

POTENT NF- κ B INHIBITORS FOR THE TREATMENT OF INFLAMMATORY DISEASES

Cross Reference to Related Applications

5 This application claims priority to and the benefit of U.S. Provisional Patent Application No. 63/614,624, filed December 24, 2023, U.S. Provisional Patent Application No. 63/614,625, filed December 24, 2023, and U.S. Provisional Patent Application No. 63/614,627, filed December 24, 2023, the contents of each of which are hereby incorporated by reference.

10

Field of the Disclosure

 The present disclosure provides certain potent compounds that inhibit nuclear factor-kappa B (NF- κ B) activation induced by inflammatory stimuli. Therefore, the compounds of the present disclosure are useful for the treatment of inflammatory disorders such as
15 rheumatoid arthritis, multiple sclerosis, asthma, and inflammatory bowel disease. Also provided are pharmaceutical compositions containing such compounds and methods of using them.

Background

20 Inflammation is an important host response to infection or injury. However, dysregulation of this response, with resulting persistent or inappropriate inflammation leads to a broad range of pathological processes. Inflammatory disorders include autoimmune diseases, allergies, asthma, chronic obstructive pulmonary disease and sepsis which are a major cause of illness and death. It is also becoming apparent that low-grade chronic
25 inflammation underlies many diseases, including diabetes, cancer, cardiovascular disease and neurodegenerative disorders. Therefore, identifying new drugs to suppress inflammation is an area of intense interest.

 NF- κ B is a ubiquitously expressed transcription factor which regulates the expression of genes involved in inflammation and pain. Activation of NF- κ B plays a central role in
30 inflammation through its ability to induce transcription of proinflammatory genes (see Tak et al. NF- κ B: a key role in inflammatory diseases. J Clin Inv 2001; 107:7-11; and Liu et al. NF- κ B signaling in inflammation. Signal Transduct Target Ther. 2017;2. pii: 17023). Synthesis of proinflammatory cytokines, such as TNF- α , IL-1 β , IL-6, and IL-8, is mediated by NF- κ B, as is the expression of cyclooxygenase 2 (COX-2), inducible nitric oxide synthase (iNOS),

adhesion molecules (ICAM-1, E-selectin, and VCAM-1), chemokines (MCP-1, KC, MIP-1) and metalloproteinases. Reciprocally, cytokines such as TNF- α and IL-1 β or prostaglandins produced by COX-2 trigger NF-kB activation generating an inflammatory cascade.

NF-kB is activated at sites of inflammation in diverse diseases including rheumatoid
5 arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, asthma, inflammatory bowel
disease, diabetes, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis,
osteoporosis, systemic lupus erythematosus, chronic obstructive pulmonary disease, stroke,
acute kidney injury, glomerulonephritis, psoriasis, atopic dermatitis, etc (Pai et al. *Immune
deficiency or hyperactivity-Nf-kappab illuminates autoimmunity*. J Autoimmun 2008;
10 31:245–251; Zhang et al. NFkB in inflammation and renal diseases. Cell Biosci 2015; 5:63;
Roman-Blas et al. NF-kB as a potential therapeutic target in osteoarthritis and rheumatoid
arthritis. OsteoArthritis and Cartilage 2006; 14:839-848).

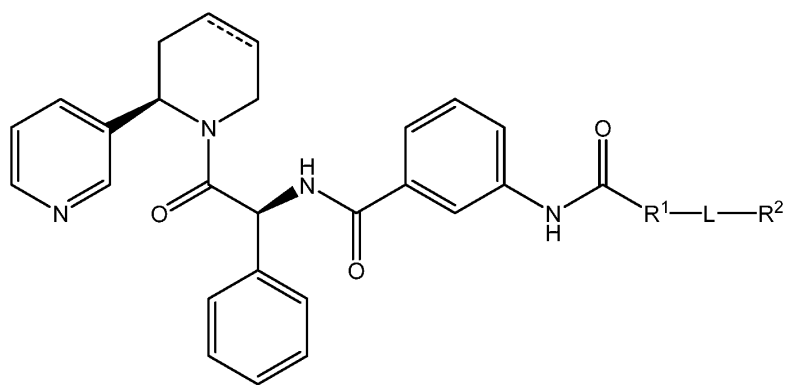
Corticosteroids have been developed to treat inflammatory conditions and have many
side effects that can be mild or serious, especially when corticosteroids are used for extended
15 periods of time. For instance, corticosteroids can cause weight gain, edema, high blood
pressure, glaucoma, hypokalemia, cataract, psychiatric disturbances, osteoporosis, and
weakening of the immune system. Non-steroidal anti-inflammatory drugs (NSAIDs) which
act via inhibition of the cyclooxygenase (COX) isozymes are widely prescribed but the
chronic use of NSAIDs is associated with common side effects including cardiovascular
20 events (hypertension, myocardial infarction, stroke, and heart failure), gastrointestinal side
effects (diffuse gastritis and discrete ulcers both gastric and duodenal) which can be fatal,
renal side effects (interstitial nephritis) as well as hepatic adverse reactions (transaminitis,
hepatitis). Biologics for targeting inflammatory cytokines have been developed. Although
biologics have been shown to ameliorate inflammatory diseases pathology and progression,
25 their use has been limited due to severe adverse reactions and to the fact that they abrogate
host defense against infection (Rider et al. Biologics for Targeting Inflammatory Cytokines,
Clinical Uses, and Limitations. Int J Cell Biol. 2016; 2016:9259646).

Certain NF-kB inhibitors are disclosed in WO/2020/154420. Still, there exists an
ongoing need for anti-inflammatory medications with greater potency and efficacy, and fewer
30 side effects, with superior properties over medications known in the art. The present
invention fulfills this and related needs.

Summary

The inventors have surprisingly discovered compounds having unexpectedly superior NF- κ B inhibitory properties relative to those known in the art, including the discovery that compounds with particular stereochemistry are markedly superior to their enantiomeric counterparts.

Accordingly, in one aspect, provided is a compound of Formula (I):

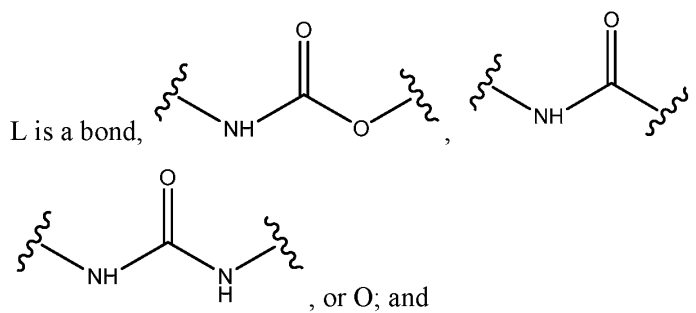


(I)

wherein:

the dashed line is an optional bond;

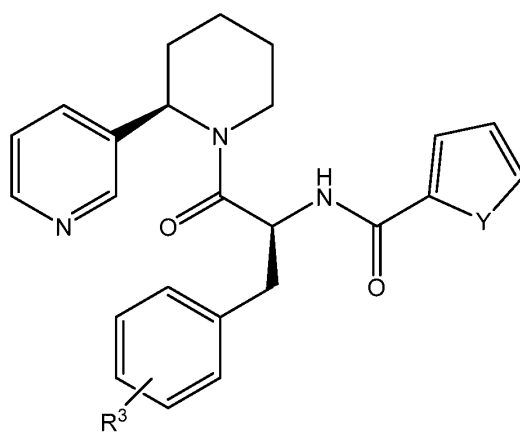
R¹ is C₃-C₅ alkyl;



R² is H or C₃-C₇ alkyl; or

a pharmaceutically acceptable salt thereof.

In a second aspect, provided is a compound of Formula (II):



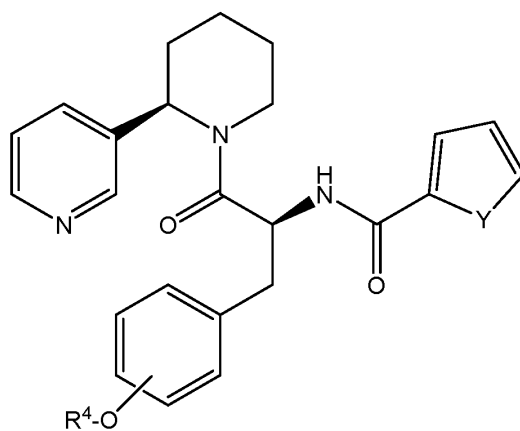
(II)

wherein:

Y is O or S; and

- 5 R³ is -H, -F, or -CX₃, wherein each X is independently -H or -F; or
a pharmaceutically acceptable salt thereof.

In a third aspect, provided is a compound of Formula (III):



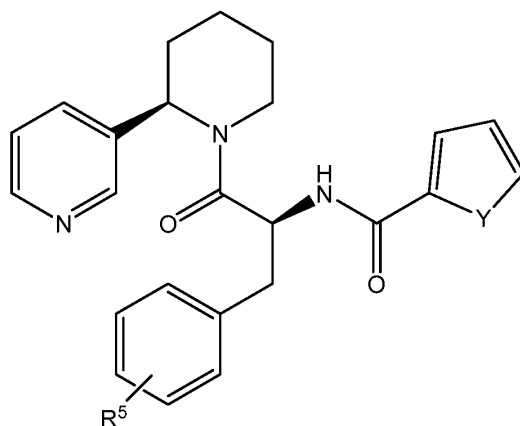
(III)

wherein:

Y is O or S; and

- 10 R⁴ is -CX₃, wherein each X is independently -H or -F; or
15 a pharmaceutically acceptable salt thereof.

In a fourth aspect, provided is a compound of Formula (IV):



(IV)

wherein:

- 5 Y is O or S; and
 R⁵ is C₂-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₃-C₄ cycloalkyl; or
 a pharmaceutically acceptable salt thereof.

10 In a fifth aspect, this disclosure is directed to a pharmaceutical composition
 comprising a compound Formula (I), a compound of Formula (II), a compound of Formula
 (III), or a compound of Formula (IV) (or any of the embodiments thereof described herein),
 or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable excipient.

15 In a sixth aspect, this disclosure is directed to a method of treating a disease treatable
 by inhibiting NF-κB activation comprising administering to a patient in need thereof a
 therapeutically effective amount of a compound of Formula (I), a compound of Formula (II),
 a compound of Formula (III), or a compound of Formula (IV) (or any of the embodiments
 thereof described herein), or a pharmaceutically acceptable salt thereof or a pharmaceutical
 composition comprising a compound of Formula (I), a compound of Formula (II), a
 compound of Formula (III), or a compound of Formula (IV) (or any of the embodiments
 thereof described herein) and a pharmaceutically acceptable excipient. In one embodiment
 the diseases are inflammatory diseases including, autoimmune diseases, pain, allergies,
 asthma, chronic obstructive pulmonary disease and sepsis. In another embodiment the
 diseases are rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, asthma,
 inflammatory bowel disease, diabetes, Parkinson's disease, Alzheimer's disease, amyotrophic
 lateral sclerosis, osteoporosis, systemic lupus erythematosus, chronic obstructive pulmonary
 disease.

disease, cystic fibrosis, stroke, acute kidney injury, glomerulonephritis, psoriasis, atopic dermatitis, Behcet's disease, tuberculosis, Crohn's disease, colitis, Pagett's disease, pancreatitis, periodontitis, inflammatory lung disease, and lupus nephritis.

In a seventh aspect, the disclosure is directed to a compound of Formula (I), a
5 compound of Formula (II), a compound of Formula (III), or a compound of Formula (IV) (or
any embodiments thereof described herein) or a pharmaceutically acceptable salt thereof for
use as a medicament. In one embodiment, the compound of Formula (I), a compound of
Formula (II), a compound of Formula (III), or a compound of Formula (IV) (and any
10 embodiments thereof described herein) or a pharmaceutically acceptable salt thereof is useful
for the treatment of inflammatory diseases including, autoimmune diseases, pain, allergies,
asthma, chronic obstructive pulmonary disease and sepsis. In another embodiment the
diseases are rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, asthma,
inflammatory bowel disease, diabetes, Parkinson's disease, Alzheimer's disease, amyotrophic
15 lateral sclerosis, osteoporosis, systemic lupus erythematosus, chronic obstructive pulmonary
disease, cystic fibrosis, stroke, acute kidney injury, glomerulonephritis, psoriasis, atopic
dermatitis, Behcet's disease, tuberculosis, Crohn's disease, colitis, Pagett's disease,
pancreatitis, periodontitis, inflammatory lung disease, and lupus nephritis.

In a eighth aspect provided a compound Formula (I), a compound of Formula (II), a
compound of Formula (III), or a compound of Formula (IV), or a pharmaceutically
20 acceptable salt thereof (and any embodiments thereof disclosed herein) for use in treating a
disease in a patient in which NF-kB activation contributes to the pathology and/or symptoms
of the disease. In one embodiment the diseases are inflammatory diseases including,
autoimmune diseases, pain, allergies, asthma, chronic obstructive pulmonary disease and
sepsis. In another embodiment the diseases are rheumatoid arthritis, osteoarthritis,
25 atherosclerosis, multiple sclerosis, asthma, inflammatory bowel disease, diabetes, Parkinson's
disease, Alzheimer's disease, amyotrophic lateral sclerosis, osteoporosis, systemic lupus
erythematosus, chronic obstructive pulmonary disease, cystic fibrosis, stroke, acute kidney
injury, glomerulonephritis, psoriasis, atopic dermatitis, Behcet's disease, tuberculosis,
Crohn's disease, colitis, Pagett's disease, pancreatitis, periodontitis, inflammatory lung
30 disease, and lupus nephritis.

Detailed Description*Definitions:*

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

5 “Alkyl” means a linear saturated monovalent hydrocarbon radical of one to eight carbon atoms or a branched saturated monovalent hydrocarbon radical of three to eight carbon atoms, e.g., methyl, ethyl, propyl, 2-propyl, butyl, pentyl, and the like. In some instances, the number of carbon atoms may be specified.

 “Alkenyl” means a C₂ to C₁₀ radical of carbon and hydrogen having at least one
10 double bond. Unless otherwise specified, alkenyl groups may be linear (i.e. unbranched) or branched, be cyclic, acyclic or part cyclic/acyclic.

 “Alkynyl” means “alkynyl” means a C₂ to C₁₀ radical which includes at least one carbon to carbon triple bond. Unless otherwise specified, alkynyl groups may be linear (i.e. unbranched) or branched, be cyclic, acyclic or part cyclic/acyclic.

15 “Cycloalkyl” means a cyclic saturated monovalent hydrocarbon radical of three to ten carbon atoms, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, and the like.

 “Patient” means a mammal, preferably a human.

The present disclosure also includes protected derivatives of compounds of the present disclosure. For example, when compounds of the present disclosure contain groups
20 such as hydroxy, carboxy, thiol or any group containing a nitrogen atom(s), these groups can be protected with a suitable protecting groups. A comprehensive list of suitable protective groups can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. (1999), the disclosure of which is incorporated herein by reference in its entirety. The protected derivatives of compounds of the present disclosure can be prepared by methods
25 well known in the art.

The present disclosure also includes polymorphic forms and deuterated forms of the compound of the present disclosure or a pharmaceutically acceptable salt thereof.

A “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the
30 parent compound. Such salts include:

 acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as formic acid, acetic acid, propionic acid, hexanoic acid,

cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, 5 benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or salts formed when an acidic proton 10 present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine, and the like. It is understood that the pharmaceutically acceptable salts are non-toxic. Additional information on suitable pharmaceutically acceptable salts can be found in *Remington's* 15 *Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, 1985, which is incorporated herein by reference in its entirety.

The compounds of the present disclosure have asymmetric centers. Unless otherwise indicated, the stereochemistry for a given compound is as denoted. It will be understood by a person of ordinary skill in the art that when a compound is denoted as an 20 (R) or (S) stereoisomer at a given position, it may contain the corresponding (S) or (R) stereoisomer as an impurity; preferably the undesired enantiomer is present in less than about 10%, preferably less than about 5% w/w. About means + or – 10% of initial value. All chiral, diastereomeric, all mixtures of chiral or diastereomeric forms, and racemic forms are within the scope of this disclosure unless the specific stereochemistry or isomeric form 25 is specifically indicated.

Certain compounds of the present disclosure can exist as tautomers and/or geometric isomers. All possible tautomers and *cis* and *trans* isomers, as individual forms and mixtures thereof are within the scope of this disclosure. Additionally, as used herein the term alkyl includes all the possible isomeric forms of said alkyl group albeit only a few 30 examples are set forth. Similarly, when the cyclic groups such as aryl, heteroaryl, heterocyclyl are substituted, they include all the positional isomers albeit only a few examples are set forth. Furthermore, all hydrates of a compound of the present disclosure are within the scope of this disclosure.

A “pharmaceutically acceptable carrier or excipient” means a carrier or an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes a carrier or an excipient that is acceptable for veterinary use as well as human pharmaceutical use. “A pharmaceutically acceptable carrier/excipient” as used in the specification and claims includes both one and more than one such excipient.

“Treating” or “treatment” of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease;

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms; or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A “therapeutically effective amount” means the amount of a compound of the present disclosure and/or a pharmaceutically acceptable salt thereof that, when administered to a patient for treating a disease, is sufficient to effect such treatment for the disease. The “therapeutically effective amount” will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

When a range is recited herein, it is to be understood that the stated range is meant to additionally encompass any sub-range within the stated range, or any individual number falling within the range, even if not explicitly enumerated herein.

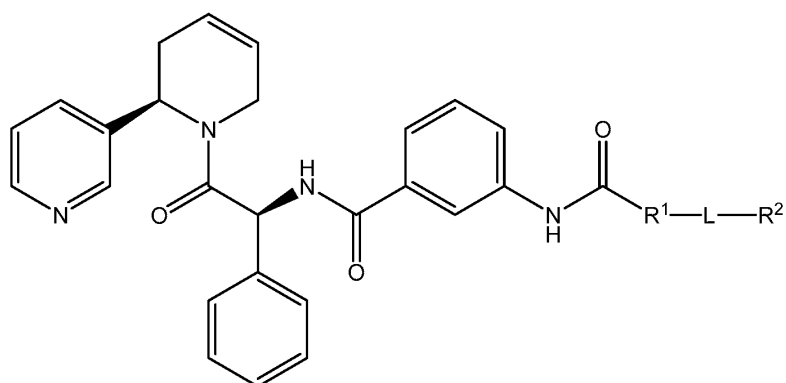
Embodiments:

Embodiment 1:

In embodiment 1, the compounds are of Formula (I), Formula (II), Formula (III), or Formula (IV) as defined in the Summary above.

Embodiment 2:

In embodiment 2, the compounds of Formula (I) are of Formula (IA):

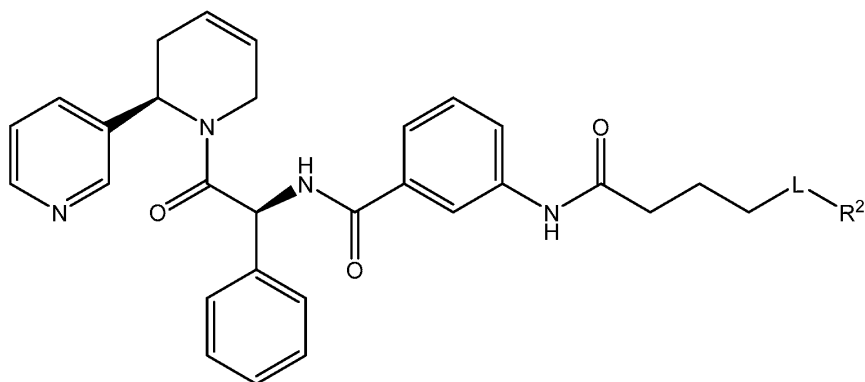


(IA)

or a pharmaceutically acceptable salt thereof, wherein R^1 , L, and R^2 are as defined in the Summary above.

5 Embodiment 3:

In embodiment 3, the compounds of Formula (I) are of Formula (IB):



(IB)

or a pharmaceutically acceptable salt thereof, wherein L and R^2 are as defined in the

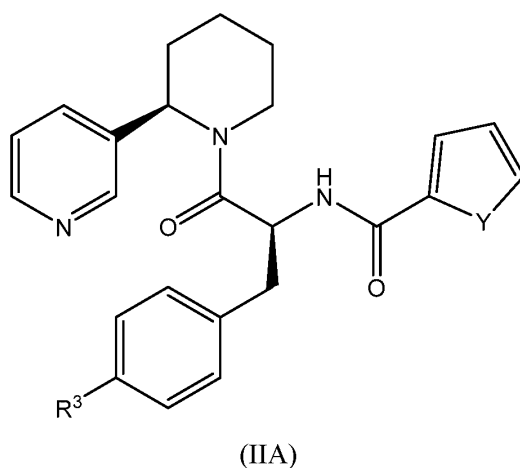
10 Summary above.

Embodiment 4:

In embodiment 4, the compounds of any of embodiments 1, 2 and 3 are those where L is a bond and R^2 is H.

Embodiment 5:

15 In embodiment 5, the compounds of Formula (II) are of Formula (IIA):



or a pharmaceutically acceptable salt thereof, wherein Y and R³ are as defined in the Summary above.

5 Embodiment 6:

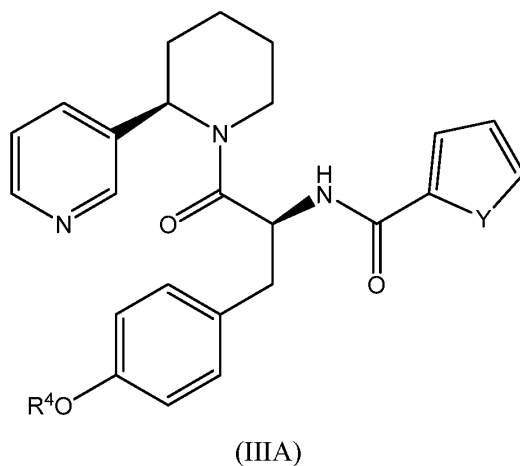
In embodiment 6, the compounds of any one of embodiments 1 and 5 are those wherein R³ is -CH₂F, -CHF₂, or -CF₃.

Embodiment 7:

10 In embodiment 7, the compounds of any one of embodiments 1, 5, and 6 are those wherein R³ is -CHF₂.

Embodiment 8:

In embodiment 8, the compounds of Formula (III) are of Formula (IIIA):



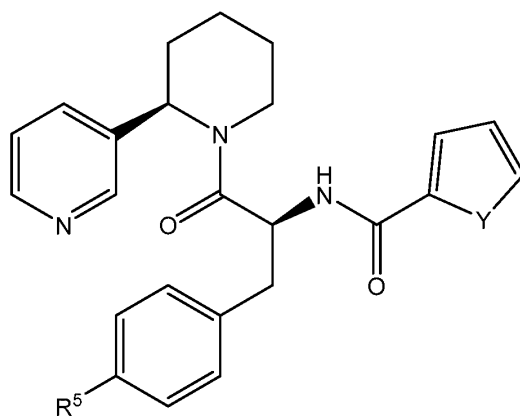
15 or a pharmaceutically acceptable salt thereof, wherein Y and R⁴ are as defined in the Summary above.

Embodiment 9:

In embodiment 9, the compounds of any one of embodiments 1 and 8 are those wherein R^4 is $-\text{CHF}_2$.

Embodiment 10:

In embodiment 10, the compounds of Formula (IV) are of Formula (IVA):



(IVA)

or a pharmaceutically acceptable salt thereof, wherein Y and R^5 are as defined in the Summary above.

Embodiment 11:

In embodiment 11, the compounds of embodiments 1 and 10 are those wherein R^5 is $\text{C}_2\text{-C}_3$ alkyl.

Embodiment 12:

In embodiment 12, the compounds of embodiments 1 and 10 are those wherein R^5 is $\text{C}_2\text{-C}_3$ alkenyl.

Embodiment 13:

In embodiment 13, the compounds of embodiments 1 and 10 are those wherein R^5 is $\text{C}_2\text{-C}_3$ alkynyl.

Embodiment 14:

In embodiment 14, the compounds of embodiments 1 and 10 are those wherein R^5 is $\text{C}_3\text{-C}_4$ cycloalkyl.

Embodiment 15:

In embodiment 15, the compounds of embodiments 1, 10, and 11 are those wherein R^5 is propyl.

Embodiment 16:

In embodiment 16, the compounds of embodiments 1, 10, and 12 are those wherein R^5 is C₂-C₃ propenyl.

Embodiment 17:

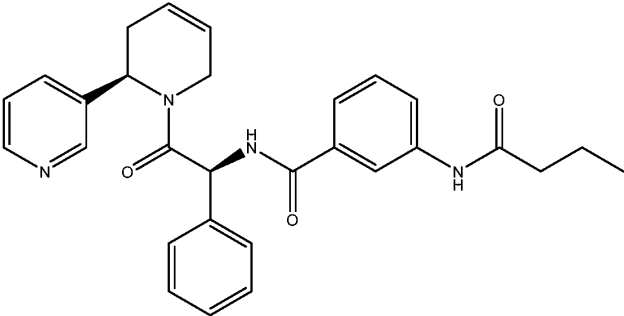
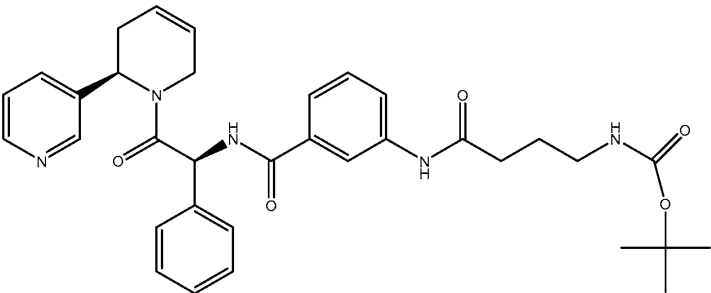
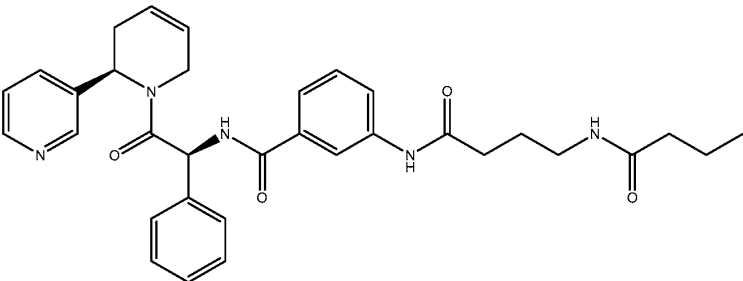
In embodiment 17, the compounds of embodiments 1, 10, and 13 are those wherein R^5 is ethynyl.

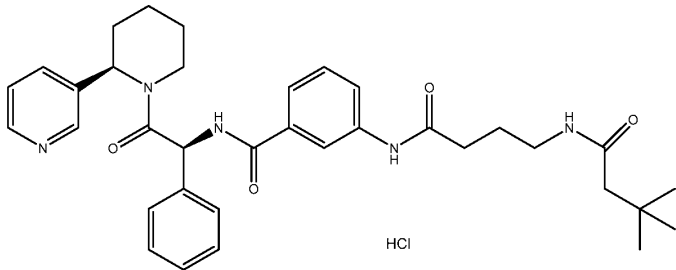
Embodiment 18:

In embodiment 18, the compounds of embodiments 1, 10, and 14 are those wherein R^5 is cyclopropanyl.

Representative compounds of Formula (I) are as indicated in Table 1 below:

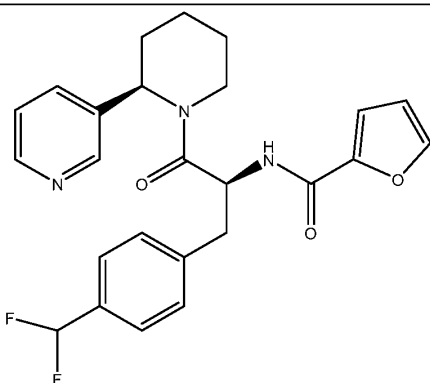
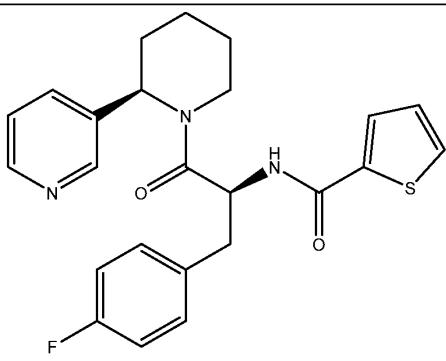
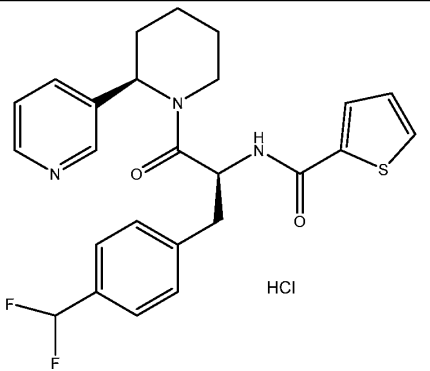
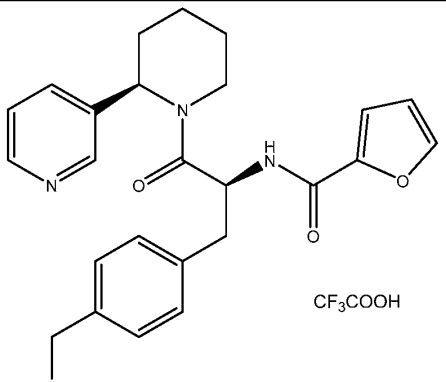
Table 1

Cpd No.	Compound
101	
102	
103	

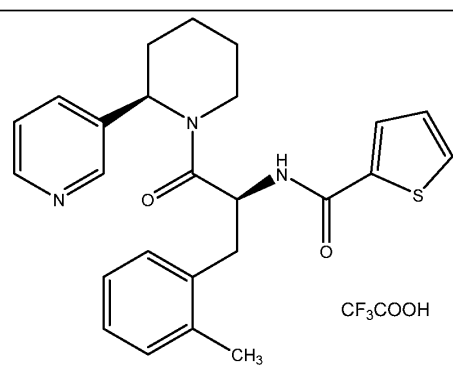
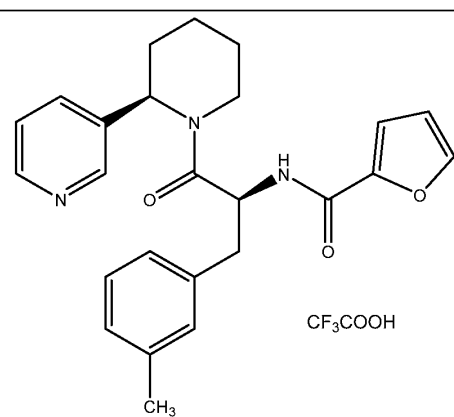
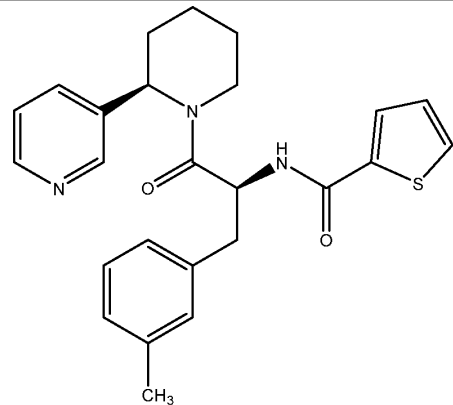
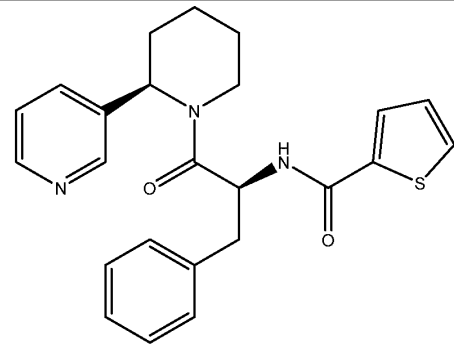
Cpd No.	Compound
112	 HCl

Representative compounds of Formula (II) are as indicated in Table 2 below:

Table 2

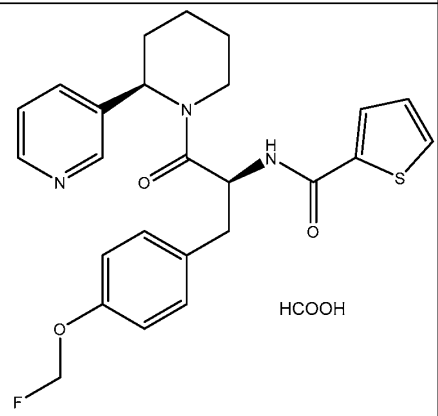
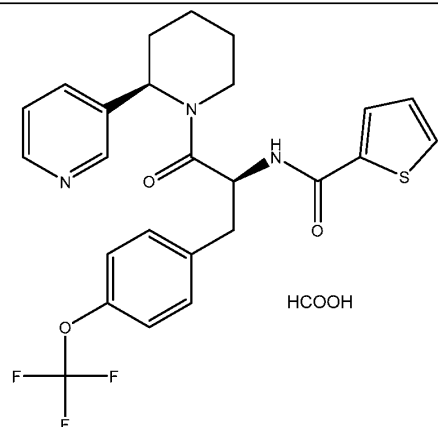
Cpd No.	Compound	Cpd No.	Compound
201	 HCl	206	
202	 HCl	207	 CF ₃ COOH

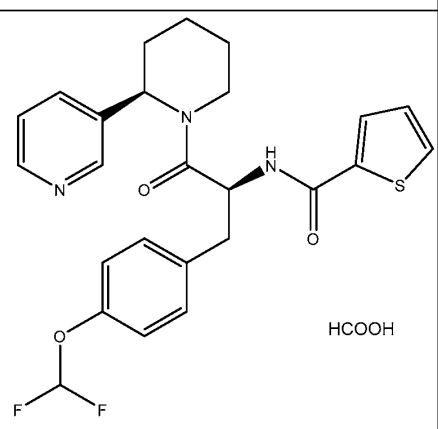
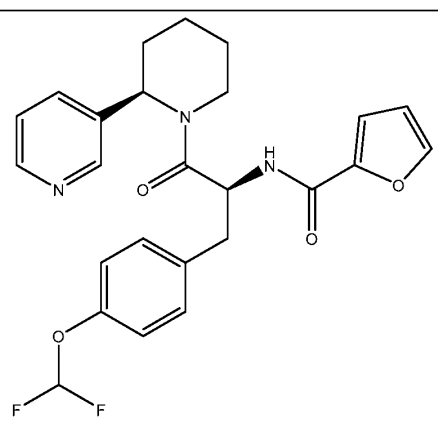
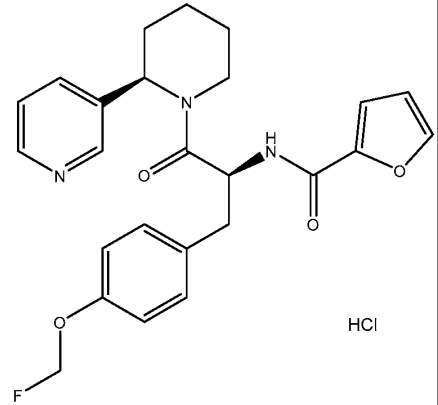
Cpd No.	Compound	Cpd No.	Compound
203	 HCOOH	208	 HCOOH
204	 CF ₃ COOH	209	 HCOOH
205	 HCOOH	210	 CH ₃

Cpd No.	Compound	Cpd No.	Compound
211	 CF ₃ COOH	212	 CF ₃ COOH
213	 CH ₃	214	

Representative compounds of Formula (III) are as indicated in Table 3 below are:

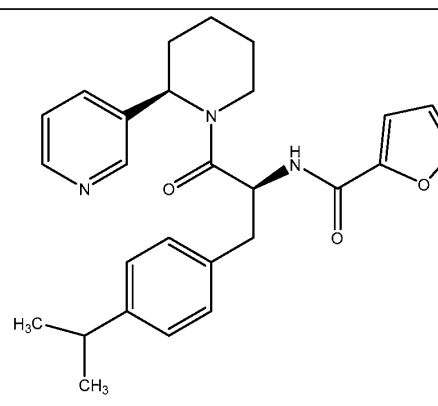
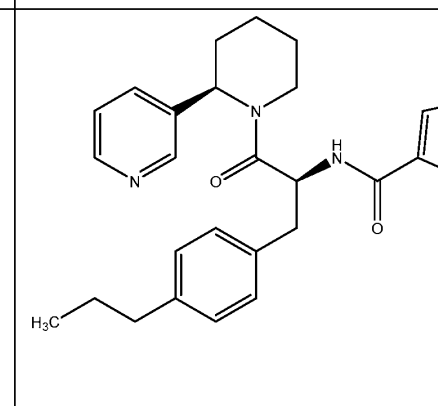
Table 3

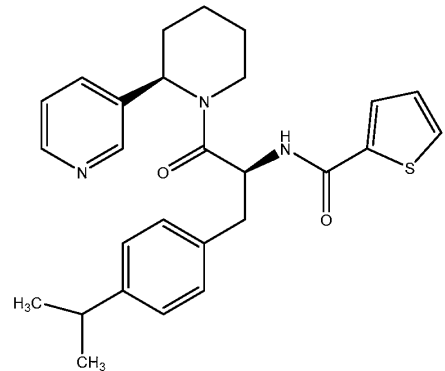
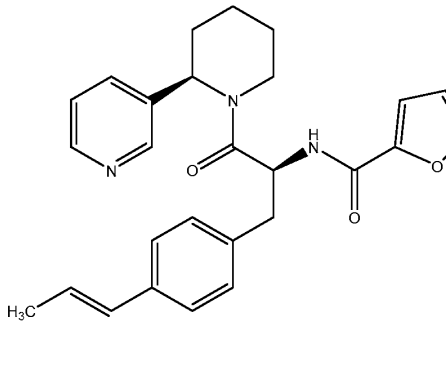
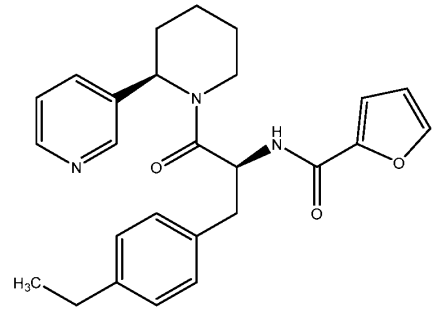
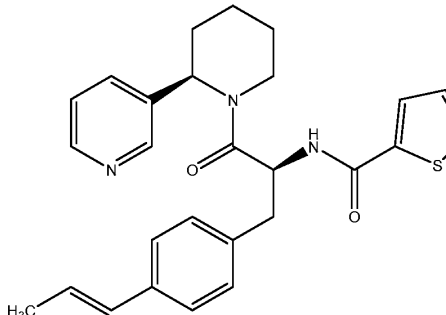
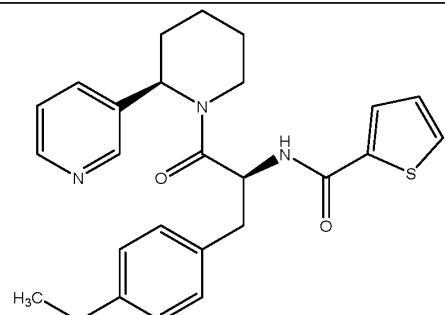
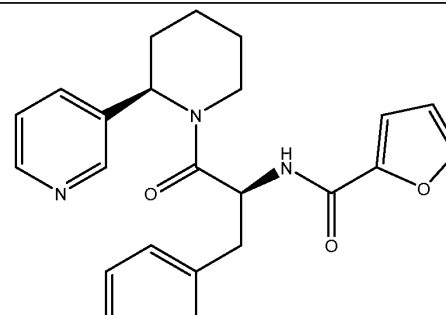
Cpd No.	Compound	Cpd No.	Compound
301	 HCOOH	303	 HCOOH

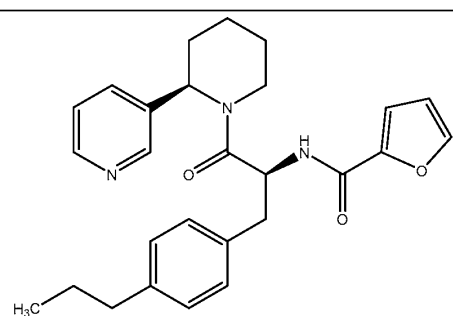
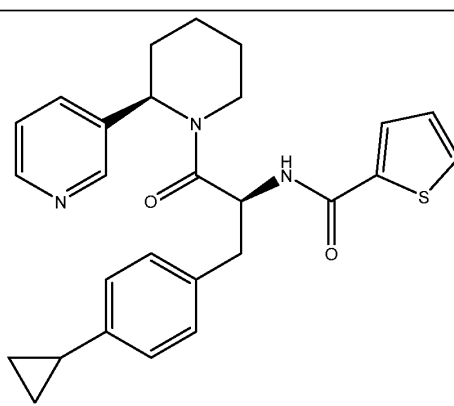
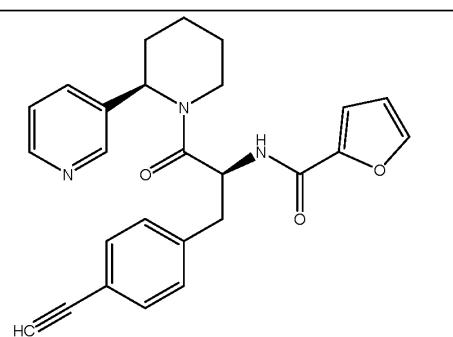
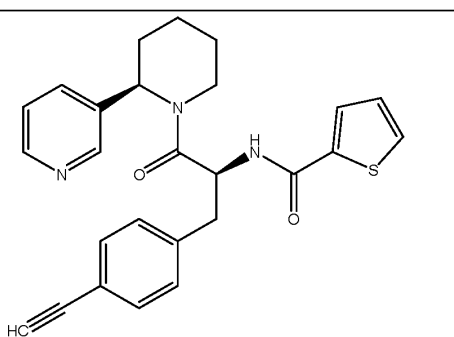
Cpd No.	Compound	Cpd No.	Compound
302	 HCOOH	304	
305	 HCl		

Representative compounds of Formula (IV) are as indicated in Table 4 below are:

Table 4

Cpd No.	Compound	Cpd No.	Compound
401		406	

Cpd No.	Compound	Cpd No.	Compound
402		407	
403		408	
404		409	

Cpd No.	Compound	Cpd No.	Compound
405		410	
411		412	

General Synthetic Scheme

Compounds of this disclosure can be made by the general methods disclosed in WO/2020/154420, the contents of which are hereby incorporated by reference in their entirety.

Administration and Pharmaceutical Composition

In general, the compounds of this disclosure will be administered in a therapeutically effective amount by any of the accepted modes of administration for agents that serve similar utilities. Therapeutically effective amounts of compounds of this disclosure may range from about 0.01 to about 500 mg per kg patient body weight per day, which can be administered in single or multiple doses. A suitable dosage level may be from about 0.1 to about 250 mg/kg per day; or about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to about 250 mg/kg per day, about 0.05 to about 100 mg/kg per day, or about 0.1 to about 50

mg/kg per day. Within this range the dosage can be about 0.05 to about 0.5, about 0.5 to about 5 or about 5 to about 50 mg/kg per day. For oral administration, the compositions can be provided in the form of tablets containing about 1.0 to about 1000 milligrams of the active ingredient, particularly about 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, 500, 5 600, 750, 800, 900, and 1000 milligrams of the active ingredient. The actual amount of the compound of this disclosure, i.e., the active ingredient, will depend upon numerous factors such as the severity of the disease to be treated, the age and relative health of the patient, the potency of the compound being utilized, the route and form of administration, and other factors.

10 In general, compounds of this disclosure will be administered as pharmaceutical compositions by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository), or parenteral (e.g., intramuscular, intravenous or subcutaneous) administration. The preferred manner of administration is oral using a convenient daily dosage regimen, which can be adjusted according to the degree of affliction. Compositions 15 can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate compositions.

The choice of formulation depends on various factors such as the mode of drug administration (e.g., for oral administration, formulations in the form of tablets, pills or capsules, including enteric coated or delayed release tablets, pills or capsules are preferred) 20 and the bioavailability of the drug substance. Recently, pharmaceutical formulations have been developed especially for drugs that show poor bioavailability based upon the principle that bioavailability can be increased by increasing the surface area i.e., decreasing particle size. For example, U.S. Pat. No. 4,107,288 describes a pharmaceutical formulation having particles in the size range from 10 to 1,000 nm in which the active material is supported on a cross-linked matrix of macromolecules. U.S. Pat. No. 5,145,684 describes the production of a 25 pharmaceutical formulation in which the drug substance is pulverized to nanoparticles (average particle size of 400 nm) in the presence of a surface modifier and then dispersed in a liquid medium to give a pharmaceutical formulation that exhibits remarkably high bioavailability.

30 The compositions are comprised of, in general, a compound of this disclosure in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the compound of this disclosure. Such excipients may be any solid, liquid, semi-solid or, in the

case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

5 Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk and the like. Liquid and semisolid excipients may be selected from glycerol, propylene glycol, water, ethanol and various oils, including those of petroleum, animal, vegetable or synthetic origin, e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc. Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose, and glycols.

10 Compressed gases may be used to disperse a compound of this disclosure in aerosol form. Inert gases suitable for this purpose are nitrogen, carbon dioxide, etc.

Other suitable pharmaceutical excipients and their formulations are described in Remington's Pharmaceutical Sciences, edited by E. W. Martin (Mack Publishing Company, 20th ed., 2000).

15 The level of the compound in a formulation can vary within the full range employed by those skilled in the art. Typically, the formulation will contain, on a weight percent (wt. %) basis, from about 0.01-99.99 wt. % of a compound of this disclosure based on the total formulation, with the balance being one or more suitable pharmaceutical excipients. For example, the compound is present at a level of about 1-80 wt. %.

20 The compounds of this disclosure may be used in combination with one or more other drugs in the treatment of diseases or conditions for which compounds of this disclosure or the other drugs may have utility. Such other drug(s) may be administered by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of the present disclosure. When a compound of this disclosure is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of the present disclosure is preferred. However, the combination therapy may also include therapies in which the compound of this disclosure and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present disclosure and the other active ingredients may be used in lower doses than when each is used singly.

25

30

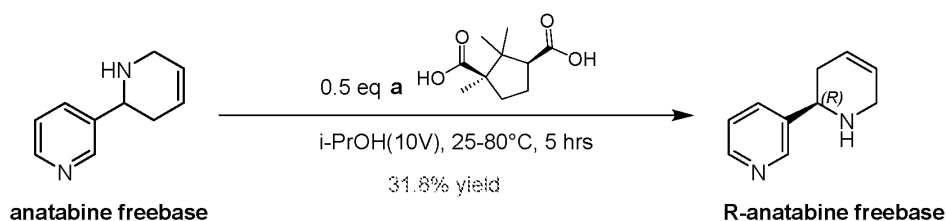
Examples

The following preparations of compounds of Formulas (I), (II), (III), and (IV) are given to enable those skilled in the art to more clearly understand and to practice the present disclosure. They should not be considered as limiting the scope of the disclosure, but merely as being illustrative and representative thereof. Synthesis of additional compounds within the scope of the disclosure, as well as starting materials and intermediates therefor, will be within the purview of one of skill in the art in view of the syntheses exemplified herein.

SYNTHETIC EXAMPLES

Example 1

Synthesis of (R)-1,2,3,6-tetrahydro-2,3'-bipyridine

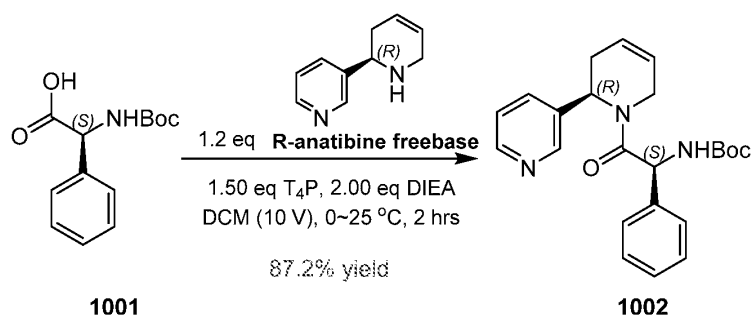


To a solution of compound **anatabine freebase** (500 g, 3.12 mol, 1.00 eq) in i-PrOH (2.50 L) was added compound **a** (312 g, 1.56 mol, 0.50 eq) at 25°C. The reaction mixture was stirred at 25 °C for 12 hrs. The mixture was filtered, and the filter cake was triturated in IPA (3L) at 60°C for 1hrs. The precipitate was filtered and the filter cake was diluted with H₂O (2.00 L), adjust pH to 10~ 11 with NaOH (1 N), extracted with DCM (1.00 L×3), dried over Na₂SO₄, filtered and concentrated to give **R-anatabine freebase** (160 g, 993 mmol, 31.8% yield, 99.5% purity, 96.9%ee) as yellow oil.

LCMS: EC28826-2-P1C2, Rt = 0.992 min, m/z +1 = 161.1

Example 2

Synthesis of tert-butyl ((S)-2-((R)-3,6-dihydro-[2,3'-bipyridin]-1(2H)-yl)-2-oxo-1-phenylethyl)carbamate

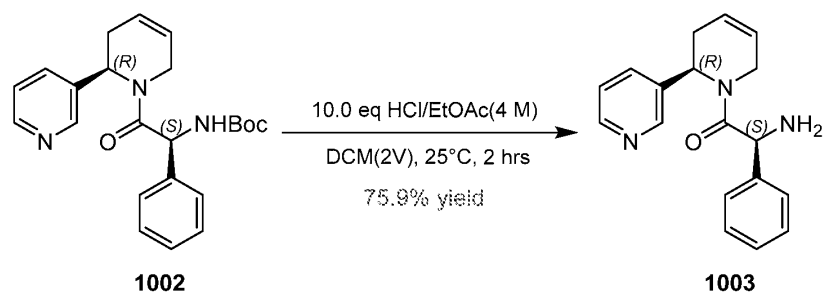


To a solution of **Cpd_1001** (200 g, 796 mmol, 1.00 eq) and **R-anatibine freebase** (153 g, 955 mmol, 1.20 eq) in DCM (2.00L) was added DIEA (205 g, 1.59 mol, 277 mL, 2.00 eq) and T4P (860 g, 1.19 mol, 50% purity, 1.50 eq) at 0°C. The reaction mixture was stirred at 25°C for 2 hrs. The reaction mixture was washed with water (2.00 L), and dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate =20:1-1:1) to give **Cpd_1002** (280 g, 694 mmol, 87.2% yield, 97.5% purity) as yellow oil.

