

INHIBITING HUMAN INTEGRIN $\alpha 4\beta 7$

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. provisional application No. 63/687,191, filed August 26, 2024, and U.S. provisional application No. 63/583,193, filed September 15, 2023, the contents of each of which are hereby incorporated by reference in their entireties.

FIELD OF THE INVENTION

[0002] This application discloses methods of treating diseases and conditions by inhibiting $\alpha 4\beta 7$ integrin. Diseases and conditions responsive to $\alpha 4\beta 7$ integrin inhibition include, for example, inflammatory bowel disease (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD).

BACKGROUND

[0003] Inflammatory bowel disease (IBD) comprises ulcerative colitis (UC) and Crohn's disease (CD), related idiopathic conditions characterized by chronic inflammation of the gastrointestinal tract. While UC affects only the colon, CD is characterized by transmural inflammation involving any portion of luminal gastrointestinal tract, from the oral cavity to the perianal area. The choice of therapy for CD varies depending upon the anatomic location, severity, and the behavior of the disease, and whether the treatment goal is to induce or maintain remission. Conventional therapies such as 5-aminosalicylates are often ineffective for moderately to severely active CD, while long-term use of corticosteroids is associated with adverse effects.

[0004] Integrins are a family of receptors known to regulate aspects of mucosal inflammation that underlie CD progression. CD is associated with activation of immune cells expressing the integrin $\alpha 4\beta 7$ and trafficking of these cells from the bloodstream into the gut and the surrounding tissue to promote chronic inflammation. Specific inhibition of $\alpha 4\beta 7$ is a validated mechanism for the treatment of IBD, as demonstrated by vedolizumab (Entyvio®), a monoclonal antibody administered via intravenous infusion.

[0005] Inhibitors of specific integrin-ligand interactions have been used for the treatment of various diseases. The mainstays of therapy over many years have been oral and topical salicylates and glucocorticoids, various immunosuppressive agents and biologics. Monoclonal

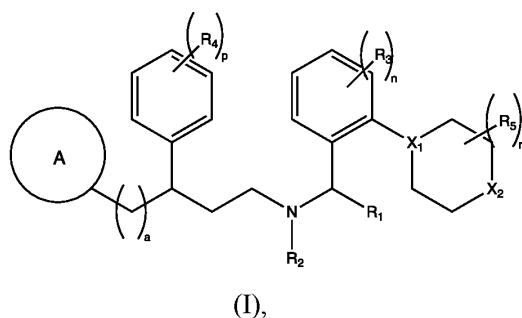
antibodies displaying high binding affinity for $\alpha_4\beta_7$ have displayed therapeutic benefits for gastrointestinal auto-inflammatory/autoimmune diseases, such as Crohn's disease, and ulcerative colitis. Anti-integrin antibody therapy for IBD was first introduced with the approval of the non-specific α_4 integrin inhibitor natalizumab for Crohn's disease, an indication approved following its initial approval for multiple sclerosis. Vedolizumab, a monoclonal antibody inhibitor of the integrin $\alpha_4\beta_7$, is approved for the induction and maintenance of remission in late-line ulcerative colitis and does not carry a black box warning. Vedolizumab is also approved as a late-line option for Crohn's disease. However, these therapies also have certain undesirable properties for the patient. A monoclonal antibody $\alpha_4\beta_7$ integrin inhibitor is administered by parenteral administration, has a long half-life with inability to rapidly modify exposures, and a reduced activity due to anti-drug antibody formation. In addition to issues with administration, monoclonal antibody therapies can be challenging to manufacture compared to small molecule therapies.

[0006] There remains a medical need for an effective and safe oral $\alpha_4\beta_7$ integrin inhibitor as an important addition to the therapeutic armamentarium for $\alpha_4\beta_7$ integrin-mediated conditions, such as inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD).

[0007] In particular, there remains an unmet need for a small molecule designed to selectively inhibit integrin $\alpha_4\beta_7$ including a need for such a small molecule for administration orally, avoiding the need for periodic therapeutic infusions and the complications associated with this form of drug administration.

