 6.95 – 6.93 (m, 1H), 6.87 (d, *J* = 9.6 Hz, 2H), 5.65 – 5.61 (m, 1H), 5.42 (t, *J* = 5.8 Hz, 1H), 3.31 – 3.26 (m, 1H), 3.20 – 3.15 (m, 1H), 2.96 – 2.81 (m, 2H), 2.75 (s, 6H), 2.70 – 2.65 (m, 1H), 2.59 – 2.54 (m, 1H), 2.19 – 1.78 (m, 8H), 1.46 – 1.40 (m, 1H), 0.97 – 0.91 (m, 6H).

FH-P2 ESI 620.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.45 – 7.42 (m, 1H), 7.18 – 7.16 (m, 1H), 7.04– 7.02 (m, 1H), 6.88 (d, *J* = 9.6 Hz, 2H), 5.67 – 5.63 (m, 1H), 5.59 – 5.56 (m, 1H), 3.46 – 3.36 (m, 1H), 3.29 – 3.22 (m, 1H), 2.98 – 2.92 (m, 1H), 2.86 – 2.84 (m, 1H), 2.82 (s, 6H), 2.62 – 2.58 (m, 1H), 2.51 – 2.41 (m, 1H), 2.03 (d, *J* = 1.5 Hz, 6H), 1.97 (t, *J* = 7.1 Hz, 1H), 1.90 – 1.78 (m, 1H), 1.41 – 1.36 (m, 1H), 0.97 – 0.74 (m, 6H).

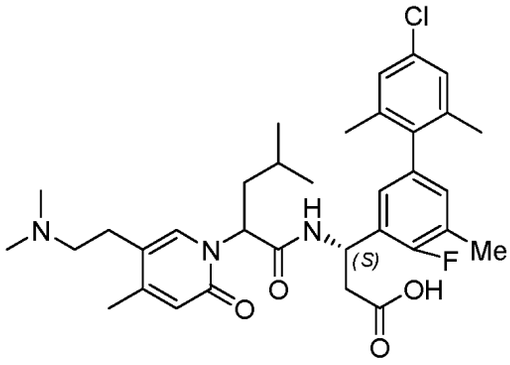
4-115. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FI-P1 and FI-P2)



FI-P1 ESI 596.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.59 (s, 1H), 6.83 (t, J = 7.2 Hz, 4H), 6.32 (s, 1H), 5.70 – 5.56 (m, 1H), 5.54 – 5.47 (m, 1H), 3.21 – 3.06 (m, 2H), 2.95 – 2.83 (m, 2H), 2.79 (s, 6H), 2.73 – 2.55 (m, 2H), 2.35 – 2.20 (m, 6H), 2.07 – 1.91 (m, 5H), 1.85 (s, 3H), 1.50 – 1.29 (m, 1H), 1.02 – 0.83 (m, 6H).

FI-P2 ESI 596.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.57 (s, 1H), 6.99 – 6.78 (m, 4H), 6.43 (s, 1H), 5.71 – 5.53 (m, 2H), 3.28 – 3.06 (m, 2H), 2.97 – 2.85 (m, 2H), 2.81 (s, 6H), 2.66 – 2.56 (m, 1H), 2.56 – 2.40 (m, 1H), 2.36 – 2.24 (m, 6H), 2.05 – 1.89 (m, 7H), 1.86 – 1.72 (m, 1H), 1.43 – 1.28 (m, 1H), 0.89 (t, J = 5.2 Hz, 6H).

4-116. (3*S*)-3-(4'-chloro-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FJ-P1 and FJ-P2)

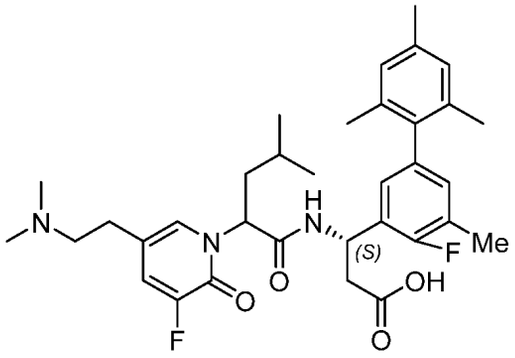


FJ-P1 ESI 612.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.58 (s, 1H), 7.11 (d, J = 2.5 Hz, 2H), 6.92 – 6.76 (m, 2H), 6.32 (s, 1H), 5.61 – 5.41 (m, 2H), 3.25 – 3.05 (m, 2H), 2.88 (t, J = 7.3 Hz, 2H), 2.78 (s, 6H), 2.71 – 2.54 (m, 2H), 2.28 (d, J = 13.0 Hz, 6H), 2.05 – 1.92 (m, 5H), 1.88 (s, 3H), 1.48 – 1.32 (m, 1H), 1.04 – 0.85 (m, 6H).

FJ-P2 ESI 612.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.55 (s, 1H), 7.13 (s, 2H), 6.93 – 6.84 (m, 2H), 6.42 (s, 1H), 5.70 – 5.54 (m, 2H), 3.24 – 3.11 (m, 2H), 2.99 – 2.76 (m, 8H), 2.64 – 2.42 (m, 2H),

2.36 – 2.20 (m, 6H), 2.03 – 1.90 (m, 7H), 1.83 – 1.72 (m, 1H), 1.47 – 1.28 (m, 1H), 0.90 (t, *J* = 6.2 Hz, 6H).

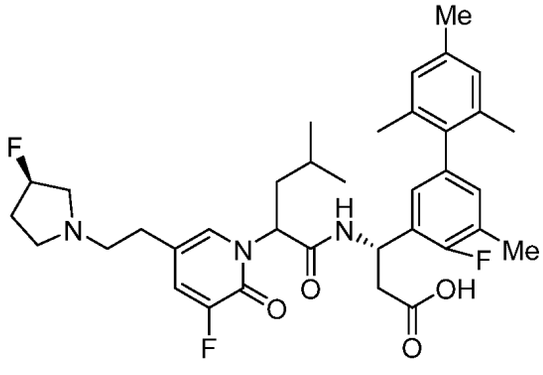
4-117. (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds FK-P1 and FK-P2)



FK-P1 ESI 596.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.59 – 7.37 (m, 2H), 6.96 – 6.64 (m, 4H), 5.76 – 5.58 (m, 1H), 5.39 (t, *J* = 5.5 Hz, 1H), 3.42 – 3.25 (m, 1H), 3.23 – 3.06 (m, 1H), 2.96 – 2.76 (m, 2H), 2.73 – 2.46 (m, 8H), 2.41 – 2.22 (m, 6H), 2.05 – 1.88 (m, 8H), 1.44 (m, *J* = 13.7, 6.7 Hz, 1H), 0.93 (m, *J* = 17.3, 6.6 Hz, 6H).

FK-P2 ESI 596.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.51 (s, 1H), 7.42 (m, *J* = 10.3, 2.1 Hz, 1H), 6.89 (m, *J* = 7.0, 4.6 Hz, 4H), 5.62 (m, *J* = 14.0, 9.4, 5.4 Hz, 2H), 3.43 – 3.30 (m, 1H), 3.23 (s, 1H), 2.93 (m, *J* = 9.6, 4.9 Hz, 1H), 2.87 – 2.75 (m, 7H), 2.59 (m, *J* = 14.9, 4.0 Hz, 1H), 2.44 (m, *J* = 14.8, 10.1 Hz, 1H), 2.34 – 2.22 (m, 6H), 2.05 – 1.91 (m, 7H), 1.84 – 1.72 (m, 1H), 1.46 – 1.22 (m, 1H), 0.91 (m, *J* = 6.6, 3.1 Hz, 6H).

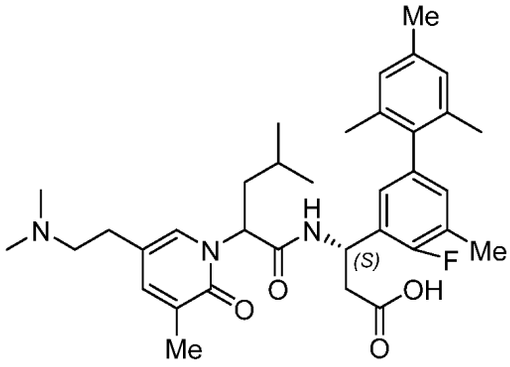
4-118. (3S)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-((R)-3-fluoropyrrolidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FL-P1 and FL-P2)



FL-P1 ESI 640.2 $(M+H)^+$. 1H NMR (400 MHz, MeOD) δ 7.50 (s, 1H), 7.41 – 7.31 (m, 1H), 6.91 (s, 2H), 6.85 (d, *J* = 7.0 Hz, 1H), 6.79 (d, *J* = 6.7 Hz, 1H), 5.70 (s, 1H), 5.49 (s, 1H), 5.24 (d, *J* = 53.7 Hz, 1H), 3.26 – 3.00 (m, 5H), 2.88 – 2.56 (m, 4H), 2.41 – 2.13 (m, 9H), 2.07 – 1.90 (m, 5H), 1.85 (s, 3H), 1.53 – 1.26 (m, 1H), 1.05 – 0.80 (m, 6H).

FL-P2 ESI 640.2 $(M+H)^+$. 1H NMR (500 MHz, MeOD) δ 7.49 (s, 1H), 7.47 – 7.36 (m, 1H), 6.90 (d, J = 8.8 Hz, 4H), 5.67 (t, J = 7.7 Hz, 1H), 5.61 – 5.52 (m, 1H), 5.33 (d, J = 54.6 Hz, 1H), 3.73 – 3.38 (m, 5H), 3.28 (s, 1H), 2.97 – 2.76 (m, 2H), 2.65 – 2.43 (m, 2H), 2.41 – 2.19 (m, 6H), 2.07 – 1.88 (m, 7H), 1.84 – 1.73 (m, 1H), 1.51 – 1.20 (m, 1H), 0.91 (d, J = 6.5 Hz, 6H).

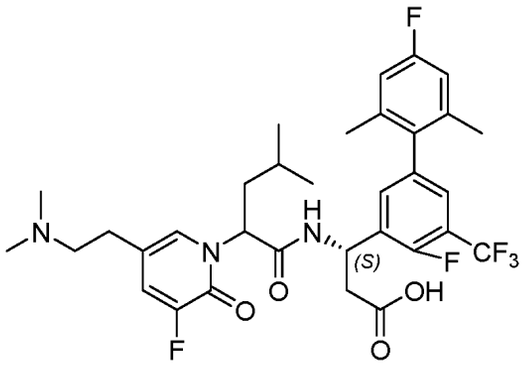
4-119. (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-3-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds FM-P1 and FM-P2)



FM-P1 ESI 592.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.35(S, 1H), 7.32(S, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.73 (d, *J* = 5.5 Hz, 1H), 6.59 (d, *J* = 6.7 Hz, 1H), 5.48-5.46 (m, 1H), 5.23 (t, *J* = 5.1 Hz, 1H), 3.08 – 2.98 (m, 1H), 2.68-2.67 (m, 2H), 2.56 (s, 6H), 2.51-2.35 (m, 3H), 2.25 – 2.11 (m, 6H), 1.97 – 1.74 (m, 11H), 1.36 – 1.24 (m, 1H), 0.88 – 0.76 (m, 6H).

FM-P2 ESI 592.3 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.40 (s, 1H), 7.29 (s, 1H), 6.78-6.74 (m, 3H), 6.67 (d, *J* = 7.0 Hz, 1H), 5.52-5.48 (m, 1H), 5.42-5.39 (m, 1H), 3.33-3.27 (m, 1H), 3.20-3.14 (m, 1H), 2.85 – 2.61 (m, 8H), 2.49-2.44 (m, 1H), 2.33-2.27 (m, 1H), 2.18 (s, 6H), 1.97 – 1.67 (m, 11H), 1.38 – 1.24 (m, 1H), 0.82-0.77 (m, 6H).

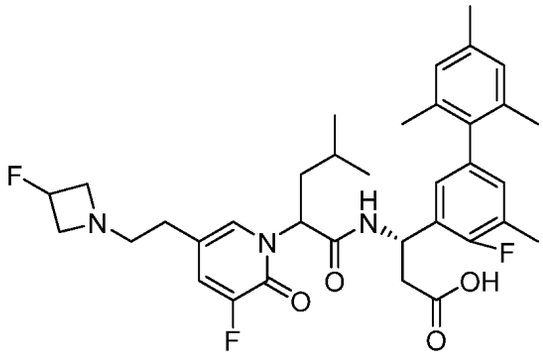
4-120. (3S)-3-(4,4'-difluoro-2',6'-dimethyl-5-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FN-P1 and FN-P2)



FN-P1 ESI 654.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.55 (s, 1H), 7.50 – 7.37 (m, 1H), 7.40 – 7.25 (m, 2H), 6.89 (d, J = 9.6 Hz, 2H), 5.73 – 5.55 (m, 1H), 5.47 (t, J = 5.9 Hz, 1H), 3.27 – 3.13 (m, 1H), 2.98 – 2.82 (m, 3H), 2.78 (s, 6H), 2.73 – 2.64 (m, 1H), 2.63 – 2.50 (m, 1H), 2.13 – 1.97 (m, 5H), 1.93 (s, 3H), 1.42 (s, 1H), 1.11 – 0.79 (m, 6H).

FN-P2 ESI 654.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.51 (s, 1H), 7.48 – 7.41 (m, 1H), 7.38 (t, J = 6.0 Hz, 2H), 6.90 (d, J = 9.6 Hz, 2H), 5.76 – 5.43 (m, 2H), 3.42 (d, J = 10.1 Hz, 1H), 3.28 (d, J = 12.8 Hz, 1H), 2.96 (d, J = 9.5 Hz, 1H), 2.85 (d, J = 7.2 Hz, 6H), 2.74 – 2.54 (m, 1H), 2.55 – 2.34 (m, 1H), 2.15 – 1.93 (m, 6H), 1.93 – 1.72 (m, 1H), 1.52 – 1.27 (m, 1H), 0.92 (t, J = 6.5 Hz, 6H).

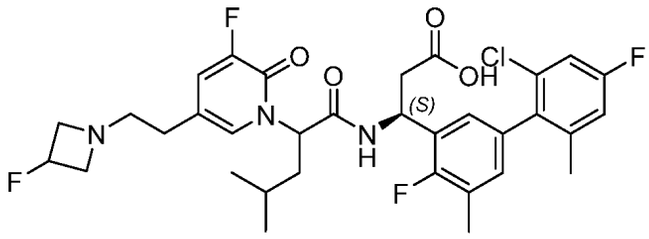
4-121. (3S)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FO-P1 and FO-P2)



FO-P1 ESI 626.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.45 – 7.33 (m, 2H), 6.96 – 6.85 (m, 3H), 6.83 – 6.75 (m, 1H), 5.69 (t, *J* = 8.1 Hz, 1H), 5.52 – 5.45 (m, 1H), 5.30 – 5.10 (m, 1H), 4.23 – 4.09 (m, 1H), 4.02 – 3.89 (m, 1H), 3.78 – 3.62 (m, 2H), 3.26 – 3.16 (m, 2H), 2.78 – 2.56 (m, 4H), 2.36 – 2.25 (m, 6H), 2.00 – 1.92 (m, 5H), 1.88 (s, 3H), 1.48 – 1.39 (m, 1H), 0.98 – 0.86 (m, 6H).

FO-P2 ESI 626.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.45 – 7.35 (m, 2H), 6.97 – 6.86 (m, 4H), 5.76 – 5.62 (m, 2H), 5.42 – 5.20 (m, 1H), 4.49 – 4.28 (m, 2H), 4.12 – 3.95 (m, 2H), 3.44 – 3.36 (m, 2H), 2.78 – 2.63 (m, 2H), 2.67 – 2.52 (m, 1H), 2.61 – 2.52 (m, 1H), 2.37 – 2.25 (m, 6H), 2.01 – 1.91 (m, 7H), 1.85 – 1.69 (m, 1H), 1.43 –1.36(m, 1H), 0.96 – 0.85 (m, 6H).

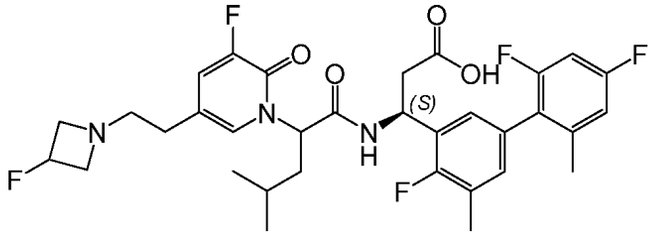
4-122. (3*S*)-3-(2'-chloro-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FP-P1 and FP-P2)



FP-P1 ESI 650.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.43 – 7.34 (m, 2H), 7.17 – 7.13 (m, 1H), 7.06 – 7.01 (m, 1H), 6.89 – 6.85 (m, 1H), 5.72 – 5.67 (m, 1H), 5.54 – 5.49 (m, 1H), 5.32 – 5.09 (m, 1H), 4.15 – 3.65 (m, 4H), 3.19 – 3.10 (m, 2H), 2.78 – 2.60 (m, 4H), 2.31 (s, 3H), 2.08 – 1.92 (m, 5H), 1.49 – 1.39 (m, 1H), 0.97– 0.93 (m, 6H).