LCMS: EC28826-3-P1A1, Rt = 0.335 min, m/z +1 = 394.1

Example 3

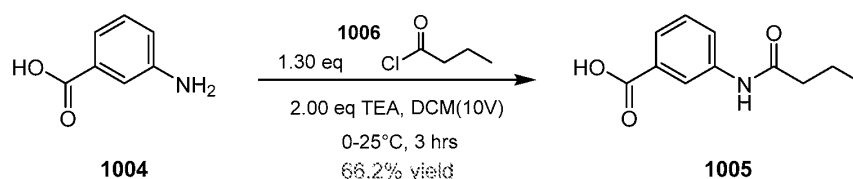
Synthesis of (S)-2-amino-1-((R)-3,6-dihydro-[2,3'-bipyridin]-1(2H)-yl)-2-phenylethan-1-one



HCl (10.0 eq) gas was bubbled into a solution of **Cpd_1002** (280 g, 711 mmol, 1.00 eq) in DCM (200 mL) and EtOAc (2.00 L) at 0 - 10 °C. After completion, the resulting mixture was stirred for 2 hrs at 25 °C. The reaction mixture was filtered and washed with MTBE (500 mL), the filter cake was dried in vacuo to give the desired product **Cpd_1003** (180 g, 540 mmol, 75.9% yield, 99% purity, HCl salt) as white solid and used to the next step directly.

LCMS: EC28826-5-P1A1, Rt = 0.123 min, m/z +1 = 294.0

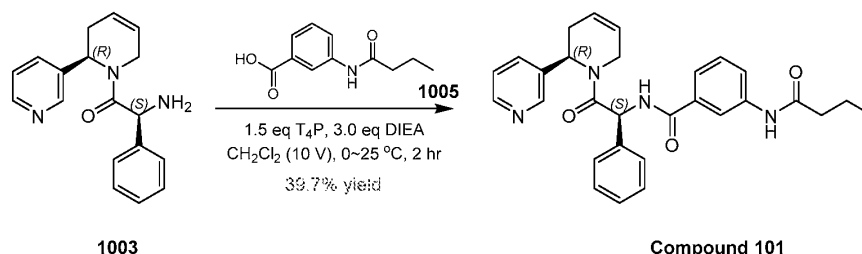
Example 4

Synthesis of 3-butylamidobenzoic acid

To a solution of **Cpd_1004** (200 g, 1.46 mol, 1.00 eq) in DCM (2.00 L) was added TEA (295 g, 2.92 mol, 406 mL, 2.00 eq) at 25 °C, the mixture was cooled to 0 °C and **Cpd_1006** (200 g, 1.88 mol, 196 mL, 1.29 eq) was added dropwise to the reaction mixture at 0 °C. After addition, the mixture was stirred at 25 °C for 3 hrs. The reaction mixture was concentrated to give a residue, the residue was triturated with 1N HCl aqueous for 1 h, filtered and washed with 1L water, the filter cake was triturated with EtOAc (1.00 L) at 25 °C for 1 hr, filtered and washed with MTBE (500 mL), the filter cake was dried in vacuo to give compound **1005** (200 g, 965 mmol, 66.2% yield, 100% purity) was obtained as white solid.

LCMS: EC28826-4-P1A1, Rt = 0.280 min, m/z +1 = 207.9

Example 5

Synthesis of 3-butylamido-N-((S)-2-((R)-3,6-dihydro-[2,3'-bipyridin]-1(2H)-yl)-2-oxo-1-phenylethyl)benzamide (Compound 101)

To a solution of **Cpd_1003** (179 g, 543 mmol, 1.00 eq, HCl salt) and **Cpd_1005** (135 g, 651 mmol, 1.20 eq) in DCM (2.00 L) was added DIEA (210 g, 1.63 mol, 283 mL, 3.00 eq) and T₄P (586 g, 814 mmol, 50.0% purity, 1.50 eq) at 0 °C. The reaction mixture was stirred at 25 °C for 2 hrs. The reaction mixture was washed with water (1.00 L), the aqueous was extracted with DCM (1.00 L), combined the organic phase and dried over Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by prep-HPLC (neutral condition) and further purified by SFC (column: Chiral-IK-50-DAICEL CHIRALPAK IK (250mm*50mm,10um); mobile phase: [CO₂-IPA: CAN = 7:3 (0.1% NH₃H₂O)]; B%:40%,

isocratic elution mode) to give desired product **Compound 101** (106 g, 215 mmol, 39.7% yield, 98.2% purity) was obtained as yellow solid.

LCMS: EC28826-6-P1A2, Rt = 1.284 min, m/z +1 = 483.1

LCMS: EC28826-6-P1D1, Rt = 1.312 min, m/z +1 = 483.1

5 **HPLC:** EC28826-6-P1D3, purity: 98.2%

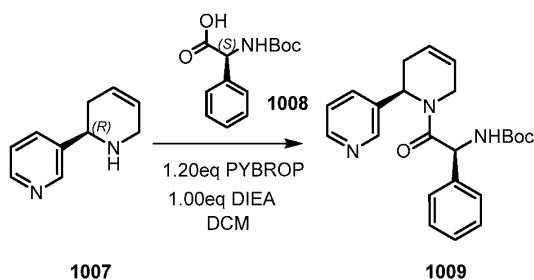
SFC: EC28826-6-P1D1 and EC28826-6-P1D3, %ee = 99.5%ee

HNMR: EC28826-6-P1D2, 400 MHz, CDCl₃-d

δ 8.70 - 8.29 (m, 2H), 8.06 - 7.90 (m, 1H), 7.87 - 7.54 (m, 4H), 7.54 - 7.44 (m, 3H), 7.41 - 7.30 (m, 3H), 7.27 (s, 2H), 6.97 - 6.76 (m, 1H), 6.22 - 6.08 (m, 1H), 6.00 (d, J = 7.4 Hz, 1H),
 10 5.88 (dt, J = 2.8, 5.0 Hz, 1H), 5.70 - 5.36 (m, 1H), 4.86 - 3.94 (m, 1H), 3.70 - 3.12 (m, 1H),
 3.00 - 2.54 (m, 2H), 2.33 (br t, J = 7.4 Hz, 2H), 1.74 (sxt, J = 7.4 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H)

Example 6

15 *Synthesis of tert-butyl ((S)-2-((R)-3,6-dihydro-[2,3'-bipyridin]-1(2H)-yl)-2-oxo-1-phenylethyl)carbamate*

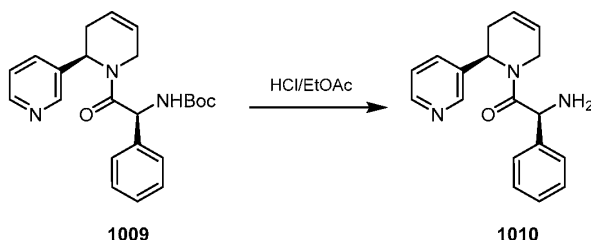


To the solution of **1008** in DCM (60 mL) was added PYBROP (19.26 g, 41.31 mmol, 1.2 eq), then added DIEA (4.46 g, 34.48 mmol, 6.01 mL, 1 eq) at 0°C, after 30 min, **1007** was
 20 added, the reaction mixture was stirred for at 25°C for 2 hrs. TLC (PE:EA=1:1) showed that reactant (R_f=0.50) was consumed and new spot (R_f=0.40) was detected. LCMS (EC10163-76-P1R2) showed that reactant was consumed and the desired MS (R_t=0.315, M+1=394) was given. The reaction mixture was partitioned between EA (60 mL*2) and water (60 mL). The organic phase was separated, washed with brine (60 mL),
 25 dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by Prep-HPLC (HCl condition). From LCMS (EC10163-76-P1A1), HPLC (EC10163-76-P1C4), **1009** was obtained as yellow solid.

LC-MS: (EC10163-76-P1A1), RT=0.321, M+1=394

HPLC:EC10163-76-P1C4,RT=0.848

Example 7

Synthesis of (S)-2-amino-1-((R)-3,6-dihydro-[2,3'-bipyridin]-1(2H)-yl)-2-phenylethan-1-one

5

To a solution of **1009** in DCM (50 mL) was added HCl/EtOAc(25ml). The reaction mixture was stirred at 20-25°C for 2 hours. LCMS(EC9891-47-P1A11) showed that reactant 1 was consumed and the desired MS ($R_t=0.526$ min, $M + 1 = 294$) was given. The reaction mixture was concentrated under vacuum. The crude product was purified by Prep-HPLC. column: Agela DuraShell C18 150*25mm*5um; mobile phase: [water(NH₃H₂O)-ACN]; B%: 14%-44%, min From LCMS(EC9891-47-P1A11)HNMR(EC9891-47-P1A), **1010** was obtained as a red oil.

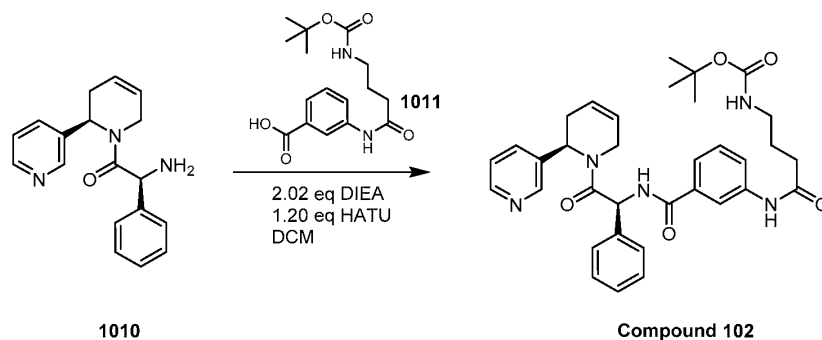
10

LC-MS: EC9891-47-P1A11, $R_t = 0.526$ min, $m/z (M+1) = 294$

15

Example 8

Synthesis of tert-butyl (4-((3-(((S)-2-((R)-3,6-dihydro-[2,3'-bipyridin]-1(2H)-yl)-2-oxo-1-phenylethyl)carbamoyl)phenyl)amino)-4-oxobutyl)carbamate (Compound 102)

**1010****Compound 102**

To a solution of **1011** (560 mg, 1.74 mmol, 1 eq) in DCM (6 mL) was added DIEA (896 mg, 6.93 mmol, 1.21 mL, 3.99 eq), then it was cooled 0-5°C, was added HATU (795 mg, 2.09 mmol, 1.2 eq), then was added **1010** (510 mg, 1.74 mmol, 1 eq). The reaction mixture was stirred at 20-25°C for 2 hours. LCMS(EC9891-81-P1A1) showed that reactant 1 was consumed and the desired MS ($R_t=0.658$ min, $M + 1 = 598$) was given. The reaction mixture

20

was diluted with DCM (5ml) and H₂O(5ml). The organic layer was washed with Saturated NaCl aqueous solution (5 mL) , dried over Na₂SO₄.The organic layer was concentrated under vacuum. The crude product was purified by Prep-HPLC (TFA condition) column: DAICEL CHIRALCEL OX (250mm*30mm,10um);mobile phase: [CO₂-EtOH(0.1%NH₃H₂O)];B%:40%, isocratic elution mode From LCMS (EC9891-81-P1A1), HPLC (EC9891-81-P1HPLC), HNMR (EC9891-81-P1A1), SFC (EC9891-81-P1A1) column: DAICEL CHIRALCEL OX (250mm*30mm,10um);mobile phase: [CO₂-EtOH(0.1%NH₃H₂O)];B%:40%. **Compound 102** (520 mg, 870.00 μ mol, 50.13% yield) was obtained as a yellow solid.

10 **LC-MS:** EC9891-50-P1A5, Rt = 0.658 min, m/z (M+1) =598

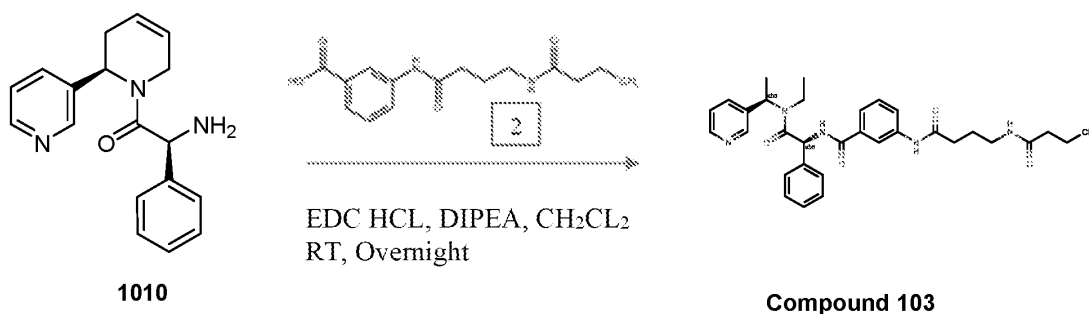
LC-MS: EC9891-81-P1A1, Rt = 0.658 min, m/z (M+1) = 598

¹H-NMR: EC9891-81-P1A1, 400 MHz, DMSO

δ 1.10 - 1.26 (m, 1 H), 1.37 (s, 9 H), 1.65 - 1.71 (m, 2 H), 2.30 (br t, J=7.44 Hz, 2 H), 2.67 (br s, 1 H), 2.93 - 2.97 (m, 2 H), 3.67 - 3.77 (m, 1 H), 4.00 - 4.12 (m, 1 H), 5.44 - 5.65 (m, 1 H), 5.72 - 5.88 (m, 2 H), 5.99 (br t, J=6.57 Hz, 1 H), 6.77 - 6.90 (m, 1 H), 7.04 - 7.12 (m, 1 H), 7.21 - 7.29 (m, 1 H), 7.33 - 7.43 (m, 4 H), 7.48 - 7.58 (m, 3 H), 7.72 - 7.84 (m, 2 H), 8.00 (s, 1 H), 8.44 - 8.58 (m, 1 H), 8.88 (br d, J=6.50 Hz, 1 H), 10.02 (s, 1 H)

Example 9

20 *Synthesis of 3-(4-butyramidobutanamido)-N-((S)-2-((R)-3,6-dihydro-[2,3'-bipyridin]-1(2H)-yl)-2-oxo-1-phenylethyl)benzamide (Compound 103)*

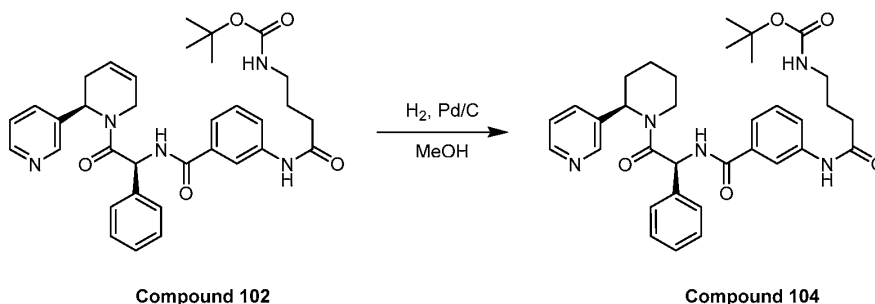


Reagent	M.W.	Eq	P(g/ml)	mmol	Amount
1010	293.38	1	-	2.653	0.7785g
2	292.34	1	-	2.653	0.7758g
EDC HCL	191.71	1.75	-	4.64	0.89g
DIPEA	129.25	2	0.742	5.31	0.92ml
CH ₂ CL ₂	-	-	-	-	25ml

Reagents were reacted overnight to prepare **Compound 103**. In the morning, the reaction mixture was washed with H₂O, NaHCO₃, and pH 6 buffer and then dried over an anhydrous MgSO₄ filter. 5 scoops of silica were added and the mixture rotovaped. The product was dry loaded on a 4g silica column and eluted to 100%. After evaporation of all the fractions, the crude purified material was vigorously stirred and dissolved in ethyl acetate (25ml) in ~50ml saturated NaHCO₃ for several hours. The final product was isolated and dried. Result: White crystalline solid; Mass – 782mg; Yield – 52%; Confirmed via mass spec.

Example 10

Synthesis of tert-butyl (4-oxo-4-((3-(((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)carbamoyl)phenyl)amino)butyl)carbamate (Compound 104)



To a solution of **Compound 102** (458 mg, 766.27 μ mol, 1 *eq*) in MeOH (20 mL), then was added Pd/C (66.18 mg, 62.19 μ mol, 10% purity, 8.12e-2 *eq*) under Ar. The reaction mixture was stirred at 20°C for 12h. LCMS (EC9891-99 -P1ACF) showed that reactant 1 was consumed and the desired MS (R_t =0.411 min) was given. The reaction mixture was concentrated under vacuum. The crude product was separated by SFC column: REGIS(S,S)WHELKO1(250mm*25mm, 10 μ m); mobile phase: [CO₂ACN/EtOH(0.1% NH₃H₂O)]; B%: 50%, isocratic elution mode. From LCMS (EC9891-99-P1ACF), HPLC (EC9891-99-P1HB2), HNMR (EC9891-99-P1HB HNMR), SFC (EC9891-99-P1A1), **Compound 104** (650 mg, 726.17 μ mol, 94.77% yield, 67% purity) was obtained as a white solid.

LC-MS: EC9891-99-P1ACF, R_t = 0.411 min, m/z ($M+1$) = 600

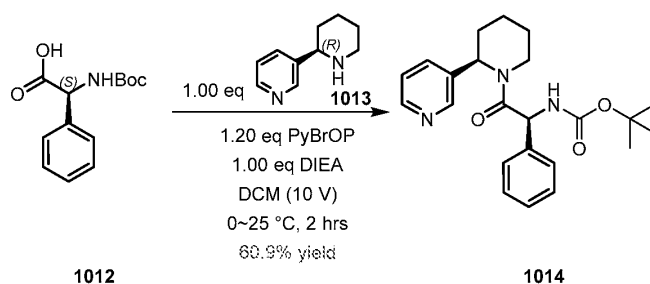
HPLC: EC9891-99-P1ACF2, R_t = 1.661 min

¹H-NMR: EC9891-99-P1BU, 400 MHz, DMSO

δ 1.23 - 1.30 (m, 2 H), 1.37 (s, 9 H), 1.65 - 1.71 (m, 2 H), 2.29 (br t, $J = 7.44$ Hz, 2 H), 2.81 - 2.90 (m, 1 H), 2.95 (q, $J = 6.55$ Hz, 2 H), 3.85 (br dd, $J = 14.26, 2.13$ Hz, 1 H), 4.34 (t, $J = 5.07$ Hz, 2 H), 5.86 (br s, 1 H), 6.12 (d, $J = 6.88$ Hz, 1 H), 6.79 - 6.85 (m, 1 H), 7.06 - 7.22 (m, 1 H), 7.32 - 7.47 (m, 6 H), 7.49 - 7.60 (m, 3 H), 7.71 (br d, $J = 7.63$ Hz, 1 H), 7.81 (br d, $J = 7.75$ Hz, 1 H), 8.01 (s, 1 H), 8.43 - 8.58 (m, 2 H), 8.78 (br d, $J = 5.88$ Hz, 1 H), 10.02 (s, 1 H)

Example 11

Synthesis of tert-butyl ((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)carbamate



To a solution of compound **1012** (5.00 g, 19.9 mmol, 1.00 eq) in DCM (50.0 mL) was added DIEA (2.60 g, 20.0 mmol, 3.5 mL, 1.00 eq) and PYBROP (11.2 g, 24.0 mmol, 1.20 eq) and compound **1013** (3.23 g, 19.9 mmol, 1.00 eq) at 0 °C stirred for 30 min, then the reaction mixture was stirred at 25 °C for 1.5 hrs. LC-MS (EC7755-2-P1A1) showed the compound **1012** was consumed and the desired mass (RT = 0.354 min, m/z (M+1) = 396.5) was detected. The reaction mixture was partitioned between DCM (100 mL) and water (50.0 mL). The organic phase was separated, washed with brine (50.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% HCl condition). From HNMR (EC7755-2-P1A) and LCMS (EC7755-2-P1B2) showed the product compound **1014** (6.20 g, 12.1 mmol, 60.9% yield, 77.3% purity) was obtained as light yellow solid.

LC-MS: EC7755-2-P1A1, RT = 0.354 min, m/z (M+1) = 396.5

LC-MS: EC7755-2-P1B2, RT = 0.360 min, m/z (M+1) = 396.4

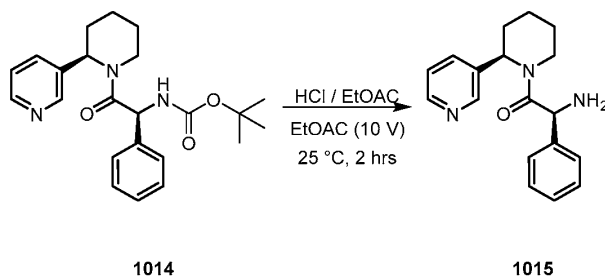
¹H-NMR: EC7755-2-P1A, 400 MHz, DMSO

δ 9.09 - 8.66 (m, 2H), 8.59 - 8.36 (m, 1H), 8.22 - 7.99 (m, 1H), 7.48 - 7.30 (m, 5H), 5.91 - 5.62 (m, 3H), 3.98 - 3.55 (m, 1H), 3.41 - 3.10 (m, 1H), 2.95 - 2.82 (m, 1H), 2.43 - 2.27 (m,

1H), 2.03 - 1.84 (m, 1H), 1.77 - 1.73 (m, 22H), 1.64 - 1.51 (m, 2H), 1.38 (s, 9H), 1.31 - 1.16 (m, 2H)

Example 12

5 *Synthesis of (S)-2-amino-2-phenyl-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethan-1-one*



To a solution of compound **1014** (6.20 g, 15.6 mmol, 1.00 *eq*) in EtOAc (60.0 mL) was added HCl/EtOAc (4 M, 39.2 mL, 10.0 *eq*) then the reaction mixture was stirred at 25 °C for 2 hrs. LC-MS (EC7755-4-P1A1) showed compound **1014** was consumed completely and the desired mass ($R_t = 0.198$ min, m/z (M+1) = 296.4) was detected. The reaction mixture was concentrated. The residue was used to next step without purification. From HNMR (EC7755-4-P1A) showed the product compound **1015** (6.00 g, crude, HCl) was obtained as yellow solid.

15 **LC-MS:** EC7755-4-P1A1, $R_t = 0.198$ min, m/z (M+1) = 296.4

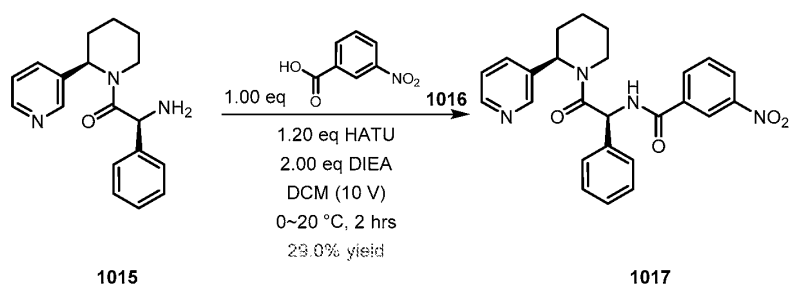
¹H-NMR: EC7755-4-P1A, 400 MHz, DMSO

δ 9.46 - 8.50 (m, 4H), 8.19 - 7.10 (m, 5H), 6.06 - 5.22 (m, 5H), 4.69 - 4.25 (m, 1H), 4.04 - 3.54 (m, 1H), 2.97 - 2.78 (m, 1H), 2.68 - 2.55 (m, 1H), 2.43 - 2.30 (m, 1H), 1.67 - 1.53 (m, 1H), 1.45 - 1.17 (m, 2H)

20

Example 13

Synthesis of 3-nitro-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide



To a solution of compound **1016** (3.40 g, 20.3 mmol, 1.02 *eq*) in DCM (40 mL) was added DIEA (5.19 g, 40.2 mmol, 7.00 mL, 2.01 *eq*) and HATU (9.10 g, 23.9 mmol, 1.20 *eq*) at 0 °C stirred for 30 min, then the compound **1015** (5.90 g, 19.9 mmol, 1.00 *eq*) was added to the solution, then the reaction mixture was stirred at 20 °C for 2 hrs. LCMS (EC7755-6-P1A1) showed the compound **1015** was consumed and the desired mass ($R_t = 0.350$ min, m/z ($M+1$) = 445.4) was detected. The reaction mixture was diluted with EtOAc (150 mL). The organic layer was washed with brine (50.0 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*10 μm ; mobile phase: [water(HCl)-ACN]; B%: 20%-50%, 20min). From HNMR (EC7755-6-P1A) and LCMS (EC7755-6-P1C1) showed the product compound **1017** (3.00 g, 5.79 mmol, 29.0% yield, 85.8% purity) was obtained as white solid.

LC-MS: EC7755-6-P1A1, $R_t = 0.350$ min, m/z ($M+1$) = 445.4

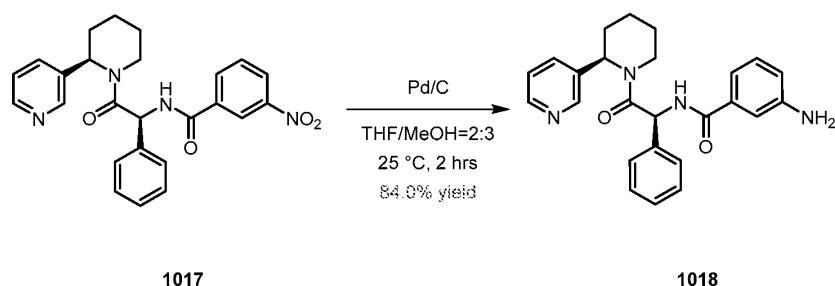
LC-MS: EC7755-6-P1C1, $R_t = 0.351$ min, m/z ($M+1$) = 445.5

$^1\text{H-NMR}$: EC7755-6-P1A, 400 MHz, DMSO

δ 9.46 (br d, $J = 6.0$ Hz, 1H), 8.85 - 8.75 (m, 2H), 8.51 - 8.31 (m, 3H), 8.11 - 8.00 (m, 1H), 7.78 (t, $J = 8.0$ Hz, 1H), 7.61 - 7.11 (m, 4H), 7.24 - 7.05 (m, 1H), 6.16 (br d, $J = 6.0$ Hz, 1H), 5.94 (br s, 1H), 4.58 - 4.35 (m, 1H), 3.90 (br d, $J = 13.0$ Hz, 2H), 3.07 - 2.87 (m, 1H), 2.47 - 2.34 (m, 1H), 1.87 - 1.69 (m, 1H), 1.46 (br d, $J = 10.6$ Hz, 1H), 1.38 - 1.15 (m, 2H), 0.87 - 0.57 (m, 1H)

Example 14

Synthesis of 3-amino-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide



To a solution of compound **1017** (3.00 g, 4.50 mmol, 1.00 *eq*) in MeOH (10.0 mL) and THF (15.0 mL) was added Pt/C (950 mg, 452 μ mol, 10% purity, 0.10 *eq*) under N₂ atmosphere. The suspension was degassed and purged with H₂ for **3** times. The mixture was stirred under H₂ (**25** Psi) at 25 °C for 2 hrs. LCMS (EC7755-8-P1A1) showed the compound **1017** was consumed and the desired mass (Rt = 0.269 min, m/z (M+1) = 415.4) was detected. The reaction mixture was filtered and the filtrate was concentrated. The residue was used to next step without purification. From HNMR (EC7755-8-P1A) and LCMS (EC7755-8-P1B1) showed the product compound **1018** (1.70 g, 3.78 mmol, 84.0% yield, 92.2% purity) was obtained as white solid.

LC-MS: EC7755-8-P1A1, Rt = 0.269 min, m/z (M+1) = 415.4

LC-MS: EC7755-8-P1B1, Rt = 0.277 min, m/z (M+1) = 415.4

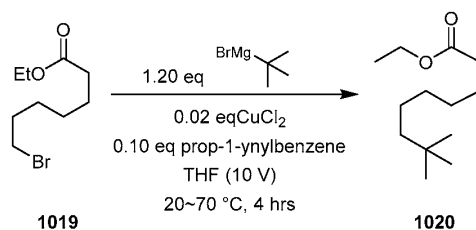
¹H-NMR: EC7755-8-P1A, 400 MHz, DMSO

δ 8.86 - 8.66 (m, 2H), 8.18 (br d, *J* = 7.6 Hz, 1H), 7.88 - 7.70 (m, 1H), 7.58 - 7.48 (m, 2H), 7.47 - 7.36 (m, 5H), 7.30 (br t, *J* = 8.0 Hz, 1H), 7.08 (br d, *J* = 7.2 Hz, 1H), 6.28 - 6.07 (m, 1H), 5.96 - 5.82 (m, 1H), 4.52 - 4.38 (m, 1H), 3.86 (br d, *J* = 12.4 Hz, 1H), 3.11 - 3.03 (m, 1H), 2.99 - 2.87 (m, 1H), 2.43 - 2.28 (m, 1H), 1.91 - 1.68 (m, 1H), 1.66 - 1.41 (m, 2H), 1.33 - 1.14 (m, 2H)

20

Example 15

Synthesis of ethyl 8,8-dimethylnonanoate



To a solution of compound **1019** (1.00 g, 4.22 mmol, 819 μ L, 1.00 *eq*) and CuCl_2 (11 mg, 81.8 μ mol, 1.94e-2 *eq*) and prop-1-ynylbenzene (50.0 mg, 430 μ mol, 1.02e-1 *eq*) in THF (1 mL) was added and bromo(*tert*-butyl)magnesium (1 M, 6.5 mL, 1.54 *eq*) slowly at 20 °C, then the reaction mixture was stirred at 70 °C for 4 hrs. TLC (Petroleum ether : Ethyl acetate = 3:1) indicated compound **1019** (R_f = 0.43) was consumed completely and two new spots (R_f = 0.43, R_f = 0.13) was formed. The reaction mixture was poured into saturated NH_4Cl aqueous solution (50.0 mL) and extracted with EA (25.0 mL*3). The combined organic layer was washed with brine (50.0 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was used to next step without purification. From HNMR (EC7755-22-P1A) showed the product compound **1020** (1.00 g, crude) was obtained as colorless oil.

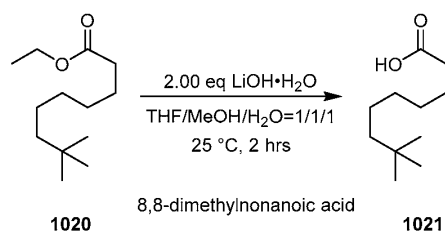
$^1\text{H-NMR}$: EC7755-22-P1A, 400 MHz, DMSO

δ 3.51 (s, 2H), 2.28 - 2.25 (m, 4H), 1.79 (br d, J = 7.2 Hz, 3H), 1.54 - 1.50 (m, 4H), 1.37 (br d, J = 7.2 Hz, 3H), 1.29 (br d, J = 7.2 Hz, 3H), 1.19 - 1.16 (m, 8H), 1.00 - 0.72 (m, 9H)

15

Example 16

Synthesis of 8,8-dimethylnonanoic acid



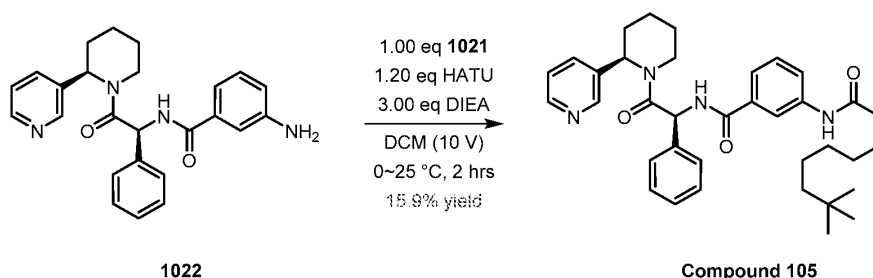
To a solution of compound **1020** (1.00 g, 4.67 mmol, 1.00 *eq*) in THF (10.0 mL), MeOH (10.0 mL) and H_2O (10.0 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (400 mg, 9.53 mmol, 2.04 *eq*), then the reaction mixture was stirred at 25 °C for 2 hrs. TLC (Dichloromethane : Methanol = 5:1) indicated compound **1020** (R_f = 0.24) was consumed completely and two new spots (R_f =0.38, 0.06) was formed. The reaction mixture was partitioned between ethyl acetate (50.0 mL) and water (25.0 mL). The organic phase was discarded, and the water phase as adjusted to pH = 3 with 1M HCl and diluted with ethyl acetate (50.0 mL), washed with brine (25.0 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was used to next step without purification. From HNMR (EC7755-24-P1A) showed the product compound **1021** (300 mg, crude) was obtained as colorless oil.

$^1\text{H-NMR}$: EC7755-24-P1A, 400 MHz, DMSO

δ 11.97 (br s, 1H), 2.21 - 2.16 (m, 6H), 1.83 - 1.74 (m, 2H), 1.50 - 1.47 (m, 5H), 1.27 (br d, J = 3.6 Hz, 5H), 0.84 (s, 9H)

Example 17

5 *Synthesis of 3-(8,8-dimethylnonanamido)-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide (Compound 105)*



To a solution of compound **1021** (100.00 mg, 536 μ mol, 1.11 *eq*) in DCM (1 mL) was added DIEA (192 mg, 1.49 mmol, 260 μ L, 3.09 *eq*) and HATU (220 mg, 578 μ mol, 1.20 *eq*) at 0 °C stirred for 30 min, compound **1022** (200 mg, 482 μ mol, 1.00 *eq*) was added to the solution, then the reaction mixture was stirred at 25 °C for 1.5 hrs. LCMS (EC7755-26-P1A1) showed the compound **1022** was consumed and the desired mass (R_t = 0.487 min, m/z ($M+1$) = 583.6) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex C18 150*25mm*10 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 54%-84%, 8min). From HNMR (EC7755-38-P1C), LCMS (EC775-38-P1C1) and HPLC (EC7755-38-P1C2) showed the product **Compound 105** (16.88 mg, 28.96 μ mol, 15.9% yield, 100% purity) was obtained as white solid.

LCMS: EC7755-26-P1A1, R_t = 0.487 min, m/z ($M+1$) = 583.6

LCMS: EC775-38-P1C1, R_t = 0.480 min, m/z ($M+1$) = 583.6

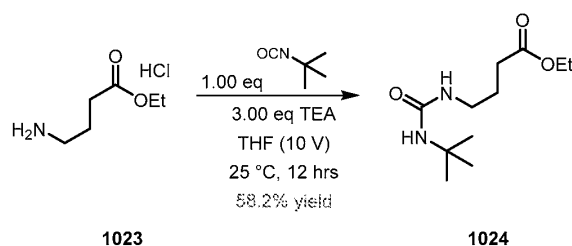
20 **HPLC:** EC7755-38-P1C2, R_t = 2.578 min, 100% purity

¹H-NMR: EC7755-38-P1C, 400 MHz, CHLOROFORM-*d*

δ 8.69 - 8.20 (m, 2H), 7.88 - 7.82 (m, 1H), 8.02 - 7.82 (m, 1H), 7.80 - 7.62 (m, 2H), 7.57 - 7.48 (m, 3H), 7.47 - 7.29 (m, 5H), 7.22 - 6.93 (m, 1H), 6.18 - 5.84 (m, 2H), 4.89 - 4.58 (m, 1H), 3.93 - 3.71 (m, 1H), 3.04 - 2.50 (m, 1H), 2.46 - 2.24 (m, 3H), 1.77 - 1.66 (m, 3H), 1.61 - 1.34 (m, 4H), 1.32 - 1.04 (m, 7H), 0.86 (s, 9H)

Example 18

Synthesis of ethyl 4-(3-(tert-butyl)ureido)butanoate

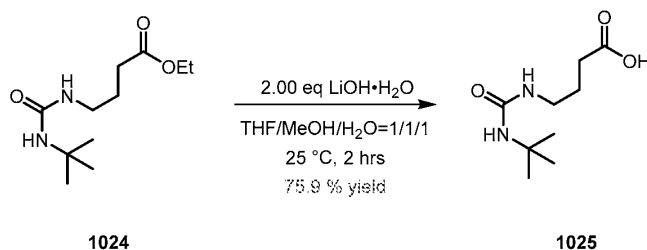


To a solution of compound **1023** (420 mg, 4.24 mmol, 500 uL, N/A purity, 1.42 *eq*) in THF (5.00 mL) was added TEA (900 mg, 8.89 mmol, 1.24 mL, 2.98 *eq*) and ethyl 4-aminobutanoate (500 mg, 2.98 mmol, N/A purity, 1.00. *eq*, HCl). The mixture was stirred at 25 °C for 12 hrs. LCMS (EC7606-21-P1A2) shows that compound **1023** was consumed, and the desired MS ($m/z = 231.1$, $R_t = 0.388$ min) was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 250*50mm*10 um; mobile phase: [water(HCl)-ACN]; B%: 20%-50%, 20min). Compound **1024** (400 mg, 1.74 mmol, 58.2% yield) was obtained as yellow oil

LC-MS: EC7606-21-P1A2, $R_t = 0.388$ min, m/z (M+1) = 231.1

Example 19

Synthesis of 4-(3-(tert-butyl)ureido)butanoic acid

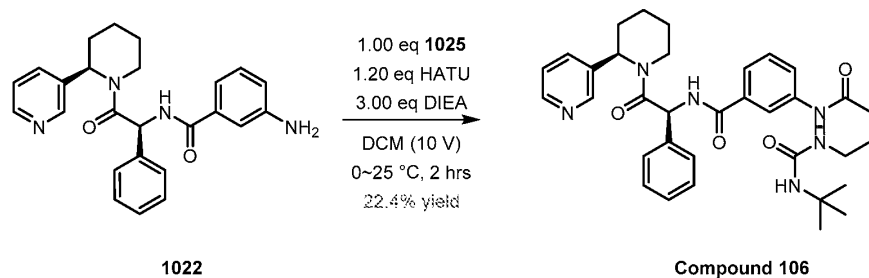


To a solution of compound **1024** (400 mg, 1.95 mmol, N/A purity, 1.00 *eq*) in H₂O (1.5 mL), MeOH (1.5 mL) THF (1.5 mL) was added LiOH·H₂O (165 mg, 3.93 mmol, 2.01 *eq*). The mixture was stirred at 25 °C for 2 hrs. LCMS (EC7606-25-P1A1) shows that compound **1024** was consumed, and the desired MS ($m/z = 203.3$, $R_t = 0.216$ min) was detected. The mixture was poured into the water (50.0 mL), adjusted to pH = 2-3 with 1M HCl, extracted with EtOAc (10.0 mL * 3). The combined organic layers were washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used to next step without purification. Compound **1025** (300 mg, 1.48 mmol, 75.9% yield) was obtained as white oil.

LC-MS: EC7606-25-P1A1, RT = 0.216 min, m/z (M+1) = 203.3

Example 20

Synthesis of 3-(4-(3-(tert-butyl)ureido)butanamido)-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide (Compound 106)



To a solution of compound **1025** (50 mg, 247 μmol , 1.02 *eq*) in DCM (1 mL) was added HATU (110 mg, 289 μmol , 1.20 *eq*) and DIEA (66.78 mg, 516 μmol , 90 μL , 2.14 *eq*) and compound **1022** (100 mg, 241 μmol , 1.00 *eq*) stirred at 0 $^\circ\text{C}$ for 30 min, then the reaction mixture was stirred at 25 $^\circ\text{C}$ for 1.5 hrs. LCMS (EC7755-13-P1A1) showed the compound **1022** was consumed and the desired mass (R_t = 0.364 min, m/z (M+1) = 599.6) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (HCl)-ACN]; B%: 20%-50%, 10 min). From HNMR (EC7755-13-P1B), LCMS (EC7755-13-P1C1) and HPLC (EC7755-13-P1C2) showed the product **Compound 106** (33.58 mg, 54.1 μmol , 22.4% yield, 96.5% purity) was obtained as off-white solid.

LCMS: EC7755-13-P1A1, R_t = 0.364 min, m/z (M+1) = 599.6

LCMS: EC7755-13-P1C1, R_t = 0.374 min, m/z (M+1) = 599.6

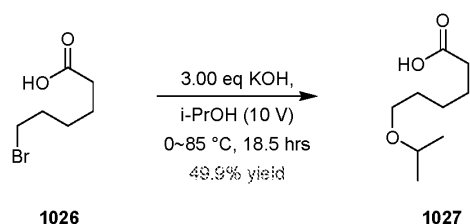
HPLC: EC7755-13-P1C2, R_t = 1.706 min, 96.5% purity

$^1\text{H-NMR}$: EC7755-13-P1B, 400 MHz, DMSO

δ 10.08 (s, 1H), 8.78 (br d, J = 6.4 Hz, 1H), 8.58 - 8.38 (m, 1H), 8.09 - 7.95 (m, 1H), 7.81 (br d, J = 8.8 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.58 - 7.33 (m, 7H), 7.28 - 7.05 (m, 1H), 6.12 (d, J = 7.2 Hz, 1H), 5.93 - 5.76 (m, 1H), 5.72 - 5.52 (m, 2H), 4.06 - 3.74 (m, 1H), 3.07 - 2.93 (m, 2H), 2.90 (br s, 1H), 2.40 - 2.26 (m, 3H), 1.71 - 1.56 (m, 3H), 1.48 - 1.26 (m, 2H), 1.20 (s, 9H), 0.68 - 0.43 (m, 1H)

Example 21

Synthesis of 6-isopropoxyhexanoic acid



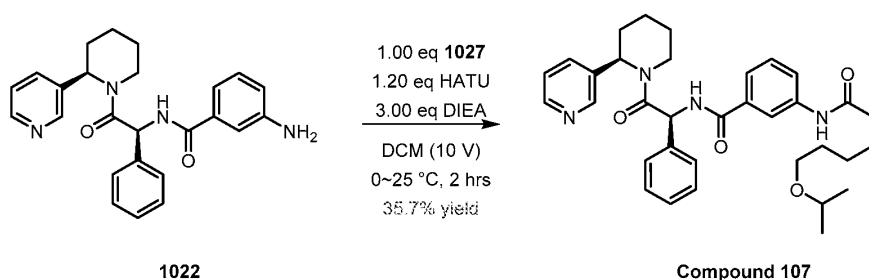
To a solution of KOH (432 mg, 7.70 mmol, 3.00 eq) in i-PrOH (3.93 g, 65.3 mmol, 5.00 mL, 25.5 eq) stirred at 0 °C for 30 min. Then the solution of compound **1026** (500 mg, 2.56 mmol, 1.00 eq) in i-PrOH (5.00 mL) was added and the resulting solution was stirred at 85 °C for 18 hrs. TLC (Petroleum ether : Ethyl acetate = 3:1) indicated compound **1026** (R_f = 0.24) was consumed completely and **two new spots** (R_f = **0.43**, R_f = **0.10**) formed. The reaction mixture was concentrated to remove i-PrOH, then the residue was partitioned between ethyl acetate (100 mL) and water (50.0 mL). The organic phase was separated, washed with brine (50.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used to the next step without purification. From HNMR (EC7755-20-P1A) showed the product compound **1027** (223 mg, 1.28 mmol, 49.9% yield) was obtained as colorless oil.

¹H-NMR: EC7755-20-P1A, 400 MHz, DMSO

δ 11.99 (br s, 1H), 5.88 - 5.66 (m, 1H), 5.08 - 4.91 (m, 1H), 3.52 - 3.44 (m, 1H), 3.32 - 3.29 (m, 2H), 2.25 - 2.14 (m, 3H), 2.06 - 1.96 (m, 1H), 1.62 - 1.39 (m, 6H), 1.33 - 1.22 (m, 4H), 1.05 (d, J = 6.0 Hz, 6H)

Example 22

Synthesis of 3-(6-isopropoxyhexanamido)-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide (Compound 107)



20

To a solution of compound **1027** (42 mg, 241.05 μ mol, 9.99e-1 eq) in DCM (1 mL) was added DIEA (96.4 mg, 746 μ mol, 130 μ L, 2.09 eq) and HATU (110 mg, 289 μ mol, 1.20eq) at 0 °C stirred for 30 min, then compound **1022** (100 mg, 241 μ mol, 1.00 eq) was added to the solution, the reaction mixture was stirred at 25 °C for 1.5 hrs. LCMS (EC7755-

21-P1A1) showed the compound **1022** was consumed and the desired mass ($R_t = 0.399$ min, m/z ($M+1$) = 571.8) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5um; mobile phase: [water(HCl)-ACN]; B%: 17%-47%, 10min). From HNMR (EC7755-21-P1A), LCMS

5 (EC7755-21-P1B1) and HPLC (EC7755-21-P1B2) showed the product **Compound 107**

(51.44 mg, 86.0 μ mol, 35.7% yield, 95.5% purity) was obtained as colorless oil.

LCMS: EC7755-21-P1A1, $R_t = 0.399$ min, m/z ($M+1$) = 571.8

LCMS: EC7755-21-P1B1, $R_t = 0.402$ min, m/z ($M+1$) = 571.4

HPLC: EC7755-21-P1B2, $R_t = 1.940$ min, 96.5% purity

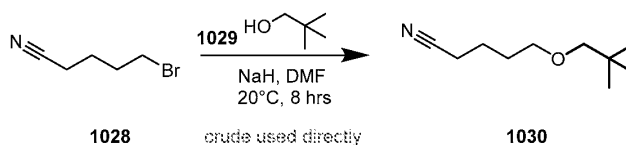
10 **¹H-NMR:** EC7755-21-P1A, 400 MHz, DMSO

δ 10.27 - 9.96 (m, 1H), 9.12 - 8.72 (m, 3H), 8.64 - 8.38 (m, 1H), 8.16 - 7.99 (m, 2H), 7.94 - 7.65 (m, 2H), 7.61 - 7.48 (m, 3H), 7.48 - 7.29 (m, 4H), 6.26 - 6.08 (m, 1H), 5.97 - 5.79 (m, 1H), 4.58 - 4.40 (m, 1H), 3.89 (br d, $J = 14.0$ Hz, 2H), 3.49 (br d, $J = 6.0$ Hz, 1H), 3.32 (t, $J =$

15 6.4 Hz, 3H), 3.02 - 2.90 (m, 1H), 2.43 - 2.29 (m, 3H), 1.65 - 1.53 (m, 3H), 1.52 - 1.42 (m, 3H), 1.37 - 1.21 (m, 4H), 1.05 (d, $J = 6.0$ Hz, 6H)

Example 23

Synthesis of 5-(neopentyloxy)pentanenitrile



20 NaH (300 mg, 7.50 mmol, 60.0% purity, 1.22 eq) was suspended in DMF (20.0 mL) at 0°C under compound **1029** (816 mg, 9.26 mmol, 998 μ L, 1.50 eq) was added over approx. 2 minutes. After stirring for a further 15 minutes, compound **1028** (1.00 g, 6.17 mmol, 1.00 eq) was introduced dropwise. Following complete addition, the resulting mixture was warmed to 20 °C and stirred at 20 °C for 8 hrs under N₂. TLC (Petroleum ether/Ethyl acetate = 3/1) showed the compound **1028** ($R_f = 0.70$) was consumed completely and one major new spot ($R_f = 0.15$) was detected. The reaction mixture was quenched with saturated NH₄Cl (50.0 mL). When suspended solids had dissolved, the solution was extracted with ethyl acetate (3 x 60.0 mL). The organic phases were dried (Na₂SO₄), filtered and concentrated under vacuum to get a residue. Compound **1030** (250 mg, crude) was obtained as a light

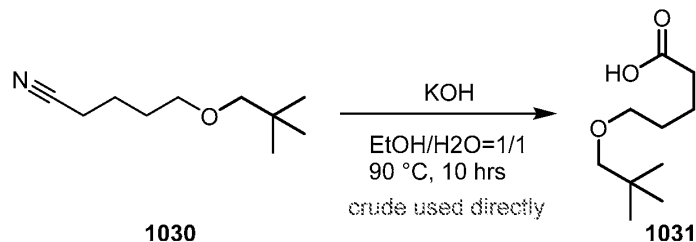
25 = 3/1) showed the compound **1028** ($R_f = 0.70$) was consumed completely and one major new spot ($R_f = 0.15$) was detected. The reaction mixture was quenched with saturated NH₄Cl (50.0 mL). When suspended solids had dissolved, the solution was extracted with ethyl acetate (3 x 60.0 mL). The organic phases were dried (Na₂SO₄), filtered and concentrated under vacuum to get a residue. Compound **1030** (250 mg, crude) was obtained as a light

30 yellow oil and confirmed by HNMR (EC9573-6-P1H).

¹H-NMR: EC9753-6-P1H, 400 MHz, DMSO

δ = 3.39 (t, J = 5.6 Hz, 2H), 3.02 (s, 2H), 2.61 (s, 1H), 2.57 (s, 1H), 2.33 - 2.30 (m, 2H), 1.63 - 1.60 (m, 2H), 0.93 - 0.84 (m, 9H).