SUMMARY

[0008] In one aspect, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:



is a 3 to 12 member heterocyclyl ring structure optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl and C₁₋₄alkyloxy are optionally substituted with one or more halogen;

a is 0, 1, 2 or 3;

X₁ is N or CR_a;

R_a is H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

X₂ is NR_b or CR_b'R_b'';

R_b is H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R_b' and R_b'' are each independently H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R₁ is H or -COOR_{1b};

R_{1b} is H or C₁₋₄ alkyl;

R₂ is H or C₁₋₄ alkyl;

R₃ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

n is 0, 1, 2, 3, or 4;

R₄ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

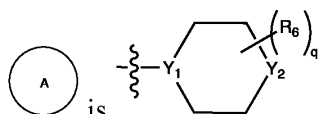
p is 0, 1, 2, 3, 4 or 5;

R₅ is H, C₁₋₄alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₇;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R₇ is independently halogen.

[0009] In one aspect, the invention features a compound of Formula (I), or a

pharmaceutically acceptable salt thereof, wherein  is , and

Y_1 is N or CR_c ;

R_c is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

Y_2 is NR_d or $CR_d'R_d''$;

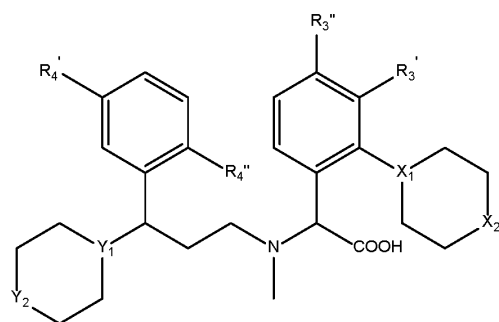
R_d is H, halogen, C_{1-4} alkyl or 3-6 member heterocycloalkyl, wherein the C_{1-4} alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

R_d' and R_d'' are each independently H, halogen, or C_{1-4} alkyl, and each C_{1-4} alkyl is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4} alkyloxy;

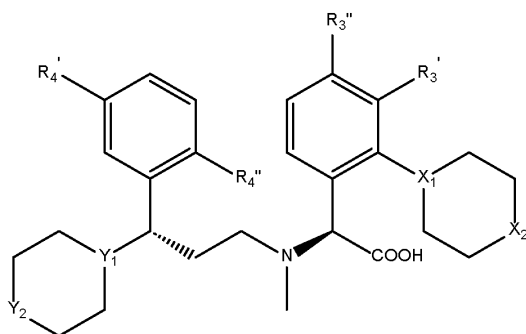
q is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

R_6 is H, C_{1-5} alkyl, halogen, C_{1-4} alkyloxy, OH, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, and each C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, is optionally substituted with 1 to 4 R_8 ; and each R_8 is independently halogen.

[00010] In one aspect, the invention features a compound of Formula (I) having a chemical structure of Formula (II) or Formula (II-A), or a pharmaceutically acceptable salt thereof,



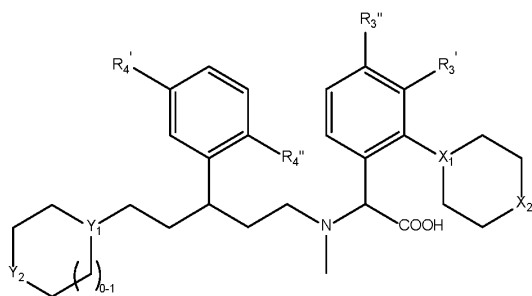
(II)



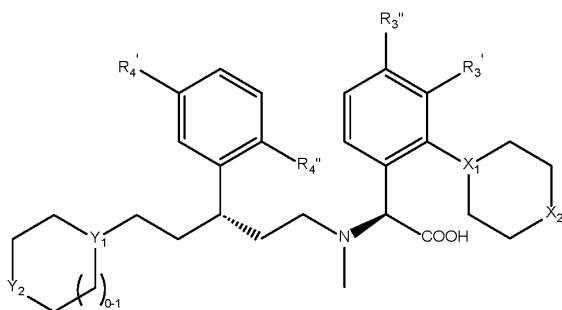
(II-A)

wherein X_1 , X_2 , Y_1 and Y_2 are each defined as described in Formula (I) and R_3' , R_3'' , R_4' , and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

[00011] In one aspect, the invention features a compound of Formula (I) having a chemical structure of Formula (III), or Formula (III-A), or a pharmaceutically acceptable salt thereof,