FP-P2 ESI 650.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.39 – 7.36 (m, 2H), 7.15 (d, J = 8.5 Hz, 1H), 7.08 – 6.96 (m, 3H), 5.73 – 5.61 (m, 2H), 5.41 – 5.22 (m, 1H), 4.48 – 4.28 (m, 2H), 4.11 – 3.94 (m, 2H), 3.42 – 3.33 (m, 2H), 2.80 – 2.47 (m, 4H), 2.34 (d, J = 1.8 Hz, 3H), 2.09 (d, J = 2.7 Hz, 3H), 2.03 – 1.90 (m, 1H), 1.83 – 1.72 (m, 1H), 1.44 – 1.30 (m, 1H), 0.94 – 0.89 (m, 6H).

4-123. (3*S*)-3-(2-(3-fluoro-5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2',4,4'-trifluoro-5,6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds FQ-P1 and FQ-P2)

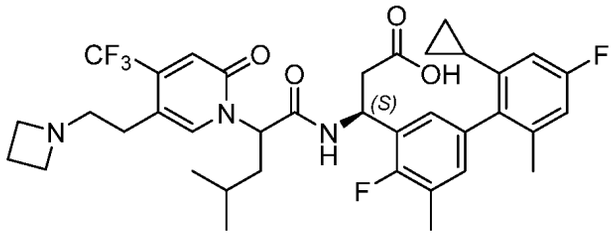


FQ-P1 ESI 634.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.43 (s, 1H), 7.36 (d, J = 10.3 Hz, 1H), 7.02 (d, J = 6.8 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.85 (t, J = 9.2 Hz, 1H), 5.69 (t, J = 8.1 Hz, 1H), 5.53 – 5.50 (m, 1H), 5.30 – 5.08 (m, 1H), 4.09 – 3.99 (m, 2H), 3.77 – 3.63 (m, 2H), 3.15 – 3.12 (m, 2H), 2.79 – 2.69 (m, 2H), 2.66 – 2.62 (m, 2H), 2.31 (s, 3H), 2.09 (s, 3H), 1.97 (t, J = 7.6 Hz, 2H), 1.51 – 1.37 (m, 1H), 0.98 – 0.93 (m, 6H).

FQ-P2 ESI 634.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.43 – 7.32 (m, 2H), 7.06 (d, J = 6.7 Hz, 2H), 6.93 (d, J = 9.3 Hz, 1H), 6.88 – 6.83 (m, 1H), 5.74 – 5.59 (m, 2H), 5.39 – 5.24 (m, 1H), 4.42 – 4.32 (m, 2H), 4.10 – 3.88 (m, 2H), 3.40 – 3.37 (m, 2H), 2.81 – 2.71 (m, 2H), 2.65 – 2.60 (m, 1H), 2.55

– 2.48 (m, 1H), 2.34 (d, *J* = 1.6 Hz, 3H), 2.16 (s, 3H), 2.03 – 1.93 (m, 1H), 1.86 – 1.75 (m, 1H), 1.45 – 1.33 (m, 1H), 0.93– 0.91(m, 6H).

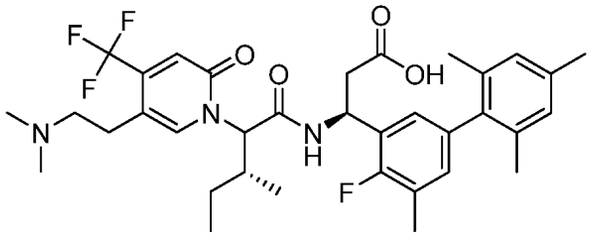
4-124. (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2'-cyclopropyl-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds FR-P1 and FR-P2)



FR-P1 ESI 688.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 6.95 (dd, *J* = 19.9, 7.2 Hz, 2H), 6.86 – 6.64 (m, 2H), 6.55 – 6.23 (m, 1H), 5.75 – 5.49 (m, 2H), 3.85 (t, *J* = 7.7 Hz, 4H), 3.33 (m, *J* = 3.2, 1.6 Hz, 2H), 3.13 (m, *J* = 6.8 Hz, 2H), 2.90 – 2.58 (m, 2H), 2.51 – 2.21 (m, 5H), 2.01 (d, *J* = 5.3 Hz, 4H), 1.87 (s, 1H), 1.40 (s, 2H), 1.07 – 0.85 (m, 6H), 0.75 (m, *J* = 8.6, 3.5 Hz, 1H), 0.66 – 0.43 (m, 3H).

FR-P2 ESI 688.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (d, *J* = 11.5 Hz, 1H), 6.94 (m, *J* = 46.9, 28.6, 8.1 Hz, 4H), 6.50 (d, *J* = 10.4 Hz, 1H), 5.78 (m, *J* = 11.0, 3.1 Hz, 1H), 5.62 (m, *J* = 7.3 Hz, 1H), 4.13 (m, *J* = 8.0 Hz, 4H), 3.50 – 3.32 (m, 2H), 2.94 (d, *J* = 16.3 Hz, 1H), 2.81 (d, *J* = 7.7 Hz, 2H), 2.68 – 2.61 (m, 1H), 2.57 – 2.42 (m, 3H), 2.34 (d, *J* = 1.1 Hz, 3H), 2.05 – 1.79 (m, 4H), 1.65 (m, *J* = 13.9, 7.1 Hz, 1H), 1.50 – 1.30 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H), 0.74 (m, *J* = 14.0, 7.3 Hz, 2H), 0.60 (m, *J* = 6.4, 5.0 Hz, 2H).

4-125. (3*S*)-3-((3*R*)-2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds FS-P1 and FS-P2)

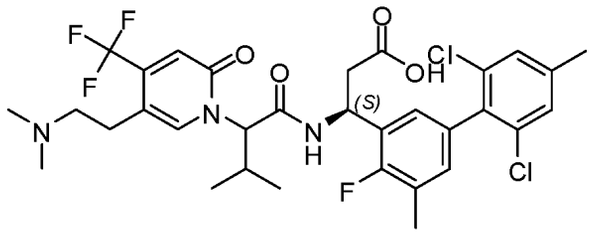


FS-P1 ESI 646.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.94 (s, 1H), 6.89 (s, 1H), 6.82 – 6.75 (m, 3H), 6.66 (s, 1H), 5.65 – 5.53 (m, 1H), 5.33 (d, *J* = 11.3 Hz, 1H), 3.05 – 2.83 (m, 5H), 2.82 – 2.62 (m,

6H), 2.40 – 2.18 (m, 8H), 2.03 – 1.88 (m, 3H), 1.78 – 1.67 (m, 1H), 1.63 (s, 3H), 1.38 – 1.21 (m, 1H), 1.07 – 0.96 (m, 3H), 0.75 (d, *J* = 6.5 Hz, 3H).

FS-P2 ESI 646.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.92 (s, 1H), 6.91 – 6.72 (m, 5H), 5.69 – 5.52 (m, 1H), 5.21 (d, *J* = 10.9 Hz, 1H), 3.14 – 2.79 (m, 3H), 2.68 (s, 6H), 2.55 – 2.36 (m, 2H), 2.22 – 2.06 (m, H), 1.84 (d, *J* = 3.6 Hz, 4H), 1.32 – 0.99 (m, 3H), 0.93 – 0.61 (m, 7H).

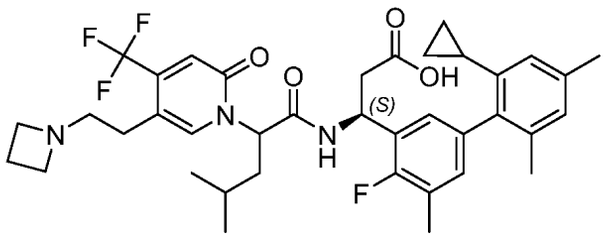
4-126. (3S)-3-(2',6'-dichloro-4-fluoro-4',5-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-3-methylbutanamido)propanoic acid (diastereomeric compounds FT-P1 and FT-P2)



FT-P1 ESI 672.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ: 7.91 (s, 1H), 7.27 (d, *J* = 6.0 Hz, 1H), 7.14 (d, *J* = 5.2 Hz, 1H), 6.90 (t, *J* = 6.0 Hz, 2H), 6.67 (d, *J* = 5.6 Hz, 1H), 5.64 – 5.60 (m, 1H), 5.29 (d, *J* = 11.2 Hz, 1H), 2.97 – 2.85 (m, 4H), 2.78 – 2.61 (m, 8H), 2.46 – 2.40 (m, 1H), 2.36 (s, 3H), 2.27 (s, 3H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H).

FT-P2 ESI 672.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ: 8.01 (s, 1H), 7.30 (s, 2H), 7.09 – 7.07 (m, 1H), 7.00 (d, *J* = 7.2 Hz, 1H), 6.90 (s, 1H), 5.78 – 5.74 (m, 1H), 5.23 (d, *J* = 11.2 Hz, 1H), 3.27 – 3.20 (m, 1H), 3.17 – 3.11 (m, 1H), 3.09 – 3.01 (m, 1H), 2.99 – 2.93 (m, 1H), 2.78 (s, 6H), 2.61 – 2.50 (m, 2H), 2.47 – 2.37 (m, 4H), 2.31 (d, *J* = 1.2 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H).

4-127. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds FU-P1 and FU-P2)

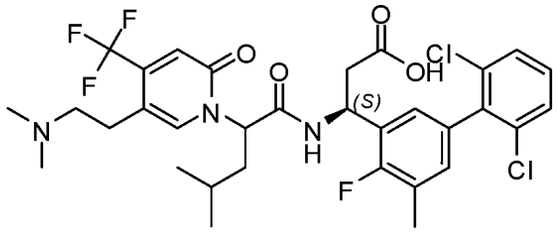


FU-P1 ESI 684.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 6.97 – 6.78 (m, 4H), 6.58 (s, 1H), 5.69 – 5.59 (m, 2H), 3.97 – 3.94 (m, 4H), 3.26 – 3.21 (m, 2H), 2.86 – 2.81 (m, 2H), 2.72 – 2.68

(m, 2H), 2.46 – 2.38 (m, 2H), 2.29 (d, *J* = 4.9 Hz, 6H), 2.03 – 1.97 (m, 3H), 1.85 (s, 2H), 1.48 – 1.31 (m, 2H), 0.98 – 0.91 (m, 6H), 0.67 (d, *J* = 8.4 Hz, 1H), 0.59 – 0.44 (m, 3H).

FU-P2 ESI 684.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.73 (d, *J* = 10.5 Hz, 1H), 7.02 – 6.96 (m, 2H), 6.91 (s, 1H), 6.90 (s, 1H), 6.59 (s, 1H), 5.78 – 5.75 (m, 1H), 5.64 – 5.59 (m, 1H), 4.14 – 4.10 (m, 4H), 3.47 – 3.38 (m, 2H), 2.97 – 2.92 (m, 1H), 2.85 – 2.75 (m, 1H), 2.69 – 2.60 (m, 1H), 2.55 – 2.45 (m, 3H), 2.34 (s, 3H), 2.29 (s, 3H), 2.05 – 1.96 (m, 4H), 1.71 – 1.61 (m, 1H), 1.49 – 1.39 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.70 – 0.66 (m, 2H), 0.58 – 0.55 (m, 2H).

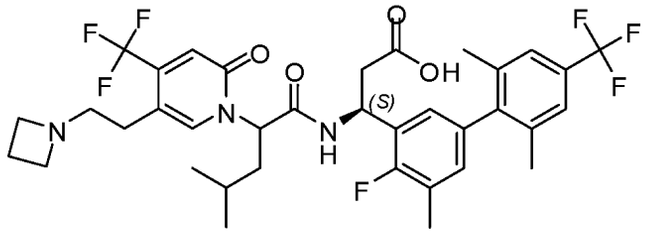
4-128. (3S)-3-(2',6'-dichloro-4-fluoro-5-methylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FV-P1 and FV-P2)



FV-P1 ESI 672.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ: 7.89 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.00 – 6.96 (m, 2H), 6.75 (s, 1H), 5.72 – 5.68 (m, 1H), 5.60 – 5.56 (m, 1H), 3.10 – 3.01 (m, 2H), 2.94 – 2.92 (m, 2H), 2.74 – 2.65 (m, 8H), 2.27 (d, *J* = 1.2 Hz, 3H), 2.01 – 1.93 (m, 2H), 1.47 – 1.41 (m, 1H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H).

FV-P2 ESI 672.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ: 7.91 – 5.88 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.08 – 7.02 (m, 2H), 6.89 (s, 1H), 5.78 – 5.74 (m, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 3.27 – 3.15 (m, 2H), 3.06 – 2.95 (m, 2H), 2.80 (s, 6H), 2.65 – 2.60 (m, 1H), 2.55 – 2.49 (m, 1H), 2.32 (s, 3H), 1.99 – 1.92 (m, 1H), 1.71 – 1.64 (m, 1H), 1.41 – 1.34 (m, 1H), 0.86 – 0.84 (m, 6H).

4-129. (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid (diastereomeric compounds FW-P1 and FW-P2)

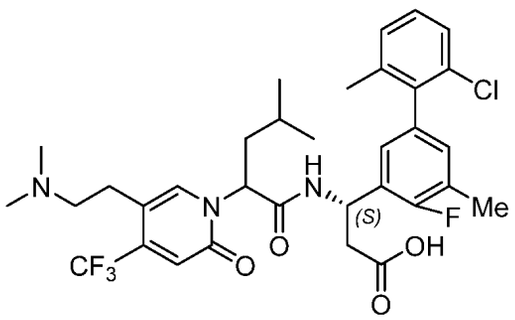


FW-P1 ESI 712.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ: 7.88 (s, 1H), 7.39 (s, 1H), 7.35 (s, 1H), 6.91 (t, *J* = 6.2 Hz, 2H), 6.70 (s, 1H), 5.66 – 5.57 (m, 2H), 4.04 (t, *J* = 8.2 Hz, 4H), 3.29 (t, *J* = 7.4 Hz, 2H),

2.84 (t, *J* = 7.2 Hz, 2H), 2.78 – 2.67 (m, 2H), 2.48 – 2.40 (m, 2H), 2.30 (d, *J* = 1.2 Hz, 3H), 2.08 (s, 3H), 2.03 – 1.99 (m, 2H), 1.91 (s, 3H), 1.47 – 1.40 (m, 1H),), 0.95 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H).

FW-P2 ESI 712.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ: 7.74 (s, 1H), 7.41 (s, 2H), 6.98 (s, 1H), 6.96 (s, 1H), 6.90 (s, 1H), 5.79 – 5.76 (m, 1H), 5.60 (t, *J* = 8.0 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 4H), 3.48 – 3.42 (m, 1H), 3.38 – 3.33 (m, 1H), 2.98 – 2.91 (m, 1H), 2.84 – 2.77 (m, 1H), 2.69 – 2.64 (m, 1H), 2.55 – 2.45 (m, 3H), 2.35 (d, *J* = 1.6 Hz, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.03 – 1.96 (m, 1H), 1.69 – 1.62 (m, 1H), 1.46 – 1.36 (m, 1H), 0.89 (d, *J* = 1.6 Hz, 3H), 0.87 (d, *J* = 2.0 Hz, 3H).

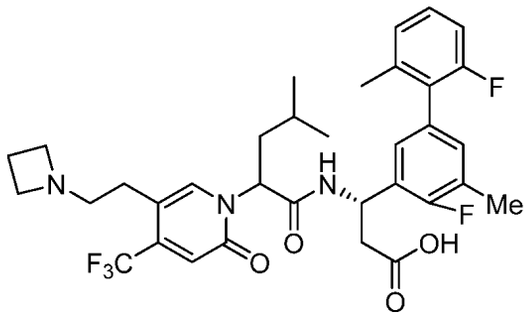
4-130. (3S)-3-(2'-chloro-4-fluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FX-P1 and FX-P2)



FX-P1 ESI 652.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (d, *J* = 4.5 Hz, 1H), 7.37 – 7.09 (m, 3H), 6.93 (m, *J* = 10.9, 4.9 Hz, 2H), 6.75 (d, *J* = 6.5 Hz, 1H), 5.68 (m, *J* = 30.2, 23.4 Hz, 2H), 3.00 (d, *J* = 50.0 Hz, 4H), 2.73 (d, *J* = 14.3 Hz, 8H), 2.30 (s, 3H), 2.13 – 1.83 (m, 5H), 1.45 (d, *J* = 6.4 Hz, 1H), 0.96 (m, *J* = 12.9, 6.6, 2.5 Hz, 6H).

FX-P2 ESI 652.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.34 – 7.09 (m, 3H), 7.11 – 6.51 (m, 3H), 5.69 (m, *J* = 21.6, 10.6, 4.3 Hz, 2H), 3.15 (s, 2H), 2.98 (s, 2H), 2.88 – 2.53 (m, 8H), 2.34 (s, 3H), 2.08 (d, *J* = 5.6 Hz, 3H), 1.98 – 1.81 (m, 1H), 1.78 (s, 1H), 1.40 (s, 1H), 0.89 (m, *J* = 6.4, 4.6 Hz, 6H).