Example 24

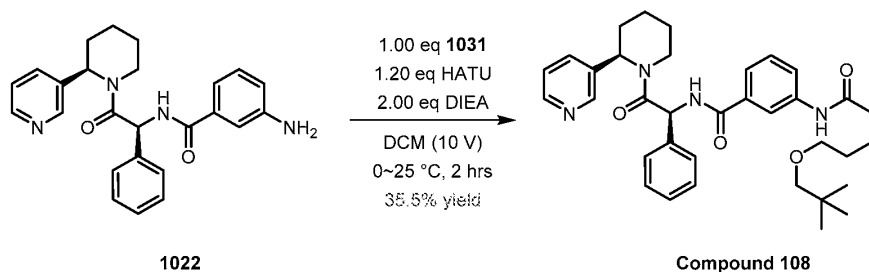
Synthesis of 5-(neopentyloxy)pentanoic acid

Compound **1030** (280 mg, 1.65 mmol, 1.00 eq) in EtOH (1.00 mL) and H₂O (1.00 mL) was added KOH (371 mg, 6.62 mmol, 4.00 eq). The mixture was stirred at 85 °C for 3 hrs under N₂. LCMS (EC9573-9-P1A2) showed that compound **1030** was consumed, and the desired MS (m/z = 187.1, R_t = 0.613 min) was detected. Upon cooling, all the volatile materials were evaporated and the solid was suspended in water (10.0 ml), the water layers were washed with MBTE (15.0 mL x 2), the pH of the solution was adjusted to 2 with HCl (1M) at 0 °C. The resulting solution was extracted with Ethyl acetate (10.0 mL x 3), dried over Na₂SO₄ and concentrated under vacuum. The product used into the next step without further purification. Compound **1031** (60.0 mg, crude) was obtained as a light yellow oil and confirmed by LCMS (EC9573-9-P1B).

LCMS: EC9573-9-P1A2, m/z (M-1) = 187.1

LCMS: EC9573-9-P1B, m/z (M-1) = 187.1

Example 25

Synthesis of 3-(5-(neopentyloxy)pentanamido)-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide (Compound 108)

To a solution of compound **1031** (54.5 mg, 289 μ mol, 1.00 eq) in DCM (1.00 mL) was added HATU (132 mg, 347 μ mol, 1.20 eq) and DIEA (74.8 mg, 579 μ mol, 101 μ L, 2.00 eq) at 0 °C stirred for 30 min, then was added compound **1022** (120 mg, 289 μ mol, 1.00 eq) to the solution and stirred at 25 °C for 5 hrs. LCMS (EC9573-10-P1A) showed the compound **1022** was consumed completely and 54.9% of desired mass (R_t = 0.429) was detected. The reaction mixture was partitioned between ethyl acetate (6.00 mL x 2) and water (4.00 mL). The organic phase was separated, washed with brine (5.00 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10 μ m; mobile phase: [water(

5 compound **1022** was consumed completely and 54.9% of desired mass (R_t = 0.429) was detected. The reaction mixture was partitioned between ethyl acetate (6.00 mL x 2) and water (4.00 mL). The organic phase was separated, washed with brine (5.00 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10 μ m; mobile phase: [water(

10 NH_4HCO_3)-ACN];B%: 48%-78%,10min). The fraction was lyophilized. **Compound 108** (60.6 mg, 103 μ mol, 35.5% yield, 99.2% purity) was obtained as a white solid and confirmed by LCMS (EC9573-10-P1C)(R_t = 2.182, 98.5% purity) and HPLC (EC9573-10-P1CP)(R_t = 2.139 min, 99.2% purity), HNMR (EC9573-10-P1CH).

LCMS: EC9573-10-P1A, R_t = 0.429 min, m/z ($M+1$) = 585.9

15 **LCMS:** EC9573-10-P1C, R_t = 2.182 min, m/z ($M+1$) = 585.4

HPLC: EC9573-10-P1CP, R_t = 2.139 min, 99.2% purity

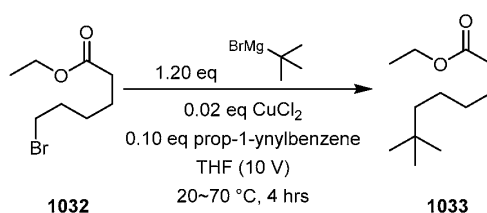
^1H NMR: EC9573-10-P1DH1, 400 MHz, DMSO

δ = 10.2 - 9.83 (m, 1H), 9.06 - 7.21 (m, 14H), 6.31 - 5.94 (m, 1H), 5.91 - 5.15 (m, 1H), 4.57 - 3.86 (m, 1H), 3.38 (br t, J = 6.2 Hz, 3H), 3.01 (s, 2H), 2.72 - 2.56 (m, 1H), 2.41 - 2.27 (m, 3H), 1.70 - 1.49 (m, 6H), 1.39 - 1.12 (m, 2H), 0.86 (s, 9H).

20

Example 26

Synthesis of ethyl 7,7-dimethyloctanoate



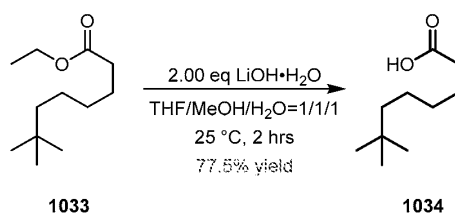
25 To a solution of compound **1032** (3.00 g, 13.4 mmol, 2.38 mL, 1.00 eq) in THF (10.0 mL) was added bromo(tert-butyl)magnesium (1 M, 18 mL, 1.34 eq) at 20 °C, then CuCl_2 (366 mg, 2.72 mmol, 2.02e-1 eq) and prop-1-ynylbenzene (160 mg, 1.38 mmol, 1.02e-1 eq) was added to the solution, then the reaction mixture was stirred at 70 °C for 4 hrs. TLC (Petroleum ether : Ethyl acetate = 2:1) showed the compound **1032** (R_f = 0.24) was

30 consumed, and two new spots (R_f = 0.43, 0.11) was formed. The reaction mixture was

poured into saturated NH_4Cl aqueous solution (50.0 mL) and extracted with EA (50.0 mL*3). The combined organic layer was washed with brine (50.0 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was used to next step without purification. Compound **1033** (3.00 g, crude) was obtained as a colorless oil.

5

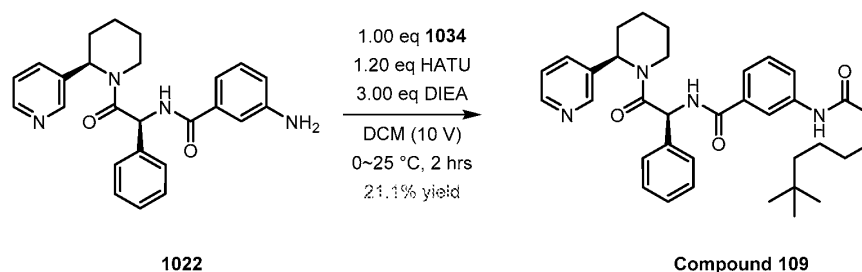
Example 27

Synthesis of 7,7-dimethyloctanoic acid

To a solution of compound **1033** (3.00 g, 14.98 mmol, 1.00 *eq*) in THF (10.0 mL) and H_2O (10.0 mL) was added $\text{LiOH}\cdot\text{H}_2\text{O}$ (1.89 g, 44.93 mmol, 2.00 *eq*) then the reaction mixture was stirred at 25 °C for 2 hrs. TLC (Dichloromethane : Methanol = 10:1) indicated the compound **1033** was consumed and two new spots (R_f = 0.13, 0.02) was formed. The reaction mixture was partitioned between ethyl acetate (50.0 mL) and water (25.0 mL). The organic phase was discarded, and the water phase as adjusted to pH = 3 with 1M HCl and diluted with ethyl acetate (50.0 mL), washed with brine (25.0 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was used to next step without purification. Compound **1034** (2.00 g, 11.6 mmol, 77.5% yield) was obtained as colorless oil.

20

Example 28

Synthesis of 3-(7,7-dimethyloctanamido)-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide (Compound 109)

To a solution of compound **1034** (150 mg, 870 μmol , 1.00 *eq*) in DCM (3.00 mL) was added DIEA (111 mg, 861 μmol , 150 μL , 3.00 *eq*) and HATU (110 mg, 289 μmol , 1.20

25

eq) at 0 °C stirred for 30 min, compound **1022** (100 mg, 241 μ mol, 1.00 *eq*) was added to the solution, then the reaction mixture was stirred at 25 °C for 1.5 hrs. LCMS (EC7755-41-P1A1) showed the compound **1022** was consumed and the desired mass ($R_t = 0.474$ min, m/z ($M+1$) = 569.6) was detected. The reaction mixture was concentrated. The residue was

5 purified by prep-HPLC (column: Welch Xtimate C18 150*25mm*5 μ m; mobile phase: [water (HCl)-ACN]; B%: 31%-61%, 10 min). From HNMR (EC7755-41-P1C), LCMS (EC7755-41-P1C1) and HPLC (EC7755-41-P1C2) showed the product **Compound 109** (15.19 mg, 50.95 μ mol, 21.1% yield, 96.6% purity) was obtained as white solid.

LCMS: EC7755-41-P1A1, $R_t = 0.474$ min, m/z ($M+1$) = 569.6

10 **LCMS:** EC7755-41-P1C1, $R_t = 0.472$ min, m/z ($M+1$) = 569.6

HPLC: EC7755-41-P1C2, $R_t = 2.407$ min, 96.6% purity

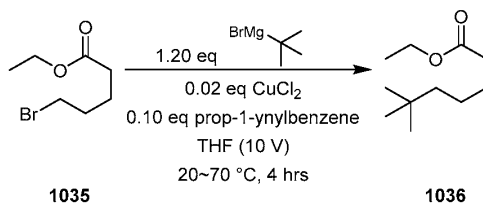
¹H-NMR: EC7755-41-P1C, 400 MHz, DMSO

δ 10.06 - 9.94 (m, 1H), 8.92 - 8.62 (m, 1H), 8.57 - 8.45 (m, 1H), 8.24 - 8.00 (m, 1H), 7.98 - 7.64 (m, 2H), 7.60 - 7.45 (m, 3H), 7.44 - 7.31 (m, 4H), 7.30 - 7.05 (m, 1H), 6.41 - 6.02 (m,

15 1H), 6.01 - 5.57 (m, 1H), 4.53 - 3.75 (m, 1H), 3.02 - 2.60 (m, 1H), 2.39 - 2.26 (m, 3H), 1.91 - 1.50 (m, 4H), 1.41 (br s, 1H), 1.36 - 1.19 (m, 6H), 1.15 (br d, $J = 8.6$ Hz, 2H), 0.85 (s, 9H), 0.75 - 0.44 (m, 1H)

Example 29

20 Synthesis of ethyl 6,6-dimethylheptanoate



To a solution of compound **1035** (1.00 g, 4.78 mmol, 763 μ L, 1.00 *eq*) in THF (10.0 mL) was added bromo(tert-butyl)magnesium (1 M, 6 mL, 1.25 *eq*) at 20 °C, then CuCl_2 (130 mg, 967 μ mol, 2.02e-1 *eq*) and prop-1-ynylbenzene (56.0 mg, 482 μ mol, 1.01e-1 *eq*) was

25 added to the solution, then the reaction mixture was stirred at 70 °C for 4 hrs. TLC (Petroleum ether : Ethyl acetate = 2:1) indicated compound **1035** ($R_f = 0.24$) was consumed completely and two new spots ($R_f = 0.09, 0.43$) was formed. The reaction mixture was poured into saturated NH_4Cl aqueous solution (50.0 mL) and extracted with EA (50.0 mL*3). The combined organic layer was washed with brine (50.0 mL), dried over Na_2SO_4 , filtered

30 and concentrated. The residue was used to next step without purification. From HNMR

(EC7755-32-P1A) showed the product compound **1036** (1.00 g, crude) was obtained as a brown oil.

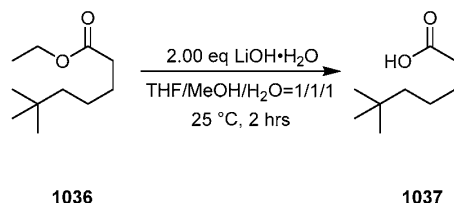
¹H-NMR: EC7755-32-P1A, 400 MHz, DMSO

δ 2.03 (s, 3H), 1.81 (br s, 4H), 1.64 (s, 4H), 1.53 - 1.44 (m, 2H), 1.18 (s, 9H), 0.84 (s, 9H)

5

Example 30

Synthesis of 6,6-dimethylheptanoic acid

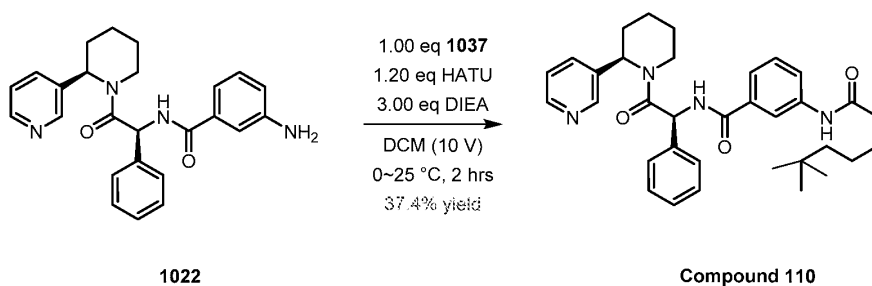


To a solution of compound **1036** (1.00 g, 5.37 mmol, 1.00 *eq*) in THF (10.0 mL) and
 10 MeOH (10.0 mL) and H₂O (10.0 mL) was added LiOH·H₂O (455 mg, 10.8 mmol, 2.02 *eq*),
 then the reaction mixture was stirred at 25 °C for 2 hrs. TLC (Dichloromethane : Methanol =
 10:1) indicated compound **1036** (R_f = 0.24) was consumed completely and two new spots (R_f
 = 0.06, R_f = 0.40) was formed. The reaction mixture was partitioned between ethyl acetate
 (50.0 mL) and water (25.0 mL). The organic phase was discarded, and the water phase as
 15 adjusted to pH = 3 with 1M HCl and diluted with ethyl acetate (50.0 mL), washed with brine
 (25.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a
 residue. The residue was used to next step without purification. Compound **1037** (200 mg,
 1.26 mmol, crude) was obtained as a colorless oil.

20

Example 31

3-(6,6-dimethylheptanamido)-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide (Compound 110)



To a solution of compound **1037** (150 mg, 947 μmol , 1.00 *eq*) in CH_2Cl_2 (2.00 mL) was added DIEA (89.0 mg, 688 μmol , 120 μL , 3.00 *eq*) and HATU (120 mg, 315 μmol , 1.20 *eq*) stirred at 0 °C for 30 min, compound **1022** (100 mg, 241 μmol , 1.00 *eq*) was added to the mixture, then the reaction mixture was stirred at 25 °C for 1.5 hrs. LCMS (EC8870-3-P1A1) showed that compound **10227** was consumed and the desired mass ($R_t = 0.450$ min, m/z ($M+1$) = 555.7) was detected. The reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: Phenomenex C18 150*25mm*10 μm ; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 46%-76%, 8 min). From HNMR (EC7755-37-P1B), LCMS (EC7755-37-P1C1) and HPLC (EC7755-37-P1C2) showed the product **Compound 110** (41.97 mg, 75.66 μmol , 37.4% yield, 99.7% purity) was obtained as white solid.

LCMS: EC8870-3-P1A1, $R_t = 0.450$ min, m/z ($M+1$) = 555.7

LCMS: EC7755-37-P1C1, $R_t = 0.446$ min, m/z ($M+1$) = 555.5

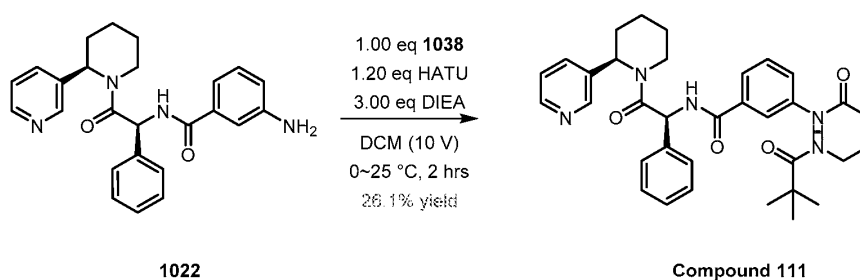
HPLC: EC7755-37-P1C2, $R_t = 2.322$ min, 99.7% purity

^1H -NMR: EC7755-37-P1B, 400 MHz, DMSO

δ 10.05 - 9.84 (m, 1H), 8.92 - 8.72 (m, 1H), 8.67 - 8.45 (m, 1H), 8.42 - 8.16 (m, 1H), 8.07 - 7.94 (m, 1H), 7.71 (br d, $J = 7.2$ Hz, 1H), 7.80 (br t, $J = 9.2$ Hz, 1H), 7.60 - 7.49 (m, 3H), 7.47 - 7.24 (m, 5H), 6.24 - 6.09 (m, 1H), 6.02 - 5.78 (m, 1H), 4.07 - 3.72 (m, 1H), 2.86 (br s, 1H), 2.70 - 2.59 (m, 1H), 2.42 - 2.26 (m, 3H), 1.64 - 1.55 (m, 3H), 1.47 - 1.39 (m, 1H), 1.35 - 1.18 (m, 8H), 1.14 (br d, $J = 8.8$ Hz, 2H), 0.84 (s, 9H), 0.63 - 0.36 (m, 1H)

Example 32

Synthesis of N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)-3-(4-pivalamidobutanamido)benzamide (Compound 111)



To a solution of compound **1038** (4-pivalamidobutanoic acid) (46 mg, 245 μmol , 1.02 *eq*) in DCM (1 mL) was added HATU (110 mg, 289 μmol , 1.20 *eq*) and DIEA (66.7 mg, 516 μmol , 90 μL , 2.14 *eq*) and compound **1022** (100 mg, 241 μmol , 1.00 *eq*) stirred at 0 °C for 30 min, then the reaction mixture was stirred at 25 °C for 1.5 hrs. LCMS (EC7755-14-P1A1)

showed the compound **1022** was consumed and the desired mass ($R_t = 0.361$ min, m/z ($M+1$) = 584.5) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (HCl)-ACN]; B%: 18%-48%, 10 min). From HNMR (EC7755-14-P1B), LCMS (EC7755-14-P1C1) and HPLC (EC7755-14-P1C2) showed the product **Compound 111** (37.63 mg, 63.1 umol, 26.1% yield, 97.8% purity) was obtained as white solid.

LCMS: EC7755-14-P1A1, $R_t = 0.361$ min, m/z ($M+1$) = 584.5

LCMS: EC7755-14-P1C1, $R_t = 0.362$ min, m/z ($M+1$) = 584.6

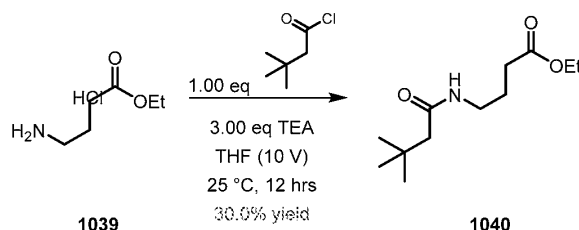
HPLC: EC7755-14-P1C2, $R_t = 1.686$ min, 99.8% purity

$^1\text{H-NMR}$: EC7755-14-P1B, 400 MHz, DMSO

δ 10.13 - 9.96 (m, 1H), 8.92 - 8.72 (m, 1H), 8.63 - 8.46 (m, 1H), 8.07 - 7.93 (m, 1H), 7.87 - 7.77 (m, 1H), 7.71 (br d, $J = 7.2$ Hz, 1H), 7.58 - 7.34 (m, 8H), 7.29 - 7.06 (m, 1H), 6.24 - 6.07 (m, 1H), 5.95 - 5.59 (m, 1H), 4.54 - 3.73 (m, 1H), 3.16 - 3.00 (m, 2H), 2.98 - 2.58 (m, 1H), 2.45 - 1.84 (m, 4H), 1.78 - 1.67 (m, 2H), 1.59 (br s, 1H), 1.51 - 1.37 (m, 1H), 1.35 - 1.17 (m, 2H), 1.08 (s, 9H), 0.74 - 0.31 (m, 1H)

Example 33

Synthesis of ethyl 4-(3,3-dimethylbutanamido)butanoate



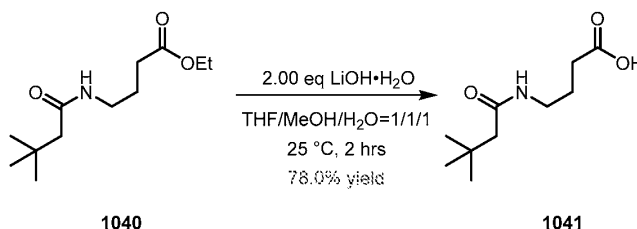
To a solution of compound **1039** (500 mg, 3.81 mmol, 1.00 eq) in THF (5.00 mL) was added TEA (1.16 g, 11.5 mmol, 1.6 mL, 3.02 eq) and 3,3-dimethylbutanoyl chloride (581 mg, 4.32 mmol, 600 uL, 1.13 eq), the reaction mixture was stirred at 25 °C for 12 hrs. LC-MS (EC7755-1-P1A1) showed the compound **1039** was consumed and the desired mass ($RT = 0.355$ min, m/z ($M+1$) = 230.5) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Waters xbridge 150*25mm 10um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 18%-48%, 8 min). From LCMS (EC7755-1-P1B1) showed the product compound **1040** (280 mg, 1.22 mmol, 30.0% yield, 100% purity) was obtained as colorless oil.

LC-MS: EC7755-1-P1A1, $RT = 0.355$ min, m/z ($M+1$) = 230.5

LC-MS: EC7755-1-P1B1, RT = 0.339 min, m/z (M+1) = 230.5

Example 34

Synthesis of 4-(3,3-dimethylbutanamido)butanoic acid



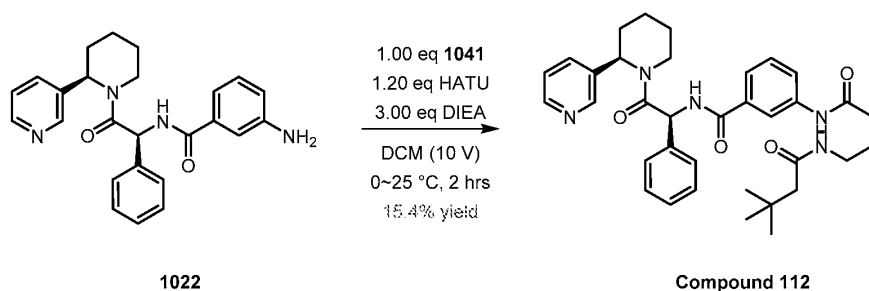
To a solution of compound **1040** (280 mg, 1.22 mmol, 1.00 *eq*) in THF (1 mL), MeOH (1 mL) and H₂O (1 mL) was added LiOH·H₂O (103 mg, 2.45 mmol, 2.01 *eq*), then the reaction mixture was stirred at 25 °C for 2 hrs. LCMS (EC7755-3-P1A1) showed the compound **1040** was consumed and the desired mass (RT = 0.268 min, m/z (M+1) = 202.4) was detected. The reaction mixture was partitioned between ethyl acetate (50.0 mL) and water (25.0 mL). The organic phase was separated, washed with brine (25.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used to next step without purification. From LCMS (EC7755-3-P1B1) showed the product compound **1041** (200 mg, 952 umol, 78.0% yield, 95.8% purity) was obtained as colorless oil.

LC-MS: EC7755-3-P1A1, RT = 0.268 min, m/z (M+1) = 202.4

LC-MS: EC7755-3-P1B1, RT = 0.269 min, m/z (M+1) = 202.4

Example 35

Synthesis of 3-(4-(3,3-dimethylbutanamido)butanamido)-N-((S)-2-oxo-1-phenyl-2-((R)-2-(pyridin-3-yl)piperidin-1-yl)ethyl)benzamide (Compound 112)



To a solution of compound **1041** (50 mg, 248 umol, 1.03 *eq*) in DCM (2.00 mL) was added DIEA (66.7 mg, 516 umol, 90 uL, 2.14 *eq*) and HATU (110 mg, 289 umol, 1.20 *eq*) at

0 °C stirred for 30 min, then compound **1022** (100 mg, 241 umol, 1.00 eq) was added to the reaction mixture and then the reaction was stirred at 25 °C for 1.5 hrs. LCMS (EC7755-9-P1A1) showed the compound **1022** was consumed and the desired mass (Rt = 0.368 min, m/z (M+1) = 598.5) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (HCl)-ACN];B%: 20%-50%, 10 min). From HNMR (EC7755-9-P1C), LCMS (EC7755-9-P1D1) and HPLC (EC7755-9-P1D2) showed the product **Compound 112** (22.78 mg, 37.04 umol, 15.4% yield, 97.2% purity) was obtained as white solid.

LCMS: EC7755-9-P1A1, Rt = 0.368 min, m/z (M+1) = 598.5

10 **LCMS:** EC7755-9-P1D1, Rt = 0.379 min, m/z (M+1) = 598.5

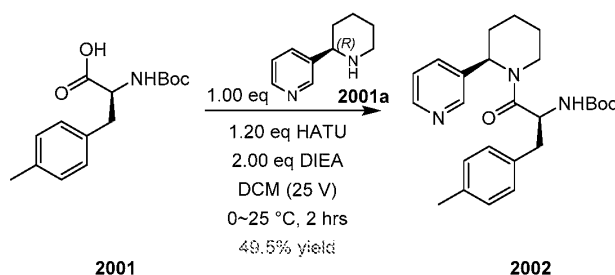
HPLC: EC7755-9-P1D2, $R_t = 1.760$ min, 97.2% purity

¹H-NMR: EC7755-9-P1C, 400 MHz, DMSO

15 $\delta = 10.30 - 10.04$ (m, 1H), 8.85 - 8.70 (m, 2H), 8.25 (br s, 1H), 8.07 (br s, 1H), 7.87 - 7.78 (m, 2H), 7.54 (br d, $J = 6.4$ Hz, 2H), 7.44 (br d, $J = 6.4$ Hz, 3H), 7.38 - 7.33 (m, 3H), 7.20 (br d, $J = 7.2$ Hz, 2H), 6.22 - 5.79 (m, 2H), 3.91 - 3.84 (m, 1H), 3.10 - 3.04 (m, 2H), 2.97 - 2.88 (m, 1H), 2.73 - 2.62 (m, 1H), 2.33 (br t, $J = 7.6$ Hz, 2H), 1.95 (s, 2H), 1.79 - 1.59 (m, 3H), 1.50 - 1.38 (m, 1H), 1.35 - 1.20 (m, 2H), 0.94 (s, 9H), 0.68 - 0.54 (m, 1H)

Example 36

20 *Synthesis of tert-butyl ((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(p-tolyl)propan-2-yl)carbamate*



To a solution of compound **2001** (200 mg, 716 μmol , 1.00 *eq*) and compound **2001a** (120 mg, 739 μmol , 1.03 *eq*) in DCM (5.0 mL) was added DIEA (185 mg, 1.43 mmol, 249 μL , 2.00 *eq*) and HATU (327 mg, 860 μmol , 1.20 *eq*) at 0°C, then the mixture was stirred at 25 °C for 2 hrs. LCMS showed compound **2001** was consumed and desired MS ($R_t = 0.428$ min, $m/z = 424.2$) was detected. The reaction solution was concentrated. The residue was purified by pre-HPLC (column: Welch Xtimate C18 150*25mm*5 μm ; mobile phase: [water

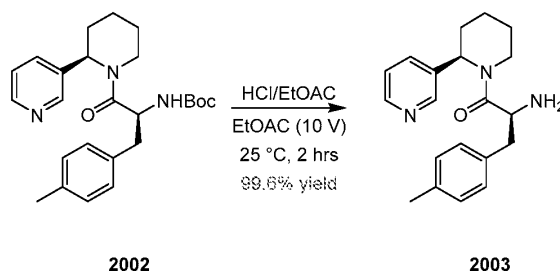
(TFA)-ACN]; B%: 25%-55%, 10min). Compound **2002** (150 mg, 354 μ mol, 49.5% yield) was obtained as a white solid.

LC-MS (reaction mixture): R_t = 0.428 min, m/z = 424.2

5

Example 37

Synthesis of (S)-2-amino-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(p-tolyl)propan-1-one



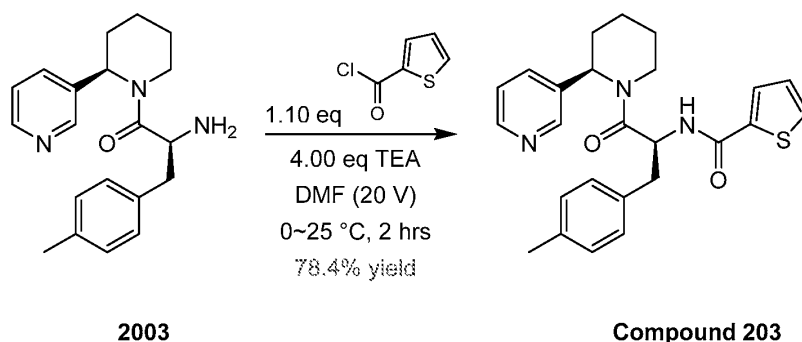
To a solution of compound **2002** (150 mg, 354 μ mol, 1.00 *eq*) in EtOAc (5.0 mL) was added HCl/EtOAc (4 M, 2.0 mL, 22.5*eq*) at 25 °C, then, the mixture was stirred at 25°C for 2 hrs. LCMS showed compound **2002** was consumed and desired MS (R_t = 0.299 min, m/z = 324.2, $M+1$) was detected. The reaction solution was concentrated. The residue was used for next step without purification. Compound **2003** (127 mg, 352 μ mol, 99.6% yield, HCl) was obtained as a white solid.

LC-MS (reaction mixture): R_t = 0.299 min, m/z = 324.2, $M+1$

15

Example 38

Synthesis of N-((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(p-tolyl)propan-2-yl)thiophene-2-carboxamide (Compound 203)



To a solution of compound **2003** (127 mg, 352 μ mol, 1.00 *eq*, HCl) and TEA (145 mg, 1.44 mmol, 0.20 mL, 4.07 *eq*) in DCM (2 mL) was added thiophene-2-carbonyl chloride (57 mg, 388 μ mol, 41.61 μ L, 1.10 *eq*) at 0 °C, then the mixture was stirred at 25°C for 2 hrs.

LCMS showed compound **2003** was consumed and desired MS ($R_t = 0.448$ min, $m/z = 434.0$, $M+1$) was detected. The reaction solution was concentrated. The residue was purified by pre-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 19%-49%, min). LCMS and HPLC showed the product **Compound 203** (120.94 mg, 278.94 umol, 78.4% yield, 99.5% purity) was obtained as white solid.

LC-MS (reaction mixture): $R_t = 0.448$ min, $m/z = 434.0$, $M+1$

LC-MS: $R_t = 0.425$ min, $m/z = 434.3$, $M+1$

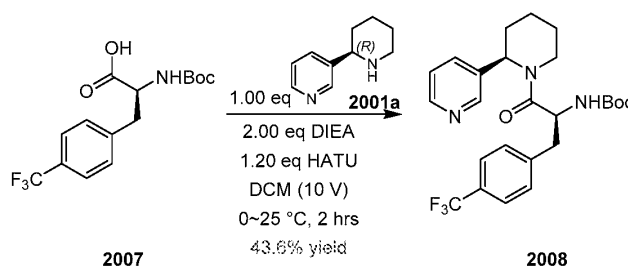
HPLC: $R_t = 1.639$ min, 99.5% purity

$^1\text{H-NMR}$: 400 MHz, DMSO: δ 9.07 - 8.87 (m, 1H), 8.48 - 8.40 (m, 2H), 7.93 (d, $J = 3.1$ Hz, 1H), 7.81 - 7.73 (m, 1H), 7.61 (br d, $J = 7.9$ Hz, 1H), 7.35 - 7.30 (m, 1H), 7.23 (br d, $J = 7.8$ Hz, 2H), 7.18 - 7.09 (m, 3H), 6.96 (s, 1H), 5.74 (br s, 1H), 5.17 - 5.02 (m, 1H), 3.90 (br d, $J = 13.6$ Hz, 1H), 3.12 - 3.00 (m, 2H), 2.37 - 2.32 (m, 1H), 2.26 (s, 3H), 1.65 - 1.34 (m, 4H), 1.28 - 1.15 (m, 1H), 1.00 - 0.75 (m, 1H)

15

Example 39

Synthesis of tert-butyl ((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-2-yl)carbamate

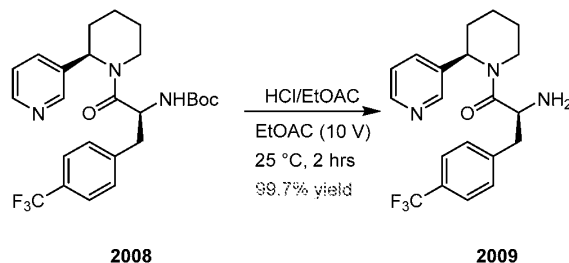


To a solution of compound **2007** (400 mg, 1.20 mmol, 1.00 eq) and compound **2001a** (200 mg, 1.23 mmol, 1.03 eq) in DCM (5.0 mL) was added DIEA (310 mg, 2.40 mmol, 417 μL , 2.00 eq) and HATU (548 mg, 1.44 mmol, 1.20 eq) at 0°C, then the mixture was stirred at 25 °C for 2 hrs. LCMS showed compound **2007** was consumed and desired MS ($R_t = 0.466$ min, $m/z = 478.2$) was detected. The reaction solution was concentrated. The residue was purified by pre-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (TFA)-ACN]; B%: 30%-60%, 10 min). Compound **2008** (250 mg, 523 umol, 43.6% yield) was obtained as a yellow solid.

LC-MS (reaction mixture): $R_t = 0.466$ min, $m/z = 478.2$

Example 40

Synthesis of (S)-2-amino-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-one

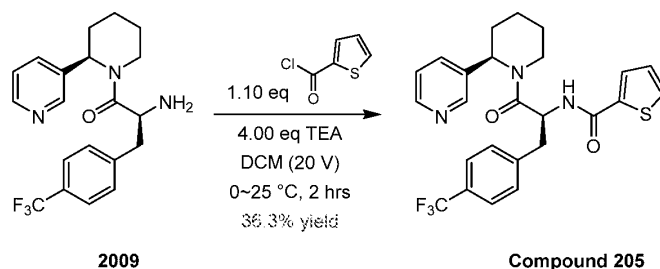


- 5 To a solution of compound **2008** (250 mg, 523 μmol , 1.00 *eq*) in EtOAc (5 mL) was added HCl/EtOAc (4 M, 5 mL, 38.2 *eq*) at 25 °C, then the mixture was stirred at 25 °C for 2 hrs. LCMS showed compound **2008** was consumed and desired MS ($R_t = 0.327$ min, $m/z = 378.1$, $M+1$) was detected. The reaction solution was concentrated. The residue was used for next step without purification. Compound **2009** (216 mg, 521 μmol , 99.7% yield, HCl) was
- 10 obtained as a yellow solid.

LC-MS (reaction mixture): $R_t = 0.327$ min, $m/z = 378.1$, $M+1$

Example 41

Synthesis of N-((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-2-yl)thiophene-2-carboxamide (Compound 205)



- To a solution of compound **2009** (100 mg, 264 μmol , 1.00 *eq*) and TEA (110 mg, 1.09 mmol, 151 μL , 4.10 *eq*) in DCM (2 mL) was added thiophene-2-carbonyl chloride (43 mg, 293 μmol , 31.4 μL , 1.11 *eq*) at 0 °C, then, the mixture was stirred at 25 °C for 2 hrs. LCMS
- 20 showed compound **2009** was consumed and desired MS ($R_t = 0.472$ min, $m/z = 488.0$, $M+1$) was detected. The reaction solution was concentrated. The residue was purified by pre-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (FA)-

ACN]; B%: 22%-52%, min). From HNMR, LCMS and HPLC showed the product

Compound 205 (50.40 mg, 96.1 umol, 36.3% yield) was obtained as a off-white gum.

LC-MS (reaction mixture): Rt = 0.472 min, m/z = 488.0, M+1

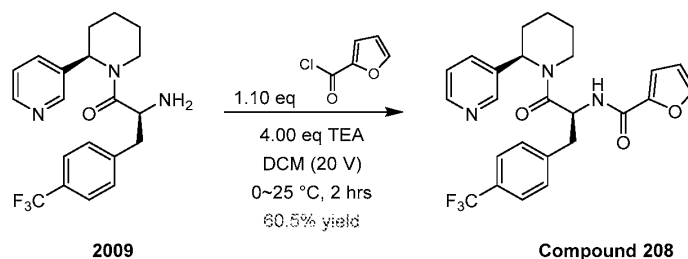
LC-MS: Rt = 0.453 min, m/z = 488.4, M+1

5 **HPLC:** Rt = 1.773 min, 97.8% purity

¹H-NMR: 400 MHz, DMSO: δ 9.22 - 8.94 (m, 1H), 8.42 (br s, 2H), 7.92 (d, J = 3.1 Hz, 1H), 7.79 - 7.74 (m, 1H), 7.68 (br d, J = 8.0 Hz, 2H), 7.62 - 7.46 (m, 3H), 7.43 - 7.23 (m, 2H), 7.16 (t, J = 4.3 Hz, 1H), 5.84 - 5.54 (m, 1H), 5.31 - 4.98 (m, 1H), 3.92 (br d, J = 14.0 Hz, 1H), 3.21 (br d, J = 7.3 Hz, 2H), 2.84 (br t, J = 12.4 Hz, 1H), 2.37 - 2.31 (m, 1H), 1.58 - 1.38 (m, 3H), 1.30 - 1.13 (m, 1H), 0.97 - 0.75 (m, 1H).

Example 42

Synthesis of N-((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-2-yl)furan-2-carboxamide (Compound 208)



15

To a solution of compound **2009** (113 mg, 274.83 umol, 1.00 eq, HCl) and TEA (114 mg, 1.13 mmol, 156 uL, 4.10 eq) in DCM (2 mL) was added furan-2-carbonyl chloride (39.4 mg, 302 umol, 29.8 uL, 1.10 eq) at 0 °C, then, the mixture was stirred at 25 °C for 2 hrs.

LCMS showed reactant 2009 was consumed and desired MS (Rt = 0.460 min, m/z = 472.1, M+1) was detected. The reaction solution was concentrated. The residue was purified by pre-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 21%-51%, min). From HNMR, LCMS and HPLC showed the product

20

Compound 208 (78.38 mg, 166.25 umol, 60.49% yield) was obtained as a white solid.

LC-MS (reaction mixture): Rt = 0.460 min, m/z = 472.1, M+1

25

LC-MS: Rt = 0.438 min, m/z = 472.3, M+1

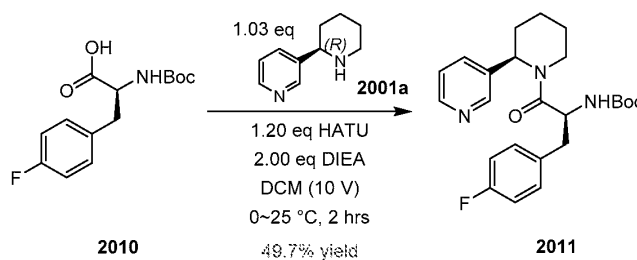
HPLC: Rt = 1.687 min, 97.1% purity

¹H-NMR: 400 MHz, DMSO: δ 8.81 (br d, J = 7.3 Hz, 1H), 8.54 - 8.32 (m, 2H), 7.85 (s, 1H), 7.76 - 7.47 (m, 5H), 7.42 - 7.16 (m, 3H), 6.68 - 6.56 (m, 1H), 5.80 - 5.56 (m, 1H), 5.20 (br d, J = 7.4 Hz, 1H), 3.91 (br d, J = 13.1 Hz, 1H), 3.20 (br d, J = 7.3 Hz, 2H), 2.84 (br

t, $J = 12.4$ Hz, 1H), 2.38 - 2.32 (m, 1H), 1.59 - 1.39 (m, 3H), 1.30 - 1.16 (m, 1H), 1.02 - 0.76 (m, 1H).

Example 43

5 *Synthesis of tert-butyl ((S)-3-(4-fluorophenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate*

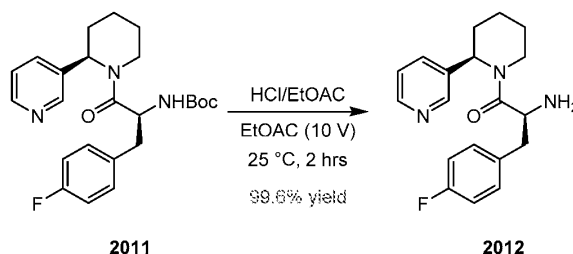


To a solution of compound **2010** (400 mg, 1.41 mmol, 1.00 eq) and compound **2011a**
 10 (236 mg, 1.45 mmol, 1.03 eq) in DCM (5 mL) was added DIEA (365 mg, 2.82 mmol, 491
 uL, 2.00 eq) and HATU (645 mg, 1.70 mmol, 1.20 eq) at 0 °C, the mixture was stirred at 25
 °C for 2 hrs. LCMS showed compound **2010** was consumed and desired MS (RT = 0.417
 min, $m/z = 428.1$) was detected. The reaction solution was concentrated. The residue was
 purified by pre-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase:
 15 [water (TFA)-ACN]; B%: 30%-60%, 10 min) to give compound **2011** (300 mg, 701 umol,
 49.7% yield) as a yellow solid.

LCMS (reaction mixture): RT = 0.417min, m/z (M+1) = 428.1

Example 44

20 *Synthesis of (S)-2-amino-3-(4-fluorophenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one*



To a solution of compound **2011** (250 mg, 584 umol, 1.00 eq) in EtOAc (5 mL) was
 added HCl/EtOAc (4 M, 5 mL, 34.2 eq) at 25 °C, the mixture was stirred at 25°C for 2 hrs.

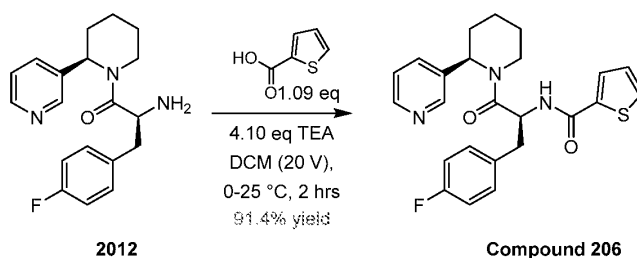
LCMS showed compound **2012** was consumed and desired MS (RT = 0.266 min, m/z = 328.1) was detected. The reaction solution was concentrated to give (212 mg, 582.65 umol, 99.64% yield, HCl) as a yellow solid.

LCMS (reaction mixture): RT=0.334 min, m/z (M+1) = 394.2

5

Example 45

Synthesis of N-((S)-3-(4-fluorophenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 206)



To a solution of compound **2012** (100 mg, 274 umol, 1.00 eq, HCl) and TEA (114 mg, 1.13 mmol, 156.81 uL, 4.10 eq) in DCM (2 mL) was added thiophene-2-carboxyl chloride (44 mg, 300 umol, 32.1 uL, 1.09 eq) at 0°C, the mixture was stirred at 25°C for 2 hrs. LCMS showed compound **2012** was consumed and desired MS (RT = 0.427 min, m/z = 438.0) was detected. The reaction solution was concentrated. The residue was purified by pre-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 16%-46%, min) to afford **Compound 206** (110 mg, 251.41 umol, 91.48% yield) as a off-white solid.

LCMS (reaction mixture): RT=0.427 min, m/z (M+1) = 438.0

¹HNMR: CDCl₃ 400 MHz: δ 8.63 - 8.32 (m, 2H), 7.52 (dd, *J* = 4.4, 10.4 Hz, 2H), 7.45 (br d, *J* = 8.0 Hz, 1H), 7.29 - 7.23 (m, 3H), 7.11 - 6.93 (m, 4H), 6.00 - 5.22 (m, 2H), 3.78 (br d, *J* = 13.6 Hz, 1H), 3.37 - 2.89 (m, 3H), 2.38 (br d, *J* = 13.8 Hz, 1H), 1.70 - 1.36 (m, 4H), 0.92 - 0.69 (m, 1H)

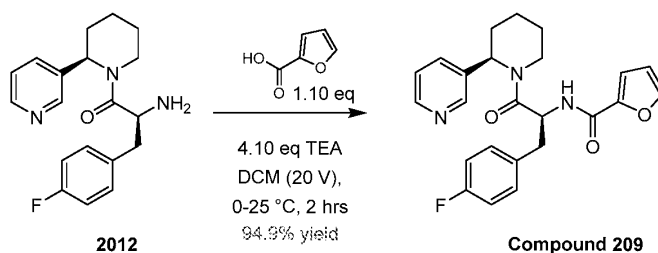
LCMS: RT = 0.403 min, m/z (M+1) = 438.3

HPLC: RT = 1.552 min

25

Example 46

Synthesis of N-((S)-3-(4-fluorophenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 209)



To a solution of compound **2012** (100 mg, 274.83 μmol , 1.00 eq, HCl) and TEA (114 mg, 1.13 mmol, 156 μL , 4.10 eq) in DCM (2 mL) was added furan-2-carboxyl chloride (39.4 mg, 302 μmol , 29.8 μL , 1.10 eq) at 0°C, the mixture was stirred at 25 °C for 2 hrs. LCMS showed compound **2012** was consumed and desired MS (RT = 0.410 min, m/z =422.1) was detected. The reaction solution was concentrated. The residue was purified by pre-HPLC (column: Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (FA)-ACN]; B%: 22%-52%, min) to give **Compound 209** (110 mg, 261.00 μmol , 94.97% yield) as a yellow solid.

LCMS (reaction mixture): RT = 0.410 min, m/z (M+1) = 422.1

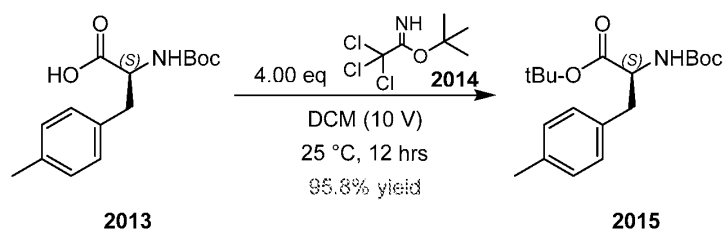
¹HNMR: CDCl₃ 400 MHz : δ 8.54 - 8.34 (m, 2H), 7.54 - 7.39 (m, 2H), 7.33 - 7.18 (m, 4H), 7.17 - 6.84 (m, 4H), 6.52 (dd, J = 1.6, 3.3 Hz, 1H), 6.06 - 5.54 (m, 1H), 5.48 - 5.22 (m, 1H), 4.59 - 4.46 (m, 1H), 3.77 (br d, J = 12.8 Hz, 1H), 3.34 - 2.80 (m, 3H), 2.36 (br d, J = 14.0 Hz, 1H), 1.99 - 1.87 (m, 1H), 1.76 - 1.25 (m, 5H), 0.89 - 0.61 (m, 1H)

LCMS: RT = 0.419 min, m/z (M+1) = 422.1

HPLC: RT = 0.821 min

Example 47

Synthesis of tert-butyl (S)-2-((tert-butoxycarbonyl)amino)-3-(p-tolyl)propanoate



To a solution of compound **2013** (10.0 g, 35.8 mmol, 1.00 eq) in DCM (100 mL) was added compound **2014** (31.3 g, 143 mmol, 25.7 mL, 4.01 eq). The mixture was stirred at 25 °C for 12 hrs. LCMS showed the main peak with desired MS (RT = 0.610 min, M-155 = 180) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by column chromatography (SiO₂, PE: EA=20:1-5:1), the fraction (Plate 1, R_f =

0.75) was collected. Compound **2015** (11.59 g, 34.30 mmol, 95.8% yield, 99.3% purity) was obtained as colourless oil, checked by LCMS and HNMR.

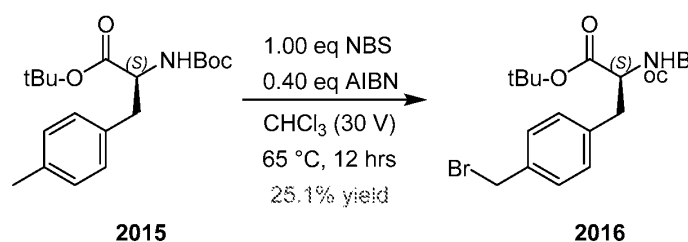
LCMS (reaction mixture): RT=0.601 min, m/z (M-155) = 180.1

LCMS (compound 2015): RT=0.603 min, m/z (M-155) = 180.1

¹H NMR: 400 MHz, CDCl₃: δ 7.08 (q, *J* = 8.1 Hz, 4H), 5.07 - 4.63 (m, 1H), 4.50 - 4.17 (m, 1H), 3.02 (br s, 2H), 2.32 (s, 3H), 1.43 (d, *J* = 2.5 Hz, 18H)

Example 48

Synthesis of tert-butyl (S)-3-(4-(bromomethyl)phenyl)-2-((tert-butoxycarbonyl)amino)propanoate

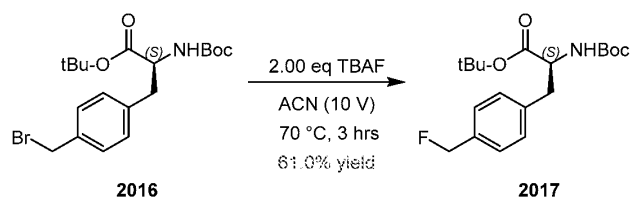


To a solution of compound **2015** (7.00 g, 20.9 mmol, 1.00 eq) in CHCl₃ (70.0 mL) was added AIBN (461 mg, 2.81 mmol, 0.14 eq) and NBS (3.34 g, 18.8 mmol, 0.90 eq), and then the reaction mixture was stirred at 50 °C for 12 hrs. TLC (Petroleum ether : Ethyl acetate = 10:1) indicated Reactant **2015** (R_f = 0.54) was consumed completely and two new spots (R_f = 0.43, R_f = 0.30) formed. The reaction mixture was concentrated to remove CHCl₃. The reaction mixture was diluted with DCM (100 mL). The organic layer was washed with brine (100 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated to give residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 50/1 to 10/1, R_f = 0.30 was collected). From HNMR showed the product compound **2016** (2.60 g, 5.25 mmol, 25.1% yield, 83.6% purity) was obtained as white solid.