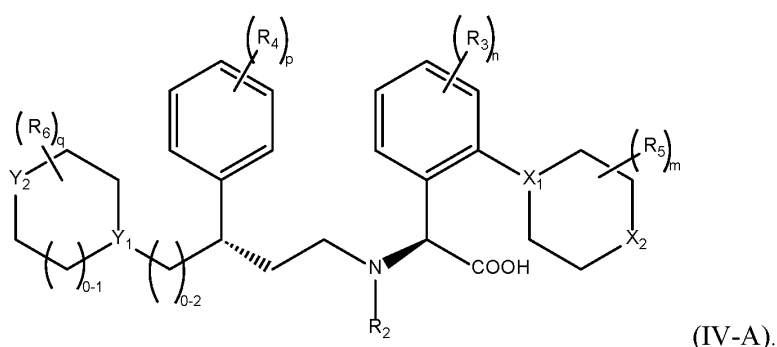
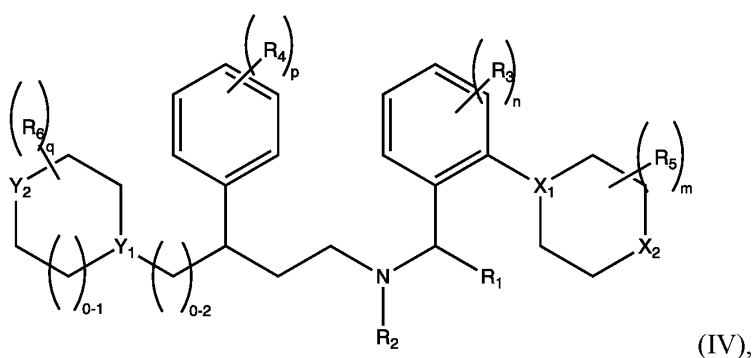
(III),



(III-A)

wherein X_1 , X_2 , Y_1 and Y_2 are each defined as described in Formula (I) and R_3' , R_3'' , R_4' , and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

[00012] In one aspect, the invention features a compound of Formula (I) having a chemical structure of Formula (IV) or Formula (IV-A), or a pharmaceutically acceptable salt thereof,



wherein

Y_1 is N or CR_c ;

R_c is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

Y_2 is NR_d or $CR_d'R_d''$;

R_d is H, halogen, C_{1-4} alkyl or 3-6 member heterocycloalkyl, wherein the C_{1-4} alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

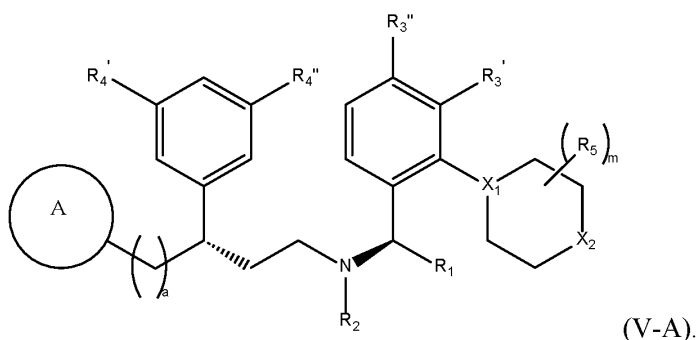
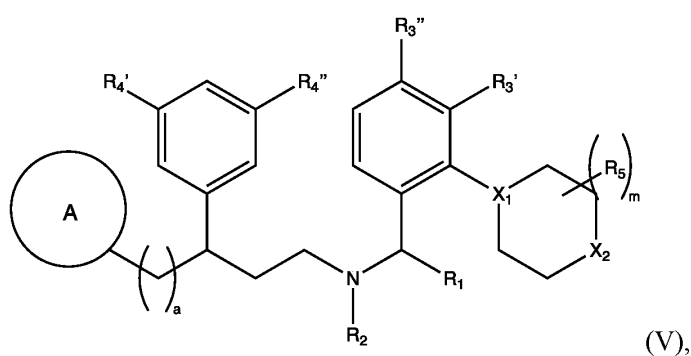
R_d' and R_d'' are each independently H, halogen, or C_{1-4} alkyl, and each C_{1-4} alkyl is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4} alkyloxy;

R_6 is H, C_{1-5} alkyl, halogen, C_{1-4} alkyloxy, OH, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, and each C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, is optionally substituted with 1 to 4 R_8 ;

q is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_8 is independently halogen.