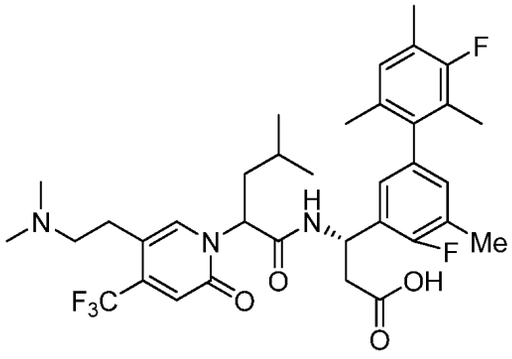
4-131. (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(2',4-difluoro-5,6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds FY-P1 and FY-P2)



FY-P1 ESI 648.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.30 – 7.23 (m, 1H), 7.16 – 7.09 (m, 1H), 7.06 –6.92 (m, 3H), 6.81 (s, 1H), 5.71 – 5.60 (m, 2H), 4.01 (t, *J* = 8.1 Hz, 4H), 3.29 (s, 2H), 2.86 (t, *J* = 6.8 Hz, 2H), 2.72 (d, *J* = 6.6 Hz, 2H), 2.46 – 2.36 (m, 2H), 2.36 – 2.31 (m, 3H), 2.10 (s, 3H), 2.00 (t, *J* = 7.6 Hz, 2H), 1.51 – 1.42 (m, 1H), 0.98 – 0.93 (m, 6H).

FY-P2 ESI 648.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 7.31 –7.19 (m, 1H), 7.15 – 7.04 (m, 3H), 6.99 (t, *J* = 8.8 Hz, 1H), 6.92 (s, 1H), 5.81 –5.75 (m, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 4.14 (t, *J* = 8.0 Hz, 4H), 3.49 – 3.35 (m, 2H), 2.94 (d, *J* = 15.7 Hz, 1H), 2.87 – 2.75 (m, 1H), 2.69 –2.56 (m, 1H), 2.57 – 2.43 (m, 3H), 2.35 (d, *J* = 1.5 Hz, 3H), 2.17 (d, *J* = 8.1 Hz, 3H), 2.04 – 1.95 (m, 1H), 1.72 – 1.62 (m, 1H), 1.46 –1.32 (m, 1H), 0.97 –0.91 (m, 6H).

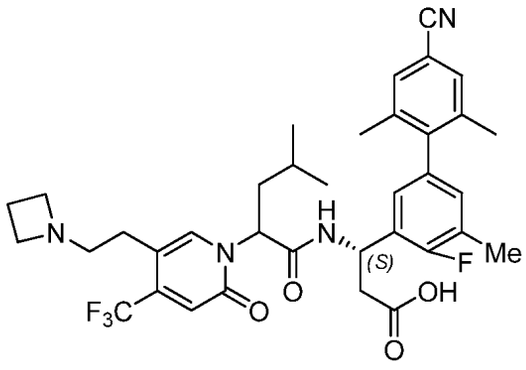
4-132. (3*S*)-3-(3',4-difluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds FZ-P1 and FZ-P2)



FZ-P1 ESI 664.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.01 – 6.79 (m, 4H), 5.78 – 5.58 (m, 2H), 3.29 – 3.07 (m, 2H), 3.04 – 2.89 (m, 2H), 2.81 (s, 6H), 2.70 – 2.42 (m, 2H), 2.33 (s, 3H), 2.26 (s, 3H), 2.13 – 1.83 (m, 7H), 1.81 – 1.60 (m, 1H), 1.52 – 1.30 (m, 1H), 1.02 – 0.81 (m, 6H).

FZ-P2 ESI 664.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 6.99 – 6.68 (m, 4H), 5.82 – 5.50 (m, 2H), 3.19 – 2.89 (m, 4H), 2.83 – 2.54 (m, 8H), 2.38 – 2.22 (m, 6H), 2.13 – 1.80 (m, 5H), 1.72 (d, *J* = 14.7 Hz, 3H), 1.51 – 1.36 (m, 1H), 1.06 – 0.84 (m, 6H).

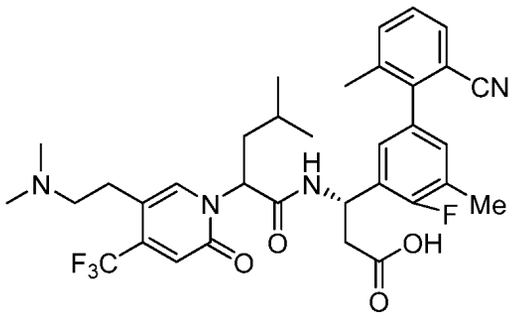
4-133. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyano-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds GA-P1 and GA-P2)



GA-P1 ESI 669.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.47 (d, *J* = 10.3 Hz, 2H), 6.91 (d, *J* = 6.7 Hz, 2H), 6.75 (s, 1H), 5.59 (d, *J* = 7.7 Hz, 2H), 4.06 (t, *J* = 8.1 Hz, 4H), 3.31 – 3.27 (m, 2H), 2.98 – 2.85 (m, 2H), 2.79 – 2.64 (m, 2H), 2.58 – 2.39 (m, 2H), 2.31 (s, 3H), 2.14 – 1.88 (m, 8H), 1.54 – 1.27 (m, 1H), 1.10 – 0.80 (m, 6H).

GA-P2 ESI 669.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.50 (s, 2H), 7.06 – 6.84 (m, 3H), 5.90 – 5.71 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 4.10 (s, 4H), 3.36 (s, 2H), 3.09 – 2.74 (m, 2H), 2.74 – 2.60 (m, 1H), 2.55 – 2.39 (m, 3H), 2.35 (s, 3H), 2.13 – 1.89 (m, 7H), 1.75 – 1.62 (m, 1H), 1.50 – 1.35 (m, 1H), 0.98 – 0.81 (m, 6H).

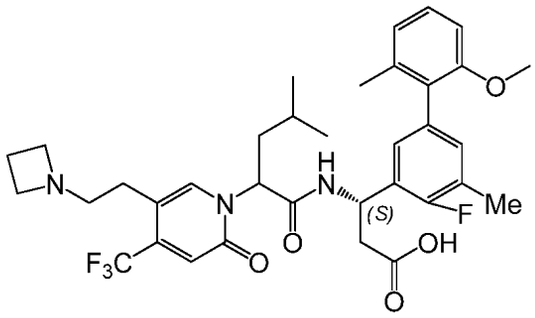
4-134. (3S)-3-(2'-cyano-4-fluoro-5,6'-dimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GB-P1 and GB-P2)



GB-P1 ESI 643.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.89 (s, 1H), 7.59 (s, 2H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.06 (s, 2H), 6.71 (d, *J* = 26.7 Hz, 1H), 5.73 (s, 1H), 5.60 (d, *J* = 7.3 Hz, 1H), 3.10 (s, 2H), 2.93 (d, *J* = 8.3 Hz, 2H), 2.80 – 2.69 (m, 8H), 2.32 (s, 3H), 2.19 (s, 2H), 2.00 (s, 3H), 1.49 – 1.42 (m, 1H), 1.00 – 0.92 (m, 6H).

GB-P1 ESI 643.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.66 – 7.52 (m, 2H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.13 (d, *J* = 6.4 Hz, 2H), 6.90 (s, 1H), 5.77 – 5.59 (m, 2H), 3.23 (s, 2H), 3.01 (s, 2H), 2.83 (s, 6H), 2.69 – 2.53 (m, 1H), 2.58 – 2.49 (m, 1H), 2.37 (d, *J* = 1.6 Hz, 3H), 2.19 (s, 3H), 2.05 – 1.96 (m, 1H), 1.81 (s, 1H), 1.42 – 1.36 (m, 1H), 0.99 – 0.91 (m, 6H).

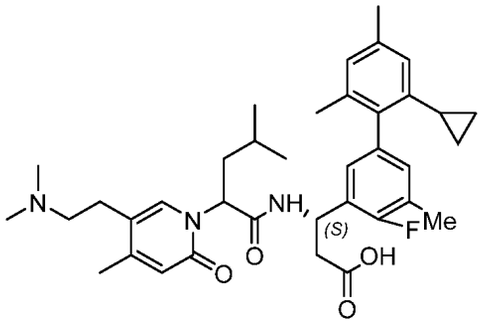
4-135. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2'-methoxy-5,6'-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds GC-P1 and GC-P2)



GC-P1 ESI 660.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.82 (s, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.99 – 6.82 (m, 5H), 5.70 – 5.62 (m, 2H), 4.01 – 3.96 (m, 4H), 3.66 (s, 3H), 3.30 – 3.27 (m, 2H), 2.88 – 2.85 (m, 2H), 2.71 (d, *J* = 7.4 Hz, 2H), 2.45 – 2.39 (m, 2H), 2.29 (s, 3H), 2.02 – 1.93 (m, 5H), 1.45 – 1.38 (m, 1H), 0.97 – 0.93 (m, 6H).

GC-P2 ESI 660.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.22 (t, *J* = 8.0 Hz, 1H), 7.00 – 6.87 (m, 5H), 5.79 – 5.75 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 4.13 (t, *J* = 7.9 Hz, 4H), 3.68 (s, 3H), 3.49 – 3.35 (m, 2H), 2.97– 2.91 (d, *J* = 16.1 Hz, 1H), 2.85 – 2.77 (m, 1H), 2.66 – 2.62(m, 1H), 2.56 – 2.42 (m, 3H), 2.32 (d, *J* = 1.7 Hz, 3H), 2.04 (s, 3H), 2.02 – 1.97 (m, 1H), 1.72 – 1.60 (m, 1H), 1.49 – 1.36 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 6H).

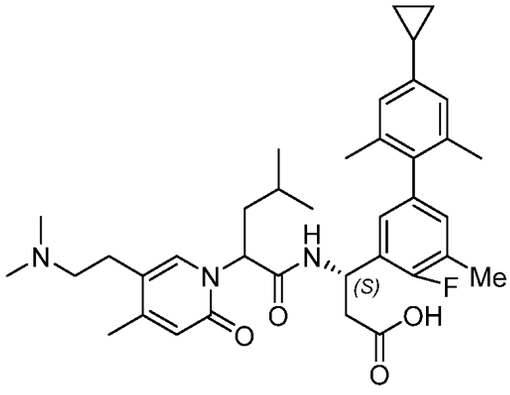
4-136. (3*S*)-3-(2'-cyclopropyl-4-fluoro-4',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GD-P1 and GD-P2)



GD-P1 ESI 618.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 1.8 Hz,1), 6.91 – 6.84 (m, 3H), 6.57 (d, *J* = 11.0 Hz, 1H), 6.38 (d, *J* = 8.9 Hz, 1H), 5.59 (d, *J* = 5.8 Hz, 1H), 5.46 (t, *J* = 5.9 Hz, 1H), 3.22 – 3.06 (m, 2H), 2.87 (t, *J* = 7.1 Hz, 2H), 2.74 (s, 6H), 2.71 – 2.56 (m, 2H), 2.27 (d, *J* = 13.3 Hz, 9H), 2.04 – 1.87 (m, 5H), 1.48 – 1.38 (m, 2H), 0.95 – 0.89 (m, 6H), 0.72 – 0.67 (m, 1H), 0.63 – 0.55 (m, 1H), 0.53 – 0.48 (m, 2H).

GD-P2 ESI 618.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.54 (d, *J* = 10.5 Hz, 1H), 6.98 – 6.89 (m, 2H), 6.89 (s, 1H), 6.59 (s, 1H), 6.44 (d, *J* = 5.1 Hz, 1H), 5.65 –5.56 (m, 2H), 3.34 – 3.26 (m, 2H), 3.20 – 3.13 (m, 2H), 2.94 – 2.88 (m, 2H), 2.81 (d, *J* = 2.0 Hz, 6H), 2.64 – 2.57 (m, 1H), 2.48 – 2.41 (m, 1H), 2.32 – 2.246 (m, 9H), 1.99 – 1.92 (m, 4H), 1.81 – 1.74 (m, 1H), 1.49 – 1.33 (m, 1H), 0.92 – 0.85 (m, 6H), 0.68 – 0.63 (m, 2H), 0.58 – 0.51 (m, 2H).

4-137. (3S)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GE-P1 and GE-P2)

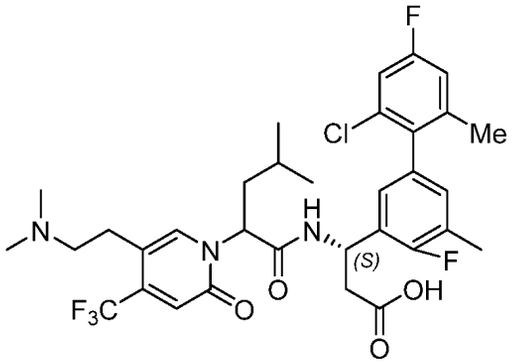


GE-P1 ESI 618.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.46 (s, 1H), 6.84 – 6.65 (m, 3H), 6.45 (d, *J* = 11.2 Hz, 1H), 6.27 (d, *J* = 8.7 Hz, 1H), 5.48-5.46 (m, 1H), 5.33 (d, *J* = 5.6 Hz, 1H), 3.15-2.95 (m, 2H), 2.78-2.74 (m, 3H), 2.60 (d, *J* = 25.4 Hz, 6H), 2.58 – 2.40 (m, 2H), 2.17 (s, 6H), 2.13(s, 3H), 1.95 – 1.73 (m, 5H), 1.34-1.28 (m, 2H), 0.86 – 0.73 (m, 6H), 0.62 – 0.32 (m, 4H).

GE-P2 ESI 618.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.43(s, 1H), 7.40(s, 1H), 6.84 (t, *J* = 6.2 Hz, 2H), 6.77 (s, 1H), 6.47 (s, 1H), 6.32 (d, *J* = 5.5 Hz, 1H), 5.52-5.44 (m, 2H), 3.09-3.06 (m, 1H), 2.88 –

2.67 (m, 8H), 2.51-2.45 (m, 1H), 2.37-2.29 (m, 1H), 2.24 – 2.09 (m, 9H), 1.85-1.81 (m, 4H), 1.70 – 1.59 (m, 1H), 1.39 – 1.16 (m, 2H), 0.78-0.76 (m, 6H), 0.54 (t, *J* = 7.6 Hz, 2H), 0.45 (d, *J* = 4.5 Hz, 2H).

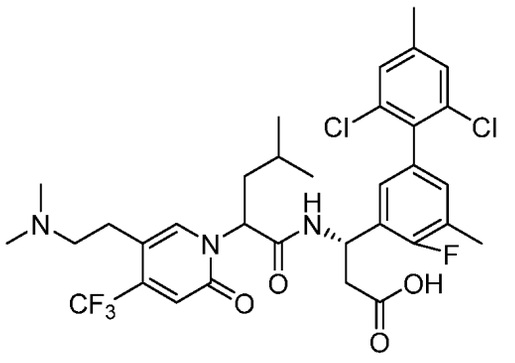
4-138. (3*S*)-3-(2'-chloro-4,4'-difluoro-5,6'-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GF-P1 and GF-P2)



GF-P1 ESI 670.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (d, *J* = 3.1 Hz, 1H), 7.14 – 6.92 (m, 4H), 6.76 (d, *J* = 5.6 Hz, 1H), 5.72 – 5.65 (m, 1H), 5.60 – 5.56 (m, 1H), 3.10 – 2.87 (m, 4H), 2.76 – 2.66 (m, 8H), 2.30 (s, 3H), 2.09 – 1.91 (m, 5H), 1.47 – 1.41 (m, 1H), 1.00 – 0.92 (m, 6H).

GF-P2 ESI 670.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.16 – 7.12 (m, 1H), 7.07 – 6.95 (m, 3H), 6.91 (d, *J* = 2.7 Hz, 1H), 5.74 – 5.59(m, 2H), 3.32 – 3.21 (m, 2H), 3.03 – 2.99 (m, 2H), 2.84 (d, *J* = 2.9 Hz, 6H), 2.67 – 2.49 (m, 2H), 2.34 (d, *J* = 1.6 Hz, 3H), 2.03 – 1.90 (m, 1H), 1.76 – 1.67 (m, 1H), 1.46 – 1.37 (m, 1H), 0.92 – 0.89 (m, 6H).