¹H NMR: 400 MHz, DMSO: δ 7.35 (br d, *J* = 7.9 Hz, 2H), 7.24 - 7.15 (m, 2H), 4.67 (s, 2H), 4.08 - 3.92 (m, 1H), 3.08 - 2.67 (m, 2H), 1.34 (s, 18H).

Example 49

Synthesis of tert-butyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(fluoromethyl)phenyl)propanoate



Under N₂ to a solution of compound **2016** (2.50 g, 6.03 mmol, 1.00 eq) in MeCN (25.0 mL) was added TBAF (1.00 M, 12.5 mL, 2.07 eq) at 25 °C, and then the mixture was stirred at 70 °C for 2 hrs. LCMS, product: Ret. Time = 0.657 min, m/z - 100 - 56 + 1 = 198.1) and HPLC, product: Ret. Time = 1.970 min) showed the starting material compound **2016** was consumed completely and desired mass was detected. The reaction mixture was quenched by addition H₂O 30.0 mL at 25 °C, and then extracted with EA 90 mL (30.0 mL * 3). The combined organic layers were washed with NaCl 100 mL (100 mL * 1), dried over NaSO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (column: 330g Flash Coulmn Welch Ultimate XB_C18 20 - 40μm; 120 Å; mobile phase: [water (TFA) - ACN]; B%: 44% 33min). From HNMR and FNMR showed the product compound **2017** (1.30 g, 3.68 mmol, 61.0% yield) was obtained as a white solid.

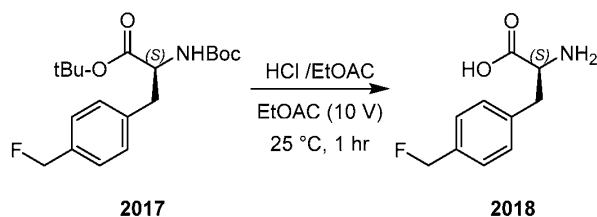
LC-MS (reaction mixture): Ret. Time = 0.657 min, m/z - 100 - 56 + 1 = 198.1

¹H NMR: 400 MHz, MeOD: δ 7.31 (s, 2H), 7.29 - 7.20 (m, 2H), 5.38 (s, 1H), 5.26 (s, 1H), 4.24 (br t, *J* = 7.3 Hz, 1H), 3.13 - 3.01 (m, 1H), 2.92 (br dd, *J* = 8.6, 13.6 Hz, 1H), 1.40 (d, *J* = 5.8 Hz, 18H).

¹⁹F NMR: 377 MHz, MeOD: δ -212.70 (s, 1F).

Example 50

Synthesis of (S)-2-amino-3-(4-(fluoromethyl)phenyl)propanoic acid



To a solution of compound **2017** (0.50 g, 1.41 mmol, 1.00 eq) in EA (5.00 mL) was added HCl/EtOAc (4.00 M, 19.0 mL, 53.7 eq), and then the mixture was stirred at 25 °C for 1 hr. LCMS, product: Ret. Time = 0.290, m/z + 1 = 198.1) showed the starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated

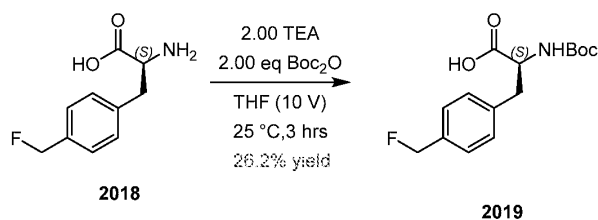
under reduced pressure to give a residue. The reaction mixture was used to the next step without purification. Compound **2018** (400 mg, crude) was obtained as a white solid.

LC-MS (reaction mixture): Ret. Time = 0.290, $m/z + 1 = 198.1$

5

Example 51

Synthesis of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(fluoromethyl)phenyl)propanoic acid



To a solution of compound **2018** (400 mg, 1.71 mmol, 1.00 *eq*, HCl) in THF (4.00 mL) and H₂O (4.00 mL) was added Boc₂O (950 mg, 4.35 mmol, 1.00 mL, 2.54 *eq*) and NaHCO₃ (440 mg, 5.24 mmol, 204 μ L, 3.06 *eq*), and then the mixture was stirred at 25 °C for 16 hrs. LCMS, product 1: Ret. Time = 0.507 min, $m/z + 23 = 320.1$ and product 2: Ret. Time = 0.665 min, $m/z + 23 = 376.2$) showed the starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 * 25mm * 5 μ m; mobile phase: [water (TFA) - ACN]; B%: 28% - 58%, 10 min). From HNMR, LCMS, HPLC and FNMR showed compound **2019** (173 mg, 448 μ mol, 26.2% yield, 77% purity) was obtained as a white solid.

LC-MS (reaction mixture): Ret. Time = 0.507 min, $m/z + 23 = 320.1$

¹H NMR: 400 MHz, MeOD: δ 7.41 - 7.19 (m, 4H), 5.40 (s, 1H), 5.28 (s, 1H), 4.37 (br dd, $J = 5.0, 8.9$ Hz, 1H), 3.24 - 3.10 (m, 1H), 2.95 (br dd, $J = 8.9, 13.8$ Hz, 1H), 1.40 (s, 10H).

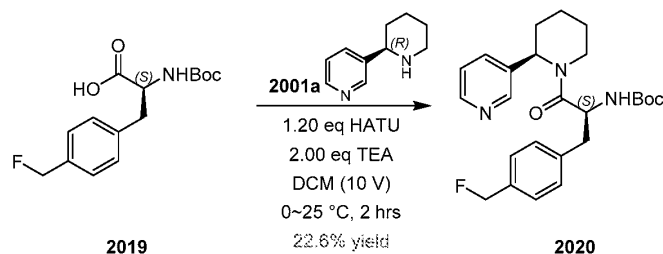
¹⁹F NMR: 400 MHz, MeOD: δ -223.12 (s, 1F).

LC-MS (compound 2019): Ret. Time = 0.499 min, $m/z + 23 = 320.1$

HPLC: Ret. Time = 1.03 min, 77.0% purity

25

Example 52

Synthesis of tert-butyl ((S)-3-(4-(fluoromethyl)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate

- 5 To a solution of compound **2019** (140 mg, 471 μmol , 1.00 eq) and compound **2001a** (84.0 mg, 518 μmol , 1.10 eq) in DCM (2.00 mL) was added DIEA (148 mg, 1.15 mmol, 200 μL , 2.44 eq) and HATU (217 mg, 571 μmol , 1.21 eq) at 0 °C, and then the mixture was stirred at 25 °C for 2 hrs. LCMS, product: Ret. Time = 0.478 min, $m/z + 1 = 442.1$) showed starting material was consumed completely and desired mass was detected. The reaction
- 10 mixture was quenched by addition DCM 2.00 mL at 25°C, and then diluted with H₂O 5.00 mL and extracted with DCM 15.0 mL (5.00 mL * 3). The combined organic layers were washed with NaCl 20.0 mL (20.0 mL * 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 150 * 25mm * 5 μm ; mobile phase: [water(TFA) - ACN]; B%: 21% -
- 15 51%, 10min). From HNMR, FNMR showed the product compound **2020** (47.0 mg, 107 μmol , 22.6% yield) was obtained as a light yellow oil.

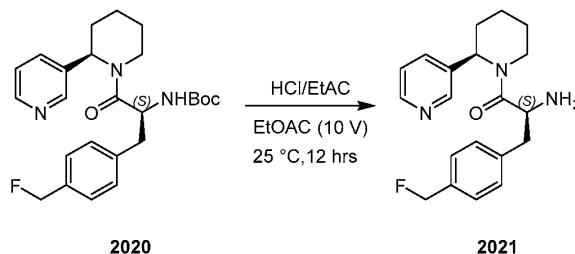
LC-MS (reaction mixture): Ret. Time = 0.478 min, $m/z + 1 = 442.1$

- ¹H NMR:** 400 MHz, MeOD: δ 8.69 (br d, $J = 6.5$ Hz, 2H), 8.46 (br d, $J = 8.0$ Hz, 1H), 8.02 - 7.85 (m, 1H), 7.50 - 7.24 (m, 4H), 5.86 (br s, 1H), 5.47 - 5.23 (m, 2H), 3.85 (br d, $J = 14.0$ Hz, 1H), 3.10 - 2.87 (m, 3H), 2.34 (br d, $J = 13.9$ Hz, 1H), 1.72 - 1.58 (m, 1H), 1.53 - 1.23 (m, 13H), 0.67 - 0.33 (m, 1H).
- 20

¹⁹F NMR: 400 MHz, MeOD: δ -73.81 (s, 1F).

Example 53

Synthesis of (S)-2-amino-3-(4-(fluoromethyl)phenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



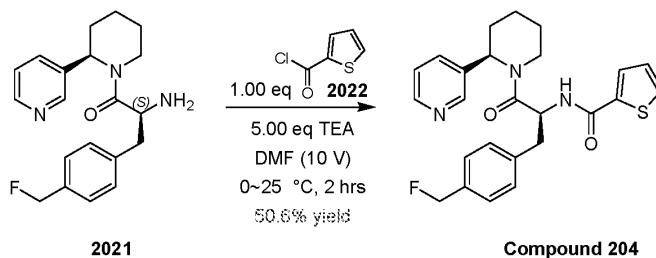
- 5 To a solution of compound **2020** (47.0 mg, 107 μmol , 1.00 eq) in EA (0.50 mL) was added HCl/EtOAc (4 M, 1.50 mL, 56.4 eq), and then the mixture was stirred at 25 °C for 1 hr. LCMS, product: Ret. Time = 0.314 min, $m/z + 1 = 342.1$) showed the starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was used to the next step without purification. From HNMR showed that compound **2021** (36.0 mg, crude) was obtained as a light yellow solid.

LC-MS (reaction mixture): Ret. Time = 0.314 min, $m/z + 1 = 342.1$

- ^1H NMR:** 400 MHz, MeOD: δ 8.89 (s, 1H), 8.79 (br d, $J = 5.5$ Hz, 1H), 8.62 (br d, $J = 8.3$ Hz, 1H), 8.10 (dd, $J = 6.0, 7.9$ Hz, 1H), 7.55 - 7.30 (m, 4H), 5.47 - 5.28 (m, 2H), 3.68 (br d, $J = 13.6$ Hz, 1H), 3.27 - 3.19 (m, 1H), 3.30 - 3.15 (m, 1H), 3.08 - 2.97 (m, 1H), 2.47 - 2.29 (m, 1H), 2.04 - 1.96 (m, 1H), 1.85 - 1.69 (m, 1H), 1.58 - 1.21 (m, 4H), 0.65 - 0.47 (m, 1H).

Example 54

- 20 *Synthesis of N-((S)-3-(4-(fluoromethyl)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 204)*



To a solution of compound **2021** (18.0 mg, 52.7 μmol , 1.00 eq) in DMF (0.50 mL) was added TEA (29.1 mg, 287 μmol , 40.0 μL , 5.45 eq) and compound **2022** (9.59 mg, 65.4

umol, 7.00 uL, 1.24 eq) at 0 °C, and then the mixture was stirred at 25 °C for 2 hrs. LCMS, product: Ret. Time = 0.457 min, $m/z + 1 = 452.1$) showed the starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch
 5 Ultimate C18 150 * 25 mm * 5 um; mobile phase: [water (TFA) - ACN]; B%: 16% - 46%, 2 min). From HNMR, FNMR, LCMS and HPLC showed that **Compound 204** (13.0 mg, 26.7 umol, 50.6% yield, 92.7% purity) was obtained as a yellow gum.

LC-MS (reaction mixture): Ret. Time = 0.457 min, $m/z + 1 = 452.1$

LC-MS: Ret. Time = 0.455 min, $m/z + 1 = 452.1$

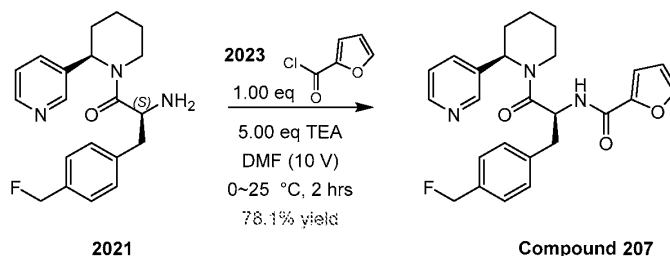
10 **HPLC:** Ret. Time = 1.563 min, 92.7% purity

¹H NMR: 400 MHz, MeOD: δ 8.62 (br d, $J = 10.1$ Hz, 2H), 8.29 (br d, $J = 8.9$ Hz, 1H), 7.84 (br s, 2H), 7.69 (d, $J = 5.0$ Hz, 1H), 7.42 (br s, 4H), 7.15 (t, $J = 4.4$ Hz, 1H), 5.85 (br s, 1H), 5.49 - 5.27 (m, 3H), 5.25 - 5.11 (m, 1H), 4.01 - 3.78 (m, 1H), 3.27 - 3.21 (m, 2H), 3.03 - 2.90 (m, 1H), 2.40 - 2.30 (m, 1H), 1.67 - 1.57 (m, 1H), 1.50 - 1.21 (m, 4H), 0.63 - 0.41
 15 (m, 1H).

¹⁹F NMR: 400 MHz, MeOD: δ -207.17 (s, 1F).

Example 55

20 *Synthesis of N-((S)-3-(4-(fluoromethyl)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 207)*



To a solution of compound **2021** (18.0 mg, 52.7 umol, 1.00 eq) in DMF (0.50 mL) was added TEA (29.1 mg, 287 umol, 40.0 uL, 5.45 eq) and compound **2023** (9.24 mg, 70.8 umol, 7.00 uL, 1.34 eq) at 0 °C, and then the mixture was stirred at 25 °C for 2 hrs. LCMS, product: Ret. Time = 0.452 min, $m/z + 1 = 436.1$) showed the starting material was consumed completely and desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch
 25 Ultimate C18 150 * 25mm * 5um; mobile phase: [water(TFA) - ACN]; B%: 16% - 46%,

2min). From HNMR, FNMR, LCMS and HPLC showed **Compound 207** (18.3 mg, 41.2 umol, 78.1% yield, 98.1% purity) was obtained as a yellow gum.

LC-MS (reaction mixture): Ret. Time = 0.452 min, $m/z + 1 = 436.1$

LC-MS: Ret. Time = 0.435 min, $m/z + 1 = 436.2$

5 **HPLC:** Ret. Time = 1.458 min, 98.1% purity

¹H NMR: 400 MHz, MeOD: δ 8.80 - 8.67 (m, 2H), 8.52 (br d, $J = 8.1$ Hz, 1H), 8.12 - 7.94 (m, 1H), 7.72 (s, 1H), 7.51 - 7.36 (m, 4H), 7.23 (br d, $J = 3.3$ Hz, 1H), 6.61 (dd, $J = 1.8$, 3.4 Hz, 1H), 5.86 (br s, 1H), 5.48 - 5.26 (m, 2H), 5.19 (dd, $J = 6.1$, 9.7 Hz, 1H), 3.92 (br d, $J = 14.0$ Hz, 1H), 3.29 - 3.17 (m, 2H), 2.98 (br t, $J = 12.2$ Hz, 1H), 2.35 (br d, $J = 13.4$ Hz, 1H),
10 1.77 - 1.56 (m, 1H), 1.51 - 1.31 (m, 2H), 1.31 - 1.20 (m, 1H), 0.61 - 0.40 (m, 1H).

¹⁹F NMR: 400 MHz, MeOD: δ -207.20 (br s, 1F).

Example 56

Synthesis of (R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)zinc(II) iodide

15

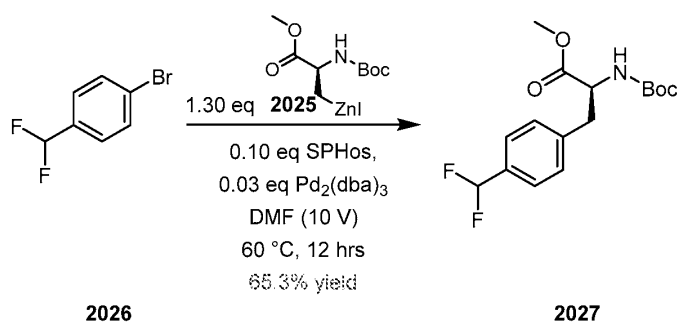


To a solution of I_2 (1.62 g, 6.38 mmol, 1.29 mL, 0.10 eq) in DMF (84.0 mL) was added Zn (12.5 g, 191 mmol, 3.00 eq) at 25 °C. The mixture was stirred at 50 °C for 3 hrs. Then the mixture cooled to 25 °C, the compound **20241** (21.0 g, 63.8 mmol, 1.00 eq) in DMF
20 (120 mL) was added. The mixture was stirred at 25 °C for 3 hrs. TLC (Petroleum ether: Ethyl acetate = 5:1) showed compound **2024** ($R_f = 0.40$) was consumed and the one new spot ($R_f = 0.50$) was formed. The reaction mixture was filtered, the filtrate was used to next step. The filtrate was used to next step without purification. Compound **2025** (24.8 g, 62.8 mmol, 98.5% yield) was obtained as a gray liquid and dissolved in DMF (300 mL).

25

Example 57

Synthesis of Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(difluoromethyl)phenyl)propanoate



- To a solution of compound **2025** (24.8 g, 62.8 mmol, 1.3 *eq*) in DMF (300 mL) was added compound **2026** (10.0 g, 48.3 mmol, 1.00 *eq*), SPhos (1.98 g, 4.83 mmol, 0.10 *eq*), and Pd₂(dba)₃ (1.33 g, 1.45 mmol, 0.03 *eq*). The mixture was stirred at 60 °C for 12 hrs under N₂.
- 5 LCMS showed the compound **2026** was consumed and the desired mass (RT = 0.521 min, m/z (M-99) = 230.1) was detected. The reaction mixture was filtered, the filtrate was diluted with Ethyl acetate (400 mL) and H₂O (500 mL). The organic layer was washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 30/1 to 5/1, R_f = 0.30 was
- 10 collected). From HNMR and LCMS showed the compound **2027** (11.0 g, 31.5 mmol, 65.3% yield, 94.4% purity) was obtained as brown yellow oil.

LC-MS (reaction mixture): RT = 0.521 min, m/z (M-99) = 230.1

LC-MS (compound 2027): RT = 0.525 min, m/z (M-99) = 230.1

- ¹H-NMR:** 400 MHz, DMSO-*d*₆: δ 7.56 - 7.30 (m, 2H), 7.12 (s, 1H), 6.98 (s, 1H), 6.84 (s, 1H), 7.15 - 6.77 (m, 1H), 4.27 - 3.97 (m, 1H), 3.62 (s, 3H), 3.22 - 2.77 (m, 2H), 1.39 - 1.26 (m, 9H)
- 15

Example 58

Synthesis of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(difluoromethyl)phenyl)propanoic acid



20

To a solution of compound **2027** (11.0 g, 31.5 mmol, 94.4% purity, 1.00 *eq*) in MeOH (100 mL) was added the solution of LiOH.H₂O (3.97 g, 94.6 mmol, 3.00 *eq*) in H₂O (100

mL) at 0 °C, then the reaction mixture was stirred at 25 °C for 12 hrs. LCMS showed the compound **2027** was consumed and the desired mass (RT = 0.466 min, m/z (M-99) = 216.1) was detected. The reaction mixture was adjusted to pH = 5 with 1M HCl, and the reaction mixture was partitioned between ethyl acetate (250 mL) and water (150 mL). The organic phase was separated, washed with brine (150 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used to next step without purification. From LCMS and HNMR showed the product compound **2028** (10.0 g, 30.9 mmol, 98.1% yield, 97.5% purity) was obtained as gray solid.

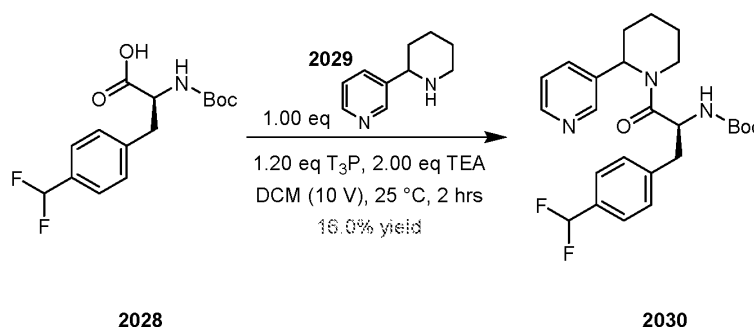
LC-MS (reaction mixture): RT = 0.466 min, m/z (M-99) = 216.1

LC-MS (compound 2028): RT = 0.468 min, m/z (M-99) = 216.1

¹H-NMR: 400 MHz, CDCl₃: δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.29 (br d, *J* = 7.6 Hz, 2H), 6.64 (t, *J* = 56.4 Hz, 1H), 4.97 (br d, *J* = 7.6 Hz, 1H), 4.65 (br d, *J* = 6.4 Hz, 1H), 3.34 - 2.95 (m, 2H), 1.45 - 1.25 (m, 9H)

Example 59

Synthesis of tert-butyl ((2S)-3-(4-(difluoromethyl)phenyl)-1-oxo-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



To a solution of compound **2028** (10.0 g, 30.9 mmol, 97.5% purity, 1.00 eq) and compound **2029** (5.02 g, 30.9 mmol, 1.00 eq) in DCM (100 mL) was added T₃P (23.5 g, 36.9 mmol, 22.0 mL, 50% purity, 1.20 eq) and DIEA (8.16 g, 63.1 mmol, 11.0 mL, 2.04 eq), then the reaction mixture was stirred at 25 °C for 2 hrs. LCMS showed the compound **2028** was consumed and the desired mass (RT = 0.441 min, m/z (M+1) = 460.3) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 10 um); mobile phase: [water (NH₄HCO₃)-ACN]; B%: 45%-70%, 20 min). From HNMR and LCMS showed the product compound **2030** (2.70 g, 4.96 mmol, 16.0% yield, 84.4% purity) was obtained as white solid.

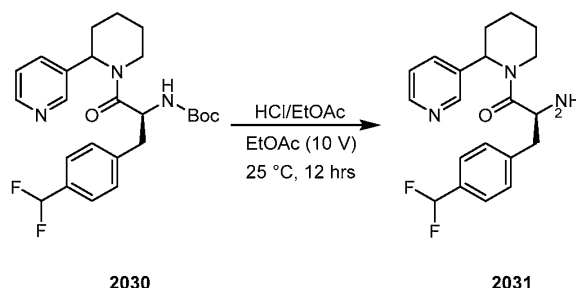
LC-MS (reaction mixture): RT = 0.441 min, m/z (M+1) = 460.3

LC-MS (compound 2030): RT = 0.430 min, m/z (M+1) = 460.4

¹H-NMR: 400 MHz, DMSO-*d*₆: δ 8.50 - 8.31 (m, 2H), 7.65 - 7.22 (m, 7H), 7.15 - 6.86 (m, 1H), 5.73 (br d, *J* = 15.6 Hz, 1H), 4.92 - 4.56 (m, 1H), 4.06 - 3.68 (m, 1H), 3.17 - 2.64 (m, 3H), 2.41 - 2.30 (m, 1H), 1.81 - 1.43 (m, 3H), 1.41 - 1.24 (m, 9H), 1.05 (br s, 2H).

Example 60

Synthesis of (2S)-2-amino-3-(4-(difluoromethyl)phenyl)-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



10

To a solution of compound **2030** (2.70 g, 4.96 mmol, 84.4% purity, 1.00 *eq*) in EtOAc (27.0 mL) was added HCl / EtOAc (4 M, 27.0 mL, 18.3 *eq*), then the reaction mixture was stirred at 25 °C for 12 hrs. LCMS showed the compound **2030** was consumed and the desired mass (RT = 0.251 min, m/z (M-99) = 360.2) was detected. The reaction mixture was concentrated. The residue was used to next step without purification. From HNMR showed the product compound **2031** (2.50 g, crude, HCl) was obtained as light brown solid.

15

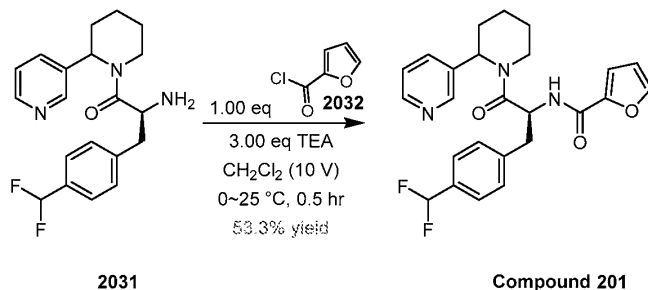
LC-MS (reaction mixture): RT = 0.250 min, m/z (M-99) = 360.2

¹H-NMR: 400 MHz, DMSO-*d*₆: δ 9.03 - 8.63 (m, 2H), 8.59 (br d, *J* = 5.2 Hz, 1H), 8.05 - 7.67 (m, 1H), 7.64 - 7.30 (m, 3H), 7.27 - 6.83 (m, 1H), 5.74 (br d, *J* = 26.8 Hz, 1H), 4.93 - 4.60 (m, 1H), 4.50 - 3.96 (m, 3H), 3.36 - 2.99 (m, 2H), 2.92 - 2.56 (m, 1H), 2.46 - 2.22 (m, 1H), 1.95 - 1.35 (m, 2H), 1.27 - 1.08 (m, 1H).

20

Example 61

Synthesis of N-((2S)-3-(4-(difluoromethyl)phenyl)-1-oxo-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 201)



- 5 To a solution of compound **2031** (2.30 g, 6.40 mmol, 1.00 *eq*) in DCM (25.0 mL) was added TEA (2.18 g, 21.5 mmol, 3 mL, 3.00 *eq*) and compound **2032** (924 mg, 7.08 mmol, 700 μ L, 1.11 *eq*) at 0 °C, and then the reaction mixture stirred at 25 °C for 30 min. LCMS showed the compound **2031** was consumed and the desired mass (RT = 0.385 min, m/z (M+1) = 454.3) was detected. The reaction mixture was concentrated. The residue was
- 10 purified by prep-HPLC (column: YMC Triart C18 250*50mm*7 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 25%-55%, 20 min). From HNMR, LCMS and HPLC showed the product **Compound 201** (1.60 g, 3.41 mmol, 53.3% yield, 96.6% purity) was obtained as gray solid.

LC-MS (reaction mixture): RT = 0.385 min, m/z (M+1) = 454.3

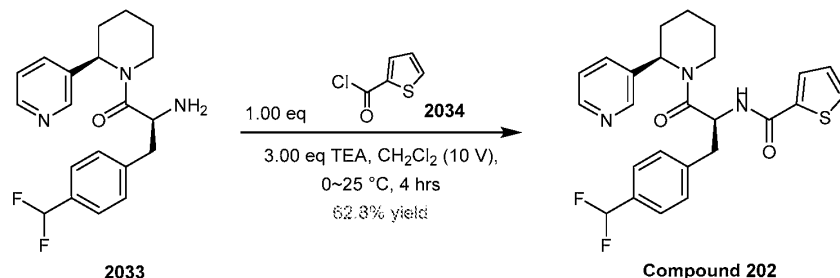
- 15 **LC-MS:** RT = 0.389 min, m/z (M+1) = 454.2

HPLC: RT = 1.428 min, 96.5% purity

- ¹H-NMR:** 400 MHz, DMSO-*d*₆: δ 9.02 - 8.65 (m, 1H), 8.59 - 8.29 (m, 2H), 7.93 - 7.68 (m, 1H), 7.65 - 7.40 (m, 4H), 7.33 - 7.20 (m, 2H), 7.16 - 6.80 (m, 1H), 6.67 - 6.43 (m, 1H), 5.87 - 5.55 (m, 1H), 5.42 - 5.02 (m, 1H), 4.53 - 3.72 (m, 1H), 3.26 - 3.05 (m, 2H), 2.94 -
- 20 2.59 (m, 1H), 2.40 - 2.30 (m, 1H), 1.78 - 0.86 (m, 5H)

Example 62

Synthesis of N-((S)-3-(4-(difluoromethyl)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 202)



- 5 To a solution of compound **2033** (80.0 mg, 202 μ mol, 1.00 *eq*, HCl) in DCM (2 mL) was added TEA (62.0 mg, 613 μ mol, 85.3 μ L, 3.03 *eq*) and compound **2034** (30.0 mg, 205 μ mol, 21.9 μ L, 1.01 *eq*) at 0 °C, and then the reaction mixture stirred at 20 °C for 4 hrs. LCMS showed that compound **2033** was consumed and the desired mass (RT = 0.366 min, m/z = 470.2) was detected. The reaction mixture was concentrated under vacuum. The crude
- 10 product was purified by reversed-phase HPLC (column: Welch Xtimate C18 150*25mm*5 μ m; mobile phase: [water (0.05% HCl)-ACN]; B%: 15%-45%, 10min). From HNMR, FNMR, LCMS, HPLC and SFC, **Compound 202** (62.68 mg, 127 μ mol, 62.8% yield, 95.1% purity) was obtained as an off-white solid.

LC-MS (reaction mixture): RT = 0.366 min, m/z = 470.2

- 15 **LC-MS:** RT = 0.370 min, m/z = 470.1

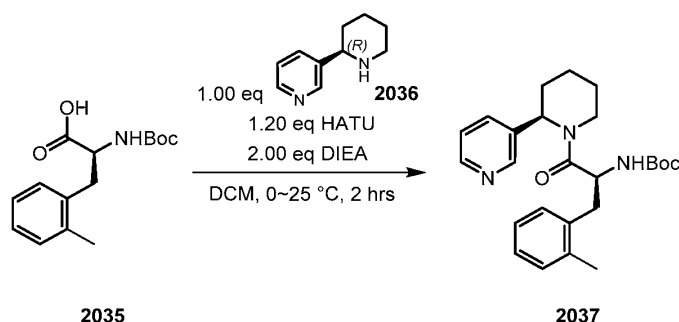
HPLC: RT = 1.610 min, 95.1% purity

SFC: 92.0% ee

- ¹H-NMR:** 400 MHz, DMSO: δ 9.03 (br d, *J* = 6.4 Hz, 1H), 8.74 - 8.52 (m, 2H), 8.21 - 8.05 (m, 1H), 7.93 (d, *J* = 3.0 Hz, 1H), 7.79 (br d, *J* = 4.8 Hz, 2H), 7.57 - 7.43 (m, 4H), 7.21 - 7.12 (m, 1H), 7.03 - 6.84 (m, 1H), 5.82 - 5.70 (m, 1H), 5.21 - 5.05 (m, 1H), 3.89 (br dd, *J* = 2.1, 13.6 Hz, 1H), 3.21 - 3.13 (m, 4H), 2.97 - 2.82 (m, 2H), 1.65 - 1.10 (m, 6H), 0.85 - 0.66 (m, 1H).
- 20

Example 63

- 25 *Synthesis of tert-butyl ((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(o-tolyl)propan-2-yl)carbamate*



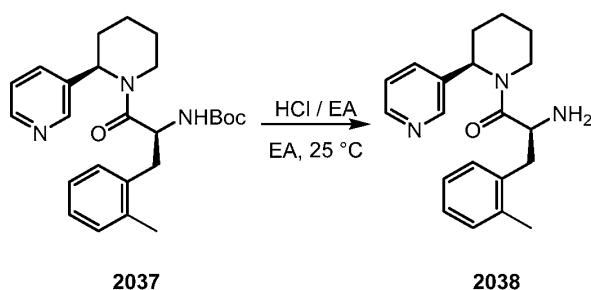
To a solution of Compound **2035** (100 mg, 358 μmol , N/A purity, 1.00 *eq*) and Compound **2036** (64 mg, 395 μmol , N/A purity, 1.10 *eq*) in DCM (1.00 mL) was added HATU (164 mg, 431 μmol , 1.20 *eq*) and DIEA (96.5 mg, 746 μmol , 130 μL , 2.08 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5857-2-P1R1, product: Ret. Time = 0.403 min, $m/z + 1 = 424.3$) showed that the reactant was consumed completely and the desired mass was detected. The reaction mixture was quenched by addition H₂O 3 mL at 25 °C, and extracted with DCM 6 mL (2 mL * 3). The combined organic layers were washed with NaCl 6 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used to the next step without the further purification. From LCMS (EC5857-2-P1A1) showed that the product Compound **2037** (150 mg, crude) was obtained as a yellow oil.

LCMS: EC5857-2-P1R1, Ret. Time = 0.403 min, m/z +1 = 424.3

LCMS: EC5857-2-P1A1, Ret. Time = 0.456 min, $m/z + 1 = 424.3$

Example 64

Synthesis of (S)-2-amino-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(o-tolyl)propan-1-one



To a solution of Compound **2037** (150 mg, 354 μ mol, N/A purity, 1.00 eq) in EtOAc (2.00 mL) was added HCl/EtOAc (4.00 M, 6.00 mL, 67.8 eq). The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5857-4-P1R1, product: Ret. Time = 0.297 min, m/z +1 = 324.3)

showed that the reactant was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was used to the next step without further purification. From HNMR (EC5857-4-P1C2) showed that the product Compound **2038** (120 mg, crude) was obtained as a yellow oil.

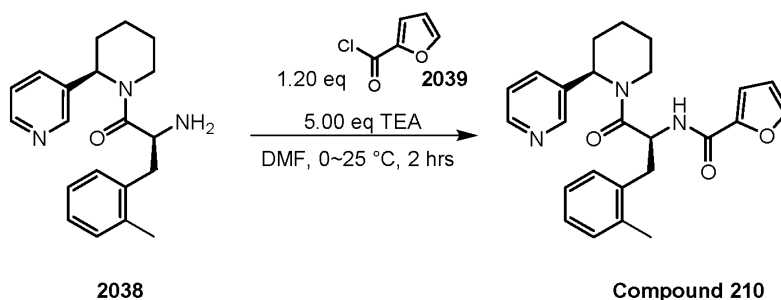
5 **LCMS:** EC5857-4-P1R1, Ret. Time = 0.297 min, $m/z + 1 = 324.3$

¹HNMR: EC5857-4-P1C2 (400 MHz, MeOD)

δ 8.75 (d, $J = 1.1$ Hz, 1H), 8.63 (d, $J = 5.6$ Hz, 1H), 8.47 (td, $J = 0.9, 8.3$ Hz, 1H), 7.94 (dd, $J = 5.8, 8.3$ Hz, 1H), 7.16 - 7.07 (m, 4H), 5.73 (brs, 1H), 3.94 (q, $J = 7.1$ Hz, 1H), 3.57 (td, $J = 6.6, 13.3$ Hz, 1H), 3.10 - 3.00 (m, 2H), 2.78 (dt, $J = 3.0, 13.4$ Hz, 1H), 2.28 (s, 3H), 1.57 - 1.42 (m, 1H), 1.25 (brs, 1H), 1.19 - 0.99 (m, 4H).

Example 65

Synthesis of N-((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(o-tolyl)propan-2-yl)furan-2-carboxamide (Compound 210)



15

To a solution of **Compound 2038** (60.0 mg, 186 μ mol, 1.00 eq) and **Compound 2039** (25.1 mg, 192 μ mol, 19.0 μ L, 1.04 eq) in DMF (1.00 mL) was added TEA (94.5 mg, 934 μ mol, 130 μ L, 5.03 eq) at 0 $^{\circ}$ C. The mixture was stirred at 25 $^{\circ}$ C for 2 hrs. LCMS (EC5857-8-P1R1, product: Ret. Time = 0.364 min, $m/z + 1 = 418.2$) showed that the reactant was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (neutral condition). From HNMR (EC5857-8-P1C1), LCMS (EC5857-8-P1A2) and HPLC (EC5857-8-P1B1) showed that the product **Compound 210** (25.69 mg, 61.2 μ mol, 33.0% yield, 99.4% purity) was obtained as a white solid.

20

25 **LCMS:** EC5857-8-P1R1, product: Ret. Time = 0.364 min, $m/z + 1 = 418.2$

¹HNMR: EC5857-8-P1C1 (400 MHz, $CDCl_3$)

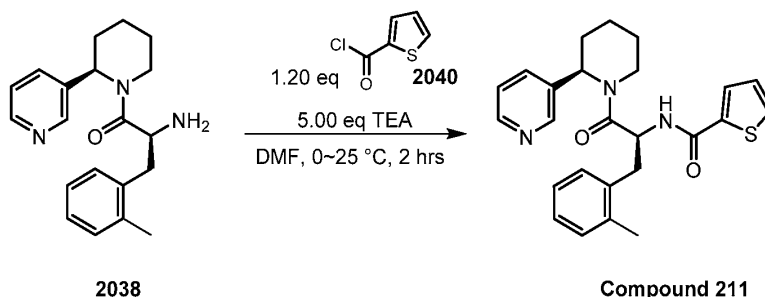
δ 8.54 (brs, 2H), 7.84 (d, J = 6.8 Hz, 1H), 7.59 - 7.52 (m, 1H), 7.50 (d, J = 0.9 Hz, 1H), 7.24 (d, J = 3.1 Hz, 1H), 7.21 (d, J = 1.8 Hz, 1H), 7.18 (d, J = 3.4 Hz, 2H), 6.53 (dd, J = 1.8, 3.5 Hz, 1H), 5.97 (s, 1H), 5.39 (ddd, J = 5.4, 7.7, 9.9 Hz, 1H), 3.66 - 3.55 (m, 1H), 3.30 - 3.15 (m, 2H), 2.86 - 2.74 (m, 1H), 2.48 (s, 3H), 2.26 (br d, J = 14.5 Hz, 1H), 1.67 - 1.57 (m, 2H),
 5 1.51 - 1.39 (m, 2H), 1.25 (d, J = 12.6 Hz, 2H).

LCMS: EC5857-8-P1A2, product: Ret. Time = 0.462 min, m/z +1 = 418.2

HPLC: EC5857-8-P1B1, product: Ret. Time = 1.542 min

Example 66

10 *Synthesis of N-((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(o-tolyl)propan-2-yl)thiophene-2-carboxamide (Compound 211)*



To a solution of Compound **2038** (60.0 mg, 186 μ mol, 1.00 eq) and Compound **2040** (27.4 mg, 187 μ mol, 20.0 μ L, 1.01 eq) in DMF (1.00 mL) was added TEA (94.5 mg, 934 μ mol, 130 μ L, 5.03 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5857-7-P1R1, product: Ret. Time = 0.375 min, m/z +1 = 434.2) showed that the reactant was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC. From HNMR (EC5857-7-P1C1), LCMS (EC5857-7-P1A1) and HPLC (EC5857-7-P1B1) showed that the product **Compound 211** (66.93 mg, 122 μ mol, 65.6% yield, 99.5% purity, TFA) was obtained as a yellow solid.

LCMS: EC5857-7-P1R1, product: Ret. Time = 0.375 min, m/z +1 = 434.2

¹HNMR: EC5857-7-P1C1 (400 MHz, CDCl₃)

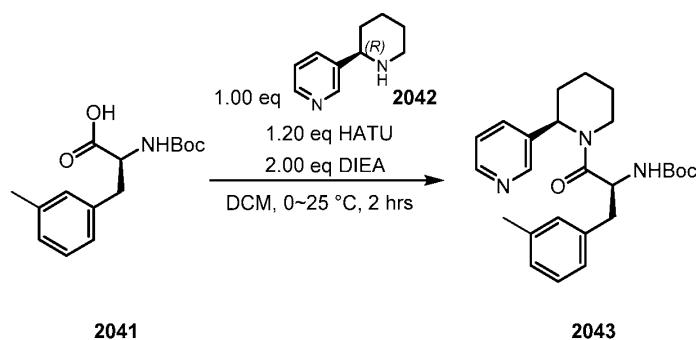
δ 8.76 (s, 1H), 8.67 (d, J = 5.4 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 7.80 (dd, J = 5.5, 8.1 Hz, 1H), 7.65 - 7.61 (m, 1H), 7.56 - 7.52 (m, 1H), 7.26 - 7.19 (m, 4H), 7.12 (dd, J = 3.9, 4.9 Hz, 1H), 6.91 (d, J = 7.1 Hz, 1H), 5.98 (d, J = 3.0 Hz, 1H), 5.39 - 5.28 (m, 1H), 3.71 - 3.63 (m, 2H), 3.28 - 3.20 (m, 2H), 2.86 - 2.76 (m, 1H), 2.27 (d, J = 15.0 Hz, 1H), 1.73 - 1.60 (m, 1H), 1.55 - 1.46 (m, 1H), 1.34 - 1.23 (m, 2H)

LCMS: EC5857-7-P1A1, product: Ret. Time = 0.466 min, m/z +1 = 434.2

HPLC: EC5857-7-P1B1, product: Ret. Time = 1.635 min

Example 67

5 *Synthesis of tert-butyl ((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(m-tolyl)propan-2-yl)carbamate*



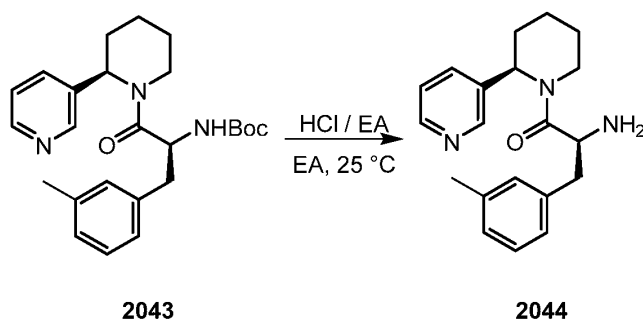
To a solution of Compound **2041** (100 mg, 358 umol, N/A purity, 1.00 *eq*) and Compound **2042** (64 mg, 395 umol, N/A purity, 1.10 *eq*) in DCM (1 mL) was added HATU (164 mg, 431 umol, 1.20 *eq*) and DIEA (96.5 mg, 746 umol, 130 uL, 2.08 *eq*) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5857-1-P1R1, product: Ret. Time = 0.407 min, m/z +1 = 424.3) showed that the reactant was consumed completely and the desired mass was detected. The reaction mixture was quenched by addition H₂O 3 mL at 25 °C, and extracted with DCM 6 mL (2 mL * 3). The combined organic layers were washed with NaCl 6 mL, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used to the next step without the further purification. From LCMS (EC5857-1-P1A1) showed that the product **Compound 2043** (150 mg, crude) was obtained as a yellow oil.

LCMS: EC5857-1-P1R1, Ret. Time = 0.407 min, m/z +1 = 424.3

LCMS: EC5857-1-P1A1, Ret. Time = 0.455 min, m/z +1 = 424.3

Example 68

Synthesis of (S)-2-amino-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(m-tolyl)propan-1-one



To a solution of Compound **2043** (150 mg, 354 μmol , N/A purity, 1.00 eq) in EtOAc (2.00 mL) was added HCl/EtOAc (4.00 M, 6.00 mL, 67.8 eq). The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5857-3-P1R1, product: Ret. Time = 0.302 min, $m/z + 1 = 324.3$)

showed that the reactant was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was used to the next step without further purification. From HNMR (EC5857-3-P1C2) showed that the product Compound **2044** (120 mg, crude) was obtained as a yellow oil.

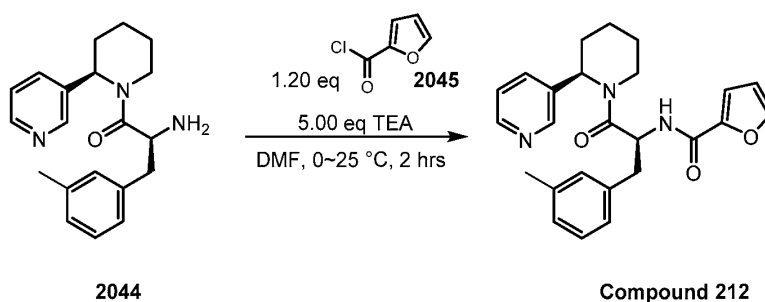
LCMS: EC5857-3-P1R1, Ret. Time = 0.302 min, $m/z + 1 = 324.3$

¹HNMR: EC5857-3-P1C2 (400 MHz, MeOD)

δ 8.90 (s, 1H), 8.79 (d, $J = 5.8$ Hz, 1H), 8.64 (d, $J = 8.3$ Hz, 1H), 8.11 (dd, $J = 5.8, 8.3$ Hz, 1H), 7.34 - 7.28 (m, 1H), 7.23 - 7.11 (m, 3H), 5.90 (brs, 1H), 3.73 (td, $J = 6.6, 13.3$ Hz, 1H), 3.31 (td, $J = 1.6, 3.3$ Hz, 5H), 3.27 - 3.17 (m, 2H), 3.16 - 3.07 (m, 1H), 3.05 - 2.95 (m, 1H), 2.39 - 2.36 (m, 3H), 1.79 - 1.65 (m, 1H), 1.57 - 1.44 (m, 1H), 1.38 (d, $J = 1.9$ Hz, 4H).

Example 69

Synthesis of N-((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(m-tolyl)propan-2-yl)furan-2-carboxamide (Compound 212)



To a solution of Compound **2044** (60.0 mg, 186 μmol , 1.00 eq) and Compound **2045** (25.1 mg, 192 μmol , 19.0 μL , 1.04 eq) in DMF (1.00 mL) was added TEA (94.5 mg, 934 μmol , 130

uL, 5.03 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5857-6-P1R1, product: Ret. Time = 0.367 min, $m/z + 1 = 418.2$) showed that the reactant was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (TFA condition).

- 5 From HNMR (EC5857-6-P1C1), LCMS (EC5857-6-P1A1) and HPLC (EC5857-6-P1B1) showed that the product **Compound 212** (38.88 mg, 72.7 umol, 39.2% yield, 99.4% purity, TFA) was obtained as a colorless oil.

LCMS: EC5857-6-P1R1, product: Ret. Time = 0.367 min, $m/z + 1 = 418.2$

¹HNMR: EC5857-6-P1C1 (400 MHz, CDCl₃)

- 10 δ 8.75 - 8.67 (m, 1H), 8.62 (d, $J = 4.6$ Hz, 1H), 8.05 (d, $J = 7.9$ Hz, 1H), 7.74 - 7.64 (m, 1H), 7.45 - 7.37 (m, 1H), 7.15 - 7.09 (m, 1H), 7.04 (brs, 4H), 6.51 - 6.43 (m, 1H), 5.96 - 5.82 (m, 1H), 5.31 - 5.15 (m, 1H), 3.73 (d, $J = 14.1$ Hz, 1H), 3.16 - 3.00 (m, 2H), 2.77 (t, $J = 12.6$ Hz, 1H), 2.29 (s, 3H), 2.26 - 2.16 (m, 1H), 1.67 - 1.55 (m, 1H), 1.47 (d, $J = 12.4$ Hz, 1H), 1.35 - 1.17 (m, 2H), 0.50 - 0.34 (m, 1H).

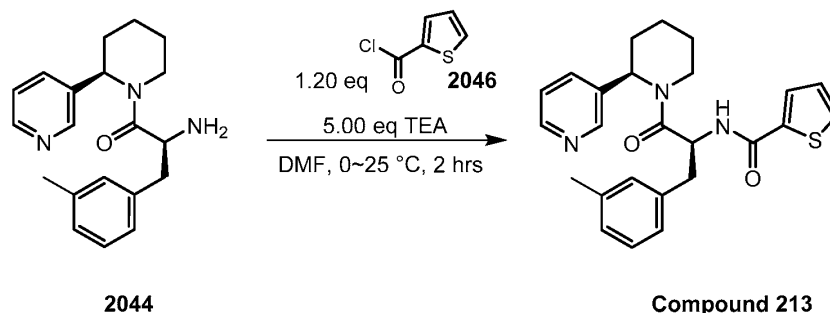
- 15 **LCMS:** EC5857-6-P1A1, product: Ret. Time = 0.450 min, $m/z + 1 = 418.2$

HPLC: EC5857-6-P1B1, product: Ret. Time = 1.526 min

Example 70

Synthesis of N-((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(m-tolyl)propan-2-yl)thiophene-2-carboxamide (Compound 213)

20



- 25 To a solution of Compound **2044** (60.0 mg, 186 umol, 1.00 eq) and Compound **2046** (27.4 mg, 187 umol, 20.0 uL, 1.01 eq) in DMF (1.00 mL) was added TEA (94.5 mg, 934 umol, 130 uL, 5.03 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5857-6-P1R1, product: Ret. Time = 0.380 min, $m/z + 1 = 434.2$) showed that the reactant was consumed completely and the desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-

HPLC (neutral condition). From HNMR (EC5857-5-P1C1), LCMS (EC5857-5-P1A1) and HPLC (EC5857-5-P1B4) showed that the product **Compound 212** (15.96 mg, 36.2 μ mol, 19.5% yield, 98.3% purity) was obtained as a white solid. The residue was purified by prep-HPLC (neutral condition). From HNMR (EC5857-12-P1C3), LCMS (EC5857-12-P1A1) and HPLC (EC5857-12-P1B1) showed that the product **Compound 212** (11.65 mg, 26.9 μ mol, 38.8% yield) was obtained as a yellow gum.

LCMS: EC5857-5-P1R1, product: Ret. Time = 0.380 min, $m/z + 1 = 434.2$

¹HNMR: EC5857-5-P1C1 (400 MHz, $CDCl_3$) and EC5857-12-P1C3 (400 MHz, $CDCl_3$)

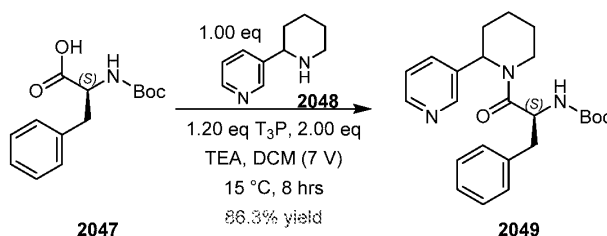
δ 8.62 - 8.48 (m, 2H), 7.87 (dd, $J = 2.4, 5.3$ Hz, 1H), 7.64 - 7.51 (m, 3H), 7.15 - 7.09 (m, 4H), 6.84 (d, $J = 7.4$ Hz, 1H), 5.98 (d, $J = 3.1$ Hz, 1H), 5.42 - 5.33 (m, 1H), 3.82 - 3.72 (m, 1H), 3.22 - 3.13 (m, 2H), 2.94 - 2.83 (m, 1H), 2.40 - 2.36 (m, 3H), 2.33 (d, $J = 16.0$ Hz, 1H), 1.58 - 1.53 (m, 2H), 1.42 - 1.35 (m, 2H), 0.62 - 0.50 (m, 1H).