[00013] In one aspect, the invention features a compound of Formula (I) having a chemical structure of Formula (V) or Formula (V-A), or a pharmaceutically acceptable salt thereof,



wherein,

a is 1 or 2;

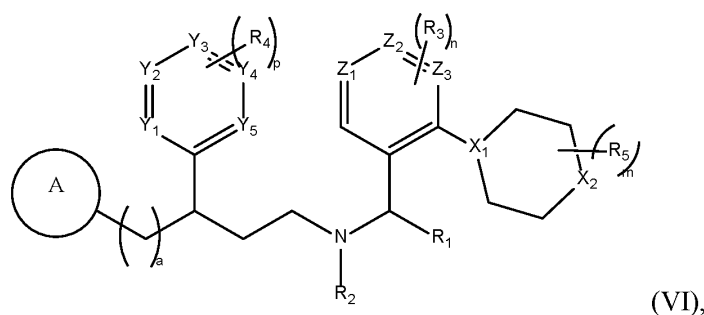
R_3' , R_3'' , R_4' , and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

R_5 is H, C_{1-4} alkyl, halogen, C_{1-4} alkyloxy, OH, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, and each C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, is optionally substituted with 1 to 4 R_7 ;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_7 is independently halogen.

[00014] In some embodiments, the compound is a compound Formula (VI) or a pharmaceutically acceptable salt thereof,



wherein

Y_1, Y_2, Y_3, Y_4, Y_5 and Z_1, Z_2 and Z_3 are each CH or N, provided that at least three of Y_1, Y_2, Y_3, Y_4 , and Y_5 are CH and at least one of Z_1, Z_2 and Z_3 is CH;



is a 3 to 12 member heterocyclcyl ring structure (including monocyclic heterocyclic, bicyclic bridged, and bicyclic spirocyclic ring structures) optionally substituted with halogen, C_{1-5} alkyl or C_{1-4} alkyloxy, wherein the C_{1-4} alkyl (e.g., methyl) and C_{1-4} alkyloxy (e.g., methoxy) are optionally substituted with one or more halogen (e.g., one or more fluoro);

a is 0, 1, 2 or 3;

X_1 is N or CR_a ;

R_a is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X_2 is NR_b or $CR_b'R_b''$;

R_b is H, halogen, C_{1-4} alkyl, C_{1-4} alkyloxy, OH, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, C_{3-6} cycloalkyloxy, or C_{1-4} alkyl- C_{3-6} cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, C_{3-6} cycloalkyloxy, or C_{1-4} alkyl- C_{3-6} cycloalkyloxy is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4} alkyloxy;

R_b' and R_b'' are each independently H, halogen, C_{1-4} alkyl, C_{1-4} alkyloxy, OH, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, C_{3-6} cycloalkyloxy, or C_{1-4} alkyl- C_{3-6} cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4}

4alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R₁ is H or -COOR_{1b};

R_{1b} is H or C₁₋₄ alkyl;

R₂ is H or C₁₋₄ alkyl;

R₃ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

n is 0, 1, 2, 3, or 4;