4-139. (3*S*)-3-(2',6'-dichloro-4-fluoro-4',5-dimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GG-P1 and GG-P2)

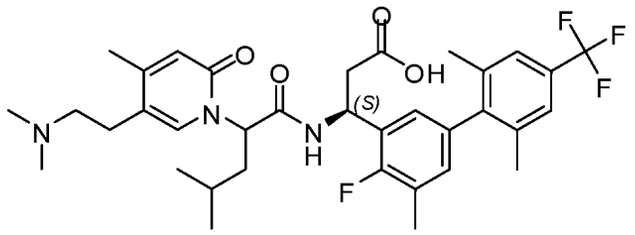


GG-P1 ESI 686.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.90 (s, 1H), 7.31 (s, 1H), 7.23 (s, 1H), 7.02 – 6.91 (m, 2H), 6.76 (s, 1H), 5.76 – 5.66 (m, 1H), 5.63 – 5.53 (m, 1H), 3.15 – 3.04 (m, 2H), 2.94 (t, *J*

= 11.0 Hz, 2H), 2.80 – 2.66 (m, 8H), 2.38 (s, 3H), 2.29 (d, *J* = 1.3 Hz, 3H), 2.04 – 1.92 (m, 2H), 1.51 – 1.42 (m, 1H), 1.01 – 0.90 (m, 6H).

GG-P2 ESI 686.1 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.32 (s, 2H), 7.09 – 6.99 (m, 2H), 6.91 (s, 1H), 5.79 – 5.71 (m, 1H), 5.65 (t, *J* = 7.7 Hz, 1H), 3.30 – 3.15 (m, 2H), 3.00 (t, *J* = 6.8 Hz, 2H), 2.81 (s, 6H), 2.67 – 2.50 (m, 2H), 2.39 (s, 3H), 2.33 (d, *J* = 1.5 Hz, 3H), 2.02 – 1.92 (m, 1H), 1.73 – 1.65 (m, 1H), 1.44 – 1.36 (m, 1H), 0.91 – 0.85 (m, 6H).

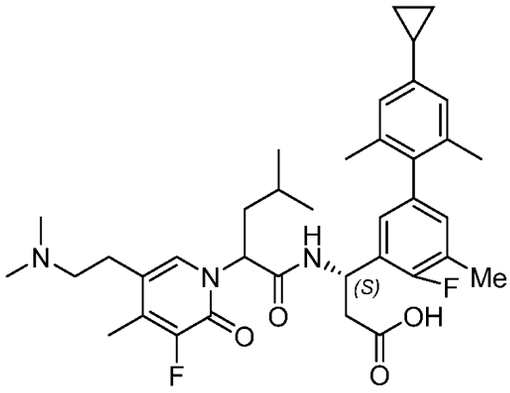
4-140. (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethyl-4'-(trifluoromethyl)biphenyl-3-yl)propanoic acid (diastereomeric compounds GH-P1 and GH-P2)



GH-P1 ESI 646.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ: 7.59 (s, 1H), 7.40 (s, 1H), 7.38 (s, 1H), 6.89 (d, *J* = 6.8 Hz, 1H), 6.84 (d, *J* = 6.4 Hz, 1H), 6.28 (s, 1H), 5.55 (t, *J* = 5.6 Hz, 1H), 5.49 (t, *J* = 6.0 Hz, 1H), 3.16 – 3.08 (m, 2H), 2.87 (t, *J* = 7.2 Hz, 2H), 2.78 (s, 6H), 2.73 – 2.68 (m, 1H), 2.65 – 2.60 (m, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.08 (s, 3H), 2.01 – 1.90 (m, 5H), 1.45 – 1.38 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H).

GH-P2 ESI 646.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ: 7.55 (s, 1H), 7.41 (s, 2H), 6.95 – 6.93 (m, 1H), 6.90 (d, *J* = 6.4 Hz, 1H), 6.41 (s, 1H), 5.63 – 5.60 (m, 1H), 5.58 – 5.56 (m, 1H), 3.38 – 3.36 (m, 1H), 3.25 – 3.19 (m, 1H), 2.95 – 2.90 (m, 2H), 2.85 (s, 6H), 2.64 – 2.59 (m, 1H), 2.50 – 2.44 (m, 1H), 2.34 (d, *J* = 1.6 Hz, 3H), 2.26 (s, 3H), 2.08 (s, 6H), 2.00 – 1.93 (m, 1H), 1.83 – 1.76 (m, 1H), 1.42 – 1.35 (m, 1H), 0.89 (t, *J* = 6.4 Hz, 6H).

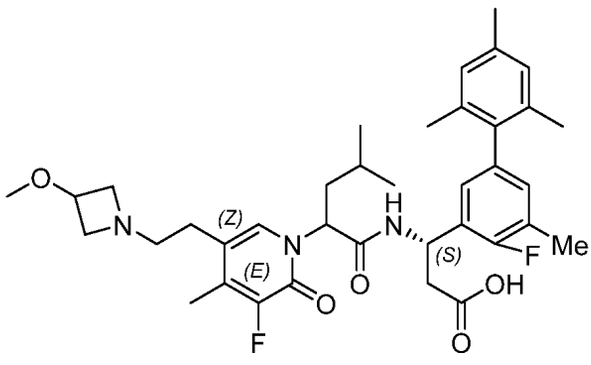
4-141. (3S)-3-(4'-cyclopropyl-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GI-P1 and GI-P2)



GI-P1 ESI 636.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.47 (s, 1H), 6.94 – 6.78 (m, 3H), 6.57 (d, *J* = 12.7 Hz, 1H), 5.74 – 5.57 (m, 1H), 5.46 (t, *J* = 5.9 Hz, 1H), 3.25-3.10(m, 2H), 2.92 (t, *J* = 6.9 Hz, 2H), 2.75 (s, 6H), 2.70 – 2.52 (m, 2H), 2.30-2.25 (m, 9H), 1.99-1.88 (m, 5H), 1.46-1.39 (m, 2H), 0.97 – 0.86 (m, 6H), 0.72 – 0.43 (m, 4H).

GI-P2 ESI 636.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.42 (d, *J* = 11.3 Hz, 1H), 6.97 (t, *J* = 8.2 Hz, 2H), 6.89 (s, 1H), 6.59 (s, 1H), 5.72 – 5.52 (m, 2H), 3.32-3.22 (m, 2H), 2.98-2.90 (m, 2H), 2.85 (s, 6H), 2.67 – 2.38 (m, 2H), 2.32-2.25 (m, 9H), 2.00-1.98 (m, 4H), 1.83 – 1.67 (m, 1H), 1.51 – 1.26 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.70 – 0.48 (m, 4H).

4-142. (3S)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GJ-P1 and GJ-P2)

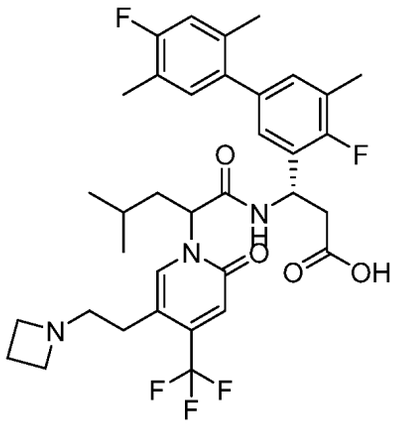


GJ-P1 ESI 652.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.26 (s, 1H), 6.84 – 6.68 (m, 4H), 5.54 – 5.45 (m, 1H), 5.41 (t, *J* = 6.3 Hz, 1H), 4.14-3.93 (m, 3H), 3.64 – 3.54 (m, 1H), 3.52-3.50 (m, 1H), 3.25-3.16(m, 5H), 2.74-2.55 (m, 4H), 2.18(s, 6H),2.12 (d, *J* = 4.0 Hz , 3H), 1.88 – 1.74 (m, 8H), 1.29-1.25 (m, 1H), 0.83-0.78 (m, 6H).

GJ-P2 ESI 652.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.20 (s, 1H), 6.85 – 6.72 (m, 4H), 5.61 – 5.43 (m, 2H), 4.36 – 4.08 (m, 3H), 3.84 – 3.61 (m, 2H), 3.32-3.22(m, 5H), 2.82-2.78 (m, 1H), 2.64-2.56 (m,

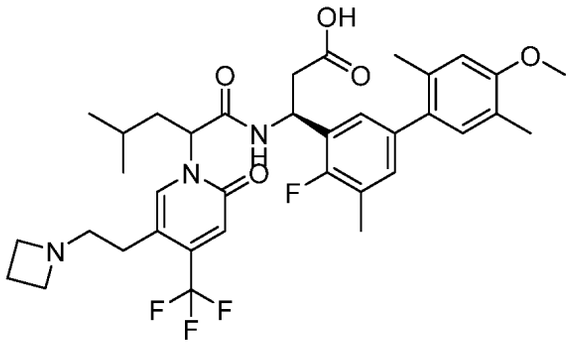
1H), 2.51-2.47 (m, 1H), 2.39-2.32 (m, 1H), 2.23 – 2.13 (m, 6H), 2.10 (d, *J* = 2.7 Hz, 3H), 1.90 – 1.73 (m, 8H), 1.68 – 1.51 (m, 1H), 1.32 – 1.20 (m, 1H), 0.79-0.74 (m, 6H).

4-143. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4,4'-difluoro-2',5,5'-trimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds GK-P1 and GK-P2)



GK-P1 ESI 662.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.03-7.00 (m, 3H), 6.93 (d, *J* = 10.6 Hz, 1H), 6.81 (s, 1H), 5.70 – 5.63 (m, 1H), 5.59 (t, *J* = 6.7 Hz, 1H), 4.02 (t, *J* = 8.2 Hz, 4H), 3.30 (s, 2H), 2.86 (t, *J* = 6.9 Hz, 2H), 2.71 (d, *J* = 6.8 Hz, 2H), 2.42 -2.39(m, 2H), 2.30 (d, *J* = 1.4 Hz, 3H), 2.25 (s, 3H), 2.15 (s, 3H), 2.02 -2.19(m, 2H), 1.48 – 1.39 (m, 1H), 0.96-0.90 (m, 6H).
GK-P2 ESI 662.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.73 (s, 1H), 7.09-7.06 (m, 2H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.99 – 6.88 (m, 2H), 5.75-5.70 (m, 1H), 5.64 (t, *J* = 7.7 Hz, 1H), 4.15 (t, *J* = 8.0 Hz, 4H), 3.42-3.40 (m, 2H), 2.95 (d, *J* = 16.2 Hz, 1H), 2.82 -2.80(m, 1H), 2.64-2.60 (m, 1H), 2.55 – 2.43 (m, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.20 (s, 3H), 2.04 – 1.97 (m, 1H), 1.71-1.68 (m, 1H), 1.43-1.38 (m, 1H), 0.92 (t, *J* = 6.3 Hz, 6H).

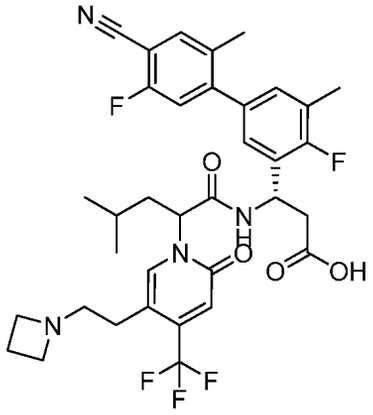
4-144. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-4'-methoxy-2',5,5'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds GL-P1 and GL-P2)



GL-P1 ESI 674.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.83 (s, 1H), 7.03 (t, *J* = 7.3 Hz, 2H), 6.90 (s, 1H), 6.83 (s, 1H), 6.78 (s, 1H), 5.67 (t, *J* = 8.0 Hz, 1H), 5.59 (t, *J* = 6.7 Hz, 1H), 3.99 (t, *J* = 8.2 Hz, 4H), 3.86 (s, 3H), 3.29 (d, *J* = 3.5 Hz, 2H), 2.85 (t, *J* = 6.7 Hz, 2H), 2.71 (d, *J* = 6.7 Hz, 2H), 2.44 – 2.34 (m, 2H), 2.29 (d, *J* = 1.6 Hz, 3H), 2.18 (s, 6H), 2.02 (t, *J* = 7.5 Hz, 2H), 1.46 – 1.39 (m, 1H), 0.96 (t, *J* = 6.2 Hz, 6H).

GL-P2 ESI 674.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.14 – 7.03 (m, 2H), 6.93 (s, 2H), 6.80 (s, 1H), 5.80 – 5.71 (m, 1H), 5.64 (t, *J* = 7.6 Hz, 1H), 4.14 (t, *J* = 8.0 Hz, 4H), 3.86 (s, 3H), 3.50 – 3.36 (m, 2H), 2.95 (d, *J* = 15.7 Hz, 1H), 2.87 – 2.78 (m, 1H), 2.67 – 2.60 (m, 1H), 2.57 – 2.42 (m, 3H), 2.33 (d, *J* = 1.6 Hz, 3H), 2.20 (d, *J* = 19.2 Hz, 6H), 2.05 – 1.96 (m, 1H), 1.73 – 1.65 (m, 1H), 1.47 – 1.37 (m, 1H), 0.92 (t, *J* = 6.7 Hz, 6H).

4-145. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(4'-cyano-4,5'-difluoro-2',5-dimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds GM-P1 and GM-P2)

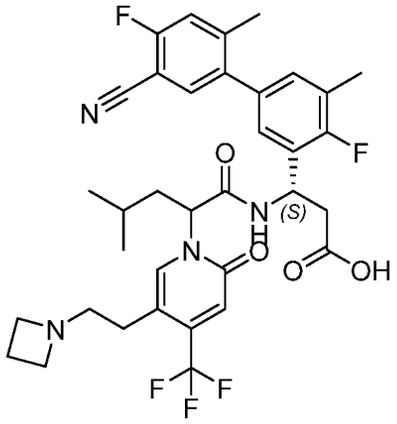


GM-P1 ESI 673.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.86 (s, 1H), 7.67 (d, *J* = 6.6 Hz, 1H), 7.24 – 7.07 (m, 3H), 6.79 (d, *J* = 7.4 Hz, 1H), 5.78 – 5.50 (m, 2H), 4.10 (t, *J* = 8.1 Hz, 4H), 3.41 – 3.34 (m, 2H), 2.92 – 2.65 (m, 4H), 2.61 – 2.40 (m, 2H), 2.32 (s, 3H), 2.23 (s, 3H), 2.15 – 1.86 (m, 2H), 1.54 – 1.38 (m, 1H), 0.97 (t, *J* = 6.6 Hz, 6H).

GM-P2 ESI 673.3 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.75 – 7.59 (m, 2H), 7.25 – 7.16 (m, 3H), 6.93 (s, 1H), 5.80 – 5.55 (m, 2H), 4.16 (t, *J* = 7.9 Hz, 4H), 3.50 – 3.37 (m, 2H), 3.04 – 2.77 (m, 2H),

2.72 – 2.43 (m, 4H), 2.36 (s, 3H), 2.28 (s, 3H), 2.06 – 1.96 (m, 1H), 1.83 – 1.64 (m, 1H), 1.53 – 1.29 (m, 1H), 0.97 – 0.89 (m, 6H).

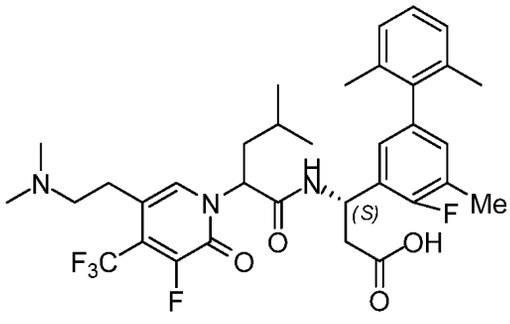
4-146. (3*S*)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)-3-(5'-cyano-4,4'-difluoro-2',5-dimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds GN-P1 and GN-P2)



GN-P1 ESI 673.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 7.55 (d, J = 6.7 Hz, 1H), 7.32 (d, J = 10.3 Hz, 1H), 7.10 (d, J = 6.4 Hz, 2H), 6.81 (s, 1H), 5.65 – 5.55 (m, 2H), 4.03 (t, J = 8.0 Hz, 4H), 3.32 – 3.26 (m, 2H), 2.84 (t, J = 7.0 Hz, 2H), 2.78 – 2.67 (m, 2H), 2.51 – 2.36 (m, 2H), 2.36 – 2.25 (m, 6H), 2.14 – 1.92 (m, 2H), 1.52 – 1.36 (m, 1H), 0.97 (t, J = 6.1 Hz, 6H).

GN-P2 ESI 673.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.57 (d, J = 6.7 Hz, 1H), 7.34 (d, J = 10.2 Hz, 1H), 7.14 (d, J = 6.7 Hz, 2H), 6.93 (s, 1H), 5.76 – 5.71 (m, 1H), 5.63 (t, J = 7.7 Hz, 1H), 4.13 (t, J = 7.9 Hz, 4H), 3.49 – 3.35 (m, 2H), 3.00 – 2.87 (m, 1H), 2.88 – 2.75 (m, 1H), 2.68 – 2.60 (m, 1H), 2.57 – 2.42 (m, 3H), 2.39 – 2.28 (m, 6H), 2.05 – 1.95 (m, 1H), 1.79 – 1.63 (m, 1H), 1.48 – 1.37 (m, 1H), 0.92 (t, J = 6.6 Hz, 6H).