LCMS: EC5857-5-P1A1 and EC5857-12-P1A1, product: Ret. Time = 0.481 min, $m/z + 1 = 434.2$

HPLC: EC5857-5-P1B4 and EC5857-12-P1B1, product: Ret. Time = 1.587 min

Example 71

Synthesis of tert-butyl ((2S)-1-oxo-3-phenyl-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



To a solution of compound **2047** (300 mg, 1.13 mmol, 1.00 eq) in DCM (2 mL) was added T_3P (864 mg, 1.36 mmol, 808 μ L, 50% purity, 1.20 eq) and TEA (229 mg, 2.26 mmol, 315 μ L, 2.00 eq), compound **2048** (183 mg, 1.13 mmol, 9.98e-1 eq) at under N_2 . The mixture was stirred at 15 °C for 8 hrs. LCMS (EC1956-3-P1A1) showed that the compound **2047** was consumed completely and the desired mass (RT = 0.399 min, $M+1 = 410.4$) was detected. The residue was diluted with H_2O (15.0 mL) and extracted with DCM 30 mL (10mL x3). The combined organic layers were washed with brine 20 mL (10 mL x 2), dried

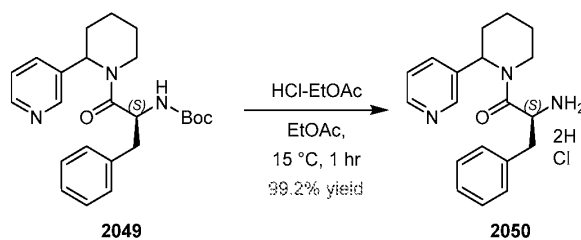
over Na₂SO₄, filtered and concentrated under reduced pressure to give compound **2049** (400 mg, 976 umol, 86.3% yield) as a yellow solid.

LCMS: EC1956-3-P1A1, RT = 0.399 min, m/z (M+1) = 410.4

5

Example 72

Synthesis of (2S)-2-amino-3-phenyl-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



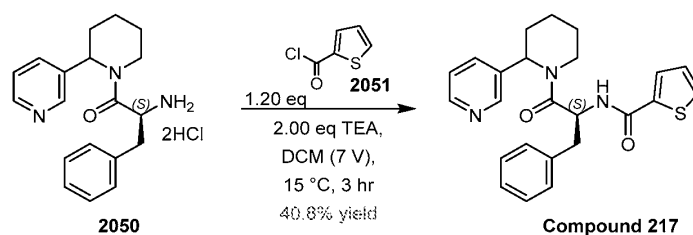
To a solution of compound **2049** (400 mg, 976 umol, 1.00 eq) in EtOAc (2 mL) was added HCl/EtOAc (4 M, 4 mL, 16.3 eq). The mixture was stirred at 15 °C for 1 hr. LCMS (EC1956-4-P1A1) showed that the compound **2049** was consumed completely and the desired mass (RT = 0.373 min, M+1 = 310.2) was detected. The reaction mixture was concentrated under vacuum to give compound **2050** (300 mg, 969.60 umol, 99.27% yield) as a yellow solid.

LCMS: EC1956-4-P1A1, RT = 0.373 min, m/z (M+1) = 310.2

15

Example 73

Synthesis of N-((2S)-1-oxo-3-phenyl-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 217)



To a solution of compound **2050** (300 mg, 969 umol, 1.00 eq) in DCM (2 mL) was added TEA (196 mg, 1.94 mmol, 270 uL, 2.00 eq) and compound **2051** (142 mg, 971 umol, 104 uL, 1.20 eq). The mixture was stirred at 15 °C for 3 hrs. LCMS (EC1956-5-P1A1) showed that the compound **2050** was consumed completely and the desired mass (RT = 0.345 min, M+1 = 420.3) was detected. The reaction mixture was concentrated under vacuum. The residue was purified by prep-HPLC (column: YMC Triart C18 250*50mm*7um; mobile phase:

[water(0.1%TFA)-ACN];B%: 23%-53%,10min) to afford the **Compound 217** (169 mg, 395.57 umol, 40.8% yield, 98.2% purity) as a white solid.

LCMS: EC1956-5-P1A1 , RT = 0.345 min, m/z (MS+1 = 420.3)

LCMS: EC1956-5-P1B2, RT = 0.359 min, m/z (M+1) = 420.1

5 **HPLC:** EC1956-5-P1B4, RT = 0.853 min,

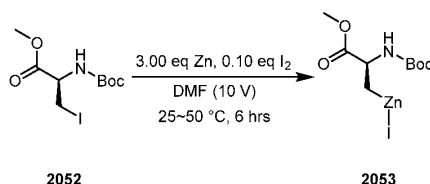
¹H NMR: EC1956-5-P1B1 (400 MHz, DMSO)

δ 9.06 - 8.93 (m, 1H), 8.76 - 8.65 (m, 1H), 8.60 (s, 1H), 8.21 (br d, J = 8.0 Hz, 1H), 7.98 - 7.65 (m, 3H), 7.40 - 7.15 (m, 6H), 5.88 - 5.70 (m, 1H), 5.17 - 4.97 (m, 1H), 3.88 (br d, J = 14.6 Hz, 2H), 3.16 - 3.07 (m, 2H), 2.96 - 2.81 (m, 1H), 1.62 - 0.60 (m, 6H)

10

Example 74

Synthesis of (R)-2-((tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)zinc(II) iodide

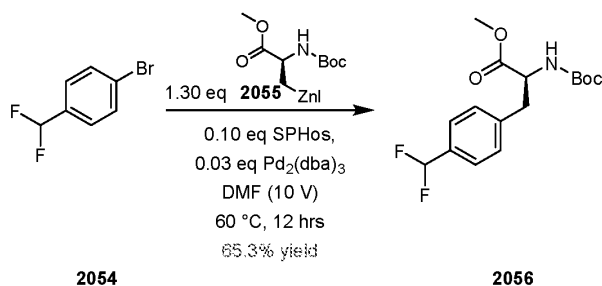


15 To a solution of I₂ (1.62 g, 6.38 mmol, 1.29 mL, 0.10 *eq*) in DMF (84.0 mL) was added Zn (12.5 g, 191 mmol, 3.00 *eq*) at 25 °C. The mixture was stirred at 50 °C for 3 hrs. Then the mixture cooled to 25 °C, the compound **2052** (21.0 g, 63.8 mmol, 1.00 *eq*) in DMF (120 mL) was added. The mixture was stirred at 25 °C for 3 hrs. TLC (Petroleum ether: Ethyl acetate = 5:1) showed compound **2052** (R_f = 0.40) was consumed and the one new spot

20 (R_f = 0.50) was formed. The reaction mixture was filtered, the filtrate was used to next step. The filtrate was used to next step without purification. Compound **2053** (24.8 g, 62.8 mmol, 98.5% yield) was obtained as a gray liquid and dissolved in DMF (300 mL).

Example 75

25 *Synthesis of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(difluoromethyl)phenyl)propanoate*



To a solution of compound **2055** (24.8 g, 62.8 mmol, 1.3 *eq*) in DMF (300 mL) was added compound **2054** (10.0 g, 48.3 mmol, 1.00 *eq*), SPHos (1.98 g, 4.83 mmol, 0.10 *eq*), and Pd₂(dba)₃ (1.33 g, 1.45 mmol, 0.03 *eq*). The mixture was stirred at 60 °C for 12 hrs under N₂.

5 LCMS (EC2762-2-P1A1) showed the compound **2054** was consumed and the desired mass (RT = 0.521 min, m/z (M-99) = 230.1) was detected. The reaction mixture was filtered, the filtrate was diluted with Ethyl acetate (400 mL) and H₂O (500 mL). The organic layer was washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 30/1 to 5/1, R_f =

10 0.30 was collected). From HNMR (EC2762-2-P1A) and LCMS (EC2762-2-P1C1) showed the compound **2056** (11.0 g, 31.5 mmol, 65.3% yield, 94.4% purity) was obtained as brown yellow oil.

LC-MS: EC2762-2-P1A1, RT = 0.521 min, m/z (M-99) = 230.1

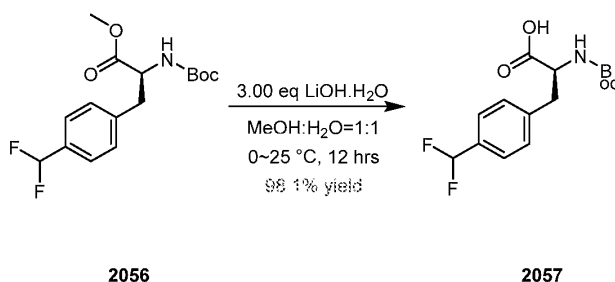
LC-MS: EC2762-2-P1C1, RT = 0.525 min, m/z (M-99) = 230.1

15 **¹H-NMR:** EC2762-2-P1A, 400 MHz, DMSO-*d*₆

δ 7.56 - 7.30 (m, 2H), 7.12 (s, 1H), 6.98 (s, 1H), 6.84 (s, 1H), 7.15 - 6.77 (m, 1H), 4.27 - 3.97 (m, 1H), 3.62 (s, 3H), 3.22 - 2.77 (m, 2H), 1.39 - 1.26 (m, 9H)

Example 76

20 *Synthesis of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(difluoromethyl)phenyl)propanoic acid*



To a solution of compound **2056** (11.0 g, 31.5 mmol, 94.4% purity, 1.00 eq) in MeOH (100 mL) was added the solution of LiOH.H₂O (3.97 g, 94.6 mmol, 3.00 eq) in H₂O (100 mL) at 0 °C, then the reaction mixture was stirred at 25 °C for 12 hrs. LCMS (EC2762-3-P1A1) showed the compound **2056** was consumed and the desired mass (RT = 0.466 min, m/z (M-99) = 216.1) was detected. The reaction mixture was adjusted to pH = 5 with 1M HCl, and the reaction mixture was partitioned between ethyl acetate (250 mL) and water (150 mL). The organic phase was separated, washed with brine (150 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used to next step without purification. From LCMS (EC2762-3-P1B1) and HNMR (EC2762-3-P1A) showed the product compound **2057** (10.0 g, 30.9 mmol, 98.1% yield, 97.5% purity) was obtained as gray solid.

LC-MS: EC2762-3-P1A1, RT = 0.466 min, m/z (M-99) = 216.1

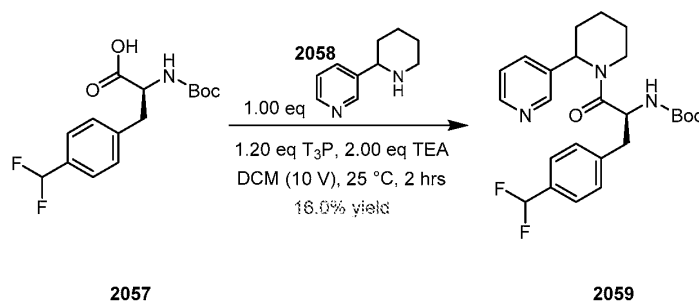
LC-MS: EC2762-3-P1B1, RT = 0.468 min, m/z (M-99) = 216.1

¹H-NMR: EC2762-3-P1A, 400 MHz, CDCl₃

δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.29 (br d, *J* = 7.6 Hz, 2H), 6.64 (t, *J* = 56.4 Hz, 1H), 4.97 (br d, *J* = 7.6 Hz, 1H), 4.65 (br d, *J* = 6.4 Hz, 1H), 3.34 - 2.95 (m, 2H), 1.45 - 1.25 (m, 9H)

Example 77

Synthesis of tert-butyl ((2S)-3-(4-(difluoromethyl)phenyl)-1-oxo-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



To a solution of compound **2057** (10.0 g, 30.9 mmol, 97.5% purity, 1.00 eq) and compound **2058** (5.02 g, 30.9 mmol, 1.00 eq) in DCM (100 mL) was added T₃P (23.5 g, 36.9 mmol, 22.0 mL, 50% purity, 1.20 eq) and DIEA (8.16 g, 63.1 mmol, 11.0 mL, 2.04 eq), then the reaction mixture was stirred at 25 °C for 2 hrs. LCMS (EC2762-4-P1A1) showed the compound **2057** was consumed and the desired mass (RT = 0.441 min, m/z (M+1) = 460.3) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 10 um); mobile phase: [water (

NH₄HCO₃)-ACN]; B%: 45%-70%, 20 min). From HNMR (EC2762-4-P1A) and LCMS (EC2762-4-P1B1) showed the product compound **2059** (2.70 g, 4.96 mmol, 16.0% yield, 84.4% purity) was obtained as white solid.

LC-MS: EC2762-4-P1A1, RT = 0.441 min, m/z (M+1) = 460.3

LC-MS: EC2762-4-P1B1, RT = 0.430 min, m/z (M+1) = 460.4

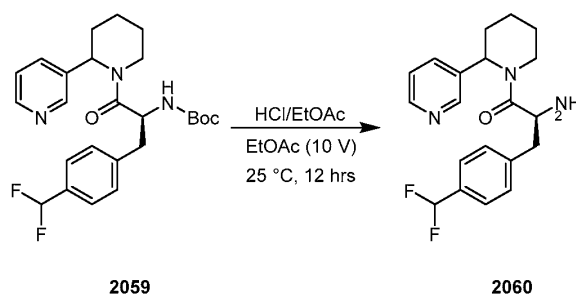
¹H-NMR: EC2762-4-P1A, 400 MHz, DMSO-*d*₆

δ 8.50 - 8.31 (m, 2H), 7.65 - 7.22 (m, 7H), 7.15 - 6.86 (m, 1H), 5.73 (br d, *J* = 15.6 Hz, 1H), 4.92 - 4.56 (m, 1H), 4.06 - 3.68 (m, 1H), 3.17 - 2.64 (m, 3H), 2.41 - 2.30 (m, 1H), 1.81 - 1.43 (m, 3H), 1.41 - 1.24 (m, 9H), 1.05 (br s, 2H)

10

Example 78

Synthesis of (2S)-2-amino-3-(4-(difluoromethyl)phenyl)-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



To a solution of compound **2059** (2.70 g, 4.96 mmol, 84.4% purity, 1.00 eq) in EtOAc (27.0 mL) was added HCl / EtOAc (4 M, 27.0 mL, 18.3 eq), then the reaction mixture was stirred at 25 °C for 12 hrs. LCMS (EC2762-5-P1A1) showed the compound **2059** was consumed and the desired mass (RT = 0.251 min, m/z (M-99) = 360.2) was detected. The reaction mixture was concentrated. The residue was used to next step without purification.

From HNMR (EC2762-5-P1A) showed the product compound **2060** (2.50 g, crude, HCl) was obtained as light brown solid.

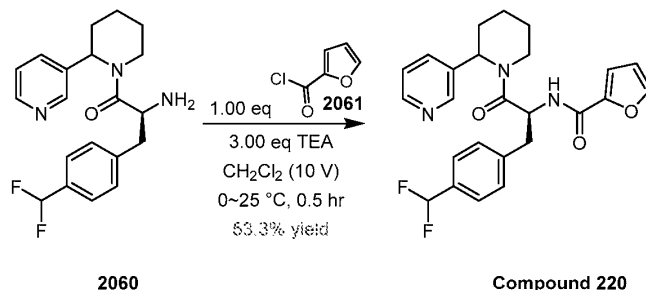
LC-MS: EC2762-5-P1A1, RT = 0.250 min, m/z (M-99) = 360.2

¹H-NMR: EC2762-5-P1A, 400 MHz, DMSO-*d*₆

δ 9.03 - 8.63 (m, 2H), 8.59 (br d, *J* = 5.2 Hz, 1H), 8.05 - 7.67 (m, 1H), 7.64 - 7.30 (m, 3H), 7.27 - 6.83 (m, 1H), 5.74 (br d, *J* = 26.8 Hz, 1H), 4.93 - 4.60 (m, 1H), 4.50 - 3.96 (m, 3H), 3.36 - 2.99 (m, 2H), 2.92 - 2.56 (m, 1H), 2.46 - 2.22 (m, 1H), 1.95 - 1.35 (m, 2H), 1.27 - 1.08 (m, 1H)

Example 79

Synthesis of N-((2S)-3-(4-(difluoromethyl)phenyl)-1-oxo-1-(2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 220)



To a solution of compound **2060** (2.30 g, 6.40 mmol, 1.00 *eq*) in DCM (25.0 mL) was added TEA (2.18 g, 21.5 mmol, 3 mL, 3.00 *eq*) and compound **2061** (924 mg, 7.08 mmol, 700 μ L, 1.11 *eq*) at 0 °C, and then the reaction mixture stirred at 25 °C for 30 min. LCMS (EC2762-7-P1A2) showed the compound **2060** was consumed and the desired mass (RT = 0.385 min, m/z (M+1) = 454.3) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: YMC Triart C18 250*50mm*7 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 25%-55%, 20 min). From HNMR (EC2762-7-P1B), LCMS (EC2762-7-P1B1) and HPLC (EC2762-7-P1B2) showed the product **Compound 220** (1.60 g, 3.41 mmol, 53.3% yield, 96.6% purity) was obtained as gray solid.

LC-MS: EC2762-7-P1A2, RT = 0.385 min, m/z (M+1) = 454.3

LC-MS: EC2762-7-P1B1, RT = 0.389 min, m/z (M+1) = 454.2

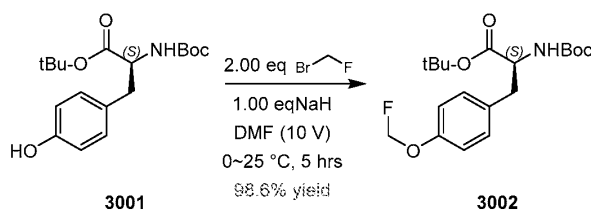
HPLC: EC2762-7-P1B2, RT = 1.428 min, 96.5% purity

¹H-NMR: EC2762-7-P1B, 400 MHz, DMSO-*d*₆

δ 9.02 - 8.65 (m, 1H), 8.59 - 8.29 (m, 2H), 7.93 - 7.68 (m, 1H), 7.65 - 7.40 (m, 4H), 7.33 - 7.20 (m, 2H), 7.16 - 6.80 (m, 1H), 6.67 - 6.43 (m, 1H), 5.87 - 5.55 (m, 1H), 5.42 - 5.02 (m, 1H), 4.53 - 3.72 (m, 1H), 3.26 - 3.05 (m, 2H), 2.94 - 2.59 (m, 1H), 2.40 - 2.30 (m, 1H), 1.78 - 0.86 (m, 5H)

Example 80

Synthesis of tert-butyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(fluoromethoxy)phenyl)propanoate



To a solution of compound **3001** (5.00 g, 14.8 mmol, 1.00 eq) in THF (50.0 mL) was added NaH (600 mg, 15.0 mmol, 60% purity, 1.01 eq) at 25 °C and the mixture was stirred at this temperature for 0.5 hr. Then bromo (fluoro) methane (3.35 g, 29.64 mmol, 2.00 eq) in THF (10 mL) was added dropwise at 0 °C. After addition, the mixture was stirred at this temperature for 2 hrs. The resulting mixture was warmed to 25 °C and stirred at 25 °C for 2 hrs. LCMS showed that compound **3001** ($m/z=337.4$) was consumed completely the desired MS ($R_t = 0.657$ min, $M-155 = 214.1$) was found. TLC (Plate 1, PE: EA = 5:1) showed the consumption of compound **3001** ($R_f = 0.45$) and the one large new spot ($R_f = 0.65$) was formed. The reaction mixture was poured into saturated NH_4Cl aqueous solution (100 mL) and extracted with EtOAc (50.0 mL*3). The combined organic layer was washed with brine (50.0 mL*2), dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (SiO_2 , PE: EA=20:1-5:1), the fraction (Plate 1, $R_f = 0.65$) was collected. Compound **3002** (5.40 g, 14.6 mmol, 98.6% yield) was obtained as yellow oil, checked by LCMS and HNMR.

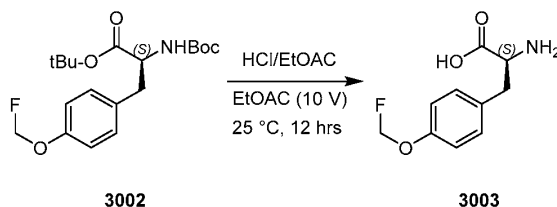
LC-MS (reaction mixture): $R_t = 0.657$ min, m/z ($M-155$) = 214.1

LC-MS (compound 3002): $R_t = 0.651$ min, m/z ($M-155$) = 214.1

$^1\text{H-NMR}$: 400 MHz, CDCl_3 : δ 7.25 - 6.86 (m, 4H), 5.89 - 5.51 (m, 2H), 5.00 (br s, 1H), 4.43 (br s, 1H), 3.02 (br s, 2H), 1.42 (br d, $J = 3.8$ Hz, 18H)

Example 81

Synthesis of (S)-2-amino-3-(4-(fluoromethoxy)phenyl)propanoic acid



To a solution of compound **3002** (5.50 g, 14.8 mmol, 1.00 eq) in EtOAc (20.0 mL) was added HCl/EtOAc (4 M, 30.0 mL, 8.06 eq). The mixture was stirred at 25 °C for 3 hrs.

LCMS showed compound **3002** ($m/z=369$) was consumed completely and the main peak with desired MS ($RT = 0.246$ min, $M-155 = 214.0$) was found. The reaction mixture was concentrated under vacuum. No need further purification to give compound **3003** (3.90 g, crude, HCl) as white solid and used to the next step. Compound **3003** (3.90 g, crude, HCl) was obtained as white solid, checked by HNMR.

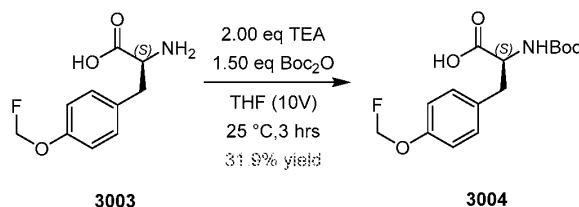
LC-MS (reaction mixture): $RT = 0.246$ min, m/z ($M-155$) = 214.0

1H -NMR: 400 MHz, $DMSO-d_6$: δ 14.10 - 13.61 (m, 1H), 8.35 (br s, 2H), 7.26 (d, $J = 8.5$ Hz, 2H), 7.07 (d, $J = 8.5$ Hz, 2H), 6.04 - 5.65 (m, 2H), 4.15 (br s, 1H), 3.09 (br d, $J = 6.1$ Hz, 2H)

10

Example 82

Synthesis of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(fluoromethoxy)phenyl)propanoic acid



To a solution of compound **3003** (3.07 g, 14.40 mmol, 1.00 eq) in THF (40.0 mL) was added (Boc)₂O (12.8 g, 58.7 mmol, 13.5 mL, 4.08 eq) and TEA (5.82 g, 57.5 mmol, 8 mL, 3.99 eq). The mixture was stirred at 25 °C for 4 hrs. LCMS showed that compound **3003** ($m/z = 214$) was consumed completely and the desired MS ($Rt = 0.488$ min, $M+23 = 336$) was found. The reaction mixture was filtered, and the filter liquor was collected and concentrated. The crude product was purified by prep-HPLC (column: YMC Triart C18 70*250mm*7um; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 13%-43%, 20 min). Compound **3004** (1.47 g, 4.60 mmol, 31.9% yield, 98% purity) was obtained as yellow oil, checked by LCMS and HNMR.

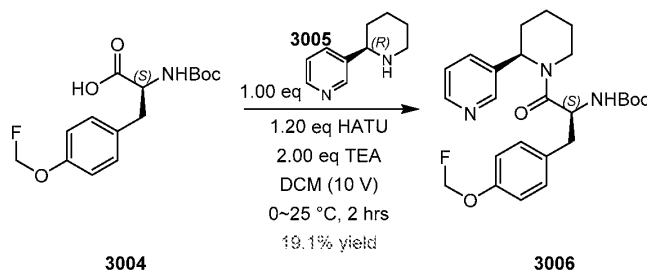
LC-MS (reaction mixture): $RT = 0.488$ min, m/z ($M+23$) = 336

LC-MS (compound 22): $RT = 0.468$ min, m/z ($M-99$) = 216.1

1H -NMR: 400 MHz, $CDCl_3$: δ 7.15 (d, $J = 8.4$ Hz, 2H), 6.94 (d, $J = 8.5$ Hz, 2H), 5.76 - 5.67 (m, 1H), 5.62 - 5.55 (m, 1H), 5.42 (br d, $J = 7.1$ Hz, 1H), 4.28 (br d, $J = 6.1$ Hz, 1H), 3.15 (br dd, $J = 4.9, 13.8$ Hz, 1H), 1.38 (s, 8H)

Example 83

Synthesis of tert-butyl ((S)-3-(4-(fluoromethoxy)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



To a solution of compound **3004** (1.10 g, 3.51 mmol, 1.00 eq) in DCM (20.0 mL) was added compound **3005** (570 mg, 3.51 mmol, 1.00 eq) and DIEA (890 mg, 6.89 mmol, 1.2 mL, 1.96 eq). Then HATU (1.65 g, 4.34 mmol, 1.24 eq) was added at 0 °C. The mixture was stirred at 25 °C for 2 hr. LCMS showed that compound **3004** ($m/z = 313$) was consumed completely and the desired MS ($R_t = 0.455$ min, $M+1 = 458.3$) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (column: YMC Triart C18 250*50mm*7um; mobile phase: [water (FA)-ACN]; B%: 15%-45%, 24min). Compound **3006** (323 mg, 670 umol, 19.1% yield, 95% purity) was obtained as yellow oil, checked by LCMS and HNMR.

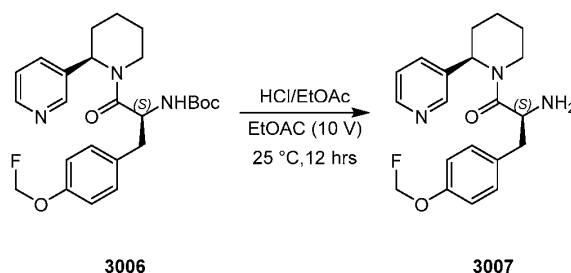
LC-MS (reaction mixture): $R_t = 0.441$ min, m/z ($M+1$) = 460.3

LC-MS (compound 23): $R_t = 0.430$ min, m/z ($M+1$) = 460.4

$^1\text{H-NMR}$: 400 MHz, CDCl_3 : δ 8.52 (br s, 1H), 8.13 (br s, 1H), 7.68 (br d, $J = 7.9$ Hz, 1H), 7.46 - 7.36 (m, 1H), 7.23 (br d, $J = 8.4$ Hz, 2H), 7.08 - 7.00 (m, 2H), 5.94 (br d, $J = 1.4$ Hz, 1H), 5.77 (s, 1H), 5.63 (s, 1H), 5.52 (br d, $J = 8.6$ Hz, 1H), 4.95 - 4.84 (m, 1H), 3.78 - 3.65 (m, 1H), 3.07 - 2.95 (m, 2H), 2.53 - 2.20 (m, 2H), 1.82 - 1.57 (m, 2H), 1.57 - 1.49 (m, 2H), 1.44 (s, 9H)

Example 84

Synthesis of (S)-2-amino-3-(4-(fluoromethoxy)phenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



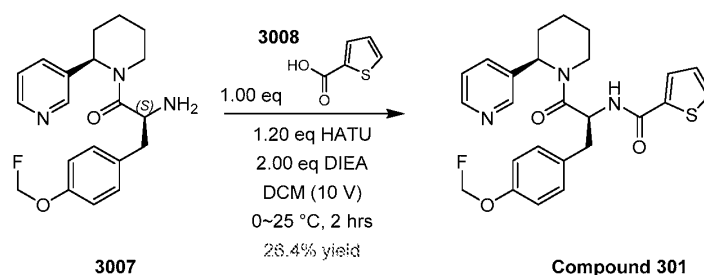
To a solution of compound **3006** (0.53 g, 1.16 mmol, 1.00 eq) in EtOAc (5 mL) was added HCl/EtOAc (4 M, 5 mL, 17.2 eq). The mixture was stirred at 25 °C for 1 hrs. LCMS showed that compound **3006** ($m/z = 457$) was consumed completely and the desired MS ($R_t = 0.317$ min, $M+1 = 358.1$) was found. The reaction mixture was concentrated under vacuum. No need further purification to give compound **3007** as white solid and used to the next step. Compound **3007** (0.528 g, crude, HCl) was obtained as white solid, checked by HNMR.

LC-MS (reaction mixture): $R_t = 0.317$ min, m/z ($M+1$) = 358.1

$^1\text{H-NMR}$: 400 MHz, $\text{DMSO}-d_6$: δ 8.91 (s, 1H), 8.75 (br d, $J = 5.4$ Hz, 1H), 8.70 - 8.58 (m, 3H), 8.52 (br d, $J = 7.9$ Hz, 1H), 7.92 (dd, $J = 5.5, 8.0$ Hz, 1H), 7.30 (br d, $J = 8.5$ Hz, 2H), 7.13 (d, $J = 8.4$ Hz, 2H), 5.95 - 5.88 (m, 1H), 5.80 - 5.76 (m, 1H), 5.73 (br s, 1H), 4.83 - 4.68 (m, 1H), 3.67 (br d, $J = 13.6$ Hz, 1H), 3.17 (br dd, $J = 5.1, 13.1$ Hz, 1H), 2.96 (br dd, $J = 9.3, 13.1$ Hz, 1H), 2.42 - 2.26 (m, 2H), 1.91 (s, 1H), 1.55 - 1.21 (m, 3H)

Example 85

Synthesis of N-((S)-3-(4-(fluoromethoxy)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 301)



To a solution of compound **3007** (0.25 g, 634.71 μmol , 1.00 eq, HCl) in DCM (5 mL) was added thiophene-2-carboxylic acid (82 mg, 639.88 μmol , 1.01 eq) and DIEA (244 mg, 1.89 mmol, 330 μL , 2.98 eq). Then HATU (290 mg, 762.70 μmol , 1.20 eq) was added at 0 °C. The mixture was stirred at 25 °C for 1 hr. LCMS showed that compound **3007** ($m/z =$

457) was consumed completely and the desired MS ($R_t = 0.429$ min, $M+1 = 468.3$) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (column: YMC Triart C18 250*50mm*7 μ m; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 27%-57%, 20 min). **Compound 301** (86 mg, 167.38 μ mol, 26.4% yield, 91.0% purity) was obtained as white solid, checked by LCMS, HPLC and HNMR.

LC-MS (reaction mixture): $R_t = 0.429$ min, m/z ($M+1$) = 468.3

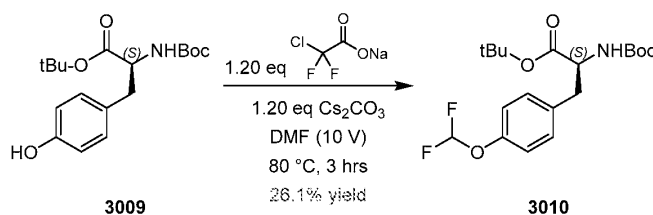
LC-MS: $R_t = 1.625$ min, m/z ($M+1$) = 468.2

HPLC: $R_t = 1.652$ min, 91.0% purity

¹H-NMR: 400 MHz, CDCl₃: δ 8.49 (br s, 2H), 7.59 - 7.44 (m, 3H), 7.25 (br s, 1H), 7.15 - 7.01 (m, 3H), 6.99 - 6.86 (m, 2H), 5.95 (br d, $J = 2.8$ Hz, 1H), 5.78 (s, 1H), 5.64 (s, 1H), 5.51 - 5.37 (m, 1H), 3.82 - 3.73 (m, 1H), 3.28 - 3.09 (m, 2H), 2.96 (br t, $J = 13.4$ Hz, 1H), 2.38 (br d, $J = 13.0$ Hz, 1H), 1.86 - 1.52 (m, 6H), 0.93 - 0.64 (m, 1H)

Example 86

Synthesis of *tert*-butyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(difluoromethoxy)phenyl)propanoate

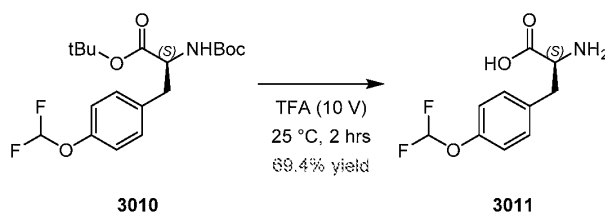


To a solution of compound **3009** (10.0 g, 29.6 mmol, 1.00 *eq*) in DMF (100 mL) was added Cs₂CO₃ (11.5 g, 35.5 mmol, 1.20 *eq*) and (2-chloro-2,2-difluoroacetyl)oxysodium (5.42 g, 35.5 mmol, 1.20 *eq*), then the reaction mixture was stirred at 80 °C for 3 hrs. LCMS showed 30% of the Reactant 1 ($R_t = 0.578$ min, m/z ($M-155$) = 182.2) remained and the desired mass ($R_t = 0.667$ min, m/z ($M-155$) = 232.1) was detected. The reaction mixture was partitioned between ethyl acetate (200 mL) and water (100 mL). The organic phase was separated, washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by reversed-phase HPLC (0.1% TFA condition). From HNMR showed the product compound **3010** (3.00 g, 7.74 mmol, 26.1% yield) was obtained as gray solid.

LC-MS (reaction mixture): $R_t = 0.667$ min, m/z ($M-155$) = 232.1

¹H-NMR: 400 MHz, DMSO: δ 7.39 - 7.25 (m, 2H), 7.19 - 7.14 (m, 1H), 7.08 (br d, J = 8.4 Hz, 2H), 4.12 - 3.76 (m, 1H), 3.03 - 2.73 (m, 2H), 1.37 - 1.31 (m, 18H)

Example 87

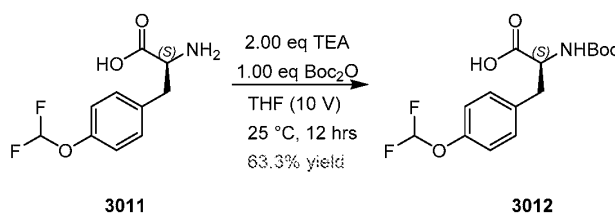
5 *Synthesis of (S)-2-amino-3-(4-(difluoromethoxy)phenyl)propanoic acid*

To a solution of compound **3010** (600 mg, 2.09 mmol, 1.00 *eq*) in TFA (5 mL) then the reaction mixture was stirred at 25 °C for 2 hrs. LCMS showed the compound **3010** was consumed and the desired mass (RT = 0.288 min, m/z (M+1) = 232.1) was detected. The reaction mixture was concentrated. The residue was used to next step without purification. From HNMR showed the product compound **3011** (500 mg, 1.45 mmol, 69.4% yield, TFA) was obtained as gray solid.

LC-MS (reaction mixture): RT = 0.288 min, m/z (M+1) = 232.1

15 **¹H-NMR:** 400 MHz, DMSO: δ 8.33 (s, 3H), 7.37 - 7.00 (m, 5H), 4.17(s, 1H), 3.13 - 3.08 (m, 2H)

Example 88

20 *Synthesis of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-(difluoromethoxy)phenyl)propanoic acid*

To a solution of compound **3011** (500 mg, 2.16 mmol, 1.00 *eq*) in THF (5 mL) and H₂O (5 mL) was added NaHCO₃ (545 mg, 6.49 mmol, 252 μ L, 3.00 *eq*) and Boc₂O (475 mg, 2.18 mmol, 500 μ L, 1.01 *eq*) and then the reaction mixture was stirred at 25 °C for 12 hrs. LC-MS showed the compound **3011** was consumed and the desired mass (RT = 0.532 min, m/z (M-99) = 232.1) was detected. The reaction mixture was poured into H₂O (50.0 mL) and adjusted to pH = 5 with citric acid, and the aqueous layer was extracted with ethyl acetate

(100 mL). The organic layer was washed with brine (20.0 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated. The residue was used to next step without purification. From HNMR and LCMS showed the product compound **3012** (500 mg, 1.37 mmol, 63.3% yield, 90.7% purity) was obtained as colourless oil.

5 **LC-MS (reaction mixture):** RT = 0.532 min, m/z (M-99) = 232.1

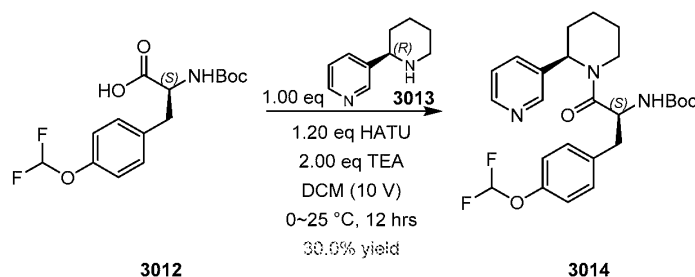
LC-MS: RT = 0.537 min, m/z (M-99) = 232.1

¹H-NMR: 400 MHz, DMSO: δ 7.25 - 6.95 (m, 4H), 6.49 (t, *J* = 74.0 Hz, 1H), 5.01 (br d, *J* = 7.1 Hz, 1H), 4.75 - 3.94 (m, 2H), 3.38 - 2.86 (m, 2H), 1.48 - 1.31 (m, 9H)

10

Example 89

Synthesis of tert-butyl ((S)-3-(4-(difluoromethoxy)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



To a solution of compound **3012** (500 mg, 1.51 mmol, 1.00 *eq*) and compound **3013** (250 mg, 1.54 mmol, 1.02 *eq*) in DCM (3 mL) was added DIEA (393 mg, 3.04 mmol, 530 μL, 2.02 *eq*) and HATU (689 mg, 1.81 mmol, 1.20 *eq*) at 0 °C, and then the reaction mixture was stirred at 25 °C for 12 hrs. LCMS showed the compound **3012** was consumed and the desired mass (RT = 0.493 min, m/z (M+1) = 476.4) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10um; mobile phase: [water (FA)-ACN]; B%: 23%-53%, 10 min). From HNMR and LCMS showed the product compound **3014** (290 mg, 453 μmol, 30.0% yield, 74.3% purity) was obtained as colorless oil.

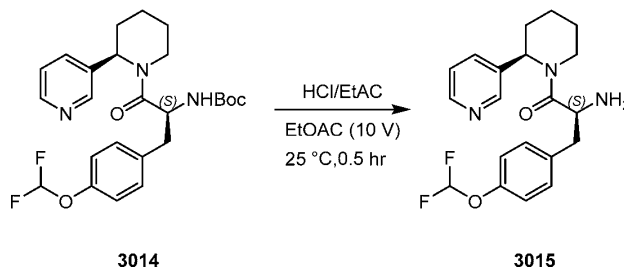
LC-MS (reaction mixture): RT = 0.493 min, m/z (M+1) = 476.4

LC-MS (compound 3014): RT = 0.498 min, m/z (M+1) = 476.3

25 **¹H-NMR:** 400 MHz, DMSO: δ 8.58 - 8.48 (m, 1H), 7.85 (br d, *J* = 7.6 Hz, 1H), 7.59 - 7.24 (m, 4H), 7.22 - 6.95 (m, 3H), 5.74 (br s, 1H), 4.91 - 4.44 (m, 1H), 2.98 - 2.71 (m, 3H), 2.45 - 2.23 (m, 2H), 1.78 - 1.44 (m, 2H), 1.43 - 1.27 (m, 9H), 1.25 - 0.65 (m, 3H)

Example 90

Synthesis of (S)-2-amino-3-(4-(difluoromethoxy)phenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



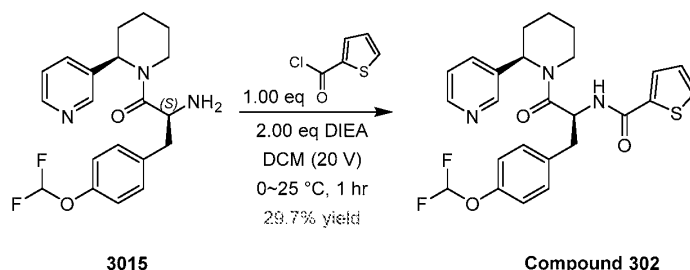
- 5 To a solution of compound **3014** (290 mg, 609 μmol , 1.00 *eq*) in EtOAc (2 mL) was added HCl/EtOAc (4 M, 2.07 mL, 13.5 *eq*) then the reaction mixture was stirred at 25 °C for 0.5 hrs. LCMS showed the compound **3014** was consumed and the desired mass (RT = 0.361 min, m/z (M^+) = 376.3) was detected. The reaction mixture was concentrated. The residue was used to next step without purification. Compound **3015** (300 mg, crude, HCl) was
- 10 obtained as colorless oil.

LCMS (reaction mixture): RT = 0.361 min, m/z (M^+) = 376.3.

Example 91

Synthesis of N-((S)-3-(4-(difluoromethoxy)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 302)

15



- To a solution of compound **3015** (150 mg, 399 μmol , 1.00 *eq*) in DCM (2 mL) was added DIEA (103 mg, 803 μmol , 140 μL , 2.01 *eq*) and thiophene-2-carbonyl chloride (61.6 mg, 420 μmol , 45 μL , 1.05 *eq*) at 0 °C, and then the reaction mixture was stirred at 25 °C for
- 20 1 hr. LCMS showed the compound **3015** was consumed and the desired mass (RT = 0.479 min, m/z ($M+1$) = 486.4) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (FA)-ACN]; B%: 20%-50%, 10 min). From HNMR, LCMS and HPLC

showed the product **Compound 302** (58.44 mg, 118 umol, 29.7% yield, 98.7% purity) was obtained as white solid.

LCMS (reaction mixture): RT = 0.479 min, m/z (M+1) = 486.4

LCMS: RT = 0.473 min, m/z (M+1) = 486.3

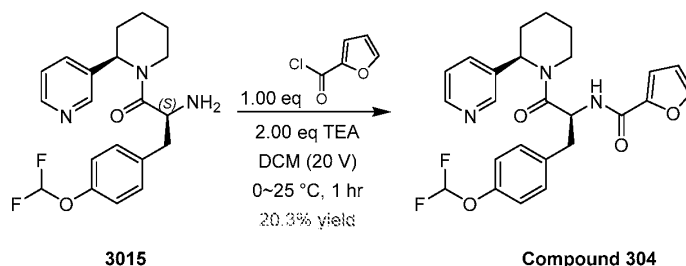
5 **HPLC:** RT = 1.661min, 98.7% purity

¹H-NMR: 400 MHz, MeOD: δ 8.45 - 8.27 (m, 2H), 7.79 - 7.53 (m, 2H), 7.39 - 7.28 (m, 4H), 7.20 - 6.92 (m, 4H), 6.86 - 6.53 (m, 1H), 5.89 - 5.30 (m, 2H), 4.60 - 3.98 (m, 1H), 3.27 - 3.09 (m, 2H), 2.84 - 2.34 (m, 2H), 2.02 - 1.84 (m, 1H), 1.75 - 1.32 (m, 4H)

10

Example 92

Synthesis of N-((S)-3-(4-(difluoromethoxy)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 304)



To a solution of compound **3015** (100 mg, 266 umol, 1.00 eq) in DCM (2 mL) was added TEA (58.1 mg, 574 umol, 80 uL, 2.16 eq) and furan-2-carbonyl chloride (39.6 mg, 303.38 umol, 30 uL, 1.14 eq) at 0 °C, and then the reaction mixture was stirred at 25 °C for 1 hr. LC-MS showed the compound **3015** was consumed and the desired mass (RT = 0.465 min, m/z (M+1) = 470.3) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (HCl)-ACN]; B%: 19%-49%, 10 min). From HNMR, LCMS and HPLC showed the product **Compound 204** (25.84 mg, 53.99 umol, 20.3% yield, 98.1% purity) was obtained as colorless oil.

LC-MS (reaction mixture): RT = 0.465 min, m/z (M+1) = 470.3

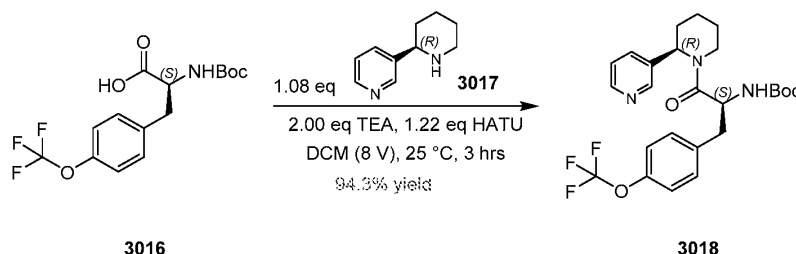
LC-MS: RT = 0.473 min, m/z (M+1) = 470.3

25 **HPLC:** RT = 1.592 min, 98.1% purity

¹H-NMR: 400 MHz, MeOD: δ 8.92 - 8.45 (m, 3H), 8.16 - 8.00 (m, 1H), 7.72 (d, J = 0.8 Hz, 1H), 7.50 - 7.07 (m, 5H), 7.03 - 6.59 (m, 2H), 5.87 (br s, 1H), 5.27 - 5.12 (m, 1H), 3.94 (br d, J = 14.0 Hz, 1H), 3.28 - 3.12 (m, 2H), 2.99 (br t, J = 12.2 Hz, 1H), 2.46 - 2.27 (m, 1H), 1.79 - 1.04 (m, 5H), 0.77 - 0.42 (m, 1H)

Example 93

Synthesis of tert-butyl ((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(4-(trifluoromethoxy)phenyl)propan-2-yl)carbamate



To the solution of compound **3016** (300 mg, 858 μmol , 1.00 eq) in DCM (2 mL) was added HATU (397 mg, 1.04 mmol, 1.22 eq), TEA (174 mg, 1.72 mmol, 240 μL , 2.01 eq) and compound **3017** (150 mg, 924 μmol , 1.08 eq) was added the reaction mixture was stirred at 25 °C for 3 hours. LCMS showed that compound **3016** was consumed and the desired mass (RT = 0.467 min, M+1 = 494.5) was given. Crude reaction mixtures were combined for workup. The combined reaction mixture was poured into water (50.0 mL) and extracted with ethyl acetate (30.0 mL x 2), the combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 200*40mm*10 μm ; mobile phase: [water(HCl)-ACN]; B%: 35%-65%, 10min) to afford **compound 3018** (400 mg, 810.51 μmol , 94.37% yield)) was obtained as a yellow solid.

10

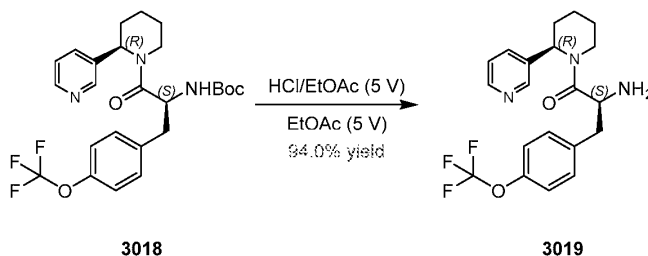
15

LCMS (reaction mixture): RT=0.467min, m/z (M+1) = 494.5

Example 94

Synthesis of (S)-2-amino-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(4-(trifluoromethoxy)phenyl)propan-1-one

20



To the solution of compound **3018** (400 mg, 810 μmol , 1.00 eq) in EtOAc (2 mL) was added HCl/EtOAc (4 M, 2 mL, 9.87 eq). The reaction mixture was stirred at 20 °C for 1 hr.

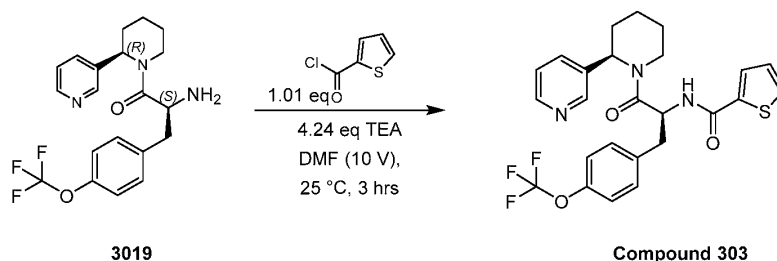
LCMS showed that compound **3018** was consumed and the desired mass (RT = 0.334 min, M+1 = 394.2) was given. The reaction mixture was concentrated under vacuum. Compound **3019** (300 mg, 762 umol, 94.0% yield) was obtained as a yellow oil.

LCMS (reaction mixture): RT=0.334 min, m/z (M+1) = 394.2

5

Example 95

Synthesis of N-((S)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)-3-(4-(trifluoromethoxy)phenyl)propan-2-yl)thiophene-2-carboxamide (Compound 303)



To the solution of compound **3019** (200 mg, 508 umol, 1.00 eq) in DMF (2 mL) was added TEA (218 mg, 2.16 mmol, 300 uL, 4.24 eq) and thiophene-2-carbonyl chloride (75.3 mg, 514 umol, 55 uL, 1.01 eq) was added the reaction mixture was stirred at 25 °C for 3 hours. LCMS showed that compound **3019** was consumed and the desired mass (RT = 0.492 min, M+1 = 504.3) was given. The reaction mixture was partitioned between 20.0 mL H₂O and 60.0 mL EtOAc and separated. The aqueous layer was then extracted with (2x30.0 mL) EtOAc. The organic layers were combined dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 150*25mm* 10um; mobile phase: [water (HCl)-ACN]; B%: 26%-56%, 10 min) to afford **Compound 303** (47 mg, 93.25 umol, 18.3% yield, 99.9% purity) as a off-white gum.

LCMS (reaction mixture): RT=0.492 min, m/z (M+1) = 504.3.