R₄ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

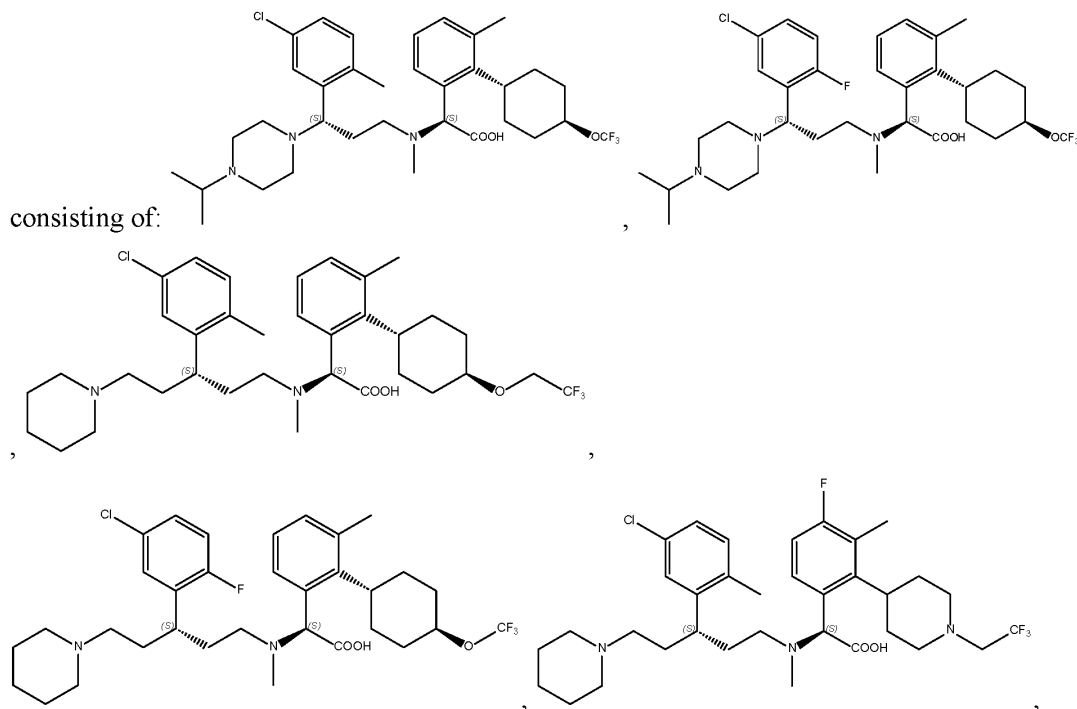
p is 0, 1, 2, 3, 4 or 5;

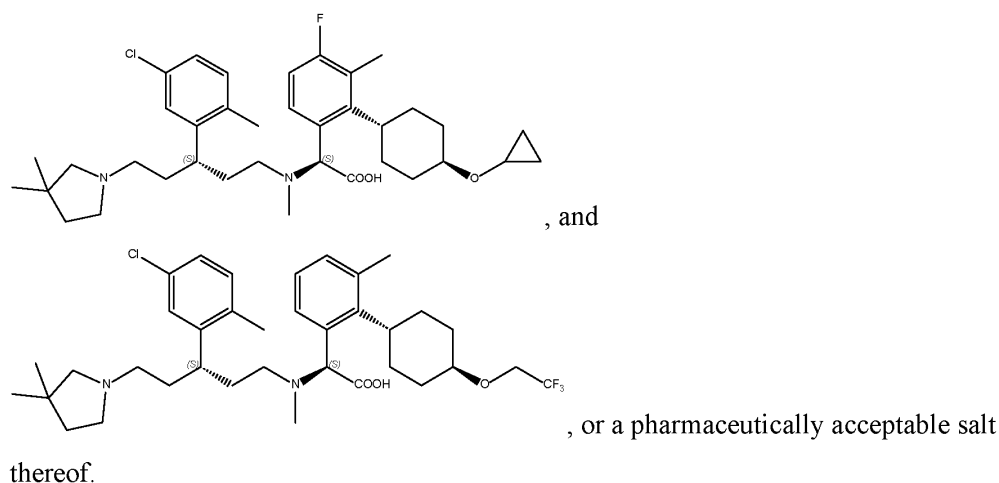
R₅ is H, C₁₋₄alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₇;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R₇ is independently halogen.

[00015] In some embodiments, the compound is a compound selected from the group





BRIEF DESCRIPTION OF THE FIGURES

[00016] Figure 1 is a table of compounds disclosed herein.

DETAILED DESCRIPTION

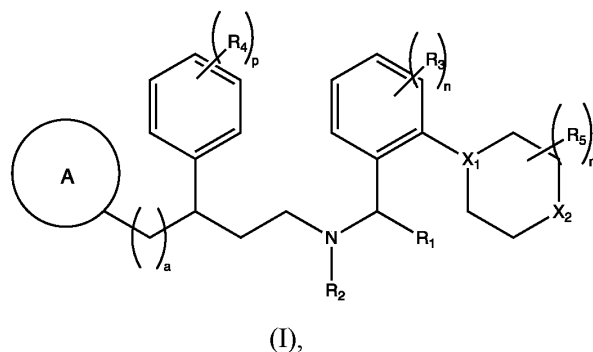
[00017] Compounds of Formula (I), which includes compounds of Formulae (Ia), (Ib), and (Ic), and their respective pharmaceutically acceptable salt forms, are small-molecule integrin therapeutics targeting $\alpha 4\beta 7$ that can be administered to treat patients with diseases and conditions that are responsive to $\alpha 4\beta 7$ integrin inhibition.