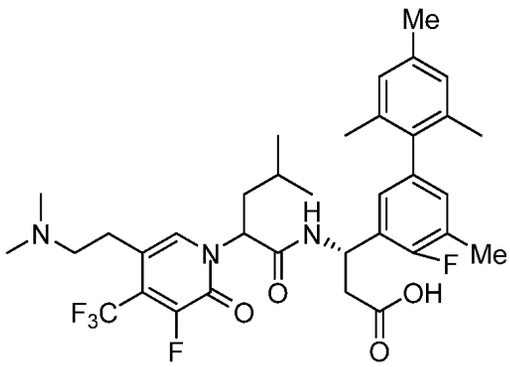
4-147. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds GO-P1 and GO-P2)



GO-P1 ESI 650.2 (M+H)+. ^{1}H NMR (500 MHz, MeOD) δ 7.70 (s, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.08 – 7.02 (m, 2H), 6.89-6.85 (m, 2H), 5.69 (t, *J* = 8.0 Hz, 1H), 5.61 – 5.54 (m, 1H), 3.09-3.02 (m, 2H), 2.99 (d, *J* = 7.3 Hz, 2H), 2.74-2.70 (m, 8H), 2.30 (s, 3H), 2.05 – 1.94 (m, 5H), 1.86 (s, 3H), 1.44 (m, 1H), 0.94-0.90 (m, 6H).

GO-P2 ESI 650.2 (M+H)+. ^{1}H NMR (500 MHz, MeOD) δ 7.62 (s, 1H), 7.18 – 7.07 (m, 3H), 6.94 (t, *J* = 6.8 Hz, 2H), 5.73-5.70 (m, 1H), 5.61 (t, *J* = 7.6 Hz, 1H), 3.31 – 3.18 (m, 2H), 3.11 – 2.95 (m, 2H), 2.84 (s, 6H), 2.65-2.60 (m, 1H), 2.52 -2.48(m, 1H), 2.35-2.32 (m, 3H), 2.08 – 1.94 (m, 7H), 1.74 – 1.64 (m, 1H), 1.42-1.39 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 6H).

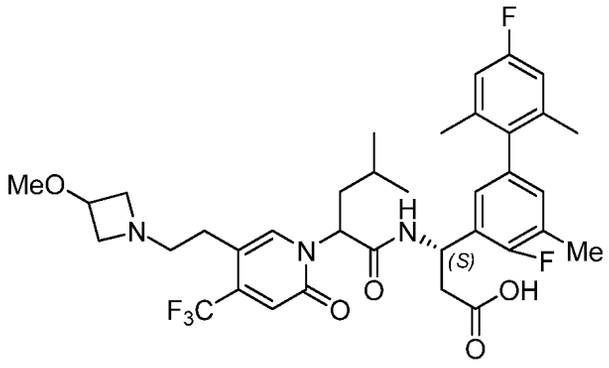
4-148. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds GP-P1 and GP-P2)



GP-P1 ESI 664.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.69 (s, 1H), 6.96 – 6.77 (m, 4H), 5.72 – 5.66 (m, 1H), 5.56 (s, 1H), 3.09 – 2.90 (m, 4H), 2.71 (d, *J* = 4.8 Hz, 8H), 2.29 (s, 6H), 2.08 – 1.91 (m, 5H), 1.82 (s, 3H), 1.44 (s, 1H), 0.95-0.90 (m, 6H).

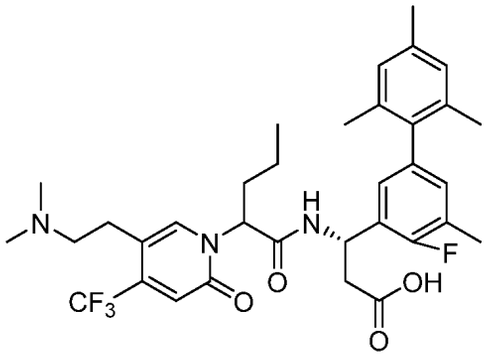
GP-P2 ESI 664.2 $(M+H)^+$. ^{1}H NMR (400 MHz, MeOD) δ 7.62 (d, *J* = 12.1 Hz, 1H), 6.97 – 6.85 (m, 4H), 5.72-5.69 (m, 1H), 5.62 (t, *J* = 7.6 Hz, 1H), 3.22 (qd, J = 13.0, 6.1 Hz, 2H), 3.13 – 2.89 (m, 2H), 2.82 (s, 6H), 2.64-2.60 (m, 1H), 2.49-2.45(m, 1H), 2.36 – 2.23 (m, 6H), 2.04 – 1.90 (m, 7H), 1.74 – 1.64 (m, 1H), 1.41-1.38 (m, 1H), 0.90-0.86 (m, 6H).

4-149. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GQ-P1 and GQ-P2)



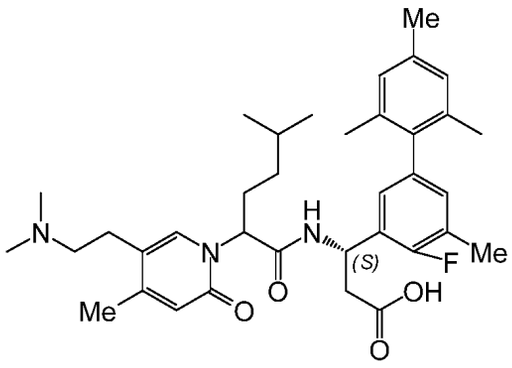
GQ-P1 ESI 692.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 6.96 – 6.68 (m, 5H), 5.75 – 5.48 (m, 2H), 4.26 – 4.01 (m, 3H), 3.74 – 3.52 (m, 2H), 3.31 (s, 3H), 3.14 (t, *J* = 6.8 Hz, 2H), 2.87 – 2.63 (m, 4H), 2.30 (s, 3H), 2.05 – 1.92 (m, 5H), 1.85 (s, 3H), 1.54 – 1.36 (m, 1H), 1.07 – 0.87 (m, 6H).
GQ-P2 ESI 692.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.74 (s, 1H), 7.04 – 6.78 (m, 5H), 5.80 – 5.70 (m, 1H), 5.62 (t, *J* = 7.7 Hz, 1H), 4.49 – 4.21 (m, 3H), 4.01 – 3.74 (m, 2H), 3.46 – 3.35 (m, 5H), 3.03 – 2.77 (m, 2H), 2.68 – 2.44 (m, 2H), 2.34 (d, *J* = 1.7 Hz, 3H), 2.12 – 1.90 (m, 7H), 1.74 – 1.57 (m, 1H), 1.53 – 1.32 (m, 1H), 0.99 – 0.83 (m, 6H).

4-150. (3S)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)pentanamido)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds GR-P1 and GR-P2)



GR-P1 ESI 632.2$(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.88 (s, 1H), 6.92 – 6.79 (m, 4H), 6.74 (s, 1H), 5.66 – 5.45 (m, 2H), 3.11 – 2.85 (m, 5H), 2.78 – 2.68 (m, 7H), 2.32 – 2.22 (m, 6H), 2.18 – 2.08 (m, 1H), 2.06 – 1.92 (m, 4H), 1.78 (s, 3H), 1.41 – 1.24 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).
GR-P2 ESI 632.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.82 (s, 1H), 6.90 (d, J = 7.1 Hz, 5H), 5.79 – 5.64 (m, 1H), 5.52 (t, J = 7.6 Hz, 1H), 3.30 – 3.15 (m, 2H), 3.00 (t, J = 6.6 Hz, 2H), 2.83 (s, 6H), 2.69 – 2.59 (m, 1H), 2.58 – 2.44 (m, 1H), 2.31 (d, J = 9.7 Hz, 6H), 2.13 – 2.01 (m, 1H), 1.97 (s, 6H), 1.91 – 1.73 (m, 1H), 1.39 – 1.02 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

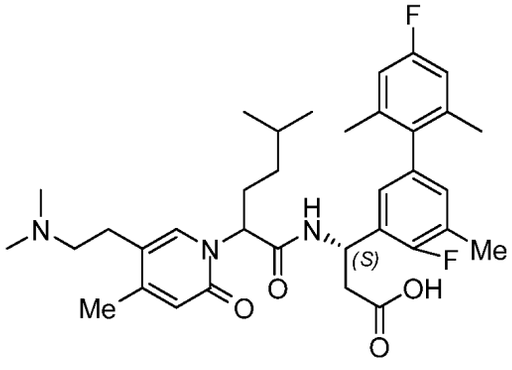
4-151. (3*S*)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)-3-(4-fluoro-2',4',5,6'-tetramethylbiphenyl-3-yl)propanoic acid (diastereomeric compounds GS-P1 and GS-P2)



GS-P1 ESI 606.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.57 (s, 1H), 6.90 (s, 2H), 6.85 – 6.80 (m, 2H), 6.34 (s, 1H), 5.48 (t, *J* = 6.0 Hz, 1H), 5.42 – 5.37 (s, 1H), 3.24 – 3.02 (m, 2H), 2.89 – 2.85 (m, 2H), 2.76 (s, 6H), 2.71 – 2.60 (m, 2H), 2.30 (d, *J* = 4.9 Hz, 6H), 2.25 (s, 3H), 2.22 – 2.14 (m, 1H), 1.95 (s, 4H), 1.87 (s, 3H), 1.60 – 1.53 (m, 1H), 1.25 – 1.14 (m, 1H), 1.12 – 1.00 (m, 1H), 0.89 – 0.87 (m, 6H).

GS-P2 ESI 606.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 6.98 – 6.78 (m, 4H), 6.44 (s, 1H), 5.66 – 5.63 (m, 1H), 5.42 (t, *J* = 7.7 Hz, 1H), 3.31 – 3.28 (m, 1H), 3.26 – 3.14 (m, 1H), 2.99 – 2.88 (m, 2H), 2.84 (s, 6H), 2.64 – 2.59 (m, 1H), 2.50 – 2.43 (m, 1H), 2.39 – 2.28 (m, 6H), 2.27 (s, 3H), 2.16 – 2.07 (m, 1H), 1.96 (s, 6H), 1.89 – 1.74 (m, 1H), 1.57 – 1.50 (m, 1H), 1.15 – 1.11 (m, 1H), 1.08 – 0.97 (m, 1H), 0.85 (t, *J* = 6.5 Hz, 6H).

4-152. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-5-methylhexanamido)propanoic acid (diastereomeric compounds GT-P1 and GT-P2)

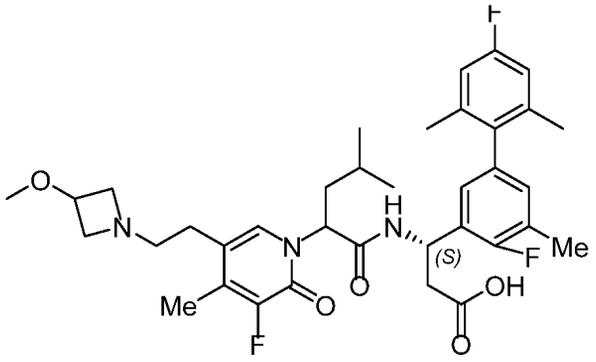


GT-P1 ESI 610.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.58 (s, 1H), 6.84 (t, *J* = 9.1 Hz, 4H), 6.32 (s, 1H), 5.50 (t, *J* = 6.2 Hz, 1H), 5.44 – 5.33 (m, 1H), 3.24 – 3.06 (m, 2H), 2.90 – 2.84 (m, 2H), 2.78 (s,

6H), 2.73 – 2.62 (m, 2H), 2.28 (d, *J* = 14.1 Hz, 6H), 2.22 – 2.11 (m, 1H), 2.00 – 1.96 (m, 4H), 1.89 (s, 3H), 1.60 – 1.54 (m, 1H), 1.29 – 1.15 (m, 1H), 1.10 – 1.03 (m, 1H), 0.89 – 0.87 (m, 6H).

GT-P2 ESI 610.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 6.90 (d, *J* = 6.9 Hz, 2H), 6.84 (d, *J* = 9.6 Hz, 2H), 6.44 (s, 1H), 5.66 – 5.62(m, 1H), 5.43 (t, *J* = 7.6 Hz, 1H), 3.38 – 3.35 (m, 1H), 3.24 – 3.20 (m, 1H), 3.00 – 2.89 (m, 2H), 2.85 (s, 6H), 2.64 – 2.59 (m, 1H), 2.50 – 2.44 (m, 1H), 2.33 (d, *J* = 4 Hz, 3H), 2.28 (s, 3H), 2.17 – 2.07 (m, 1H), 2.01 (s, 6H), 1.87 – 1.77 (m, 1H), 1.57 – 1.51 (m, 1H), 1.20 – 1.09 (m, 1H), 1.08 – 0.97 (m, 1H), 0.85 (t, *J* = 6.4 Hz, 6H).

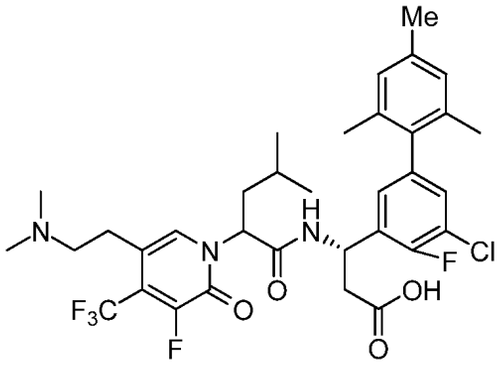
4-153. (3*S*)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(3-fluoro-5-(2-(3-methoxyazetidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GU-P1 and GU-P2)



GU-P1 ESI 656.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.40 (s, 1H), 6.95 – 6.72 (m, 4H), 5.71 – 5.47 (m, 2H), 4.27 – 4.16 (m, 2H), 4.16 – 4.07 (m, 1H), 3.81 – 3.69 (m, 1H), 3.70 – 3.58 (m, 1H), 3.30 (s, 3H), 3.25 (t, *J* = 6.8 Hz, 2H), 2.88 – 2.63 (m, 4H), 2.37 – 2.16 (m, 6H), 2.06 – 1.82 (m, 8H), 1.49 – 1.28 (m, 1H), 0.97 – 0.90 (m, 6H).

GU-P2 ESI 656.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.33 (s, 1H), 6.96 – 6.89 (m, 2H), 6.84 (d, *J* = 9.7 Hz, 2H), 5.72 – 5.58 (m, 2H), 4.39 – 4.14 (m, 3H), 3.85 – 3.65 (m, 2H), 3.31 – 3.20 (m, 5H), 2.93 – 2.78 (m, 1H), 2.77 – 2.55 (m, 2H), 2.54 – 2.45 (m, 1H), 2.33 (d, *J* = 1.7 Hz, 3H), 2.22 (d, *J* = 2.7 Hz, 3H), 2.06 – 1.86 (m, 7H), 1.81 – 1.66 (m, 1H), 1.344 – 1.32 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 6H).

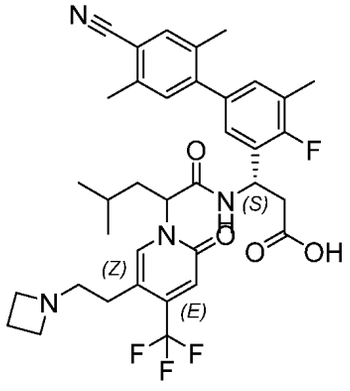
4-154. (3*S*)-3-(5-chloro-4-fluoro-2',4',6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-3-fluoro-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GV-P1 and GV-P2)



GV-P1 ESI 684.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.65 (s, 1H), 7.13 (d, J = 6.3 Hz, 1H), 7.08 (d, J = 6.1 Hz, 1H), 6.93 (s, 2H), 5.66 (d, J = 5.4 Hz, 2H), 3.13 – 2.89 (m, 4H), 2.70 (s, 6H), 2.67 – 2.62 (m, 1H), 2.62 – 2.53 (m, 1H), 2.30 (s, 3H), 1.98 (d, J = 6.9 Hz, 7H), 1.74 -1.70(m, 1H), 1.40 – 1.33 (m, 1H), 0.89 (d, J = 5.6 Hz, 6H).

GV-P2 ESI 684.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.67 (s, 1H), 7.10 (d, J = 6.9 Hz, 1H), 7.02 (d, J = 6.1 Hz, 1H), 6.91 (d, J = 13.0 Hz, 2H), 5.68 (t, J = 8.1 Hz, 1H), 5.55 (t, J = 7.0 Hz, 1H), 3.08 (s, 2H), 2.98 (d, J = 7.7 Hz, 2H), 2.73 (d, J = 9.7 Hz, 8H), 2.30 (s, 3H), 2.04 – 1.93 (m, 5H), 1.83 (s, 3H), 1.44-1.40 (m, 1H), 0.96 -0.92(m, 6H).