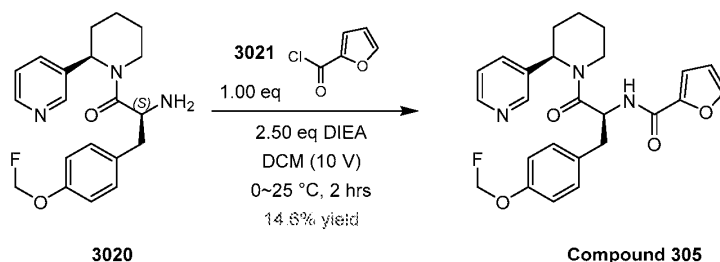
¹HNMR CDCl₃ 400 MHz: δ 8.60 - 8.52 (m, 2H), 7.89 (br dd, *J* = 1.6, 4.2 Hz, 1H), 7.66 - 7.43 (m, 3H), 7.35 (br d, *J* = 8.4 Hz, 2H), 7.26 - 7.20 (m, 2H), 7.13 - 7.03 (m, 2H), 6.93 (br d, *J* = 6.8 Hz, 1H), 5.94 (br d, *J* = 1.2 Hz, 1H), 5.44 - 5.24 (m, 1H), 3.93 - 3.63 (m, 1H), 3.31 - 3.15 (m, 2H), 3.05 - 2.85 (m, 1H), 2.39 - 2.26 (m, 1H), 1.70 - 1.27 (m, 5H), 0.95 - 0.43 (m, 1H)

LCMS: RT = 0.463 min, m/z (M+1) = 504.4

HPLC: RT = 1.838 min

Example 96

Synthesis of N-((S)-3-(4-(fluoromethoxy)phenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 305)



To a solution of compound **3020** (0.165 g, 461.64 μmol , 1.00 eq) in DCM (3 mL) was
 5 added DIEA (148.40 mg, 1.15 mmol, 200 μL , 2.49 eq). Then compound **3021** (60.72 mg, 465.18 μmol , 46 μL , 1.01 eq) was added at 0°C. The mixture was stirred at 25 °C hr for 3 hrs. LCMS (EC3956-24-P1A1) showed that reactant 1 ($m/z = 357$) was consumed completely and the desired MS ($R_t = 0.439$ min, $M+1 = 452.4$) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (column:
 10 Phenomenex luna C18 150*25mm* 10 μm ; mobile phase: [water (FA)-ACN]; B%: 12%-42%, 9 min). **Compound 305** (0.035 g, 67.44 μmol , 14.6% yield, 87.8% purity) was obtained as white solid, checked by HPLC (EC3956-24-P1A9), LCMS (EC3956-24-P1A7) and HNMR (EC3956-24-P1A1)

LCMS: EC3956-24-P1A1, $R_t=0.439$ min, m/z ($M+1$) = 452.4

15 **LCMS:** EC1557-136-P1A4, $R_t= 1.575$ min, m/z ($M+1$) = 452.3

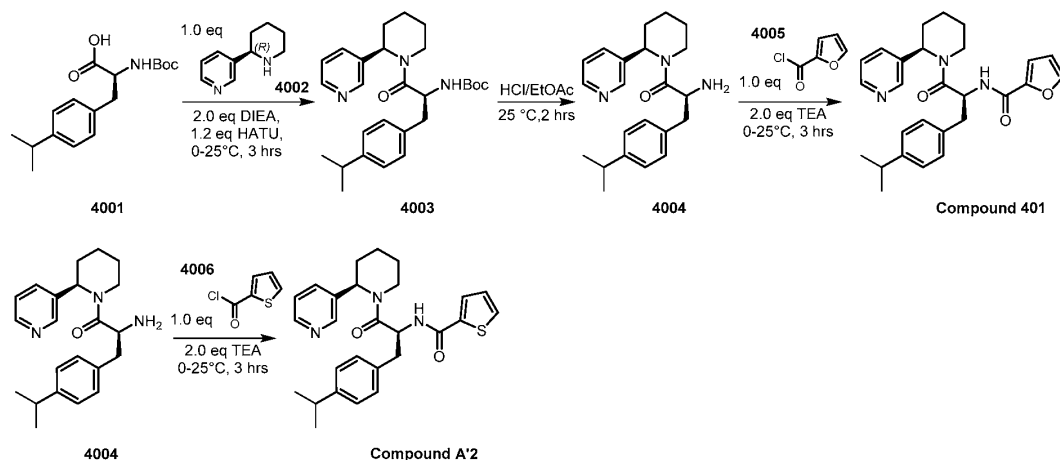
HPLC: EC1557-136-P1A5, $R_t = 1.549$ min, 87.8% purity

^1H NMR: EC1557-136-P1A1, 400 MHz, CDCl_3

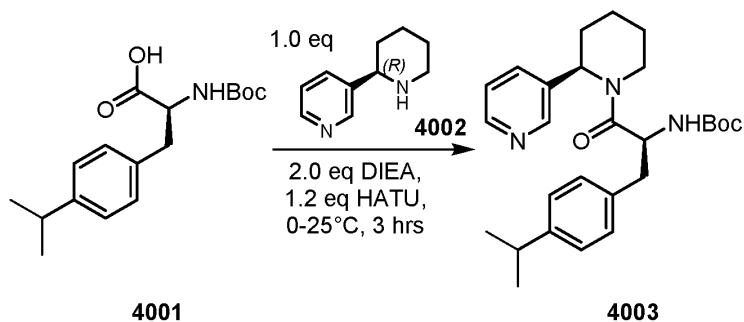
δ 8.60 - 8.34 (m, 2H), 7.57 - 7.43 (m, 2H), 7.32 (br s, 1H), 7.22 (br d, $J = 8.3$ Hz, 1H), 7.15 (br d, $J = 3.5$ Hz, 1H), 7.10 - 7.02 (m, 2H), 6.95 - 6.84 (m, 1H), 6.52 (dd, $J = 1.7, 3.4$ Hz,
 20 1H), 5.95 (br d, $J = 2.8$ Hz, 1H), 5.80 - 5.74 (m, 1H), 5.66 - 5.61 (m, 1H), 5.41 (dt, $J = 5.5, 8.4$ Hz, 1H), 3.85 - 3.68 (m, 1H), 3.32 - 3.03 (m, 2H), 3.00 - 2.87 (m, 1H), 2.40 - 2.18 (m, 4H), 1.78 - 1.34 (m, 5H), 0.83 - 0.61 (m, 1H)

Example 97

Synthetic Protocol for Compound 401 and Compound 402



Example 98

5 *Synthesis of tert-butyl ((S)-3-(4-isopropylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate*

To a solution of compound **4001** (300 mg, 975 μmol , 1.00 eq) and compound **4002** (160 mg, 986 μmol , 1.01 eq) in DCM (3.00 mL) was added DIEA (256 mg, 1.98 mmol, 345 μL , 2.03 eq) and HATU (450 mg, 1.18 mmol, 1.21 eq) at 0 °C. The mixture was stirred at 25°C for 2 hrs. LCMS (EC5892-20-P1A1) showed that compound **4001** ($m/z=307$) was consumed completely and the desired MS ($R_t=0.502$ min, $M+1=452.4$) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (column: Phenomenex C18 250*50mm*10 μm ; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 46%-76%, 8 min). Compound **4003** (0.36 g, 805 μmol , 82.4% yield, 99.6% purity) was obtained as yellow oil, checked by LCMS (EC5892-20-P1A1) and HNMR (EC5892-20-P1A1).

LCMS: EC5892-20-P1A1, $R_t = 0.502$ min, $m/z + 1 = 452.4$

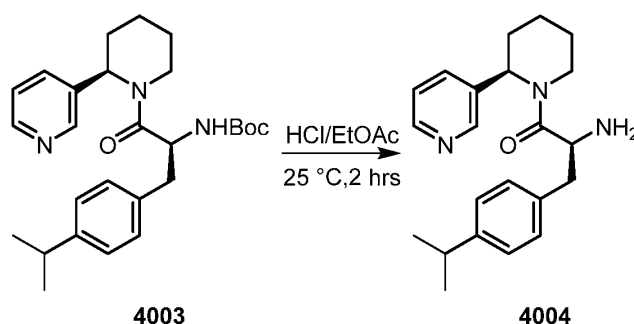
HNMR: EC5892-20-P1A1, (400 MHz, CDCl₃)

δ = 8.48 (br s, 2H), 7.62 - 7.43 (m, 1H), 7.20 (s, 4H), 7.12 - 6.90 (m, 1H), 5.93 (br d, J = 1.1 Hz, 1H), 5.37 (br d, J = 8.0 Hz, 1H), 4.91 (q, J = 7.9 Hz, 1H), 3.63 (br d, J = 13.9 Hz, 1H), 3.09 - 2.96 (m, 2H), 2.94 - 2.77 (m, 2H), 2.27 (br d, J = 14.3 Hz, 1H), 1.64 - 1.54 (m, 1H),
 5 1.46 (s, 9H), 1.41 (br s, 2H), 1.36 - 1.29 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H), 0.41 - 0.19 (m, 1H)

Example 99

Synthesis of (S)-2-amino-3-(4-isopropylphenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one

10



To a solution of compound **4003** (360 mg, 797.17 μmol , 1 eq) in EtOAc (2 mL) was added HCl/EtOAc (4 M, 1.73 mL, 8.67 eq). The mixture was stirred at 25°C for 2 hrs.

15 LCMS (EC5892-21-P1A1) showed that compound **4003** (m/z =451) was consumed completely and the desired MS (R_t = 0.375 min, $M+1$ =352.3) was found. The reaction mixture was concentrated under vacuum. No need further purification to give compound **4004** (335 mg, crude, HCl) as white solid and used to the next step. Compound **4004** (335 mg, crude, HCl) was obtained as white solid, checked by HNMR (EC5892-21-P1A1).

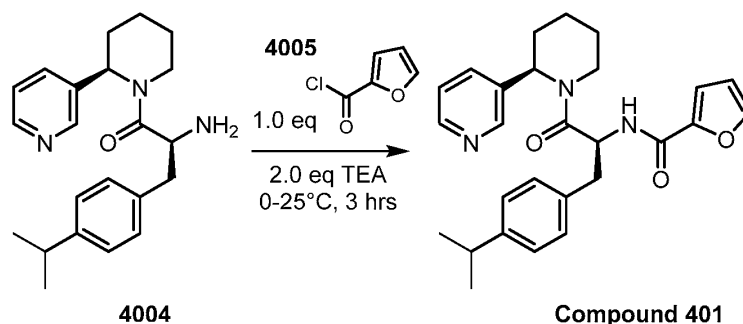
20 **LCMS:** EC5892-21-P1A1, Ret. Time = 0.375 min, m/z +1 = 352.3

¹HNMR: EC5857-3-P1A1 (400 MHz, DMSO)

δ = 8.93 - 8.83 (m, 1H), 8.72 (br d, J = 5.1 Hz, 1H), 8.62 (br s, 2H), 8.53 - 8.37 (m, 1H), 7.88 (br d, J = 5.4 Hz, 1H), 7.28 - 7.23 (m, 2H), 7.23 - 7.17 (m, 2H), 5.72 (br s, 1H), 4.78 - 4.70 (m, 1H), 3.58 (br d, J = 13.0 Hz, 1H), 3.18 (br dd, J = 4.6, 12.8 Hz, 1H), 2.94 - 2.85 (m, 2H),
 25 2.80 - 2.69 (m, 1H), 2.37 - 2.26 (m, 1H), 2.04 - 1.84 (m, 1H), 1.45 - 1.34 (m, 1H), 1.23 (br s, 1H), 1.18 (d, J = 6.9 Hz, 6H), 1.15 - 1.05 (m, 2H)

Example 100

Synthesis of N-((S)-3-(4-isopropylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 401)



To a solution of compound **4004** (165 mg, 469 μ mol, 1.00 eq) and TEA (95.2 mg, 941 μ mol, 131 μ L, 2.00 eq) in DCM (3.00 mL) was added compound **4005** (62.0 mg, 475 μ mol, 47.0 μ L, 1.01 eq) at 0°C. The mixture was stirred at 25 °C for 2 hr. LCMS (EC5892-22-P1A1) showed that compound **4004** (m/z =351) was consumed completely and the desired MS (R_t =0.475 min, $M+1$ =446.2) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (column: Waters xbridge 150*25mm 10 μ m; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 40%-70%, 9min).

Compound 401 (140 mg, 313 μ mol, 66.6% yield, 99.6% purity) was obtained as yellow solid, checked by LCMS(EC5892-22-P1A4), HPLC(EC5892-22-P1A2), HNMR(EC5892-22-P1A1) and Chiral SFC(EC5892-22-P1A3)

LCMS: EC5892-22-P1A1, product: Ret. Time = 0.475 min, m/z +1 = 446.2

$^1\text{HNMR}$: EC5892-22-P1A1 (400 MHz, CDCl_3)

δ = 8.56 - 8.37 (m, 2H), 7.50 - 7.41 (m, 2H), 7.24 (s, 2H), 7.23 - 7.19 (m, 2H), 7.16 - 7.10 (m, 1H), 7.09 - 6.90 (m, 1H), 6.51 (dd, J = 1.7, 3.4 Hz, 1H), 5.94 (br d, J = 3.4 Hz, 1H), 5.53 - 5.20 (m, 1H), 4.95 - 4.92 (m, 1H), 3.68 (br d, J = 13.6 Hz, 1H), 3.17 (d, J = 7.4 Hz, 2H), 3.00 - 2.74 (m, 2H), 2.29 (br d, J = 14.4 Hz, 1H), 1.62 (tt, J = 4.8, 13.5 Hz, 1H), 1.47 - 1.31 (m, 2H), 1.23 (d, J = 6.9 Hz, 7H), 0.41 - 0.21 (m, 1H)

LCMS: EC5892-22-P1A4, product: Ret. Time = 1.776 min, m/z +1 = 446.4

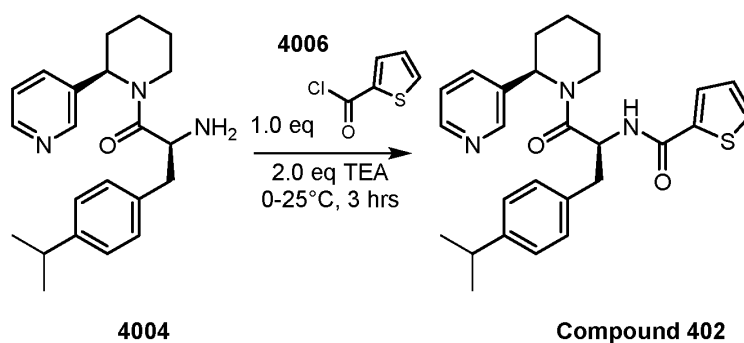
HPLC: EC5892-22-P1A2, product: Ret. Time = 2.065 min

Chiral SFC: EC5892-22-P1A3, ee%=100

25

Example 101

Synthesis of N-((S)-3-(4-isopropylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 402)



To a solution of compound **4004** (165 mg, 425 μ mol, 1 eq, HCl) and TEA (87.2 mg, 862 μ mol, 120 μ L, 2.03 eq) in DCM (3.00 mL) was added compound **4006** (63.0 mg, 430 μ mol, 46.0 μ L, 1.01 eq) at 0°C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5892-23-P1A1) showed that compound **4004** (m/z =351) was consumed completely and the desired MS (R_t =0.496 min, $M+1$ =462.4) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (column: Waters xbridge 150*25mm 10 μ m; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 45%-75%, 9 min).

Compound 402 (110 mg, 237 μ mol, 55.9% yield, 99.8% purity) was obtained as yellow solid, checked by LCMS(EC5892-23-P1A3), HPLC(EC5892-23-P1A2), HNMR(EC5892-23-P1A1) and Chiral SFC(EC5892-23-P1A3).

LCMS: EC5892-23-P1A1, product: Ret. Time = 0.496 min, $m/z + 1 = 462.4$

$^1\text{HNMR}$: EC5892-23-P1A1 (400 MHz, CDCl_3)

δ = 8.48 (br s, 2H), 7.56 - 7.53 (m, 1H), 7.50 (d, $J = 4.1$ Hz, 1H), 7.30 (br dd, $J = 5.1, 7.9$ Hz, 1H), 7.26 - 7.23 (m, 2H), 7.23 - 7.18 (m, 2H), 7.09 - 7.01 (m, 2H), 6.03 - 5.58 (m, 1H), 5.49 - 5.25 (m, 1H), 3.69 (br d, $J = 13.9$ Hz, 1H), 3.27 - 3.07 (m, 2H), 2.98 - 2.79 (m, 2H), 2.31 (br d, $J = 14.5$ Hz, 1H), 1.78 - 1.53 (m, 1H), 1.50 - 1.32 (m, 2H), 1.24 (d, $J = 6.9$ Hz, 7H), 0.47 - 0.26 (m, 1H)

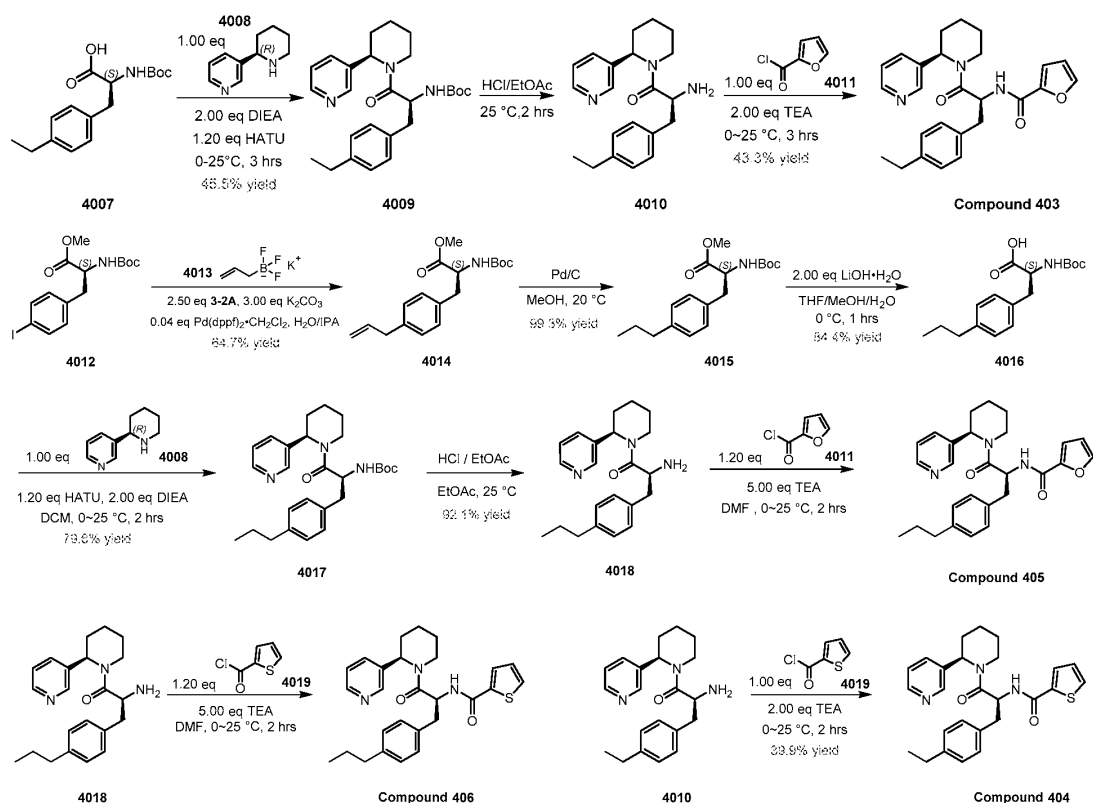
LCMS: EC5892-23-P1A3, product: Ret. Time = 1.882 min, $m/z + 1 = 462.5$

HPLC: EC5857-6-P1A2, product: Ret. Time = 2.152 min

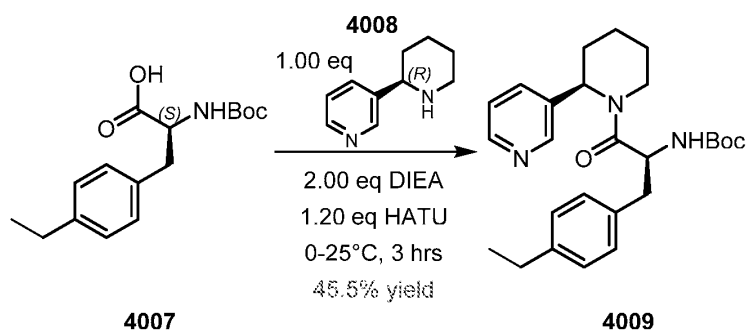
Chiral SFC: EC5892-23-P1A3, ee%= 100

Example 102

Synthetic Protocol for Compound 403, Compound 404, Compound 405, and Compound 406



Example 103

5 Synthesis of *tert*-butyl ((*S*)-3-(4-ethylphenyl)-1-oxo-1-((*R*)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate

To a solution of compound 4007 (4.00 g, 13.6 mmol, 1.00 eq) and DIEA (3.52 g, 27.3 mmol, 4.75 mL, 2.00 eq) and HATU (6.22 g, 16.4 mmol, 1.20 eq) in DCM (40.0 mL) was added compound 4008 (2.21 g, 13.6 mmol, 1.00 eq) at 0 °C, and then the reaction mixture was stirred at 20 °C for 3 hrs. LCMS (EC7706-1-P1A1) showed the compound 4007 was consumed and the desired mass (RT = 0.396min, m/z (M+1) = 438.9) was detected. The

reaction mixture was concentrated. The crude product was purified by reversed-phase HPLC (0.1% HCl condition). Compound **4009** (2.80 g, 6.21 mmol, 45.5% yield, 97.0% purity) was obtained as brown solid.

LC-MS: EC7706-1-P1A1, RT = 0.396 min, m/z (M+1) = 438.9

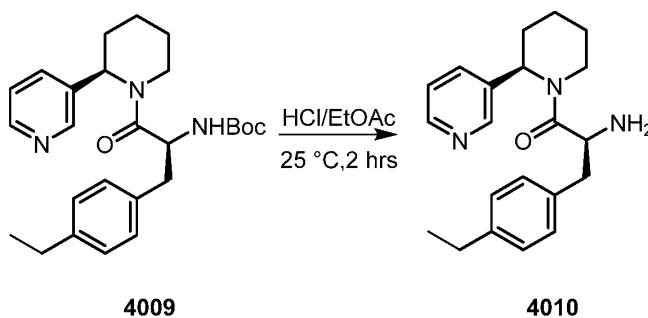
5 **LC-MS:** EC7706-1-P1B1, RT = 0.396 min, m/z (M+1) = 438.9

¹H-NMR: EC7706-1-P1A, 400 MHz, DMSO

10 δ 8.91 (s, 1H), 8.78 - 8.77 (m, 1H), 8.78 - 8.65 (m, 3H), 8.53 - 8.24 (m, 1H), 7.99 - 7.88 (m, 1H), 7.45 (br d, J = 6.4 Hz, 1H), 7.46 - 7.21 (m, 2H), 5.78 - 5.71 (m, 1H), 4.86 - 4.54 (m, 2H), 3.85 - 3.57 (m, 2H), 3.26 - 3.07 (m, 1H), 2.96 - 2.71 (m, 3H), 2.62 - 2.55 (m, 2H), 2.36 - 2.29 (m, 1H), 1.59 (s, 2H), 1.60 - 1.58 (m, 1H), 1.38 (s, 3H), 1.17 - 1.12 (m, 4H)

Example 104

Synthesis of (S)-2-amino-3-(4-ethylphenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



15

To a solution of compound **4009** (2.80 g, 6.40 mmol, 1.00 eq) in EtOAc (28.0 mL) was HCl/EtOAc (4 M, 16.0 mL, 10.0 eq), then the reaction mixture was stirred at 25 °C for 2 hrs. LCMS (EC7706-5-P1A1) showed the compound **4009** was consumed and the desired mass (RT = 0.293 min, m/z (M+1) = 338.4) was detected. The reaction mixture was concentrated. The residue was used to next step without purification. From HNMR (EC7706-5-P1A) showed the product compound **4010** (2.40 g, crude, HCl) was obtained as brown solid.

20

LC-MS: EC7706-5-P1A1, RT = 0.293 min, m/z (M+1) = 338.4

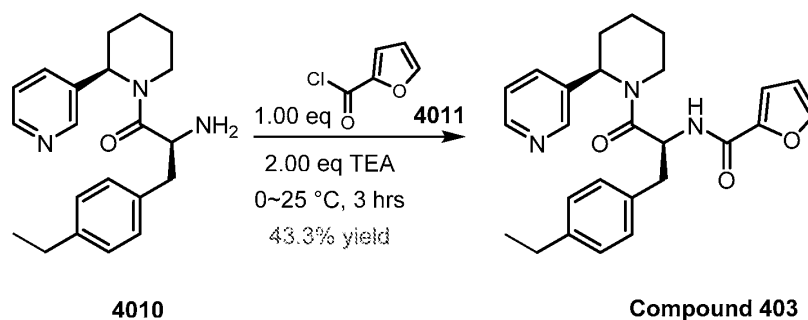
¹H-NMR: EC7706-5-P1A, 400 MHz, DMSO

25 δ 8.91 (s, 1H), 8.75 (d, J = 5.6 Hz, 1H), 8.67 (br s, 3H), 8.54 (br d, J = 8.2 Hz, 1H), 7.98 - 7.90 (m, 1H), 7.24 - 7.16 (m, 4H), 5.72 (br s, 1H), 4.87 - 4.52 (m, 2H), 3.43 (d, J = 7.0 Hz,

1H), 3.20 - 3.16 (m, 1H), 3.00 - 2.83 (m, 2H), 2.81 - 2.72 (m, 1H), 1.50 - 1.37 (m, 1H), 1.33 - 1.17 (m, 2H), 1.16 - 1.12 (m, 3H), 1.11 - 1.02 (m, 2H), 0.27 - -0.07 (m, 1H)

Example 105

5 *Synthesis of N-((S)-3-(4-ethylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 403)*



To a solution of compound **4010** (2.00 g, 5.93 mmol, 1.00 *eq*) in DCM (10.0 mL) was added TEA (1.89 g, 18.7 mmol, 2.60 mL, 3.15 *eq*) and compound **4011** (792 mg, 6.07 mmol, 600 μ L, 1.02 *eq*) at 0 °C, then the reaction mixture was stirred at 25 °C for 3 hrs. LCMS (EC7706-19-P1A1) showed the compound **4010** was consumed and the desired mass (R_t = 0.379 min, m/z ($M+1$) = 433.0) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 250*50mm*10 μ m; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 30%-50%, 20min). **Compound 403** (1.11 g, 2.57 mmol, 43.3% yield, 99.6% purity) was obtained as white solid.

LC-MS: EC7706-19-P1A1, R_t = 0.379 min, m/z ($M+1$) = 433.0

LC-MS: EC7706-19-B1, R_t = 0.376 min, m/z ($M+1$) = 432.8

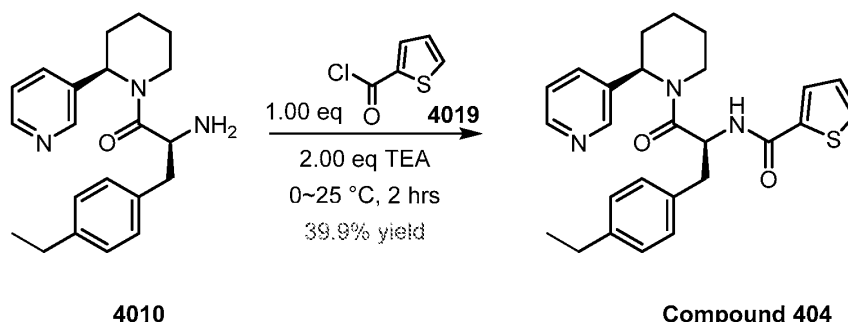
HPLC: EC7706-19-P1B2, R_t = 1.799 min, 99.6% purity

$^1\text{H-NMR}$: EC7706-19-P1A, 400 MHz, DMSO

20 δ 8.68 (br d, J = 7.2 Hz, 1H), 8.51 - 8.29 (m, 2H), 7.85 (s, 1H), 7.59 (br d, J = 8.0 Hz, 1H), 7.38 - 7.29 (m, 1H), 7.25 - 7.22 (m, 2H), 7.15 (br d, J = 8.0 Hz, 2H), 6.99 (br s, 1H), 6.70 - 6.54 (m, 1H), 5.82 - 5.57 (m, 1H), 5.20 - 4.92 (m, 1H), 3.86 (br d, J = 13.3 Hz, 1H), 3.06 (br d, J = 7.6 Hz, 2H), 2.83 (br t, J = 12.4 Hz, 1H), 2.63 - 2.52 (m, 2H), 2.32 (br d, J = 13.2 Hz, 1H), 1.59 - 1.47 (m, 1H), 1.37 (br s, 2H), 1.27 - 1.09 (m, 4H), 0.83 - 0.62 (m, 1H)

Example 106

Synthesis of N-((S)-3-(4-ethylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 404)



To a solution of compound **4010** (2.00 g, 5.93 mmol, 1.00 *eq*) in DCM (10.0 mL) was added TEA (1.89 g, 18.7 mmol, 2.60 mL, 3.15 *eq*) and compound **4019** (869 mg, 5.93 mmol, 635 μL , 1.00 *eq*) at 0 $^{\circ}\text{C}$, then the reaction mixture was stirred at 25 $^{\circ}\text{C}$ for 2 hrs. LCMS (EC7706-20-P1A1) showed the compound **4010** was consumed and the desired mass ($R_t = 0.385$ min, m/z ($M+1$) = 448.9) was detected. The reaction mixture was concentrated. The residue was purified by prep-HPLC (column: Phenomenex luna C18 (250*70mm, 10 μm); mobile phase: [water(NH_4HCO_3)-ACN]; B%: 35%-65%, 31min). **Compound 404** (1.09 g, 2.36 mmol, 39.9% yield, 97.4% purity) was obtained as off-white solid.

LC-MS: EC7706-20-P1A1, $R_t = 0.385$ min, m/z ($M+1$) = 448.9

LC-MS: EC7706-20-P1B2, $R_t = 0.393$ min, m/z ($M+1$) = 448.8

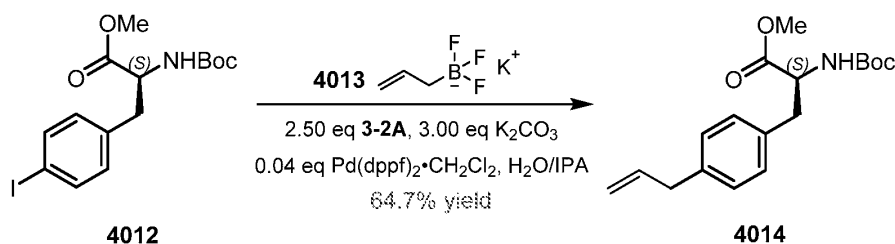
HPLC: EC7706-20-P1B1, $R_t = 1.897$ min, 97.4% purity

$^1\text{H-NMR}$: EC7706-20-P1A, 400 MHz, DMSO

δ 9.14 - 8.85 (m, 1H), 8.52 - 8.33 (m, 2H), 8.02 - 7.87 (m, 1H), 7.77 (d, $J = 4.8$ Hz, 1H), 7.59 (br d, $J = 8.0$ Hz, 1H), 7.35 - 7.30 (m, 1H), 7.25 (br d, $J = 8.0$ Hz, 2H), 7.18 - 7.14 (m, 2H), 6.99 (br s, 1H), 5.80 - 5.50 (m, 1H), 5.22 - 4.84 (m, 1H), 3.86 (br d, $J = 12.4$ Hz, 1H), 3.07 (br d, $J = 5.6$ Hz, 2H), 2.82 (br t, $J = 12.4$ Hz, 1H), 2.60 - 2.53 (m, 2H), 2.31 (br d, $J = 13.2$ Hz, 1H), 1.59 - 1.46 (m, 1H), 1.36 (br s, 2H), 1.26 - 1.07 (m, 4H), 0.79 - 0.56 (m, 1H)

Example 107

Synthesis of methyl (S)-3-(4-allylphenyl)-2-((tert-butoxycarbonyl)amino)propanoate



To a solution of compound **4012** (38.0 g, 93.7 mmol, N/A purity, 1.00 eq) in IPA (275 mL) /H₂O (125 mL) was added potassium;allyl(trifluoro)boranuide (34.6 g, 234 mmol, 2.50 eq) and K₂CO₃ (39.5 g, 286 mmol, 3.00 eq) then added Pd(dppf).CH₂Cl₂ (3.06 g, 3.75 mmol, 0.04 eq) at 25 °C. The mixture was stirred at 90 °C for 2 hrs. LCMS (EC7606-10-P1A1) showed that compound **4012** was consumed, and the desired MS (m/z (M+1) = 220.1, Rt = 0.588 min) was detected. The mixture was poured into the water (100 mL), extracted with EtOAc (150 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether: Ethyl acetate = 50: 1 to 5: 1), the fraction (Plate 1, R_f = 0.40) was collected. Compound **4014** (20.0 g, 60.7 mmol, 64.7% yield, 97.0% purity) was obtained as a yellow solid.

LC-MS: EC7606-10-P1A1, Rt = 0.588 min, m/z (M+1) = 220.1

LC-MS: EC7606-10-P1ACP, Rt = 0.509 min, m/z (M+1) = 220.5

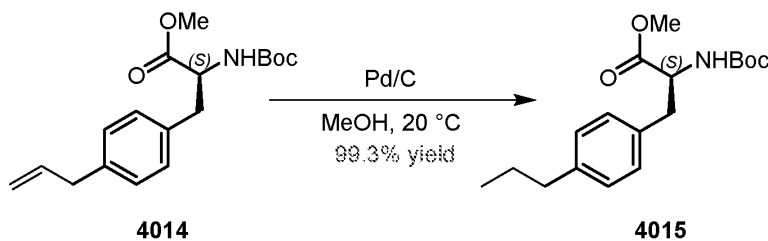
HPLC: EC7606-10-P1BCP2, Rt = 2.856 min, 97.1% purity

¹H-NMR: EC7606-10-P1N1, 400 MHz, CDCl₃

δ 7.40 (d, *J* = 8.4 Hz, 1H), 7.19 - 7.01 (m, 4H), 6.05 - 5.87 (m, 1H), 5.13 - 5.01 (m, 2H), 4.64 - 4.51 (m, 1H), 4.13 (q, *J* = 7.2 Hz, 1H), 3.72 (s, 3H), 3.36 (d, *J* = 6.6 Hz, 2H), 3.08 (dt, *J* = 5.6, 13.8 Hz, 2H), 1.42 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 1H)

Example 108

Synthesis of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-propylphenyl)propanoate



To a solution of compound **4014** (20.0 g, 62.6 mmol, N/A purity, 1.00 eq) in MeOH (150 mL) was added Pd/C (62.6 mmol, 10.0% purity, 1.00 eq). The mixture was stirred at 20

°C for 2 hrs. LCMS (EC7606-13-P1A1) showed that reactant 4014 was consumed, and the desired MS (m/z ($M+1$) = 222.2, R_t = 0.504 min) was detected. The reaction mixture was filtered through kieselguhr, the filtrate was concentrated under reduced pressure. The residue was used for next step directly. Compound **4015** (20.0 g, 62.2 mmol, 99.3% yield) was

5 obtained as yellow oil.

LC-MS: EC7606-10-P1ACP, R_t = 0.504 min, m/z ($M+1$) = 222.3

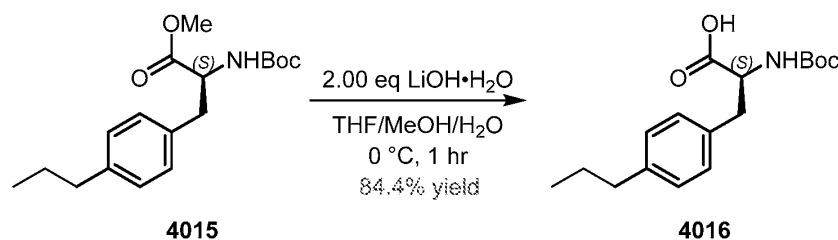
¹H-NMR: EC7606-13-P1N1, 400 MHz, CDCl₃

δ 7.18 - 7.09 (m, 2H), 7.08 - 7.01 (m, 2H), 4.98 (br d, J = 7.6 Hz, 1H), 4.57 (br d, J = 7.6 Hz, 1H), 3.73 - 3.70 (m, 3H), 3.05 (dq, J = 6.0, 13.6 Hz, 2H), 2.62 - 2.50 (m, 2H), 1.67 - 1.59

10 (m, 2H), 1.42 (s, 9H), 0.94 (t, J = 7.2 Hz, 3H)

Example 109

Synthesis of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-propylphenyl)propanoic acid



15 To the solution of compound **4015** (20.0 g, 62.2 mmol, N/A purity, 1.00 *eq*) in THF (150 mL) and MeOH (50.0 mL) and H₂O (50.0 mL) was added LiOH·H₂O (5.22 g, 124 mmol, 2.00 *eq*) at 0 °C and the mixture was stirred at 0 °C for 1 hr. LCMS (EC7606-20-P1A1) showed that compound **4015** was consumed, and the desired MS (m/z ($M+1$) = 208.2, R_t = 0.500 min) was detected. The mixture was poured into the water (100 mL), adjusted to

20 pH = 5~6 with 1M HCl, extracted with EtOAc (100 mL * 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used to next step without purification. Compound **4016** (19.0 g, 52.5 mmol, 84.4% yield, 85.0% purity) was obtained as white oil.

LC-MS: EC7606-20-P1A1, R_t = 0.500 min, m/z ($M+1$) = 208.2

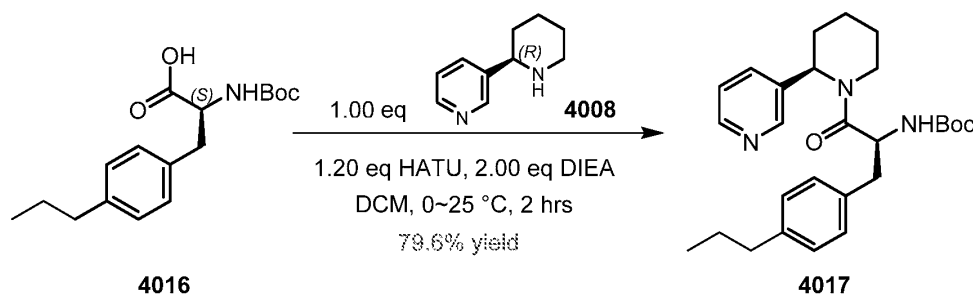
25 **HPLC:** EC7606-20-P1B1, R_t = 2.567 min, 85.6% purity

¹H-NMR: EC7606-20-P1NCP, 400 MHz, CDCl₃

δ 7.22 - 7.07 (m, 5H), 6.06 (br s, 1H), 4.94 (br d, J = 7.4 Hz, 1H), 4.60 (br d, J = 5.4 Hz, 1H), 3.20 - 3.13 (m, 1H), 3.11 - 3.01 (m, 1H), 2.62 - 2.53 (m, 2H), 1.63 (sxt, J = 7.4 Hz, 2H), 1.43 (br s, 9H), 0.95 (t, J = 7.2 Hz, 3H)

Example 110

Synthesis of tert-butyl ((S)-1-oxo-3-(4-propylphenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



5

To the solution of compound **4016** (5.00 g, 16.2 mmol, N/A purity, 1.00 eq) in DCM (60 mL) was added DIEA (4.21 g, 32.5 mmol, 5.67 mL, 2.00 eq) at 25 °C and then HATU (7.43 g, 19.5 mmol, 1.20 eq) was added at 0 °C. Then added compound **4008** (2.91 g, 17.9 mmol, N/A purity, 1.00 eq) at 0 °C. And the mixture was stirred at 25 °C for 2 hrs under N₂. LCMS (EC7606-23-P1A1) showed that compound **4016** was consumed, and the desired MS (m/z (M+1) = 452.3, Rt = 0.504 min) was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by reversed-phase HPLC (0.10% HCl condition). Compound **4017** (6.50 g, 12.9 mmol, 79.6% yield, 90.0% purity) was obtained as a white solid.

10

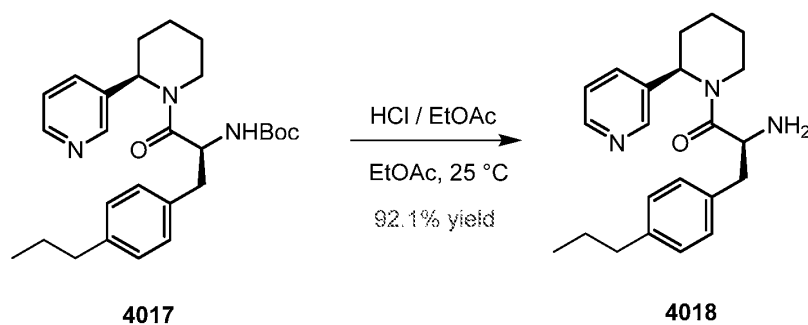
LC-MS: EC7606-23-P1A1, Rt = 0.504 min, m/z (M+1) = 452.3

HPLC: EC7606-23-P1BCP1, Rt = 2.141 min, 90.4% purity

Example 111

Synthesis of (S)-2-amino-3-(4-propylphenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one

20



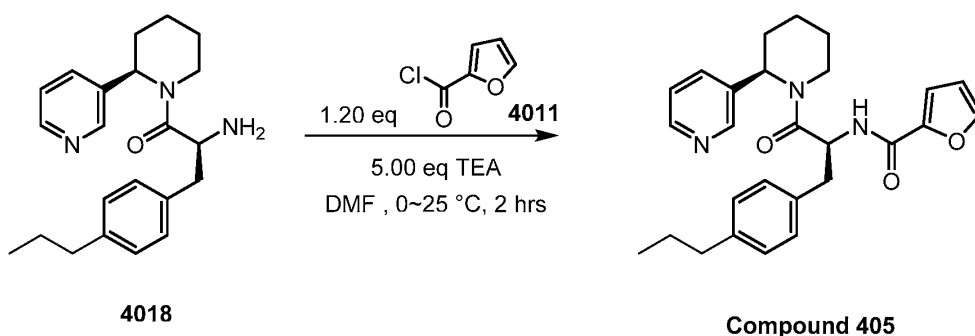
To a solution of compound **4017** (5.00 g, 11.0 mmol, N/A purity, 1.00 eq) was added HCl/EtOAc (4.00 M, 2.77 mL, 1.00 eq). The mixture was stirred at 25 °C for 6 hrs. LCMS (EC7606-28-P1A2) showed that compound **4017** was consumed, and the desired MS (m/z (M+1) = 352.4, R_t = 0.317 min) was detected. The reaction mixture was concentrated under reduced pressure to remove HCl/EtOAc. The residue was used to next step without purification. Compound **4018** (4.30 g, 10.2 mmol, 92.1% yield, 92.0% purity, HCl) was obtained as a yellow solid.

LC-MS: EC7606-28-P1A2, R_t = 0.317 min, m/z (M+1) = 352.4

10

Example 112

Synthesis of N-((S)-1-oxo-3-(4-propylphenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 405)



To the solution of compound **4018** (3.00 g, 7.73 mmol, N/A purity, 1.00 eq, HCl) in DCM (30 mL) was added TEA (3.91 g, 38.7 mmol, 5.39 mL, 5.00 eq) at 25 °C, and compound **4011** (1.21 g, 9.31 mmol, 920 uL, 1.20 eq) was added at 0 °C and the mixture was stirred at 25 °C for 2 hrs. LCMS (EC7606-32-P1A1) showed that compound **4018** was consumed, and the desired MS (m/z (M+1) = 446.2, R_t = 0.403 min) was detected. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: YMC Triart C18 70*250mm*7um; mobile phase: [water (NH₄HCO₃) - ACN]; B%: 45%-75%, 15min). **Compound 405** (807 mg, 1.65 mmol, 91.0% purity) was obtained as a yellow solid.

LC-MS: EC7606-32-P1A1, R_t = 0.412 min, m/z (M+1) = 446.2

Special LC-MS: EC8519-3-P1S1, R_t = 10.514 min, m/z (M+1) = 446.4

HPLC: EC8519-3-P1B1, R_t = 1.875 min, 94.7% purity

SFC: EC8519-3-P1X1

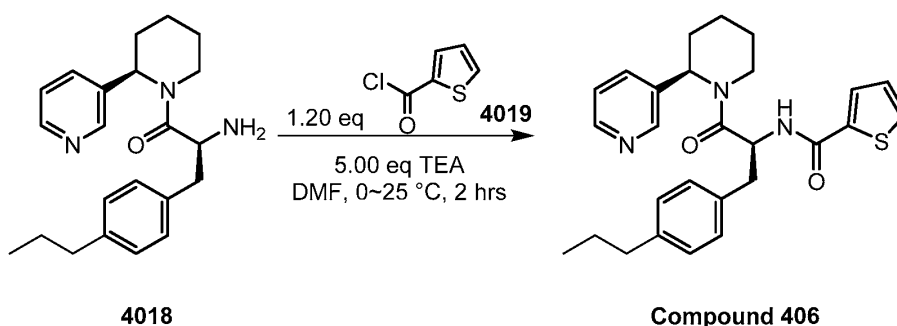
25

¹H-NMR: EC8519-3-P1N1, 400 MHz, CDCl₃

δ 8.68 (br d, *J* = 7.0 Hz, 1H), 8.45 - 8.35 (m, 2H), 7.85 (s, 1H), 7.59 (br d, *J* = 7.8 Hz, 1H), 7.33 (br dd, *J* = 4.8, 7.6 Hz, 1H), 7.27 - 7.17 (m, 3H), 7.16 - 7.06 (m, 2H), 7.05 - 6.90 (m, 1H), 6.66 - 6.59 (m, 1H), 5.80 - 5.58 (m, 1H), 5.10 (q, *J* = 7.2 Hz, 1H), 3.86 (br d, *J* = 13.4 Hz, 1H), 3.06 (br d, *J* = 7.2 Hz, 2H), 2.82 (br t, *J* = 12.2 Hz, 1H), 2.31 (br d, *J* = 13 Hz, 1H), 1.62 - 1.23 (m, 6H), 1.17 (br d, *J* = 7.0 Hz, 1H), 0.87 (br t, *J* = 7.2 Hz, 3H), 0.67 (br d, *J* = 12.6 Hz, 1H).

Example 113

10 *Synthesis of N-((S)-1-oxo-3-(4-propylphenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 406)*



To the solution of compound **4018** (3.00 g, 7.73 mmol, N/A purity, 1.00 *eq*, HCl) in DCM (30.0 mL) was added TEA (3.91 g, 38.7 mmol, 5.39 mL, 5.00 *eq*) at 25 °C, and compound **4019** (1.36 g, 9.31 mmol, 996 uL, N/A purity, 1.20 *eq*) was added at 0 °C and the mixture was stirred at 25 °C for 2 hrs. LCMS (EC7606-33-P1A1) showed that compound **4018** was consumed, and the desired MS (*m/z* (*M*+1) = 462.3, *Rt* = 0.413 min) was detected. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: YMC Triart C18 70*250mm*7um; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 47%-77%, 15min). Compound **406** (1.05 g, 2.12 mmol, 93.0% purity) was obtained as a yellow solid.

LC-MS: EC7606-33-P1A1, *Rt* = 0.413 min, *m/z* (*M*+1) = 462.3.

Special LC-MS: EC8519-4-P1S1, *Rt* = 11.186 min, *m/z* (*M*+1) = 462.3

25 **HPLC:** EC8519-4-P1B1, *Rt* = 1.972 min, 94.1% purity

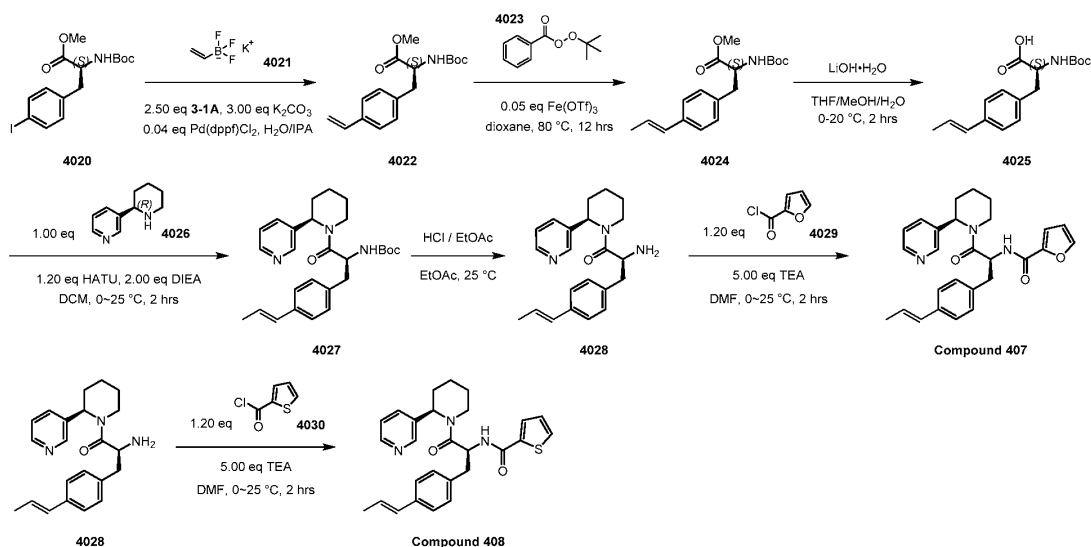
SFC: EC8519-4-P1X1

¹H-NMR: EC8519-4-P1N1, 400 MHz, CDCl₃

δ 8.95 (br d, $J = 7.0$ Hz, 1H), 8.41 (s, 2H), 7.94 (d, $J = 3.0$ Hz, 1H), 7.77 (d, $J = 4.4$ Hz, 1H), 7.59 (br d, $J = 8.0$ Hz, 1H), 7.32 (br dd, $J = 4.8, 7.6$ Hz, 1H), 7.24 (br d, $J = 7.8$ Hz, 2H), 7.13 (br d, $J = 8.0$ Hz, 3H), 6.98 (br s, 1H), 5.73 (br s, 1H), 5.11 (br d, $J = 7.2$ Hz, 1H), 3.86 (br d, $J = 13.0$ Hz, 1H), 3.22 - 2.89 (m, 3H), 2.82 (br t, $J = 12.4$ Hz, 1H), 2.30 (br d, $J = 14.2$ Hz, 1H), 1.58 - 1.45 (m, 3H), 1.40 - 1.09 (m, 3H), 0.87 (br t, $J = 7.2$ Hz, 3H), 0.73 - 0.55 (m, 1H).