[00018] In particular, methods described herein can be effective in the treatment of inflammatory bowel disease such as ulcerative colitis or Crohn's disease. For example, administration of a compound of Formula (I) according to methods described herein provides unexpected therapeutic benefit within twelve weeks of therapy to subjects with moderately to severely active ulcerative colitis, including patients who have received prior advanced therapy (AT) for ulcerative colitis and/or those with a baseline endoscopy of 3. Further, methods described herein show that administration of a compound according to Formula (I) can be well-tolerated and with a favorable safety profile.

[00019] Accordingly, methods as described herein can expand the therapies available for subjects with inflammatory bowel disease such as ulcerative colitis or Crohn's disease.

Compounds of Formula (I)

[00020] In one aspect, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:



is a 3 to 12 member heterocyclyl ring structure (including monocyclic heterocyclic, bicyclic bridged, and bicyclic spirocyclic ring structures) optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl (e.g., methyl) and C₁₋₄alkyloxy (e.g., methoxy) are optionally substituted with one or more halogen (e.g., one or more fluoro);

a is 0, 1, 2 or 3;

X₁ is N or CR_a;

R_a is H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

X₂ is NR_b or CR_{b'}R_{b''};

R_b is H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R_{b'} and R_{b''} are each independently H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R₁ is H or -COOR_{1b};

R_{1b} is H or C₁₋₄ alkyl;

R₂ is H or C₁₋₄ alkyl;

R₃ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

n is 0, 1, 2, 3, or 4;

R₄ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

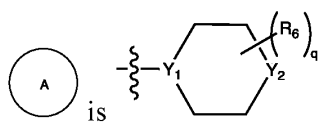
p is 0, 1, 2, 3, 4 or 5;

R₅ is H, C₁₋₄alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₇;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R₇ is independently halogen.

[00021] In one aspect, the invention features a compound of Formula (I), or a

pharmaceutically acceptable salt thereof, wherein  is , and

Y₁ is N or CR_c;

R_c is H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

Y₂ is NR_d or CR_{d'}R_{d''};

R_d is H, halogen, C₁₋₄ alkyl or 3-6 member heterocycloalkyl, wherein the C₁₋₄ alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

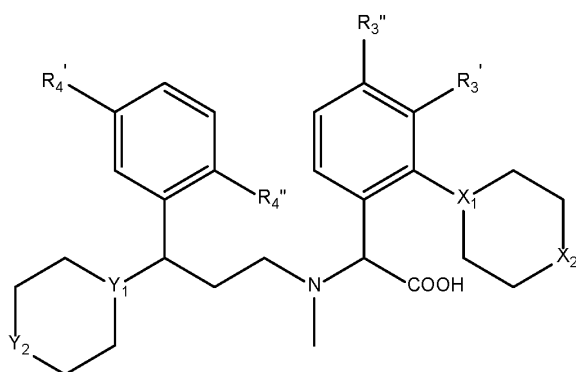
R_{d'} and R_{d''} are each independently H, halogen, or C₁₋₄ alkyl, and each C₁₋₄ alkyl is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

q is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

R₆ is H, C₁₋₅alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₈; and

each R₈ is independently halogen.

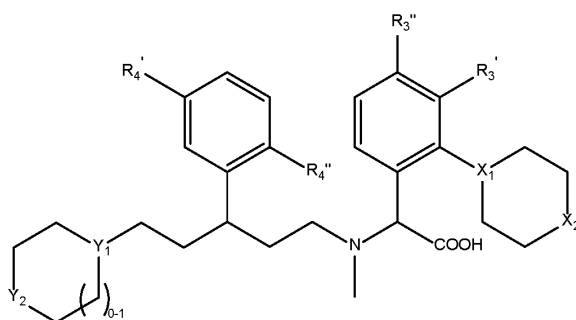
[00022] In one aspect, the invention features a compound of Formula (I) having a chemical structure of Formula (II), or a pharmaceutically acceptable salt thereof,