4-155. (3S)-3-(2-(5-(2-(azetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2H)-yl)-4-methylpentanamido)-3-(4'-cyano-4-fluoro-2',5,5'-trimethyl-[1,1'-biphenyl]-3-yl)propanoic acid (diastereomeric compounds GW-P1 and GW-P2)

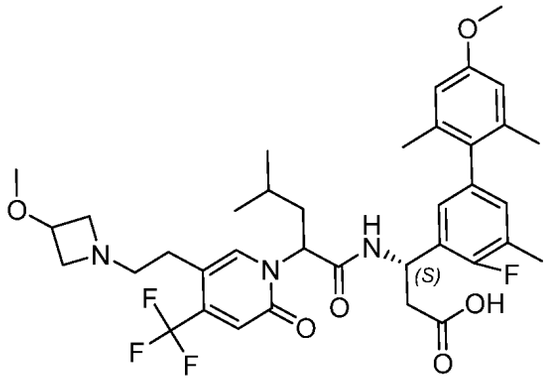


GW-P1 ESI 669.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.72 (s, 1H), 7.45 (s, 1H), 7.10 (s, 1H), 7.06 – 6.92 (m, 2H), 6.65 (s, 1H), 5.57 – 5.40 (m, 2H), 3.92 (t, J = 8.1 Hz, 4H), 2.73-2.70 (m, 2H), 2.60 (d, J = 7.6 Hz, 2H), 2.40 (s, 3H), 23.0-2.33(m, 2H), 2.36-2.30 (m, 2H), 2.19 (s, 3H), 2.09 (s, 3H), 1.94-1.88 (m, 2H), 1.35 – 1.21 (m, 1H), 0.86-0.83 (m, 6H).

GW-P2 ESI 669.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.61 (s, 1H), 7.47 (s, 1H), 7.13 (s, 1H), 7.10 – 6.98 (m, 2H), 6.80 (s, 1H), 5.65-5.62 (m, 1H), 5.52 (t, J = 7.7 Hz, 1H), 4.04 (t, J = 8.1 Hz, 4H), 3.40

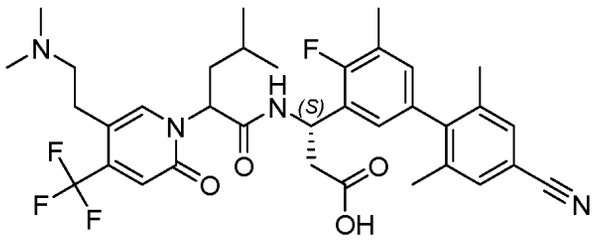
– 3.25 (m, 2H), 2.86 – 2.64 (m, 2H), 2.54-2.49 (m, 1H), 2.45 – 2.30 (m, 6H), 2.23 (d, *J* = 1.5 Hz, 3H), 2.14 (s, 3H), 1.95 – 1.81 (m, 1H), 1.63 – 1.52 (m, 1H), 1.31-1.26 (m, 1H), 0.84-0.78 (m, 6H).

4-156. (3*S*)-3-(4-fluoro-4'-methoxy-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-methoxyazetidin-1-yl)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GX-P1 and GX-P2)



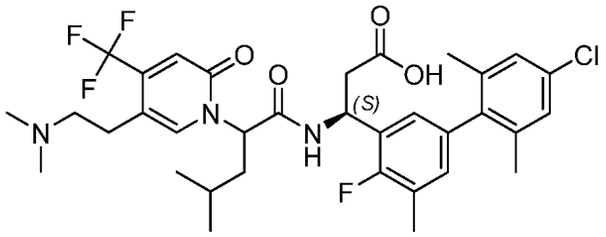
GX-P1 ESI 704.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.85 (s, 1H), 6.86 (t, *J* = 6.2 Hz, 2H), 6.77 (s, 1H), 6.65 (s, 1H), 6.62 (s, 1H), 5.67 (t, *J* = 8.0 Hz, 1H), 5.61 – 5.56 (m, 1H), 4.25 – 4.09 (m, 3H), 3.79 (s, 3H), 3.71 – 3.61 (m, 2H), 3.31(s, 3H), 3.17 (t, *J* = 6.8 Hz, 2H), 2.81 (t, *J* = 6.9 Hz, 2H), 2.76 – 2.69 (m, 2H), 2.28 (s, 3H), 2.04 – 1.97 (m, 5H), 1.82 (s, 3H), 1.48 – 1.41 (m, 1H), 0.98 – 0.93 (m, 6H).
GX-P2 ESI 704.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.75 (s, 1H), 6.96 – 6.90 (m, 3H), 6.67 (s, 2H), 5.76 – 5.72(m, 1H), 5.63 (t, *J* = 7.7 Hz, 1H), 4.44 – 4.26 (m, 3H), 3.98 – 3.92 (m, 1H), 3.88 – 3.83 (m, 1H), 3.80 (s, 3H), 3.42 – 3.35 (m, 5H), 2.97 – 2.80 (m, 2H), 2.67 – 2.62 (m, 1H), 2.56 – 2.50 (m, 1H), 2.33 (d, *J* = 1.6 Hz, 3H), 2.04 – 1.94 (m, 7H), 1.73 – 1.64 (m, 1H), 1.47 – 1.39 (m, 1H), 0.92 – 0.89 (m, 6H).

4.157. (3*S*)-3-(4'-cyano-4-fluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GY-P1 and GY-P2)



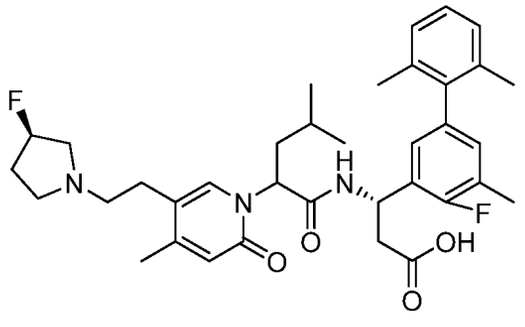
GY-P1 ESI 657.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.45 (d, *J* = 21.6 Hz, 2H), 6.88 (d, *J* = 5.6 Hz, 2H), 6.71 (s, 1H), 5.72 – 5.47 (m, 2H), 3.08 – 2.85 (m, 4H), 2.79 – 2.57 (m, 8H), 2.30 (d, *J* = 1.4 Hz, 3H), 2.11 – 1.93 (m, 5H), 1.88 (s, 3H), 1.50 – 1.37 (m, 1H), 1.06 – 0.86 (m, 6H).
GY-P2 ESI 657.4 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.84 (s, 1H), 7.49 (s, 2H), 7.02 – 6.74 (m, 3H), 5.75 – 5.53 (m, 2H), 3.25 – 3.06 (m, 2H), 2.98 (t, *J* = 6.9 Hz, 2H), 2.78 (s, 6H), 2.70 – 2.48 (m, 2H), 2.34 (d, *J* = 1.4 Hz, 3H), 2.14 – 1.86 (m, 7H), 1.79 – 1.62 (m, 1H), 1.46 – 1.31 (m, 1H), 0.95 – 0.82 (m, 6H).

4-158. (3*S*)-3-(4'-chloro-4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-(dimethylamino)ethyl)-2-oxo-4-(trifluoromethyl)pyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds GZ-P1 and GZ-P2)



GZ-P1 ESI 666.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.91 (s, 1H), 7.08 (d, *J* = 24.1 Hz, 2H), 6.91 – 6.80 (m, 2H), 6.72 (s, 1H), 5.68 (t, *J* = 8.0 Hz, 1H), 5.59 – 5.48 (m, 1H), 3.18 – 3.02 (m, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.82 – 2.63 (m, 8H), 2.29 (s, 3H), 2.04 – 1.91 (m, 5H), 1.79 (s, 3H), 1.58 – 1.30 (m, 1H), 1.04 – 0.86 (m, 6H).
GZ-P2 ESI 666.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.88 (s, 1H), 7.13 (s, 2H), 6.94 – 6.83 (m, 3H), 5.81 – 5.68 (m, 1H), 5.62 (t, *J* = 7.7 Hz, 1H), 3.30 – 3.16 (m, 2H), 3.01 (t, *J* = 6.8 Hz, 2H), 2.83 (s, 6H), 2.72 – 2.45 (m, 2H), 2.33 (d, *J* = 1.1 Hz, 3H), 1.98 (d, 7H), 1.75 – 1.63 (m, 1H), 1.51 – 1.33 (m, 1H), 0.87 (d, *J* = 6.6 Hz, 6H).

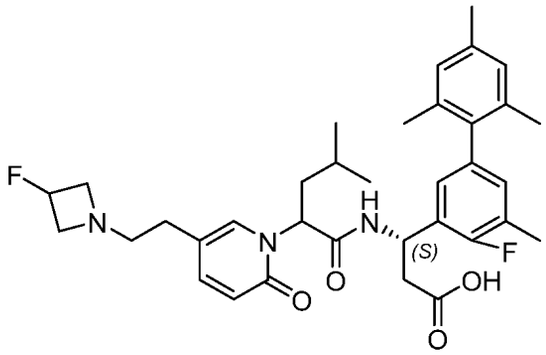
4-159. ((3*S*)-3-(4-fluoro-2',5,6'-trimethylbiphenyl-3-yl)-3-(2-(5-(2-((*R*)-3-fluoropyrrolidin-1-yl)ethyl)-4-methyl-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds HA-P1 and HA-P2)



HA-P1 ESI 622.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.54 (s, 1H), 7.16 – 7.02 (m, 3H), 6.87 – 6.78 (m, 2H), 6.27 (s, 1H), 5.73 – 5.50 (m, 2H), 5.34 – 5.15 (m, 1H), 3.31 – 3.23 (m, 1H), 3.22 – 3.00 (m, 2H), 2.94 – 2.80 (m, 3H), 2.78 – 2.59 (m, 4H), 2.36 – 2.09 (m, 8H), 2.01 – 1.91 (m, 5H), 1.83 (s, 3H), 1.50 – 1.37 (m, 1H), 0.97 – 0.89 (m, 6H).

HA-P2 ESI 622.2 $(M+H)^+$. ^1H NMR (500 MHz, MeOD) δ 7.56 (s, 1H), 7.22 – 7.02 (m, 3H), 6.91 (d, *J* = 6.8 Hz, 2H), 6.42 (s, 1H), 5.65 – 5.57 (m, 2H), 5.41 – 5.24 (m, 1H), 3.62 – 3.35 (m, 3H), 3.31 – 3.09 (m, 3H), 2.94 – 2.74 (m, 2H), 2.68 – 2.49 (m, 2H), 2.39 – 2.22 (m, 8H), 2.10 – 1.89 (m, 7H), 1.82 – 1.70 (m, 1H), 1.49 – 1.31 (m, 1H), 0.95 – 0.85 (m, 6H).

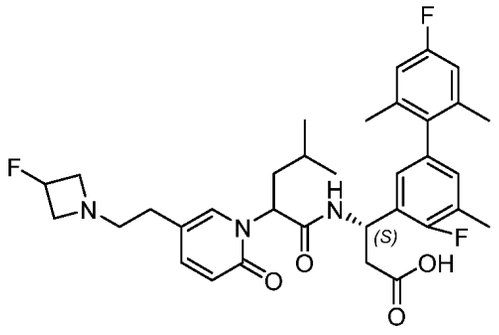
4-160. (3*S*)-3-(4-fluoro-2',4',5,6'-tetramethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2*H*)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds HB-P1 and HB-P2)



HB-P1 ESI 608.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.52 (s, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 6.96 – 6.79 (m, 3H), 6.73 (s, 1H), 6.43 (d, *J* = 9.5 Hz, 1H), 5.74 – 5.46 (m, 2H), 5.14 (d, *J* = 57.6 Hz, 1H), 3.77 (s, 2H), 3.50 (s, 2H), 2.88 (s, 2H), 2.79 – 2.60 (m, 2H), 2.51 (s, 2H), 2.29 (d, *J* = 14.1 Hz, 6H), 1.96 (d, *J* = 12.7 Hz, 5H), 1.80 (s, 3H), 1.42 (s, 1H), 1.03 – 0.79 (m, 6H).

HB-P2 ESI 608.3 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.60 – 7.40 (m, 2H), 6.90 (d, *J* = 7.8 Hz, 4H), 6.57 (d, *J* = 9.2 Hz, 1H), 5.70 – 5.57 (m, 2H), 5.32 (d, *J* = 57.4 Hz, 1H), 4.51 – 4.26 (m, 2H), 4.14 – 3.87 (m, 2H), 3.39 (d, *J* = 5.3 Hz, 2H), 2.85 – 2.44 (m, 4H), 2.35 – 2.17 (m, 6H), 2.04 – 1.86 (m, 7H), 1.86 – 1.73 (m, 1H), 1.48 – 1.33 (m, 1H), 0.90 (t, *J* = 6.3 Hz, 6H).

4-161. (3S)-3-(4,4'-difluoro-2',5,6'-trimethyl-[1,1'-biphenyl]-3-yl)-3-(2-(5-(2-(3-fluoroazetidin-1-yl)ethyl)-2-oxopyridin-1(2H)-yl)-4-methylpentanamido)propanoic acid (diastereomeric compounds HC-P1 and HC-P2)



HC-P1 ESI 612.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.54 (s, 1H), 7.43 (dd, J = 9.2, 2.3 Hz, 1H), 6.87-6.82 (m, 3H), 6.76 (d, J = 6.7 Hz, 1H), 6.46 (d, J = 9.3 Hz, 1H), 5.63 (d, J = 7.9 Hz, 1H), 5.54 – 5.43 (m, 1H), 5.20 (d, J = 57.2 Hz, 1H), 4.09-3.88 (m, 2H), 3.71-3.55 (m, 2H), 3.10-3.02 (m, 2H), 2.80 – 2.53 (m, 4H), 2.29 (s, 3H), 2.03 – 1.92 (m, 5H), 1.87 (s, 3H), 1.50 – 1.36 (m, 1H), 0.97-0.92 (m, 6H).
HC-P2 ESI 612.2 $(M+H)^+$. ^1H NMR (400 MHz, MeOD) δ 7.41 (s, 1H), 7.38-7.35 (m, 1H), 6.79 (t, J = 6.1 Hz, 2H), 6.73 (d, J = 9.7 Hz, 2H), 6.45 (d, J = 9.3 Hz, 1H), 5.53-5.48 (m, 2H), 5.20 (d, J = 57.2 Hz, 1H), 4.39 – 4.14 (m, 2H), 3.99-3.87 (m, 2H), 3.32 – 3.25 (m, 2H), 2.67 – 2.48 (m, 3H), 2.40-2.34 (m, 1H), 2.21 (d, J = 1.7 Hz, 3H), 1.90 – 1.81 (m, 7H), 1.72 – 1.64 (m, 1H), 1.33 – 1.22 (m, 1H), 0.79 (t, J = 6.6 Hz, 6H).

Introduction to the *In Vitro* Assays Described in Examples 5-7

Three *in vitro* assays were used to examine the $\alpha_4\beta_7$ mechanistic process used by cells: 1) ligand:receptor affinity, 2) the avidity of those interactions on a cell's surface, and 3) how those interactions fare under an imposing force. In Example 5, a Fluorescence Polarization (FP) assay is used to measure compound activity through binding competition with the fluorescein-labeled peptide. In Example 6, the potency of compounds against $\alpha_4\beta_7$ is measured in the cell-based ligand binding assay (LBA), using RPMI 8866 cells incubated with the compound samples in competition with soluble MAdCAM-1 ligand. In Example 7, activity of compounds is evaluated in a cell adhesion assay that mechanistically tests what occurs in vivo when trafficking cells utilize $\alpha_4\beta_7$ to adhere to MAdCAM-1 expressing HEVs of the gut during the extravasation process. In the cell adhesion assay of Example 7, a MAdCAM1-(Fc) is coated on plastic, and α4β7 expressing cells (RPMI-8866) are allowed to adhere to the coated surface in the presence of the test compounds. Next, the force of washing with buffer is applied to cells thereby testing the strength of that adhesion. Unattached cells are removed and the remaining adherent cells are quantified.

Example 5: Fluorescence polarization assays of compounds for $\alpha_4\beta_7$ binding

Fluorescence Polarization (FP) assays were used to measure compound activity through binding competition with the fluorescein-labeled peptide CRSDTLCGE{Lys(FITC)}. In the assay, 6.5 nM of integrin $\alpha_4\beta_7$ was incubated with the test compound in 2 mM manganese chloride, 0.1 mM calcium chloride, 20 mM HEPES buffer at pH 7.3, 150 mM sodium chloride, 0.01% Triton X-100, 2% DMSO, and 3 nM of the fluorescein-labeled peptide. Running the assays in 384-well plates, the integrin protein was pre-incubated with the test compounds for 15 minutes at 22^{0}C before the fluorescein-labeled peptide was added. After the fluorescein-labeled peptide was added, the assay was incubated at 22^{0}C for 1 hour and fluorescence polarization was measured. IC_{50} values were determined by non-linear regression, four-parameter curve fitting.

An $\alpha_4\beta_7$ inhibition potency measurement for compounds including certain compounds in Figure 1, Figure 3 and Figure 4 was made using the FP assay of Example 5. In Figure 1, the IC_{50} value obtained using the FP assay of Example 5 is provided as a numerical range (A: <5.55 nM; B: 5.55-500 nM; C: >500 nM in Figure 1). In Figure 3 and Figure 4, the IC_{50} value obtained using the FP assay of Example 5 is provided as a numerical range (A: <5 nM; B: 5-500 nM; C: >500 nM in Figure 3 and Figure 4).