Example 114

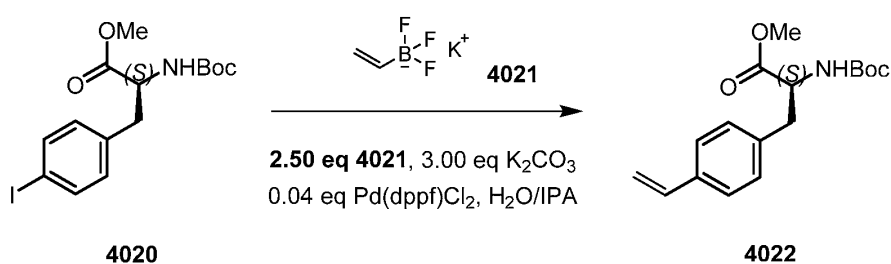
Synthetic Protocol for Compound 407 and Compound 408



10

Example 115

Synthesis of methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(4-vinylphenyl)propanoate



To the solution of Compound **4020** (2.00 g, 4.94 mmol, 1.00 eq) and Compound **4021** (1.65 g, 12.3 mmol, 2.50 eq) in IPA (32 mL) and H_2O (16 mL) was added K_2CO_3 (2.05 g, 14.8 mmol, 3.00 eq) and $Pd(dppf)Cl_2$ (360 mg, 492 μ mol, 0.10 eq) at 20 °C and the mixture was stirred at 80 °C for 2 hrs under N_2 . The mixture was poured into the water (30 mL), extracted with EtOAc (30 mL * 2). The combined organic layers were washed with brine (60

mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 1/0 to 5/1), TLC (Petroleum ether : Ethyl acetate = 5 : 1) showed the spot (R_f = 0.46) was collected. Compound **4022** (1.10 g, 3.60 mmol, 72.9% yield) was obtained as yellow oil which was confirmed by HNMR (EC6159-13-P1A1).

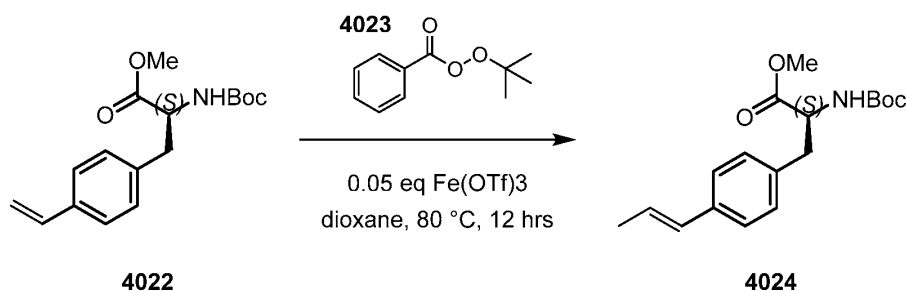
LCMS: EC6159-13-P1A1, RT = 0.487 min, M/Z - 100 = 206

¹HNMR: EC6178-13-P1C1, 400MHz, CDCl₃-d₆

δ 7.35 (d, *J*=8.00 Hz, 2H), 7.09 (d, *J*= 8.00 Hz, 2H), 6.69 (dd, *J*= 17.6, 10.8 Hz, 1H), 5.73 (dd, *J*= 17.6, 0.80 Hz, 1H), 5.16-5.33 (m, 1H), 4.98 (br d, *J*= 7.60 Hz, 1 H), 4.52-4.67 (m, 1H), 3.72 (s, 3H), 2.93-3.20 (m, 2H), 1.43 (s, 9H).

Example 116

Synthesis of methyl (S,E)-2-((tert-butoxycarbonyl)amino)-3-(4-(prop-1-en-1-yl)phenyl)propanoate



15

To the solution of Compound **4022** (500 mg, 1.64 mmol, 1.00 *eq*) and Compound **4023** (635 mg, 3.27 mmol, 616 uL, 2.00 *eq*) in dioxane (10 mL) was added Fe(OTf)₃ (82 mg, 163 umol, 0.10 *eq*) at 20 °C and the mixture was stirred at 80 °C for 12 hrs. The mixture was poured into the water (20 mL), extracted with EtOAc (20 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was purified by prep-HPLC (water (0.05% HCl)-ACN). Compound **4024** (118 mg, 369 umol, 22.5% yield) was obtained as yellow oil which was confirmed by HNMR (EC6159-19-P1A1).

20

LCMS: EC6159-19-P1A1, RT = 0.466 min, M/Z - 100 = 220

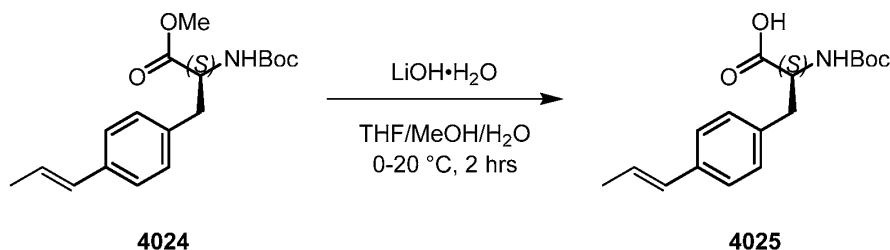
¹HNMR: EC6178-19-P1A1, 400MHz, CDCl₃-d₆

25

δ 7.29 (s, 2H), 7.07 (d, *J*= 8.00 Hz, 2H), 6.34-6.47 (m, 1H), 6.16-6.31 (m, 1H), 4.98 (br d, *J*= 8.00 Hz, 1H), 4.51-4.66 (m, 1H), 3.74 (s, 3H), 2.97-3.18 (m, 2H), 1.90 (d, *J*= 6.40 Hz, 3H), 1.45 (s, 9H).

Example 117

Synthesis of (S,E)-2-((tert-butoxycarbonyl)amino)-3-(4-(prop-1-en-1-yl)phenyl)propanoic acid



5

To the solution of methyl Compound **4024** (118 mg, 369 μmol , 1.00 *eq*) in THF (1.5 mL) and MeOH (0.5 mL) and H₂O (0.5 mL) was added LiOH·H₂O (31 mg, 738 μmol , 2.00 *eq*) at 0 °C and the mixture was stirred at 0 °C for 1 hr. The mixture was poured into the water (5 mL), adjusted to pH = 5~6 with 2 M HCl, extracted with EtOAc (10 mL * 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used for next step directly. Cpd **4025** (100 mg, 327 μmol , 88.6% yield) was obtained as yellow oil.

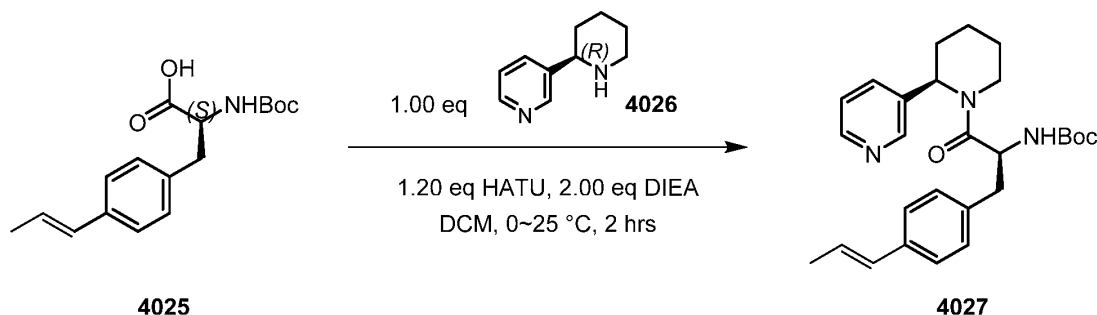
10

LCMS: EC6159-20-P1A2, RT = 0.463 min, M/Z - 100 = 206

15

Example 118

Synthesis of tert-butyl ((S)-1-oxo-3-(4-((E)-prop-1-en-1-yl)phenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



To the solution of compound **4025** (100 mg, 327 μmol , 1.00 *eq*) and compound **4026** (54 mg, 333 μmol , 1.02 *eq*) in DCM (2 mL) was added DIEA (85 mg, 657 μmol , 114 μL , 2.01 *eq*) at 20 °C and then HATU (149 mg, 392 μmol , 1.20 *eq*) was added at 0 °C. And the mixture was stirred at 20 °C for 2 hrs under N₂. The mixture was poured into the water (10

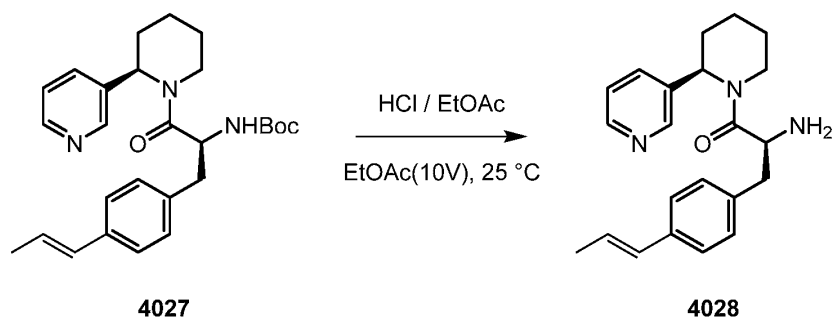
20

mL), extracted with DCM (10 mL * 3). The combined organic layers were washed with brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used for next step directly. Compound **4027** (160 mg, crude) was obtained as red oil.

5 **LCMS:** EC6159-21-P1A1, RT = 0.435 min, M/Z + 1 = 450

Example 119

Synthesis of (S)-2-amino-3-(4-((E)-prop-1-en-1-yl)phenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



10

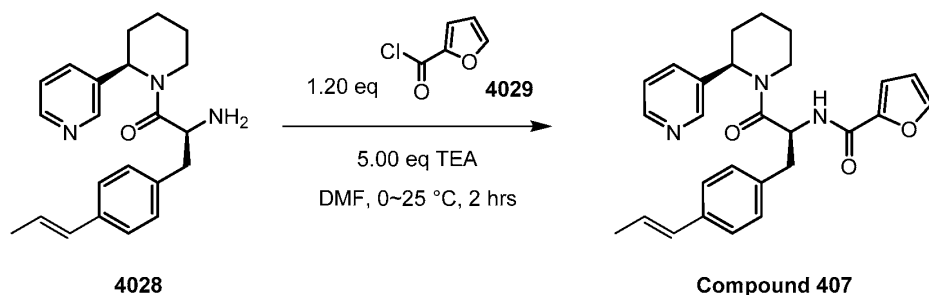
To the solution of Compound **4027** (160 mg, 355 μ mol, 1.00 *eq*) in HCl/EtOAc (4 M, 4 mL, 45.0 *eq*) at 20 °C and the mixture was stirred at 20 °C for 0.5 hr. The reaction mixture was concentrated under reduced pressure. The residue was used for next step directly.

Compound **4028** (160 mg, crude, HCl) was obtained as yellow oil.

15 **LCMS:** EC6159-22-P1A1, RT = 0.301 min, M/Z + 1 = 350

Example 120

Synthesis of N-((S)-1-oxo-3-(4-((E)-prop-1-en-1-yl)phenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 407)



20

To the solution of Compound **4028** (80 mg, 207 μ mol, 1.00 *eq*, HCl) in DMF (1.5 mL) was added TEA (109 mg, 1.08 mmol, 150 μ L, 5.20 *eq*) at 20 °C, and Compound **4029**

(29 mg, 222 μmol , 20 μL , 1.07 *eq*) was added at 0 °C and the mixture was stirred at 20 °C for 3 hrs. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 150 * 25 mm * 10 μm ; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 41%-71%, 8 min).

- 5 **Compound 407** (22.41 mg, 49.6 μmol , 23.9% yield, 98.3% purity) was obtained as white solid which was confirmed by QC of Compound 407.

LCMS: EC6159-23-P1A1, RT = 0.394 min, M/Z + 1 = 444

¹HNMR: EC6159-23-P1C1, 400MHz, CDCl_3-d_6

- δ 8.39-8.53 (m, 2H), 7.39-7.54 (m, 2H), 7.28-7.32 (m, 2H), 7.19-7.26 (m, 3H), 7.12-7.18 (m, 1H), 6.93-7.10 (m, 1H), 6.51 (dd, J = 2.00, 1.69 Hz, 1H), 6.33-6.45 (m, 1H), 6.12-6.29 (m, 1H), 5.57-6.02 (m, 1H), 5.22-5.51 (m, 1H), 3.60-3.85 (m, 1H), 3.05-3.34 (m, 2H), 2.84-2.98 (m, 1H), 2.24-2.48 (m, 1H), 1.89 (br dd, J = 6.40, 1.20 Hz, 3H), 1.63-1.78 (m, 2H), 1.33-1.46 (m, 2H), 0.49-0.79 (m, 1H).

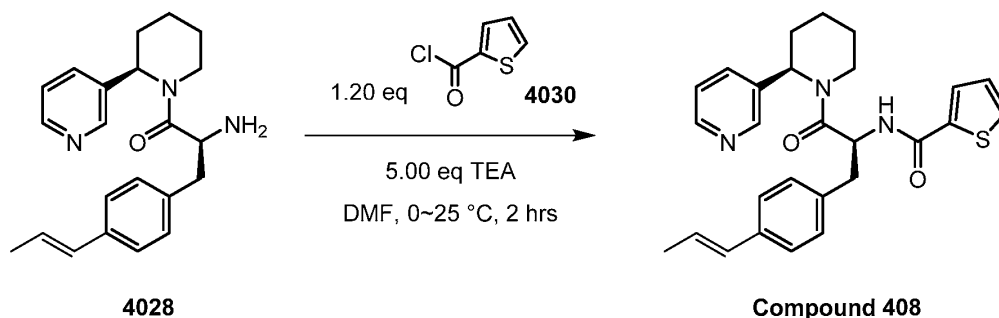
LCMS: EC6159-23-P1C2, RT = 0.402 min, m/z + 1 = 444

- 15 **HPLC:** EC6159-23-P1C1, RT = 1.844 min, purity = 98.3%

SFC: EC6159-23-P1H1_b2

Example 121

20 *Synthesis of N-((S)-1-oxo-3-(4-((E)-prop-1-en-1-yl)phenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 408)*



- 25 To the solution of **Compound 4028** (80 mg, 207 μmol , 1.00 *eq*, HCl) in DMF (1.5 mL) was added TEA (109 mg, 1.08 mmol, 150 μL , 5.20 *eq*) at 20 °C, and **Compound 4030** (32 mg, 218 μmol , 23.3 μL , 1.05 *eq*) was added at 0 °C and the mixture was stirred at 20 °C for 3 hrs. The reaction mixture was filtered, the filtrate was concentrated under reduced pressure. The crude product was purified by prep-HPLC (column: Phenomenex Luna C18 150 * 25 mm * 10 μm ; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 39%-69%, 8 min).

Compound 408 (19.27 mg, 41.3 μ mol, 19.9% yield, 98.7% purity) was obtained as white solid which was confirmed by QC of Compound 408.

LCMS: EC6159-24-P1A1, RT = 0.406 min, M/Z + 1 = 460

¹HNMR: EC6159-24-P1C1, 400MHz, CDCl₃-d₆

5 δ 8.48 (br s, 2H), 7.40-7.61 (m, 3H), 7.28-7.33 (m, 2H), 7.19-7.26 (m, 2H), 7.16 (br d, J = 8.00 Hz, 1H), 6.94-7.15 (m, 2H), 6.31-6.46 (m, 1H), 6.22 (dq, J = 16.0, 6.80 Hz, 1H), 5.59-6.01 (m, 1H), 5.26-5.51 (m, 1H), 3.75 (br d, J = 13.2 Hz, 1H), 3.07-3.32 (m, 2H), 2.84-3.01 (m, 1H), 2.28-2.44 (m, 1H), 1.89 (br dd, J = 6.40, 1.20 Hz, 3H), 1.72 (m, 2H), 1.34-1.49 (m, 2H), 0.60-0.80 (m, 1H).

10 **LCMS:** EC6159-24-P1C2, RT = 0.418 min, m/z + 1 = 460

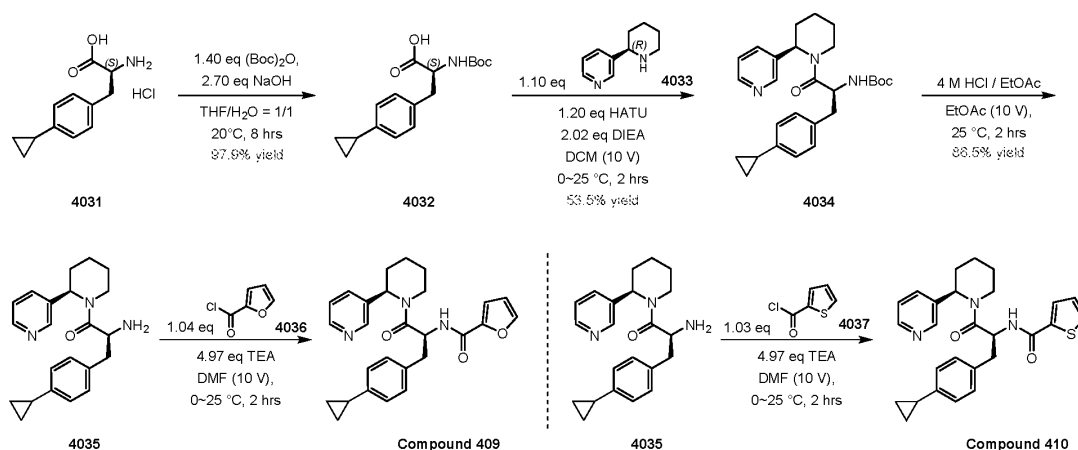
HPLC: EC6159-24-P1C1, RT = 1.933 min, purity = 98.9%

SFC: EC6159-24-P1H1_b2

Example 122

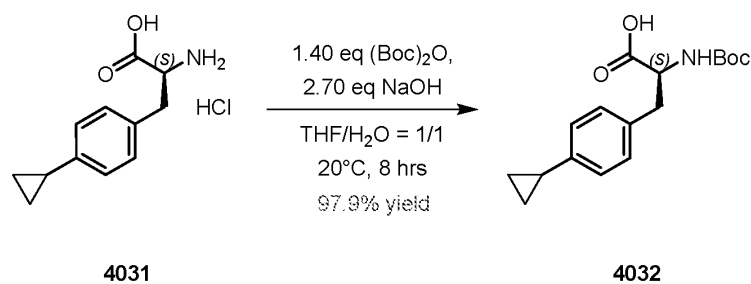
15

Synthetic Protocol for Compound 409 and Compound 410



Example 123

Synthesis of (S)-2-((tert-butoxycarbonyl)amino)-3-(4-cyclopropylphenyl)propanoic acid



20

To a solution of compound **4031** (4.00 g, 16.5 mmol, N/A purity, 1.00 eq, HCl) in THF (20.0 mL) /H₂O (20.0 mL) was added (Boc)₂O (5.06 g, 23.2 mmol, 5.32 mL, 1.40 eq) and NaOH (1.79 g, 44.6 mmol, 2.70 eq). The mixture was stirred at 20 °C for 8 hrs. LCMS (EC7606-3-P1A2) showed that compound **4031** was consumed, and the desired MS (m/z (M+1) = 206.1, Rt = 0.528 min) was detected. The reaction mixture was diluted with water (20.0 mL) and extracted with ethyl acetate 15.0 mL (5.00 mL x 3). The combined extracts were washed with brine (10.0 mL), dried over sodium sulfate and concentrated under reduced pressure. The residue was used to next step without purification. Compound **4032** (5.00 g, 16.2 mmol, 97.9% yield, 99.0% purity) was obtained as yellow oil.

LC-MS: EC7606-3-P1A2, Rt = 0.528 min, m/z (M+1) = 206.1.

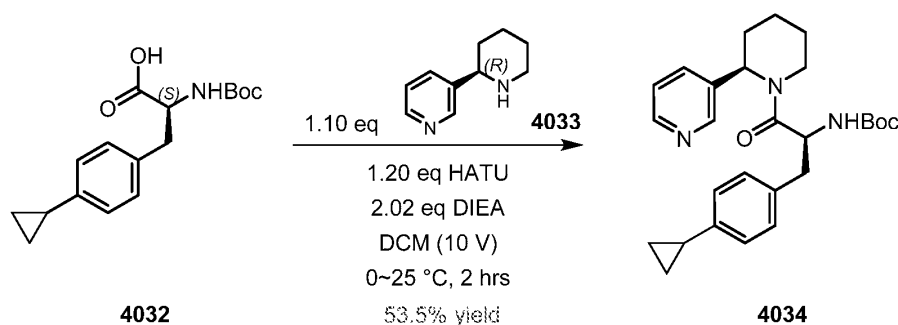
LC-MS: EC7606-3-P1A2, Rt = 0.528 min, m/z (M+1) = 206.1.

HPLC: EC7606-3-P1B1, Rt = 1.972 min, 94.1% purity

15

Example 124

Synthesis of tert-butyl ((S)-3-(4-cyclopropylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



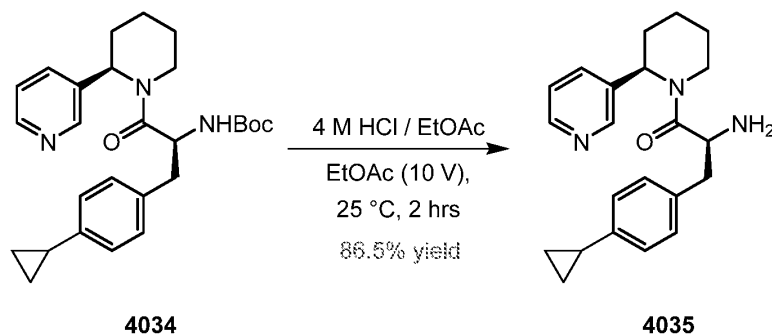
To a solution of compound **4032** (7.50 g, 24.5 mmol, N/A purity, 1.00 eq) in DCM (75.0 mL) was added HATU (11.2 g, 29.5 mmol, 1.20 eq) and DIEA (6.48 g, 50.2 mmol, 8.74 mL, 2.04 eq) at 0 °C then added compound **4033** (4.02 g, 24.8 mmol, N/A purity, 1.01 eq). The mixture was stirred at 25 °C for 2 hrs. LCMS (EC7606-6-P1A1) showed that compound **4032** was consumed, and the desired MS (m/z (M+1) = 450.2, Rt = 0.476 min) was detected. The reaction mixture was concentrated under reduced pressure to remove DCM. The residue was used to next step without purification. Compound **4034** (6.50 g, 13.1 mmol, 53.5% yield, 91.0% purity) was obtained as a white solid.

LC-MS: EC7606-6-P1A1, Rt = 0.475 min, m/z (M+1) = 450.2.

Example 125

Synthesis of (S)-2-amino-3-(4-cyclopropylphenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one

5



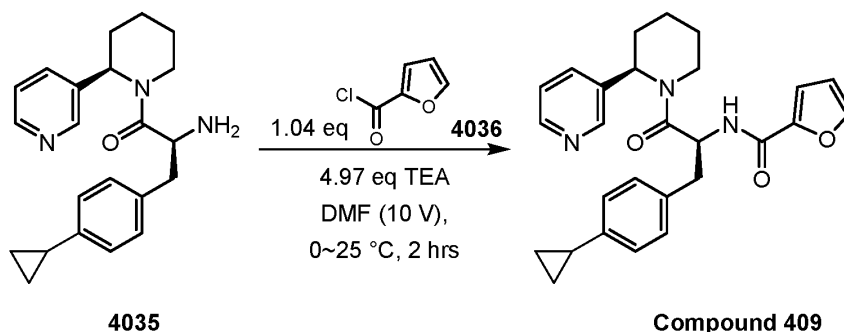
To a solution of compound **4034** (3.50 g, 7.78 mmol, N/A purity, 1.00 eq) was added HCl/EtOAc (4 M, 100 mL, 51.3 eq). The mixture was stirred at 25 °C for 2 hrs. LCMS (EC7606-14-P1A1) showed that compound **4034** was consumed, and the
 10 desired MS (m/z (M+1) = 350.2, Rt = 0.337) was detected. The reaction mixture was concentrated under reduced pressure to remove HCl/EtOAc. The residue was used to next step without purification. Compound **4035** (2.60 g, 6.74 mmol, 86.5% yield, HCl) was obtained as a white solid.

LC-MS: EC7606-14-P1A1, Rt = 0.337 min, m/z (M+1) = 350.2.

15

Example 126

Synthesis of N-((S)-3-(4-cyclopropylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 409)



20 To a solution of compound **4035** (2.40 g, 6.22 mmol, N/A purity, 1.00 eq, HCl) in DCM (24.0 mL) was added TEA (3.15 g, 31.1 mmol, 4.33 mL, 5.01 eq). Then

added compound **4036** (1.32 g, 10.1 mmol, 1.00 mL, N/A purity, 1.03 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC7606-18-P1A1) showed that compound **4035** was consumed, and the desired MS (m/z (M+1) = 444.2, R_t = 0.453 min) was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 250*50mm*10 um; mobile phase: [water (HCl) -ACN]; B%: 20%-50%, 20 min). The crude product was purified by SFC (column: DAICEL CHIRALPAK IC (250mm*30mm, 10 um); mobile phase: [ACN/EtOH (0.1%NH₃H₂O)]; B%: 40%-40%, A4.8;191min). **Compound 409** (1.00 g, 2.16 mmol, 96.0% purity, 1.00 eq) was obtained as a yellow solid.

LC-MS: EC7606-18-P1A1, R_t = 0.453 min, m/z (M+1) = 444.2.

LCMS: EC8519-1-P1A1, R_t = 0.357 min, m/z (M+1) = 444.3.

HPLC: EC8519-1-P1B1, R_t = 1.728 min, 97.9% purity

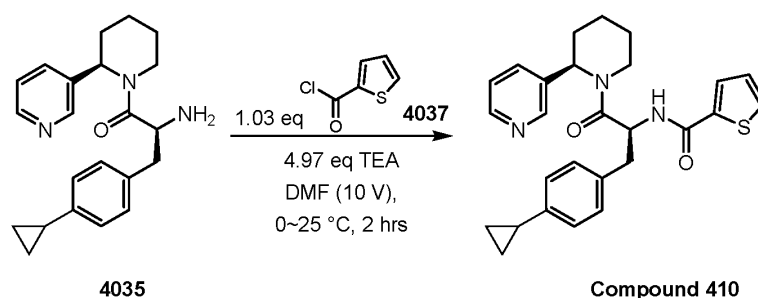
¹H-NMR: EC8519-1-P1N1, 400 MHz, DMSO

δ 8.68 (br d, J = 6.8 Hz, 1H), 8.45 - 8.35 (m, 2H), 7.85 (s, 1H), 7.59 (br d, J = 7.8 Hz, 1H), 7.33 (br dd, J = 4.8, 7.6 Hz, 1H), 7.27 - 7.17 (m, 3H), 7.16 - 7.06 (m, 2H), 7.05 - 6.90 (m, 1H), 6.66 - 6.59 (m, 1H), 5.80 - 5.58 (m, 1H), 5.10 (q, J = 7.2 Hz, 1H), 3.86 (br d, J = 13.4 Hz, 1H), 3.06 (br d, J = 7.4 Hz, 2H), 2.82 (br t, J = 12.2 Hz, 1H), 2.31 (br d, J = 13.2 Hz, 1H), 1.62 - 1.23 (m, 6H), 1.17 (br d, J = 7.0 Hz, 1H), 0.87 (br t, J = 7.2 Hz, 3H), 0.67 (br d, J = 12.6 Hz, 1H)

SFC: EC8519-1-P1S2

Example 127

Synthesis of N-((S)-3-(4-cyclopropylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 410)



To a solution of compound **4035** (2.40 g, 6.22 mmol, N/A purity, 1.00 eq, HCl) in DCM (24.0 mL) was added TEA (3.16 g, 31.2 mmol, 4.35 mL, 5.02 eq). Then

added compound **4037** (1.37 g, 9.35 mmol, 1 mL, N/A purity, 1.00 eq) at 0 °C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC7606-19-P1A1) showed that compound **4035** was consumed, and the desired MS (m/z (M+1) = 460.3, R_t = 0.461 min) was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The crude product was purified by reversed-phase HPLC (column: Phenomenex luna C18 250*50mm*10 um; mobile phase: [water (HCl) -ACN]; B%: 20%-50%, 20 min). The crude product was purified by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm, 10 um); mobile phase: [ACN/MeOH(0.1%NH₃H₂O)]; B%: 60%-60%, A4.7;75min). **Compound 410** (640 mg, 1.32 mmol, 95.0% purity, 1.00 eq) was obtained as a yellow solid.

LC-MS: EC7606-19-P1A1, R_t = 0.461 min, m/z (M+1) = 460.3.

LCMS: EC8519-2-P1A1, R_t = 0.357 min, m/z (M+1) = 444.3.

HPLC: EC8519-2-P1B1, R_t = 1.826 min, 97.9% purity

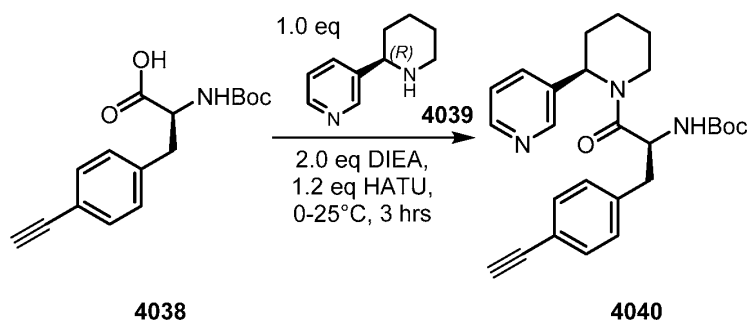
¹H-NMR: EC8519-2-P1N1, 400 MHz, DMSO

δ 8.95 (br d, J = 7.0 Hz, 1H), 8.41 (s, 2H), 7.94 (d, J = 3.0 Hz, 1H), 7.77 (d, J = 4.4 Hz, 1H), 7.59 (br d, J = 8.0 Hz, 1H), 7.32 (br dd, J = 4.8, 7.6 Hz, 1H), 7.24 (br d, J = 7.8 Hz, 2H), 7.13 (br d, J = 8.0 Hz, 3H), 6.98 (br s, 1H), 5.73 (br s, 1H), 5.11 (br d, J = 7.2 Hz, 1H), 3.86 (br d, J = 13.2 Hz, 1H), 3.22 - 2.89 (m, 3H), 2.82 (br t, J = 12.4 Hz, 1H), 2.30 (br d, J = 14.2 Hz, 1H), 1.58 - 1.45 (m, 3H), 1.40 - 1.09 (m, 3H), 0.87 (br t, J = 7.2 Hz, 3H), 0.73 - 0.55 (m, 1H)

SFC: EC8519-1-P1S2

Example 128

Synthesis of tert-butyl ((S)-3-(4-ethynylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)carbamate



To a solution of compound **4038** (0.20 g, 691 umol, 1.00 eq) and compound **4039** (113 mg, 696 umol, 1.01 eq) in DCM (3.00 mL) was added DIEA (178 mg, 1.38 mmol, 241

uL, 2.00 eq) and HATU (315 mg, 830 umol, 1.20 eq) at 0 °C. The mixture was stirred at 25°C for 2 hrs. LCMS (EC5892-1-P1A1) showed that compound **4038** ($m/z=289$) was consumed completely and the desired MS ($R_t=0.451$ min, $M+1=434.4$) was found. The reaction mixture was concentrated under vacuum. No need further purification to give compound **4040** (0.50 g, crude) as yellow oil and used to the next step. Compound **4040** (0.50 g, crude) was obtained as yellow oil, checked by LCMS (EC5892-1-P1A2) and HNMR (EC5892-1-P1A1)

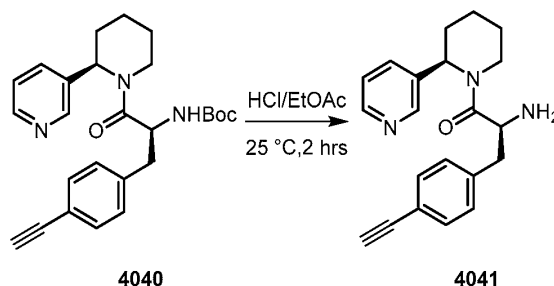
LCMS: EC5892-1-P1A1, Ret. Time = 0.451 min, $m/z +1 = 434.4$

HNMR: EC5892-1-P1A1 (400 MHz, $CDCl_3$)

$\delta = 8.49 - 8.45$ (m, 2H), 7.46 (br d, $J = 8.0$ Hz, 3H), 7.23 (br d, $J = 7.9$ Hz, 3H), 5.92 (br d, $J = 2.8$ Hz, 1H), 5.38 (br d, $J = 8.6$ Hz, 1H), 4.98 - 4.88 (m, 1H), 3.16 (q, $J = 7.4$ Hz, 3H), 3.08 (s, 1H), 2.91 (dt, $J = 2.5, 13.4$ Hz, 1H), 1.49 - 1.45 (m, 6H), 1.42 (s, 9H)

Example 129

Synthesis of (S)-2-amino-3-(4-ethynylphenyl)-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-1-one



To a solution of compound **4040** (0.3 g, 692 umol, 1.00 eq) in EtOAc (2.00 mL) was added HCl/EtOAc (4 M, 1.50 mL, 8.67 eq). The mixture was stirred at 25°C for 2 hrs.

LCMS (EC5892-14-P1A1) showed that compound **4040** ($m/z=433$) was consumed completely and the desired MS ($R_t=0.316$ min, $M+1=334.3$) was found. The reaction mixture was concentrated under vacuum. No need further purification to give compound **4041** (0.58 g, crude, HCl) as white solid and used to the next step. Compound **4041** (0.58 g, crude, HCl) was obtained as white solid, checked by HNMR (EC5892-14-P1A1)

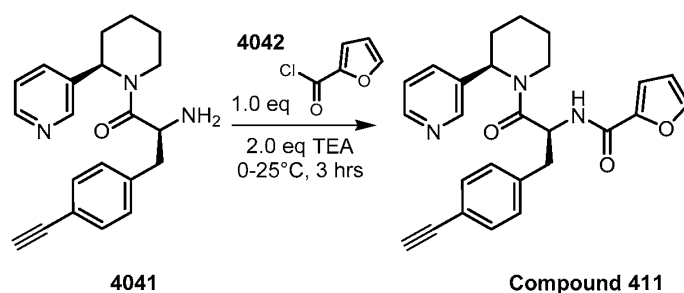
LCMS: EC5892-14-P1A1, Ret. Time = 0.316 min, $m/z +1 = 334.3$

¹HNMR: EC5892-14-P1A1 (400 MHz, DMSO)

δ = 8.96 (s, 1H), 8.80 - 8.76 (m, 1H), 8.70 (br s, 3H), 8.61 (br d, J = 8.3 Hz, 1H), 7.99 (dd, J = 5.6, 8.1 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.72 (br s, 1H), 4.84 - 4.75 (m, 1H), 3.68 (br d, J = 13.5 Hz, 1H), 3.59 (dtd, J = 4.0, 6.6, 13.1 Hz, 1H), 3.21 (br dd, J = 5.2, 13.1 Hz, 1H), 3.11 (dq, J = 4.3, 7.4 Hz, 1H), 3.00 (br dd, J = 9.3, 12.9 Hz, 1H), 2.89 - 2.78 (m, 1H), 1.30 (d, J = 6.6 Hz, 4H), 1.28 - 1.26 (m, 4H)

Example 130

Synthesis of N-((S)-3-(4-ethynylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)furan-2-carboxamide (Compound 411)



10

To a solution of compound **4041** (0.29 g, 869 μ mol, 1.00 eq) and TEA (180 mg, 1.79 mmol, 248 μ L, 2.05 eq) in DCM (3.00 mL) was added compound **4042** (114 mg, 879 μ mol, 87.0 μ L, 1.01 eq) at 0°C. The mixture was stirred at 25 °C for 2 hr. LCMS (EC5892-15-P1A1) showed that compound **4041** (m/z =333) was consumed completely and the desired

MS (R_t =0.400 min, $M+1$ =428.3) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (column: Waters xbridge 150*25mm 10 μ m; mobile phase: [water (NH_4HCO_3)-ACN]; B%: 28%-58%, 9min).

Compound 411 (80.0 mg, 182 μ mol, 20.9% yield, 97.5% purity) was obtained as yellow solid, checked by LCMS(EC5892-15-P1A3), HPLC(EC5892-15-P1A5), HNMR(EC5892-15-P1A1) and Chiral SFC(EC5892-15-P1A6).

20

LCMS: EC5892-15-P1A1, product: Ret. Time = 0.400 min, m/z +1 = 428.3

$^1\text{HNMR}$: EC5892-15-P1A1 (400 MHz, CDCl_3)

δ = 8.55 - 8.35 (m, 2H), 7.47 (br d, J = 7.0 Hz, 3H), 7.35 - 7.27 (m, 2H), 7.22 (br d, J = 8.1 Hz, 2H), 7.14 (br d, J = 3.3 Hz, 1H), 7.11 - 6.66 (m, 1H), 6.56 - 6.48 (m, 1H), 5.94 (br d, J = 3.1 Hz, 1H), 5.44 (dt, J = 5.5, 8.3 Hz, 1H), 4.00 - 3.88 (m, 1H), 4.60 - 3.63 (m, 1H), 3.28 - 3.21 (m, 1H), 3.18 - 3.11 (m, 1H), 3.09 (s, 1H), 3.01 - 2.46 (m, 1H), 2.35 (br d, J = 14.3 Hz, 1H), 2.16 - 1.85 (m, 2H), 1.77 - 1.52 (m, 2H), 1.50 - 1.40 (m, 2H), 0.82 - 0.48 (m, 1H)

25

LCMS: EC5892-15-P1A3, product: Ret. Time = 1.601 min, m/z +1 = 428.3

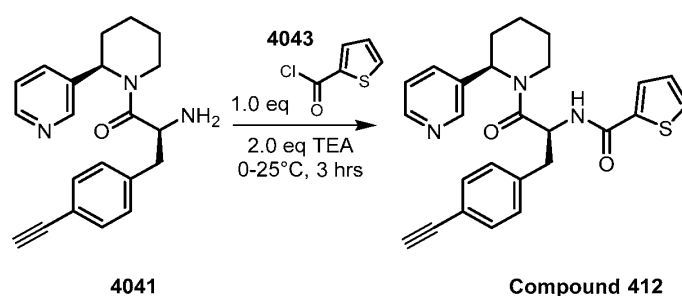
HPLC: EC5892-15-P1A5, product: Ret. Time = 1.726 min

Chiral SFC: EC5892-15-P1A6, ee%=98.4

5

Example 131

Synthesis of N-((S)-3-(4-ethynylphenyl)-1-oxo-1-((R)-2-(pyridin-3-yl)piperidin-1-yl)propan-2-yl)thiophene-2-carboxamide (Compound 412)



To a solution of compound **4041** (0.24 g, 720 μ mol, 1.00 eq) and TEA (150 mg, 1.48 mmol, 205 μ L, 2.05 eq) in DCM (3.00 mL) was added compound **4043** (108 mg, 737 μ mol, 78.8 μ L, 1.02 eq) at 0°C. The mixture was stirred at 25 °C for 2 hrs. LCMS (EC5892-7-P1A1) showed that compound **4041** (m/z=333) was consumed completely and the desired MS (Rt=0.483 min, M+1=444.0) was found. The reaction mixture was concentrated under vacuum. The crude product was purified by prep-HPLC (column: Welch Ultimate AQ-C18 150*30mm*5 μ m; mobile phase: [water (HCl)-ACN]; B%: 19%-49%, 10min). **Compound 412** (30.0 mg, 65.6 μ mol, 9.11% yield, 96.9% purity) was obtained as white solid, checked by LCMS (EC5892-7-P1A7), HPLC (EC5892-7-P1A6) HNMR (EC5892-7-P1A1) and SFC (EC5892-7-P1A7).

LCMS: EC5892-7-P1A1, product: Ret. Time = 0.483 min, m/z +1 = 444.0

¹HNMR: EC5892-7-P1A1 (400 MHz, CDCl₃)

δ = 8.68 (br s, 1H), 8.55 (br d, J = 1.5 Hz, 1H), 8.21 (br d, J = 6.5 Hz, 1H), 7.86 - 7.77 (m, 1H), 7.69 (d, J = 3.4 Hz, 1H), 7.53 (d, J = 4.9 Hz, 1H), 7.49 (d, J = 7.9 Hz, 2H), 7.30 - 7.27 (m, 1H), 7.27 - 7.17 (m, 2H), 7.14 - 7.07 (m, 2H), 5.95 (br s, 1H), 5.34 - 5.20 (m, 1H), 3.92 - 3.72 (m, 1H), 3.30 - 3.17 (m, 2H), 3.11 (s, 1H), 2.95 - 2.80 (m, 1H), 2.39 - 2.19 (m, 2H), 1.80 - 1.71 (m, 1H), 1.66 - 1.59 (m, 1H), 1.50 (br d, J = 12.5 Hz, 1H), 1.33 - 1.25 (m, 1H), 0.78 - 0.62 (m, 1H)

LCMS: EC5892-7-P1A7, product: Ret. Time = 1.666 min, m/z +1 = 444.3

HPLC: EC5892-7-P1A6, product: Ret. Time = 1.757 min

Chiral SFC: EC5892-7-P1A7, ee%=97.4

BIOLOGICAL EXAMPLES

5 Example 1

Determination of inhibition of NF-kB activation induced by TNF α ... *in vitro* assay

The ability of a compound disclosed herein to inhibit NFkB activation induced by TNF α was determined using the TNF α Luciferase assay. The HEK293/NF-kB luciferase cell
10 line was obtained by cotransfection of pNFkB-luc vector with pHyg (Panomics, CA, USA) followed by hygromycin selection. HEK293/NFkB Luciferase cells were grown in DMEM medium supplemented with 10% fetal bovine serum, 100U/ml of penicillin, 100 μ g/ml of streptomycin/ Fungizone, and 100 μ g/ml of hygromycin B as the selecting agent. HEK293 NFkB Luciferase cells were grown in T75 flasks (Nunc™ Cell Culture Treated
15 EasYFlasks™) in a cell culture incubator at 37°C and 5%CO₂.

Confluent T75 cell culture flasks (approximately 8-10 million of cells per flask) were washed with 10 ml of sterile PBS (without calcium and magnesium) under a biosafety cabinet. After aspiration of the PBS with a sterile glass pipette, the layer of cells (for each T75 flask) was covered with 1 ml of TrypLE™ Express without phenol red (Gibco) at room
20 temperature. After one minute of incubation, HEK293 were mechanically resuspended in the TrypLE by tapping the side of the flask. The cells were then resuspended with 10 ml of pre-warmed complete culture medium and transferred to a conical tube. Cells were centrifuged for 5 minutes at 4000 rpm (1000g) at room temperature. The cellular pellet was resuspended with 24 ml of pre-warmed cell culture media and 200 ml of cell suspension (approximately
25 80,000 cells per well) was plated per well in 96-well cell culture plates (Costar #3599, Corning, NY, USA) using a multichannel pipette and reversed pipetting to prevent air bubble formation. After plating, the cells were maintained overnight in the cell culture incubator before being treated. For each 96 well cell culture plate, 8 wells were used as “control wells” (only culture medium added) and to 8 wells only TNF α was added. The NF-kB Luciferase
30 reporter cell line was challenged with 25 ng/ml of TNF- α for four hours in the presence and absence (control conditions) of a dose range of the different compounds to be tested. For each compound, a dose range of concentrations was tested in quadruplicate and used to determine an IC₅₀.

Luciferase activity was monitored using the Luc-Screen® Extended-Glow Luciferase Reporter Gene Assay System by chemoluminescence according to the instruction of the manufacturer (Invitrogen) and a BioTek Synergy HT plate reader (BioTek Instruments, VT, USA). The IC₅₀, concentration at which NF-κB activation was reduced by 50%, for a
 5 representative number of compounds is provided in Tables 5-8 below.

Table 5

Cpd No. (see Cpd Table 1 above)	IC ₅₀ (μM)	Cpd No. (see Cpd Table 1 above)	IC ₅₀ (μM)	Cpd No. (see Cpd Table 1 above)	IC ₅₀ (μM)
101	0.008667	102	0.001764	103	0.01273
104	0.0031	105	0.0172	106	0.0082
107	0.0073	108	0.0075	109	0.0105
110	0.0065	111	0.0123	112	0.0108

10

Table 6

Cpd No. (see Cpd Table 2 above)	IC ₅₀ (μM)	Cpd No. (see Cpd Table 2 above)	IC ₅₀ (μM)	Cpd No. (see Cpd Table 2 above)	IC ₅₀ (μM)
201	0.0598	204	0.06008	207	0.0548
202	0.06965	205	0.1373	208	0.23
203	0.08975	206	0.2124	209	0.5863
210	0.1833	211	0.1647	212	0.26
213	0.3464	214	0.312		

Table 7

Cpd No. (see Cpd Table 3 above)	IC ₅₀ (μM)	Cpd No. (see Cpd Table 3 above)	IC ₅₀ (μM)	Cpd No. (see Cpd Table 3 above)	IC ₅₀ (μM)
302	0.1896	303	0.6575	304	0.397
305	0.1274				

Table 8

Cpd No. (see Cpd Table 4 above)	IC ₅₀ (μM)	Cpd No. (see Cpd Table 4 above)	IC ₅₀ (μM)	Cpd No. (see Cpd Table 4 above)	IC ₅₀ (μM)
401	0.1069	405	0.08535	409	0.01952
402	0.1086	406	0.07393	410	0.02295
403	0.01038	407	0.3008	411	0.2822
404	0.00961	408	0.5666	412	0.5026

Example 2

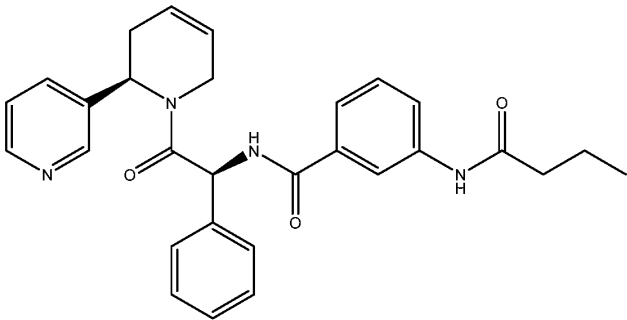
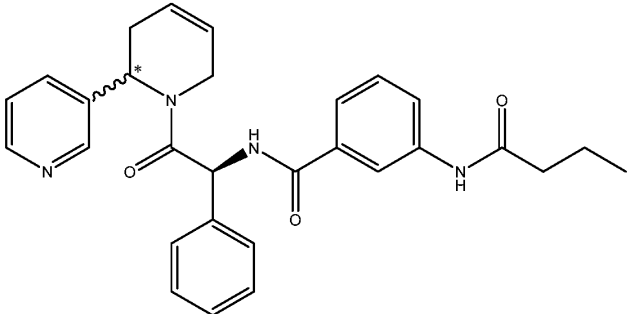
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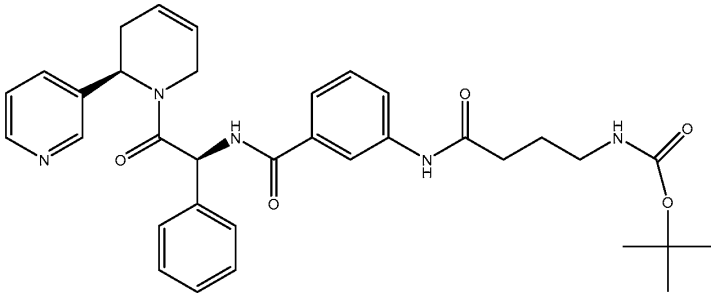
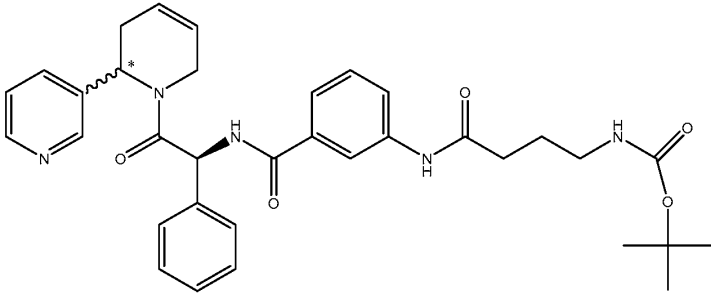
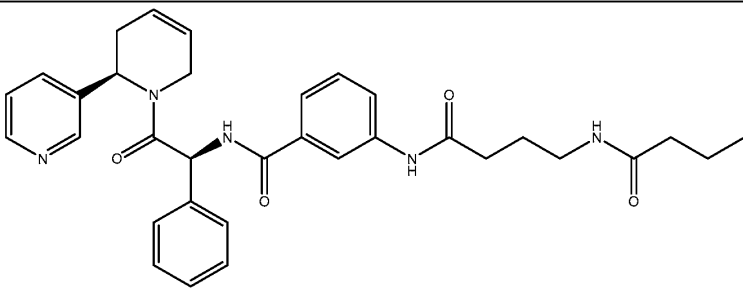
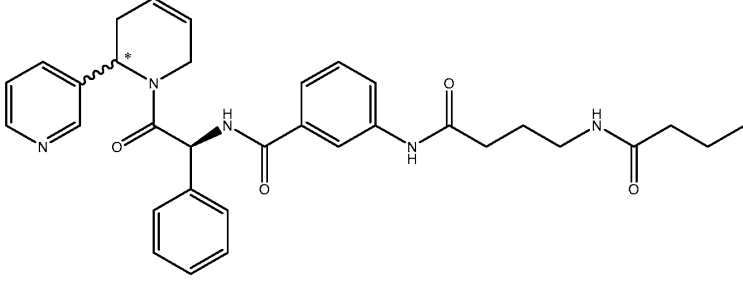
Comparative Inhibitory Activity

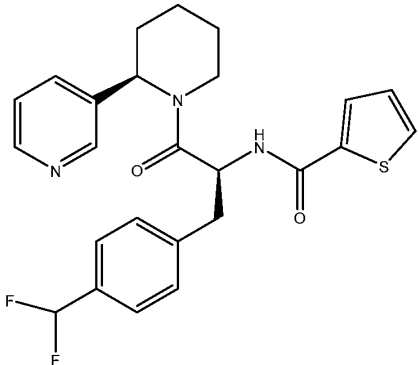
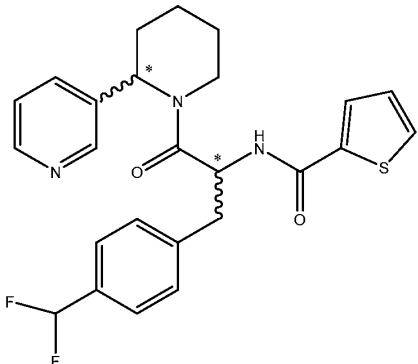
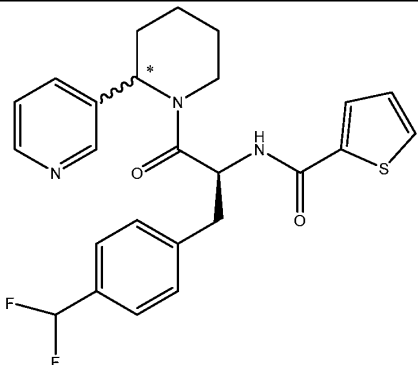
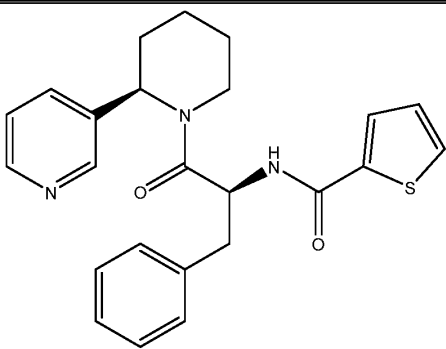
The inventors surprisingly discovered that the R,S enantiomers as disclosed herein are unexpectedly superior to their alternative isomers or mixtures thereof. Exemplary findings are provided in Table 9.