An $\alpha_4\beta_7$ inhibition potency measurement was also performed using the FP assay of Example 5 for compounds in Table 3A, Table 3B and (comparative) Table 4 below, with results provided as a numerical range of the resulting IC_{50} value (A: ≤10 nM; B: >10-500 nM; C: >500 nM in Table 3A, Table 3B and Table 4).

Example 6: Ligand binding assays

To measure the potency of compounds against $\alpha_4\beta_7$ in the cell-based ligand binding assay (LBA), RPMI 8866 cells were incubated with the compound samples in a volume of 10 µl at room temperature for 15 minutes in buffer containing 50 mM HEPES pH 7.3, 150 mM sodium chloride, 1% bovine serum albumin, 3 mM manganese chloride, 0.15 mM calcium chloride, 15 mM glucose, 1.5% dimethyl sulfoxide, and 0.025% e780 fixable viability dye. 5 ul of 33 nM MAdCAM-1-Fc fluorescently labeled with Dylight 650 in 50 mM HEPES pH 7.3, 150 mM sodium chloride, and 1% bovine serum albumin was added to the cells. The samples were incubated for 45 minutes at room temperature, fixed with 0.8% formaldehyde for 30 minutes at room temperature, and washed with 50 mM Tris pH 7.5, 150 mM NaCl, 1 mM EDTA, and 1% bovine serum albumin. Fluorescence intensity for each cell was measured via flow cytometry. Dead cells were excluded from further analysis based on staining with the 780

fixable viability dye. Median fluorescence intensity for Dylight 650 was determined for each sample and concentration-response curves were analyzed for IC50 values using 4-parameter non-linear regression analysis.

An $\alpha_4\beta_7$ ligand binding assay measurement was performed with the ligand binding assay of Example 6 for compounds listed in Figure 1, Figure 3 and Figure 4. In Figure 1, Figure 3 and Figure 4, the IC_{50} value obtained using the LB assay of Example 6 is provided by numerical range (A: <5 nM; B: 5-500 nM; C: >500 nM in Figure 1, Figure 3 and Figure 4).

An $\alpha_4\beta_7$ ligand binding assay measurement was also performed using the ligand binding assay of Example 6 for compounds in Table 3A, Table 3B and (comparative) Table 4 below, with the resulting IC_{50} value provided as a numerical range (A: ≤ 10nM; B: >10-500 nM; C: >500 nM in Table 3A, Table 3B and Table 4).

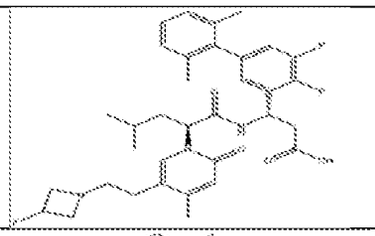
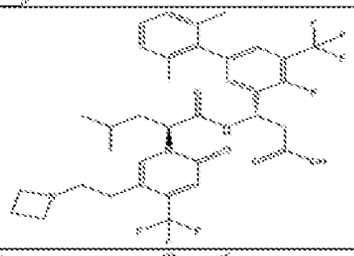
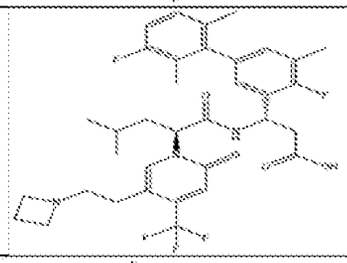
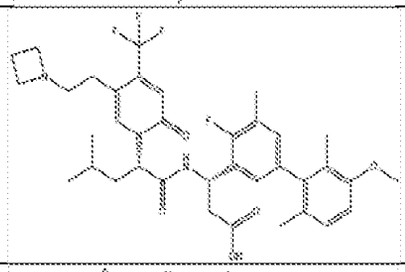
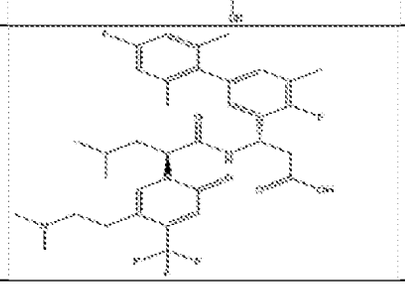
Example 7: Cell Adhesion Assay

Example 7 describes a cell adhesion assay. The $\alpha_4\beta_7$ cell adhesion measurement from the assay of Example 7 was obtained from compounds in the Table 3A and Table 3B below, as well as for the comparative compounds in Table 4, with results presented as a numerical range of the resulting IC_{50} value (A: < 5 nM; B: 5 to <10 nM; C10-50 nM; D: >50 nM; E:>100nM and F>500nM for Table 3A, Table 3B and Table 4).

To each well of a 96 well plate, 100 ug of recombinant human MAdCAM in 100ul PBS is added and incubated overnight at 4°C. After incubation MAdCAM is removed by aspiration and 200 ul of PBS+ 1%BSA is added to block the plate for 2 hours at 37°C and 5% CO2. During this incubation dilution curves of compound are made in 100% DMSO in 96 well V bottom plates. 1.75ul of diluted compounds are then transferred to a new 96 well U bottom plate containing 20 ul of assay media (phosphate free DMEM + 25 mM HEPES + 1%BSA). To this an additional 155 ul of assay media is added with mixing by pipetting up and down. This mixture is allowed to incubate for 15 minutes at 37°C and 5% CO2. After incubation 175ul of assay media containing 2e6/mL RPMI8866 cells is added to compound containing wells without mixing and plate is allowed to incubate for another 15 minutes at 37°C and 5% CO2. During this incubation MAdCAM coated plates are removed from incubator and washed twice with 200 ul PBS+0.1%BSA. After cells have incubated with compound for 15 minutes they are mixed by pipetting up and down and 100 ul of mixture is

transferred to the washed MAdCAM coated plates in triplicate. This plate is then incubated at 37ºC and 5% CO2 for 1 hour. After incubation plates are washed twice with 200 ul and once with 50 ul of phenol free RPMI + 1%BSA. A final 50ul of phenol free RPMI +1%BSA is added to wells after last wash. Next 50 ul of Promega cell titer glow is added to the wells. Plate is incubated on shaker for 2 minutes at 200 RPM followed by another 8 minutes off shaker before having the luminescence read on a Biotek Citation 5 plate reader. Raw data is converted to % inhibition compared to bottom of curve and analyzed using a 4-parameter non linear curve in Prism to determine IC_{50} and IC_{90}.

Table 3A. Selected Exemplary Compounds.

Compound	Example	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
	3-1 (D-P2)	A	A	A
	3-4 (G-P2)	A	A	A
	3-27 (AF-P2)	A	A	A
	3-28 (AG-P2)	A	A	A
	3-32 (AK-P2)	A	A	A

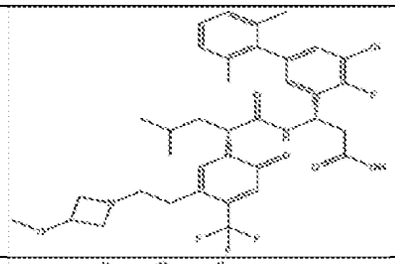
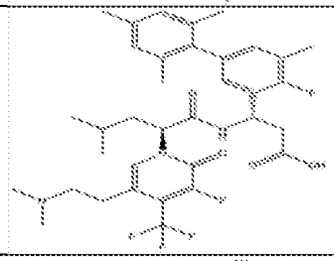
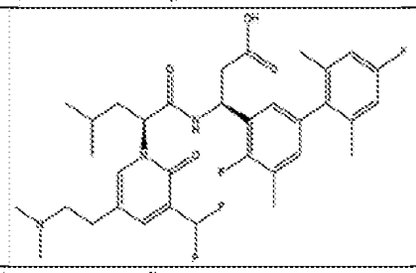
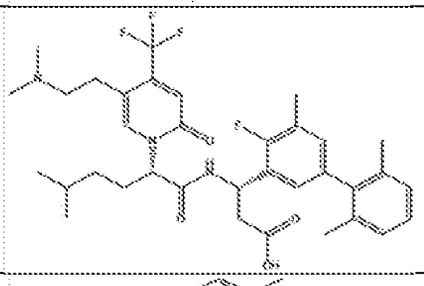
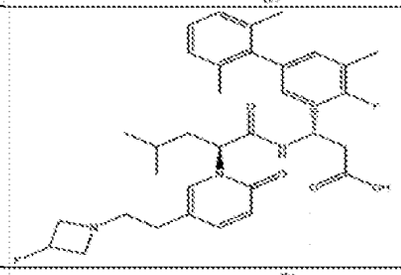
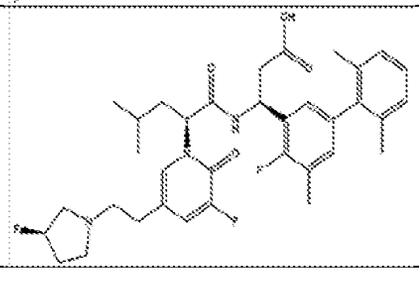
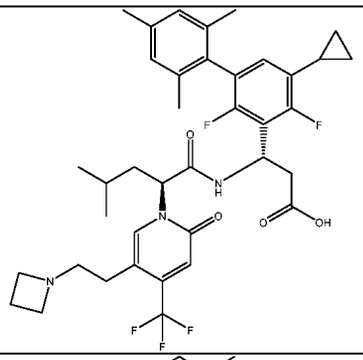
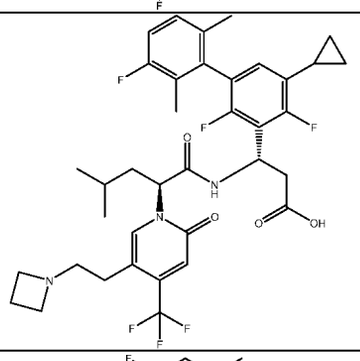
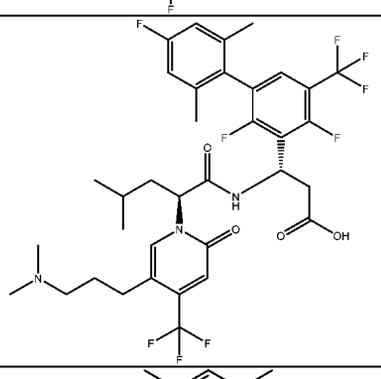
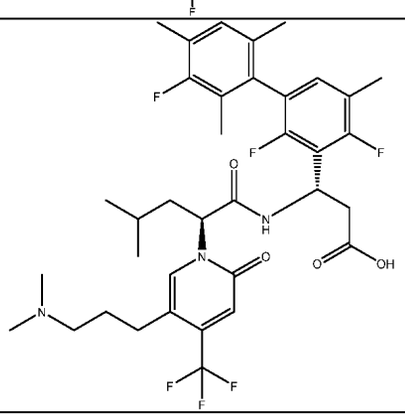
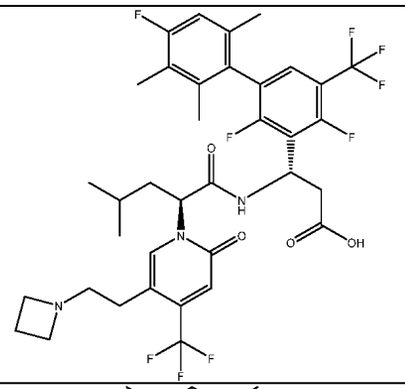
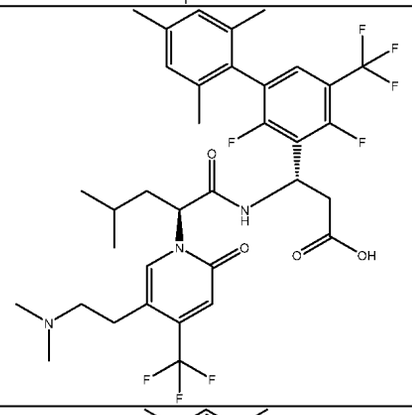
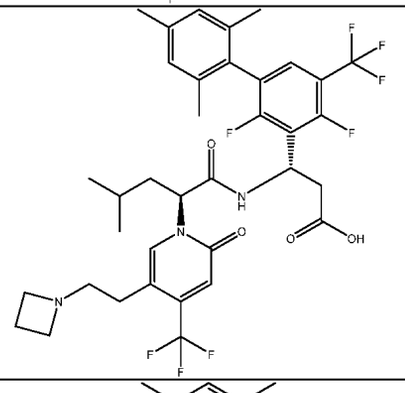
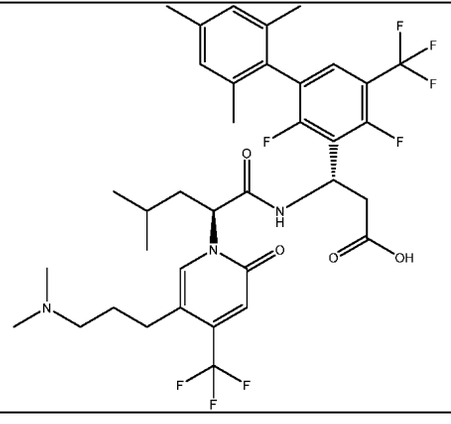
Compound	Example	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
	3-18 (W-P2)	A	A	A
	3-24 (AC-P2)	A	A	A
	3-6 (I-P2)	A	A	A
	3-7 (J-P2)	A	A	A
	3-43 (AV-P2)	A	A	A
	3-42 (AU-P2)	A	A	A

Table 3B. Selected Exemplary Compounds.

Compound	Example	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
	3-57 (HM-P2)	A	A	A
	3-52 (HH-P2)	A	A	B
	3-67 (HW-P2)	A	A	A
	3-93 (IW-P2)	A	B	B

Compound	Example	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
	3-142 (KT-P2)	A	B	A.
	3-76 (IF-P2)	A	B	A
	3-77 (IG-P2)	A	B	A
	3-70 (HZ-P2)	A	B	B

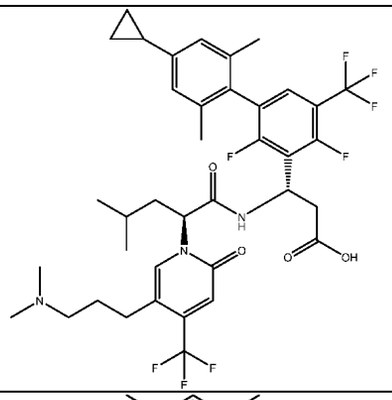
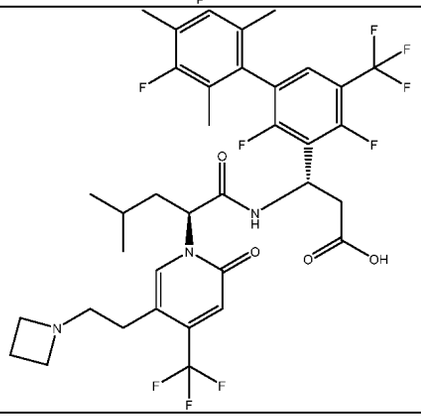
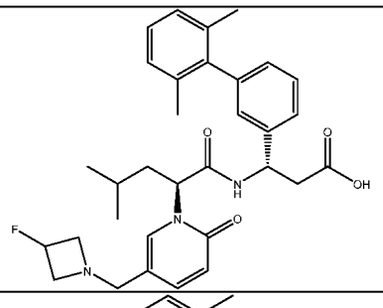
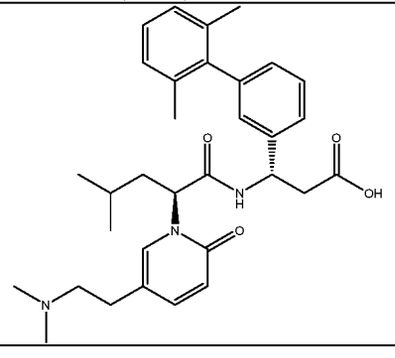
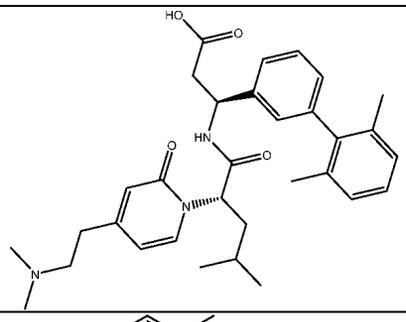
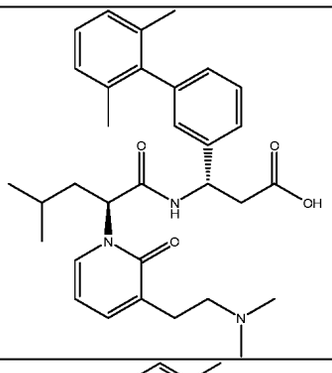
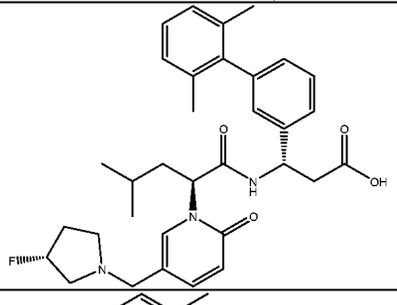
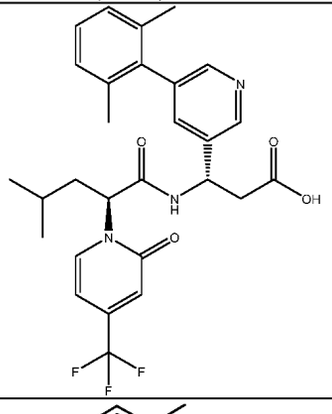
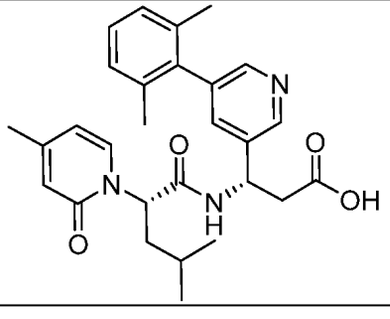
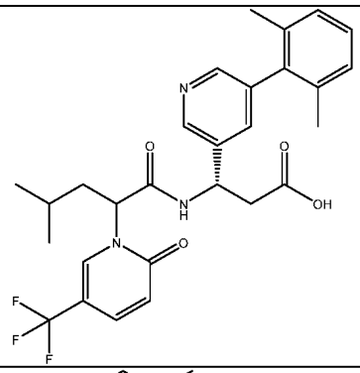
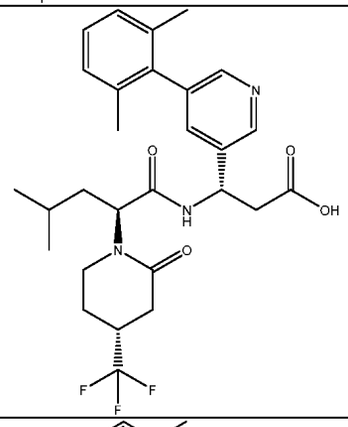
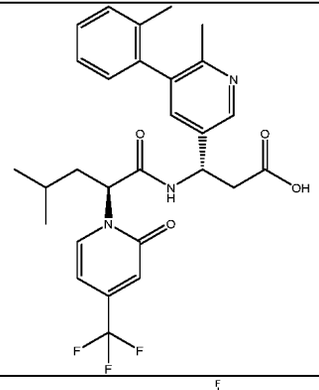
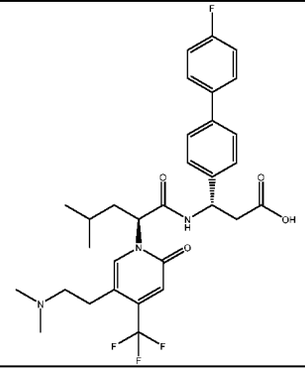
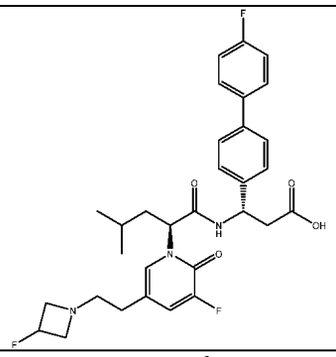
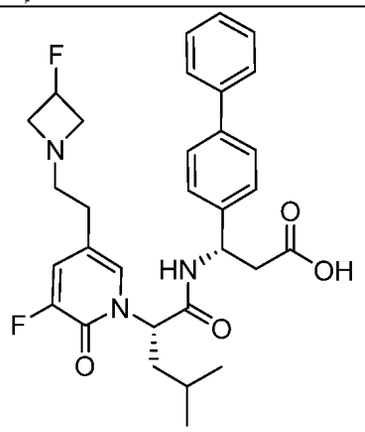
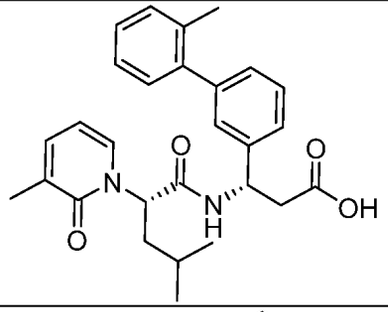
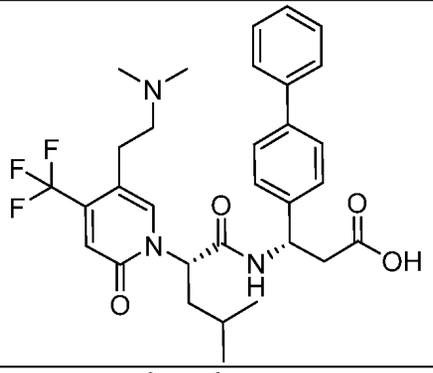
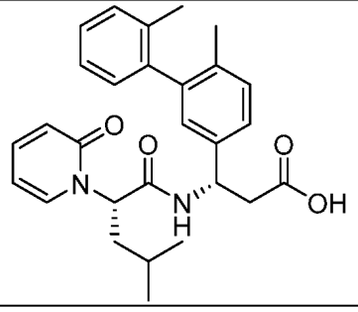
Compound	Example	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
	3-65 (HU-P2)	A	B	B
	3-64 (HT-P2)	A	B	A

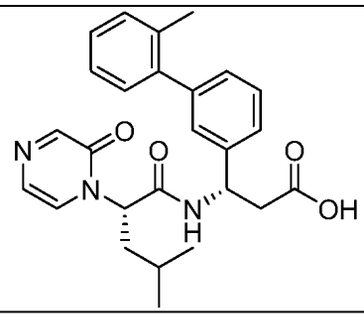
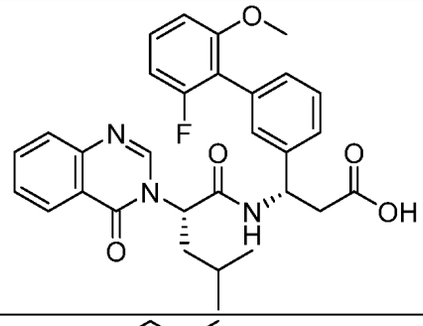
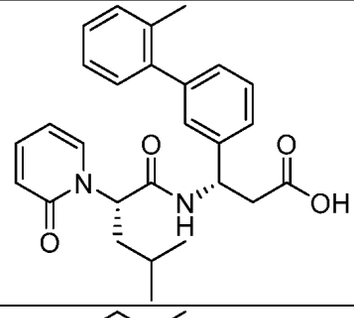
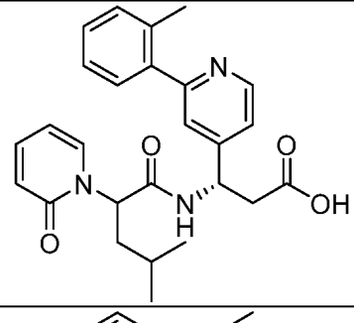
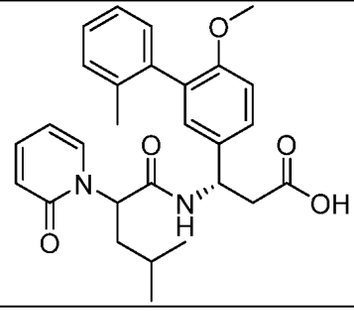
Table 4. Comparative Compounds

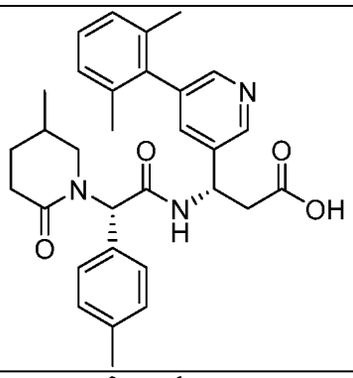
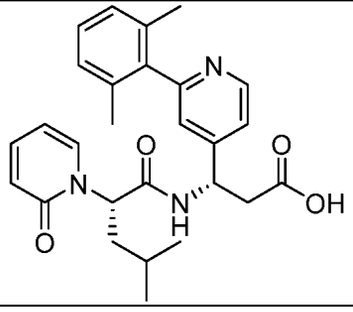
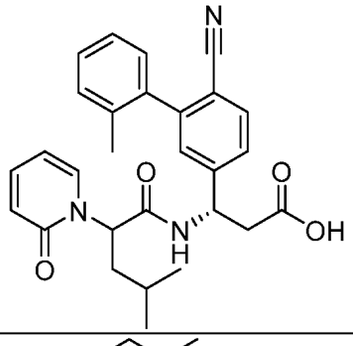
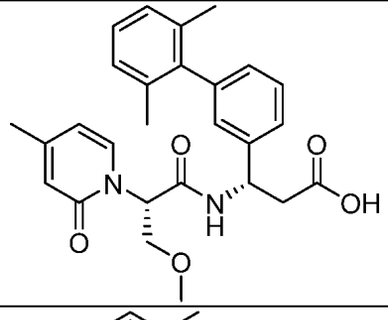
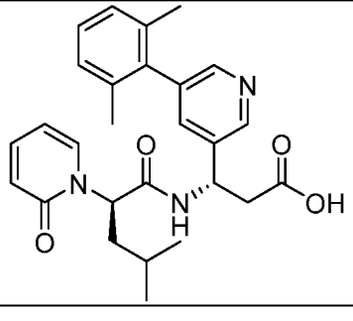
No.	Comparator Compound	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
C-1		A	A	D
C-2		A	A	B

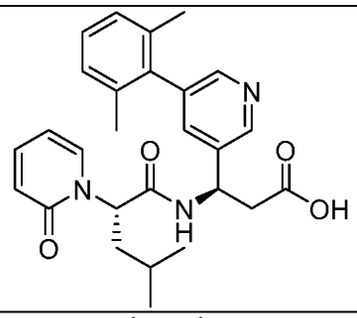
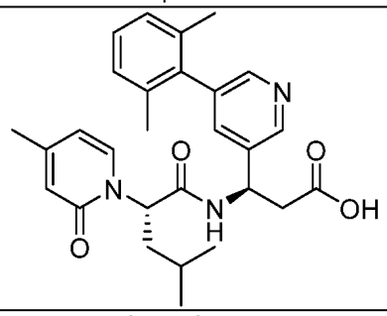
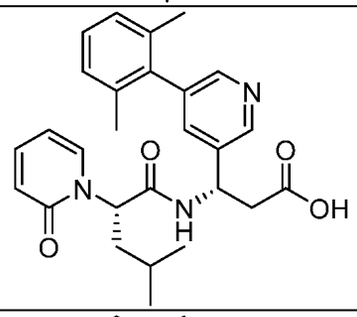
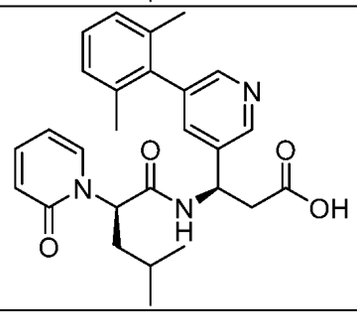
No.	Comparator Compound	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
C-3		A	A	C
C-4		A	B	E
C-5		A	A	C
C-6		A	A	C
C-7		A	A	C

No.	Comparator Compound	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
C-8		A		D
C-9		A	B	D
C-10			B	E
C-11		A	B	F

No.	Comparator Compound	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
C-12		A	B	F
C-13		A	B	F
C-14		A	B	F
C-15		B	B	F
C-16		B		F

No.	Comparator Compound	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
C-17		B		F
C-18		B		F
C-19		B		F
C-20		B		F
C-21		B		F

No.	Comparator Compound	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
C-22		A	B	F
C-23		B		F
C-24		A		F
C-25		B	B	F
C-26		B		

No.	Comparator Compound	FP Assay (Example 5)	LB Assay (Example 6)	CA Assay (Example 7)
C-27		C		
C-28		B	B	
C-29		A		E
C-30		C		

INCORPORATION BY REFERENCE

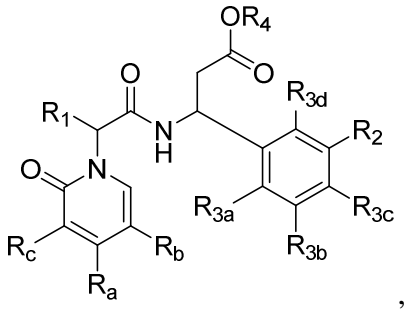
All of the U.S. patents and U.S. and PCT patent application publications cited herein are hereby incorporated by reference.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

Claims:

1. A compound of Formula (I):



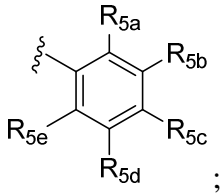
(I)

or a pharmaceutically acceptable salt thereof, wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and substituted or unsubstituted $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$; provided that at least one of R_a, R_b, and R_c is $-(C_1\text{-}C_5)$alkylene-N-$(R_x)(R_y)$;

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl; or R_x and R_y taken together with the N to which they are attached form an unsubstituted 4-6 membered ring or a substituted 4-6 membered ring, substituted with at least one halide, unsubstituted $(C_1\text{-}C_4)$-alkyl, or OMe;

R_1 is substituted or unsubstituted $(C_1\text{-}C_6)$-alkyl, substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_3\text{-}C_6)$-cycloalkyl, or substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy;

R_2 is  ;

R_{3a} and R_{3b} are independently selected from the group consisting of H, substituted or unsubstituted $(C_1\text{-}C_5)$-alkyl, substituted or unsubstituted $(C_3\text{-}C_6)$-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, -OH, -CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, $-(C_1\text{-}C_4)$-alkoxy, $-OCF_3$, and substituted or unsubstituted $(C_1\text{-}C_4)$-alkylene-$(C_1\text{-}C_4)$-alkoxy; provided that R_{3a} and R_{3b} are not both H;

R_{3c} is H;

R_{3d} is H;

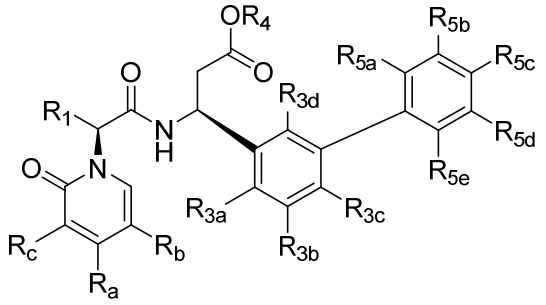
R_4 is H, or substituted or unsubstituted $(C_1\text{-}C_4)$-alkyl;

R_{5a}, and R_{5e} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy; and

R_{5b}, R_{5c}, and R_{5d} are independently selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

wherein, unless otherwise specified, substituted means substituted with one or more substituents selected from alkyl, cycloalkyl, heterocyclylalkyl, halogen, OH, OMe, $C(H)F_2$, $C(F)H_2$, CF_3, $C(H)_2CF_3$, SF_5 $CHFCH_2$amine, CH_2amine, and CN.

2. The compound of claim 1, wherein the compound is a compound of Formula (Ia):



(Ia)

wherein

at least one of R_a, R_b, and R_c is –(C_1-C_3)alkylene-N(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H and methyl; or

R_x and R_y taken together with the N to which they are attached form a substituted or unsubstituted 4-6 membered ring; and

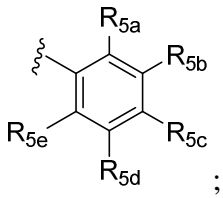
R_{3a}, and R_{3b} are each independently selected from the group consisting of methyl and F.

3. The compound of claim 1, wherein

R_a, R_b, and R_c are independently selected from the group consisting of H, Me, halide, CF_3, $C(H)F_2$, $C(F)H_2$, and –(C_1-C_5)alkylene-N-(R_x)(R_y); provided that at least one of R_a, R_b, and R_c is -(C_1-C_5)alkylene-N-(R_x)(R_y);

R_x and R_y are independently selected from the group consisting of H and substituted or unsubstituted (C_1-C_6)-alkyl; or R_x and R_y taken together with the N to which they are attached form a 4-6 membered ring;

R_1 is methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, or t-butyl;

R_2 is 

;

R_{3a} and R_{3b} are independently selected from the group consisting of halide, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_4)-alkoxy, CF_3, $C(H)F_2$, and $C(F)H_2$;

R_{3c}, and R_{3d} are H;

R_4 is H;

R_{5a} is methyl;

R_{5b} is selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_1-C_5)-alkyl, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted 3-6 membered heterocycloalkyl, hydroxyl, and (C_1-C_4)-alkoxy;

R_{5c} is methyl;

R_{5d} is H; and

R_{5e} is selected from the group consisting of H, CN, halide, CF_3, $C(H)F_2$, $C(F)H_2$, substituted or unsubstituted (C_3-C_6)-cycloalkyl, substituted or unsubstituted (C_1-C_5)-alkyl, hydroxyl, and (C_1-C_4)-alkoxy.

4. A pharmaceutical composition comprising a compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient.

5. Use of the compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

6. Use of the pharmaceutical composition of claim 4, in the manufacture of a medicament for treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease.

7. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, for use as a medicament.

Abstract

Disclosed are small molecule antagonists of human α4β7 integrin, and methods of using them to treat a number of diseases and conditions.

[Fig. 1]