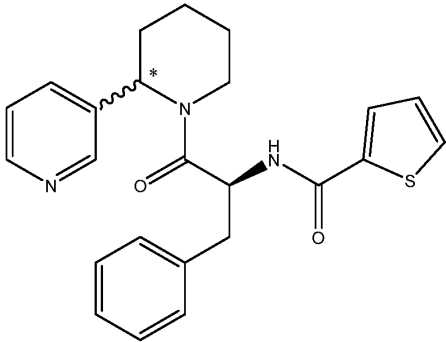
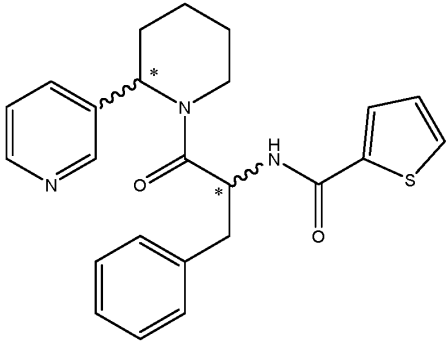
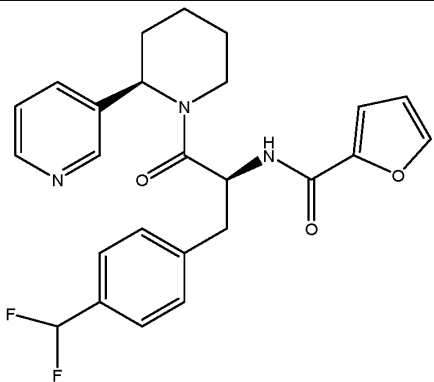
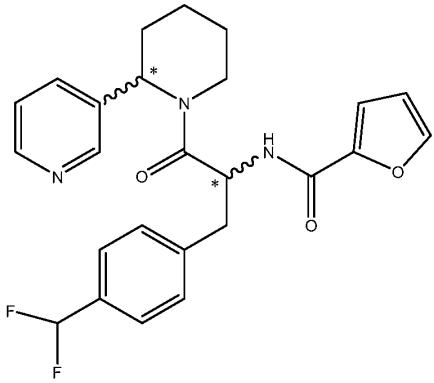
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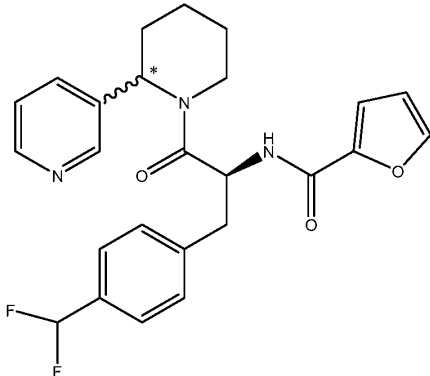
Table 9

Cpd No.	Compound*	IC ₅₀ (μM)
101		0.008667
113		0.053

Cpd No.	Compound*	IC ₅₀ (μM)
102		0.001764
114		0.00896
103		0.01273
115		0.0504

Cpd No.	Compound*	IC ₅₀ (μM)
202		0.06965
215		0.1709
216		0.1628
214		0.312

Cpd No.	Compound*	IC ₅₀ (μM)
217		0.5228
218		0.5121
201		0.0598
219		0.1801

Cpd No.	Compound*	IC ₅₀ (μM)
220		0.08557

* An asterisk with a wavy bond indicates a mixture of isomers at the carbon with the asterisk.

Example 3

Determination of Anti-inflammatory Activity using Acute LPS Model of Inflammation in Mice... *in vivo* model

5

The ability of the compounds disclosed herein to reduce inflammation was determined *in vivo* by using the above mouse model. The impact of the compounds on the production of proinflammatory cytokines induced by LPS can be evaluated in various tissues (e.g., plasma, brain, intestine, spleen, lung, etc). Adult C57Bl6/J wild-type mice were used to assess the impact of a compound disclosed herein ("test" compound) on cytokines production induced by an intraperitoneal injection of LPS (lipopolysaccharide) [LPS from *Escherichia coli* O111:B4, Sigma-Aldrich # L4391]. Prior to treatment with LPS (1mg/Kg (intraperitoneal injection) dissolved in sterile PBS), mice were randomized into a placebo/control group receiving an intraperitoneal (IP) injection of the vehicle used to dissolve the test compound (50% PEG4000/50% DMSO) and into a treatment group (receiving 20 mg/Kg of the test compound IP). Mice were injected with the test compound or the vehicle 15 minutes prior to the LPS injection.

Mice were then humanely euthanatized four hours after the intraperitoneal injection of LPS. Following euthanasia, blood was collected by an intracardiac puncture using EDTA as an anticoagulant. Blood was immediately centrifuged at 1500g for 4 minutes and the plasma collected and snap frozen in liquid nitrogen. All the other tissues were rapidly dissected out and snap frozen in liquid nitrogen. Samples were stored at -80°C.

Tissue homogenates were prepared by sonication in ice-cold M-PER Reagent (Pierce Biotechnology, Rockford, IL, USA) containing 1mM phenylmethanesulfonyl fluoride, 1X of

protease cocktail inhibitor (Roche, Inc., USA) and 1mM sodium orthovanadate (Sigma-Aldrich, MO, USA). Cytokines were quantified by electrochemiluminescence using MULTI-SPOT plates from a V-Plex assay kit Pro-Inflammatory Panel 1 (mouse) kit (Mesoscale discovery, USA). All LPS treated samples were diluted 10X with diluent 41 from the kit and control samples were assayed without dilution. The amount of proinflammatory cytokines interferon-gamma, IL-1 β , and TNF α produced was less in the treatment group versus the control group.

Formulation Examples

The following are representative pharmaceutical formulations containing a compound of the present disclosure.

Tablet Formulation

The following ingredients are mixed intimately and pressed into single scored tablets.

	Ingredient	Quantity per tablet
		mg
	compound of this disclosure	400
	cornstarch	50
	croscarmellose sodium	25
	lactose	120
	magnesium stearate	5

Capsule Formulation

The following ingredients are mixed intimately and loaded into a hard-shell gelatin capsule.

	Ingredient	Quantity per capsule
		mg
	compound of this disclosure	200
	lactose spray dried	148
	magnesium stearate	2

Injectable Formulation

Compound of the disclosure (e.g., compound 1) in 2% HPMC, 1% Tween 80 in DI water, pH 2.2 with MSA, q.s. to at least 20 mg/mL

Inhalation Composition

- 5 To prepare a pharmaceutical composition for inhalation delivery, 20 mg of a compound disclosed herein is mixed with 50 mg of anhydrous citric acid and 100 mL of 0.9% sodium chloride solution. The mixture is incorporated into an inhalation delivery unit, such as a nebulizer, which is suitable for inhalation administration.

10 Topical Gel Composition

- To prepare a pharmaceutical topical gel composition, 100 mg of a compound disclosed herein is mixed with 1.75 g of hydroxypropyl cellulose, 10 mL of propylene glycol, 10 mL of isopropyl myristate and 100 mL of purified alcohol USP. The resulting gel mixture is then incorporated into containers, such as tubes, which are suitable for topical
15 administration.

Ophthalmic Solution Composition

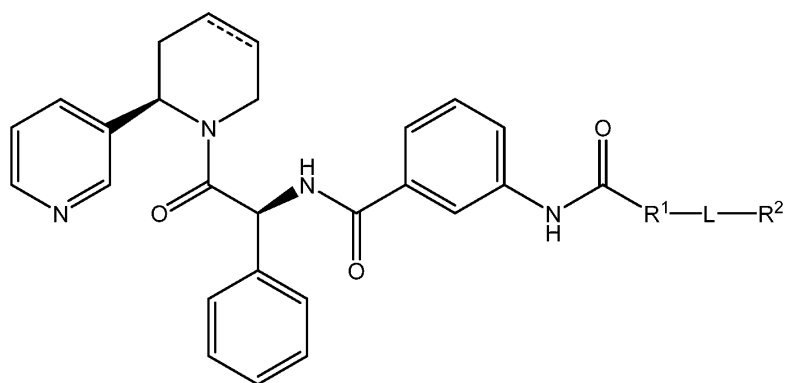
- To prepare a pharmaceutical ophthalmic solution composition, 100 mg of a compound disclosed herein is mixed with 0.9 g of NaCl in 100 mL of purified water and filtered using a
20 0.2 micron filter. The resulting isotonic solution is then incorporated into ophthalmic delivery units, such as eye drop containers, which are suitable for ophthalmic administration.

Nasal spray solution

- To prepare a pharmaceutical nasal spray solution, 10 g of a compound disclosed
25 herein is mixed with 30 mL of a 0.05M phosphate buffer solution (pH 4.4). The solution is placed in a nasal administrator designed to deliver 100 ul of spray for each application.

We claim:

1. A compound of Formula (I), Formula (II), Formula (III) or Formula (IV):

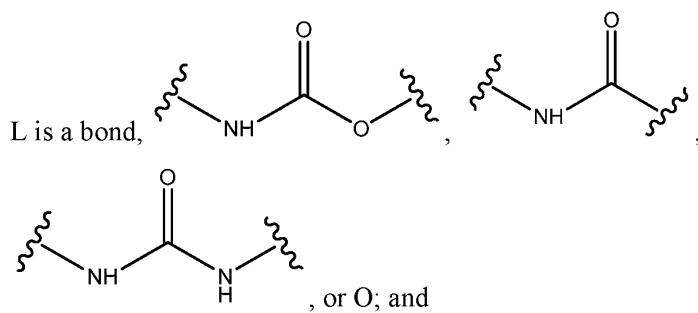


(I)

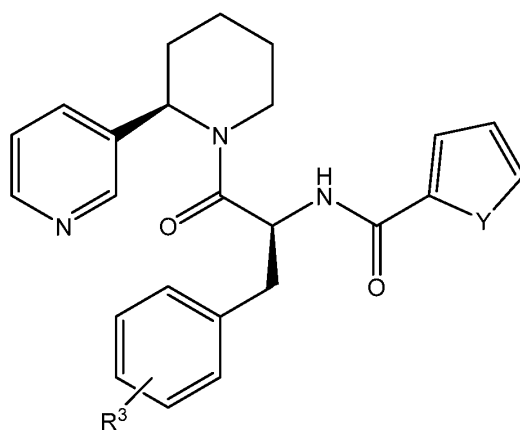
- 5 wherein:

the dashed line is an optional bond;

R¹ is C₃-C₅ alkyl;



- 10 R² is H or C₃-C₇ alkyl;

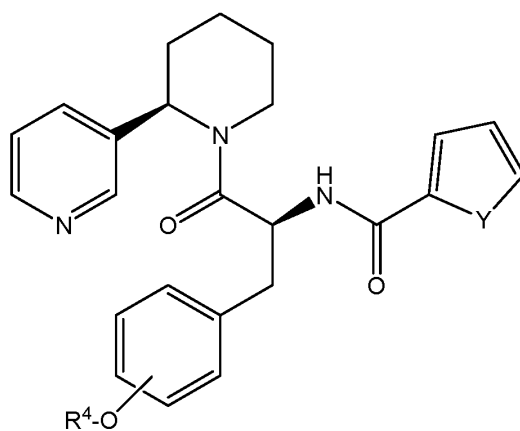


(II)

wherein:

Y is O or S; and

R³ is -H, -F, or -CX₃, wherein each X is independently -H or -F;

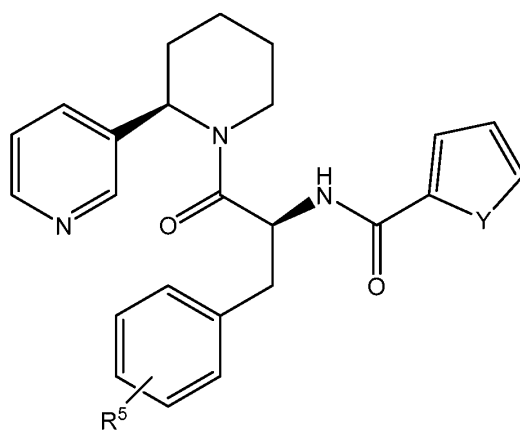


(III)

5 wherein:

Y is O or S; and

R⁴ is -CX₃, wherein each X is independently -H or -F;



(IV)

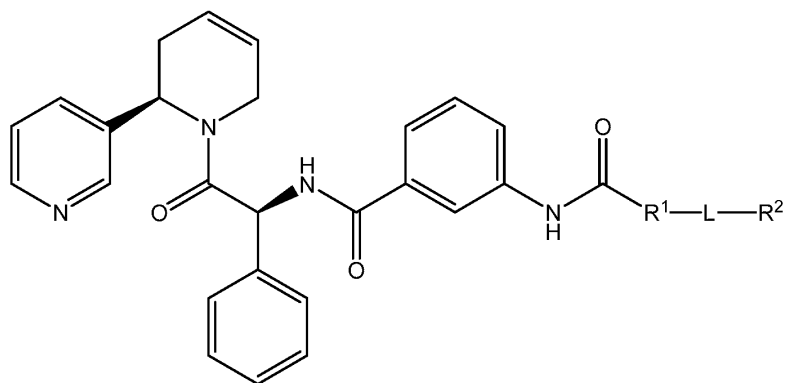
10 wherein:

Y is O or S; and

R⁵ is C₂-C₃ alkyl, C₂-C₃ alkenyl, C₂-C₃ alkynyl, or C₃-C₄ cycloalkyl;
or a pharmaceutically acceptable salt thereof.

15 2. The compound of claim 1, wherein the compound is of Formula (I) or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1 or 2, wherein the compound is of Formula (IA):

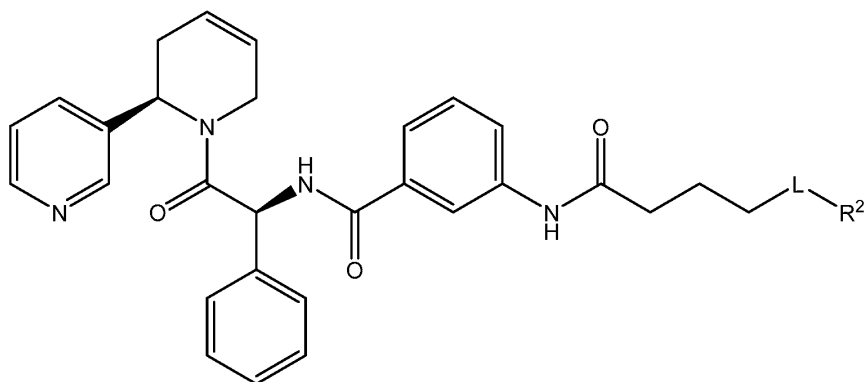


(IA)

or a pharmaceutically acceptable salt thereof.

5

4. The compound of any one of claims 1-3, wherein the compound is of Formula (IB):



(IB)

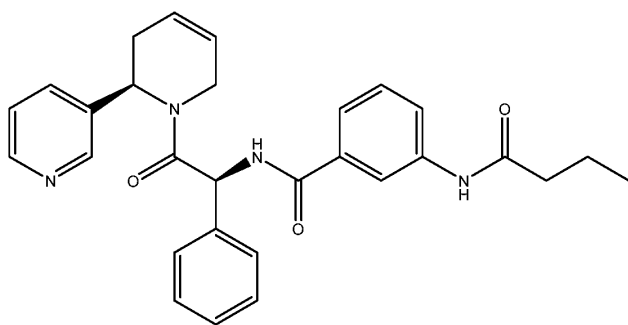
or a pharmaceutically acceptable salt thereof.

10

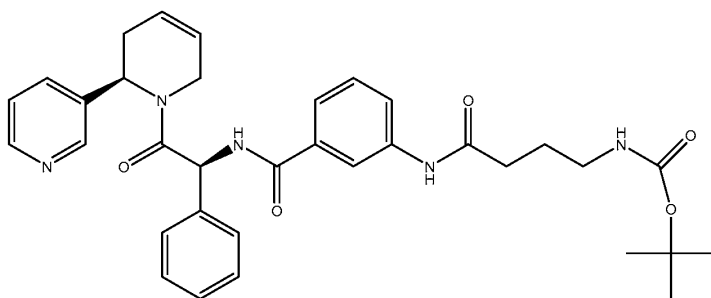
5. The compound of any one of claims 1-4 wherein L is a bond.

6. The compound of any one of claims 1-5 wherein R² is H.

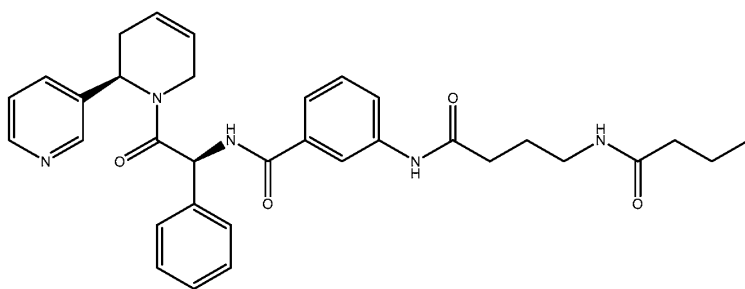
- 15 7. The compound of any one of claims 1-4, wherein the compound is



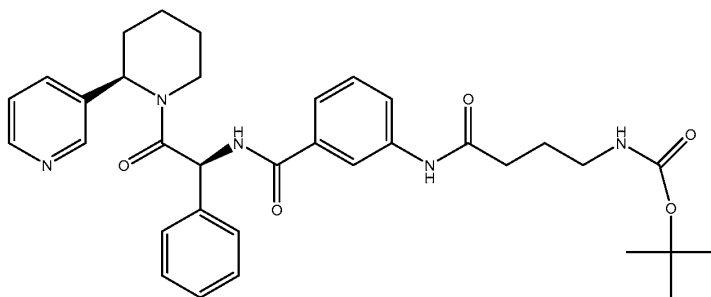
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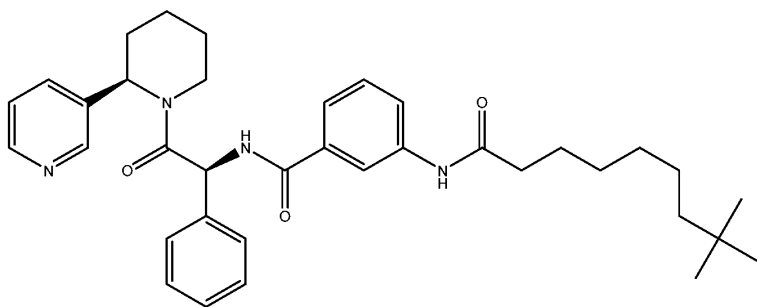
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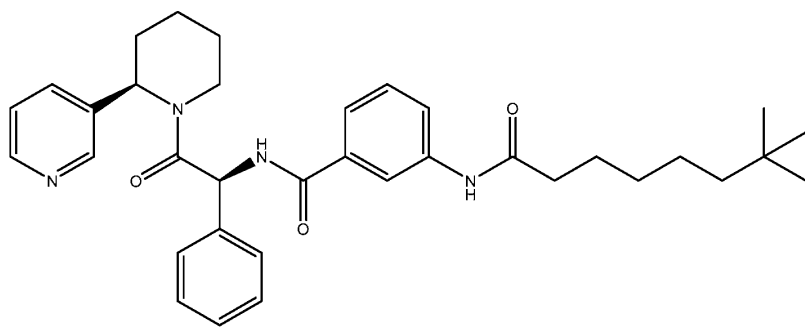
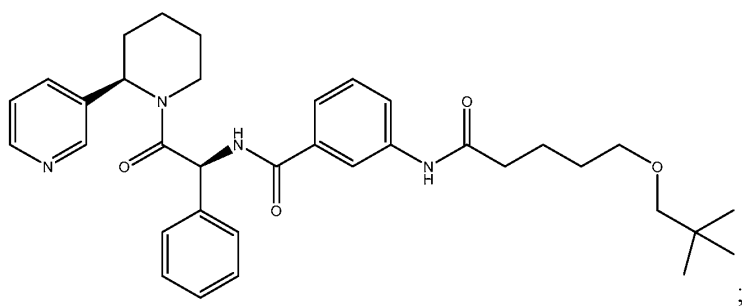
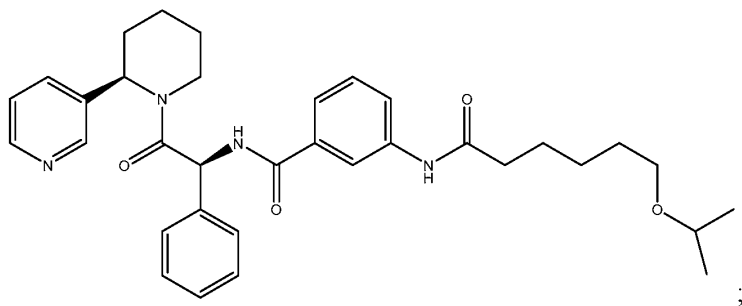
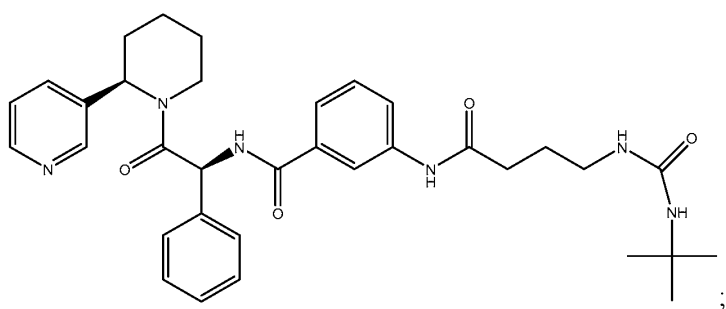
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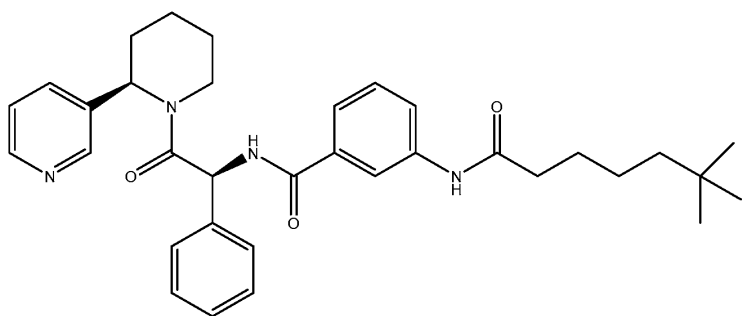


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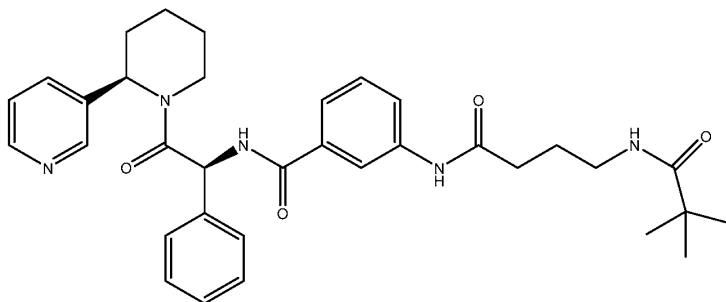


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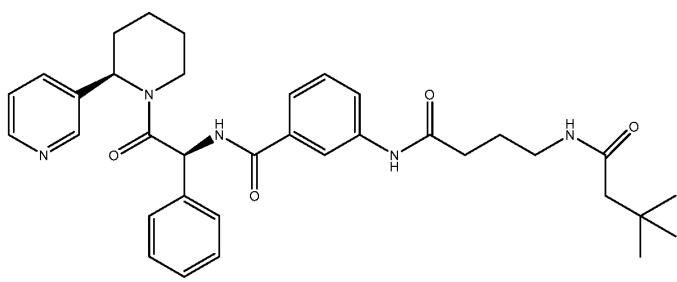




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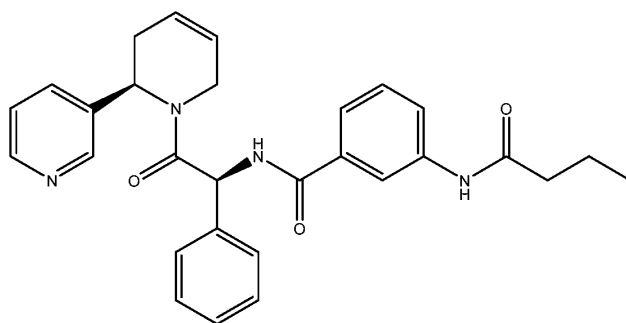
; or



;

or a pharmaceutically acceptable salt thereof.

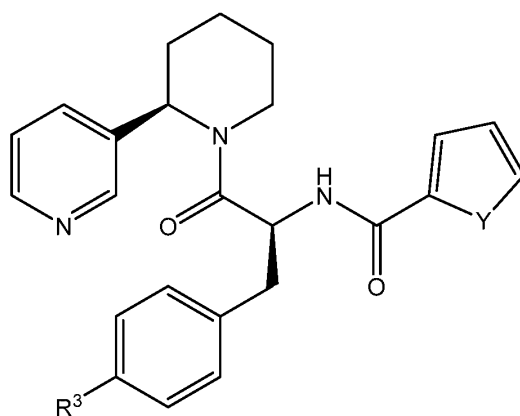
8. The compound according to claim 7, wherein the compound is



5 or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, wherein the compound is of Formula (II) or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 1 or claim 9, wherein the compound is of Formula (IIA)



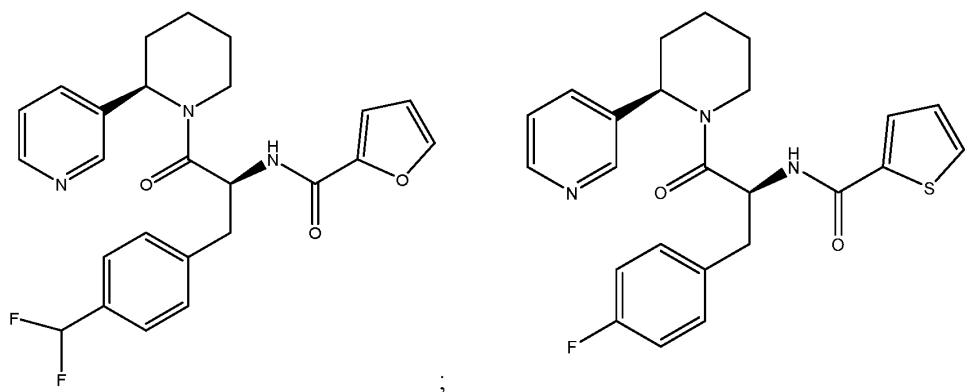
(IIA)

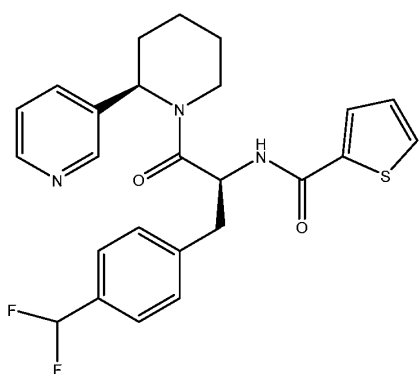
- 5 or a pharmaceutically acceptable salt thereof.

11. The compound of any one of claims 1 and 9-10, wherein R^3 is $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, or $-\text{CF}_3$.

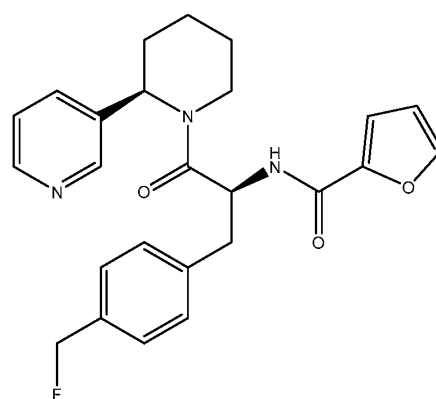
- 10 12. The compound of any one of claims 1 and 9-11, wherein R^3 is $-\text{CHF}_2$.

13. The compound of any one of claims 1 and 9-10, wherein the compound is

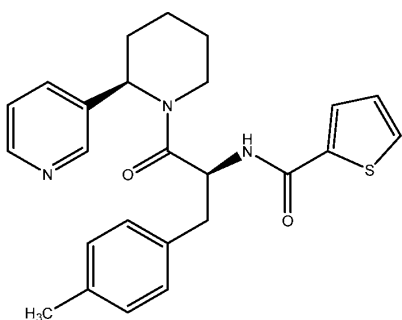




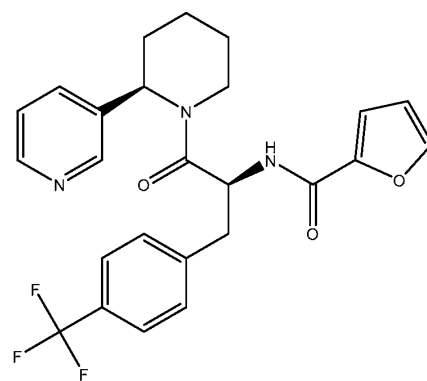
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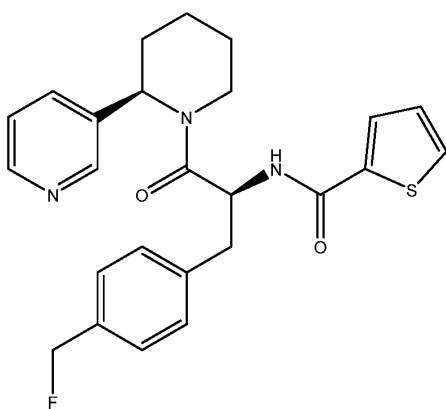
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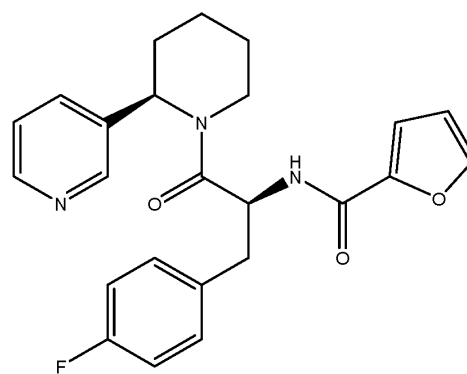
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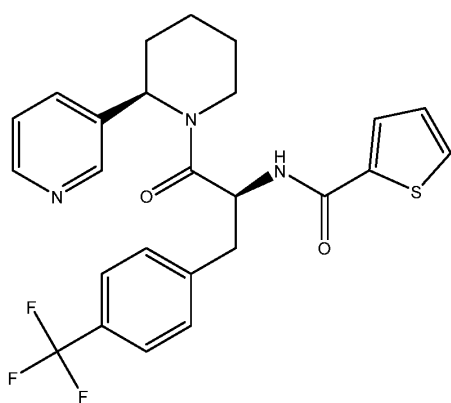
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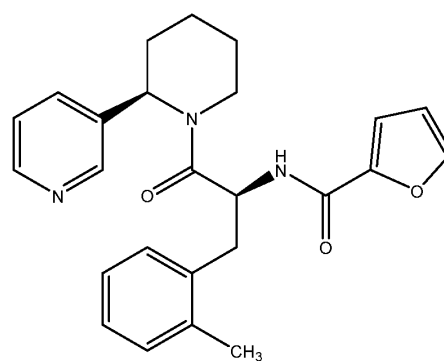
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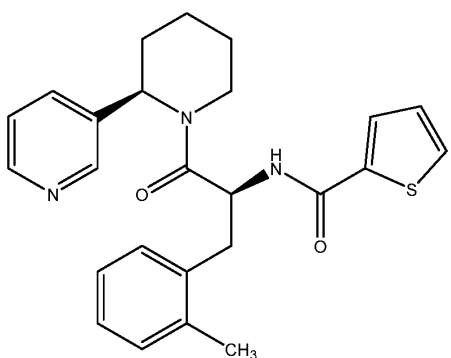
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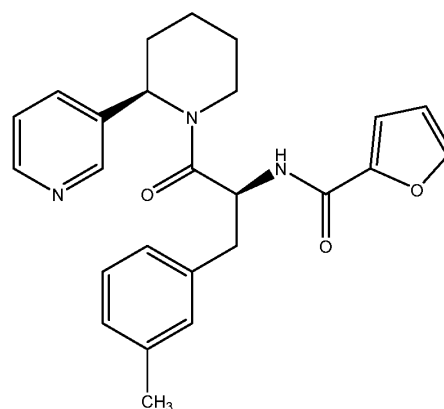
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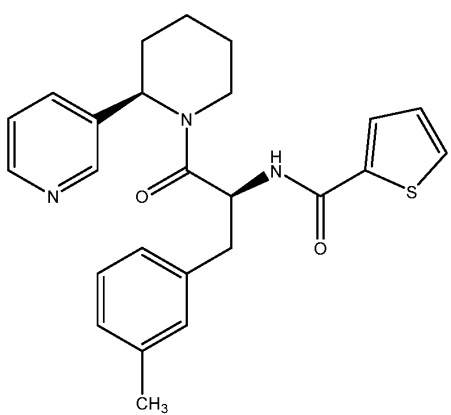
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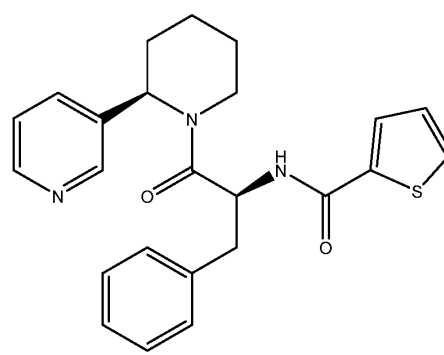
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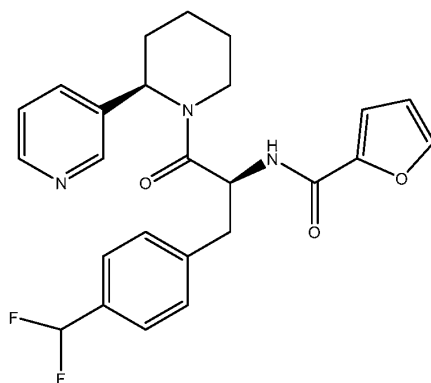
; or



;

or a pharmaceutically acceptable salt thereof.

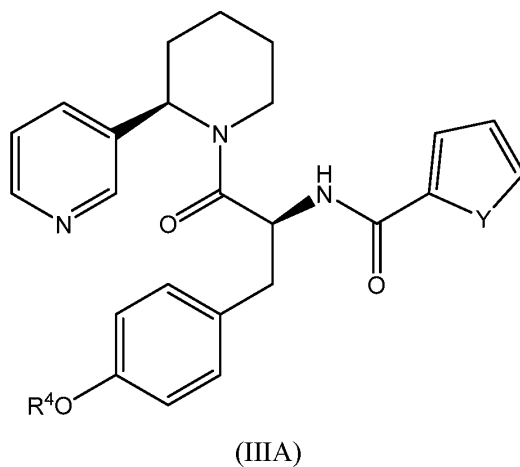
14. The compound according to claim 13, wherein the compound is



or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1, wherein the compound is of Formula (III) or a
5 pharmaceutically acceptable salt thereof.

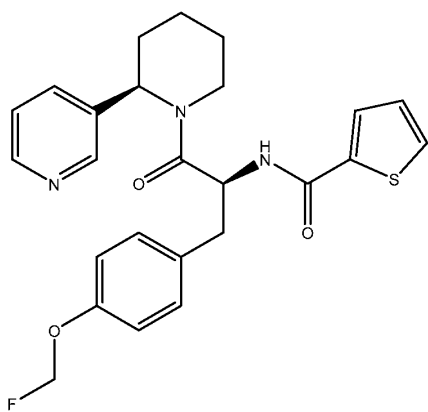
16. The compound of claim 1 or claim 15, wherein the compound is of Formula (IIIA)



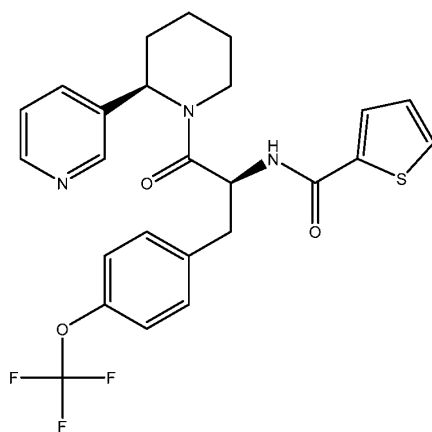
- 10 or a pharmaceutically acceptable salt thereof.

17. The compound of any one of claims 1 and 15-16, wherein R⁴ is -CHF₂.

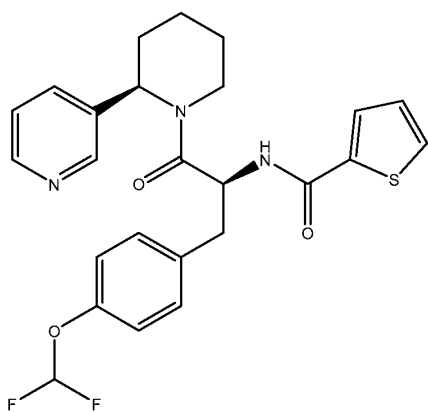
18. The compound of any one of claims 1 and 15-16, wherein the compound is
15



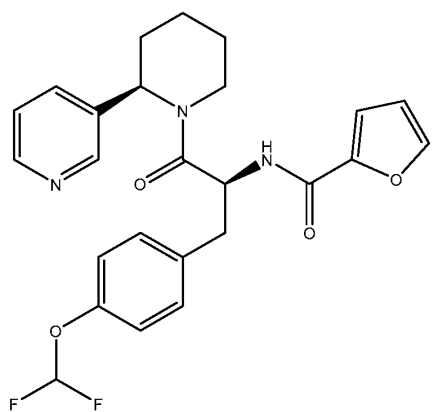
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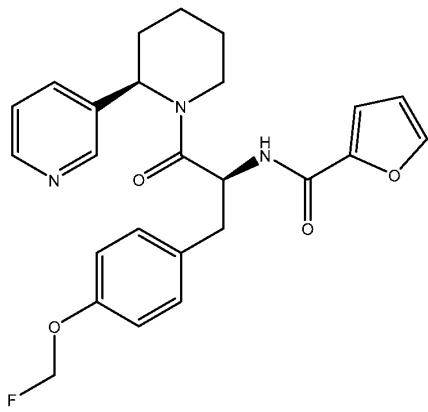
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; or



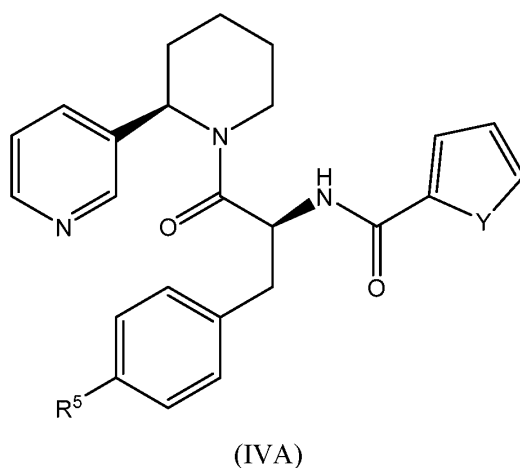
;

or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, wherein the compound is of Formula (IV) or a pharmaceutically acceptable salt thereof.

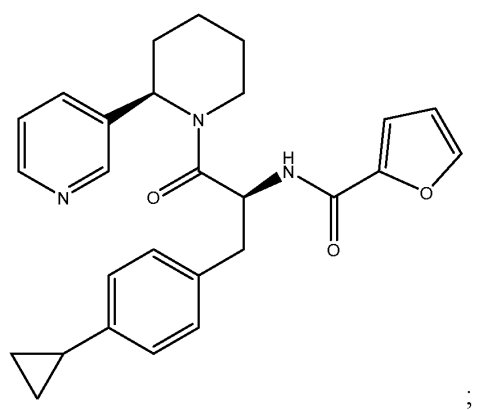
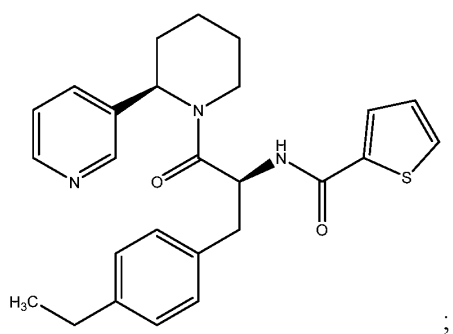
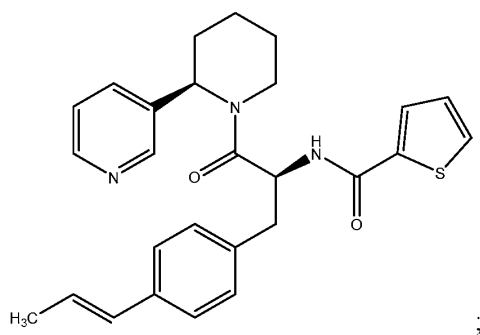
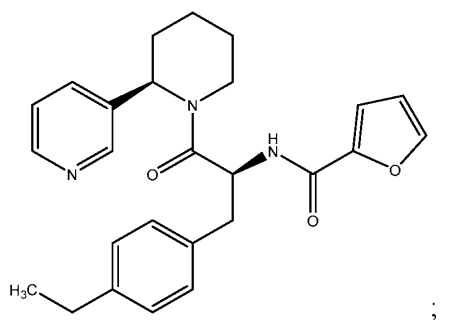
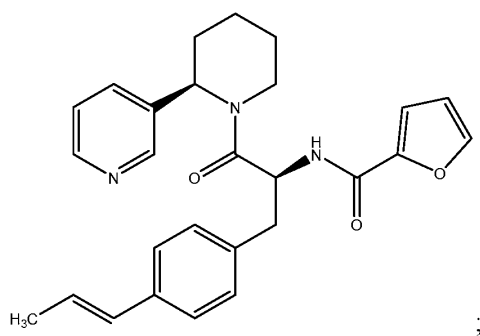
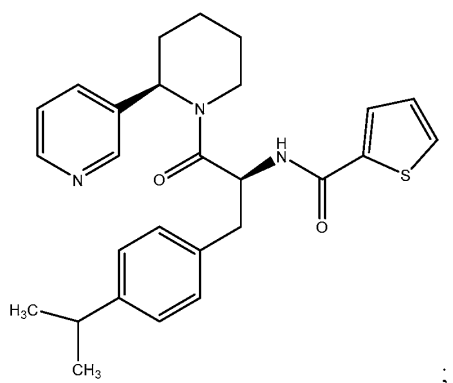
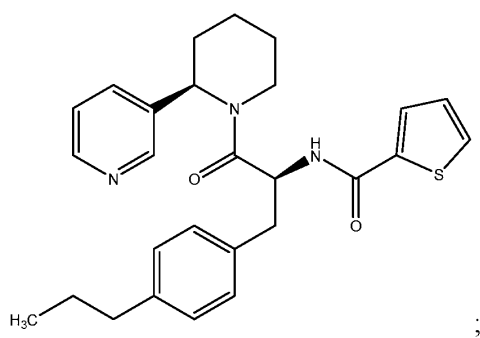
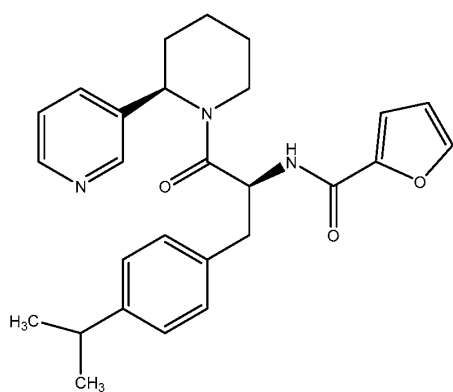
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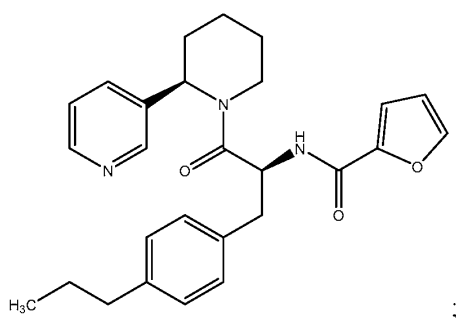
20. The compound of claim 1 or claim 19, wherein the compound is of Formula (IVA)



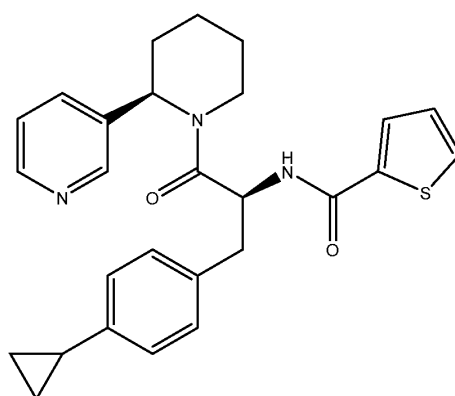
or a pharmaceutically acceptable salt thereof.

21. The compound of any one of claims 1 and 19-20, wherein R^5 is C_2 - C_3 alkyl.
22. The compound of any one of claims 1 and 19-20, wherein R^5 is C_2 - C_3 alkenyl.
23. The compound of any one of claims 1 and 19-20, wherein R^5 is C_2 - C_3 alkynyl.
24. The compound of any one of claims 1 and 19-20, wherein R^5 is C_3 - C_4 cycloalkyl.
25. The compound of any one of claims 1 and 19-21, wherein R^5 is propyl.
26. The compound of any one of claims 1, 19-20, and 22, wherein R^5 is C_2 - C_3 propenyl or ethynyl.
27. The compound of any one of claims 1, 19-20, and 24, wherein R^5 is cyclopropyl.
28. The compound of any one of claims 1 and 19-20, wherein the compound is

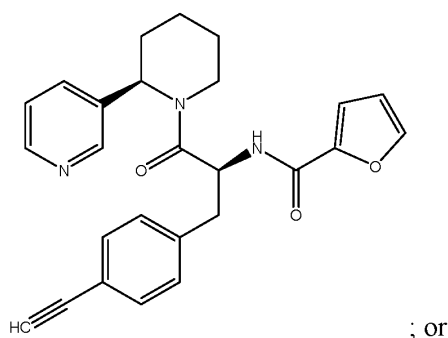




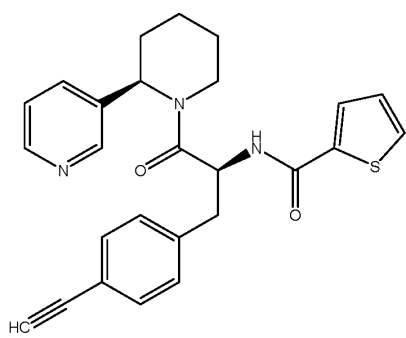
;



;



; or



;

or a pharmaceutically acceptable salt thereof.

29. A pharmaceutical composition comprising a compound of any one of claims 1-28 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

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30. A method of treating a disease treatable by inhibiting NF- κ B activation comprising administering to a patient in need thereof, the pharmaceutical composition of claim 29.

31. The method of claim 30 wherein the disease is an inflammatory disease.

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32. The method of claim 31 wherein the disease is selected from the group consisting of autoimmune disease, pain, allergies, asthma, chronic obstructive pulmonary disease and sepsis.

15 33. The method of claim 30 wherein the disease is selected from the group consisting of rheumatoid arthritis, osteoarthritis, atherosclerosis, multiple sclerosis, asthma, inflammatory

- bowel disease, diabetes, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, osteoporosis, systemic lupus erythematosus, chronic obstructive pulmonary disease, cystic fibrosis, stroke, acute kidney injury, glomerulonephritis, psoriasis, atopic dermatitis, Behcet's disease, tuberculosis, Crohn's disease, colitis, Pagett's disease, pancreatitis,
- 5 periodontitis, inflammatory lung disease, and lupus nephritis.