(II)

wherein X_1 , X_2 , Y_1 and Y_2 are each defined as described in Formula (I) and R_3' , R_3'' , R_4' , and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

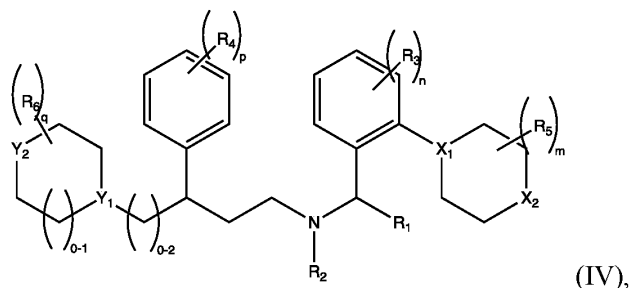
[00023] In one aspect, the invention features a compound of Formula (I) having a chemical structure of Formula (III), or a pharmaceutically acceptable salt thereof,



(III)

wherein X_1 , X_2 , Y_1 and Y_2 are each defined as described in Formula (I) and R_3' , R_3'' , R_4' , and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

[00024] In one aspect, the invention features a compound of Formula (IV), or a pharmaceutically acceptable salt thereof:



wherein:

X_1 is N or CR_a ;

R_a is H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

X_2 is NR_b or $CR_b'R_b''$;

R_b is H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R_b' and R_b'' are each independently H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

Y_1 is N or CR_c ;

R_c is H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

$$Y_2 \text{ is } \mathbf{NR}_d \text{ or } \mathbf{CR}_d' \mathbf{R}_d'';$$

R_d is H, halogen, C₁₋₄ alkyl or 3-6 member heterocycloalkyl, wherein the C₁₋₄ alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

R_d' and R_d'' are each independently H, halogen, or C₁₋₄ alkyl, and each C₁₋₄ alkyl is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R₁ is H or -COOR_{1b};

R_{1b} is H or C₁₋₄ alkyl;

R₂ is H or C₁₋₄ alkyl;

R₃ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

n is 0, 1, 2, 3, or 4;

R₄ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

p is 0, 1, 2, 3, 4 or 5;

R₅ is H, C₁₋₄alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₇;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

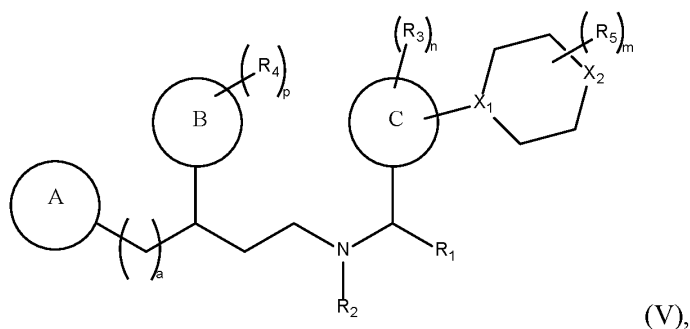
R₆ is H, C₁₋₅alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₈;

q is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

each R₇ is independently halogen; and

each R₈ is independently halogen.

[00025] In one aspect, the invention features a compound of Formula (V), or a pharmaceutically acceptable salt thereof:



Ⓐ is a 3 to 12 member heterocyclyl ring structure (including monocyclic heterocyclic, bicyclic bridged, and bicyclic spirocyclic ring structures) optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl (e.g., methyl) and C₁₋₄alkyloxy (e.g., methoxy) are optionally substituted with one or more halogen (e.g., one or more fluoro);

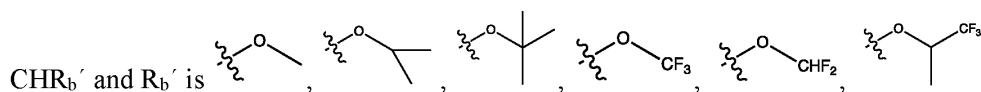
Ⓑ and Ⓒ are each independently a 5-6 member aryl or heteroaryl ring structure; and a, R₄, p, R₂, R₁, R₃, n, X₁, X₂, R₅ and m are as described from Formula (I) herein.

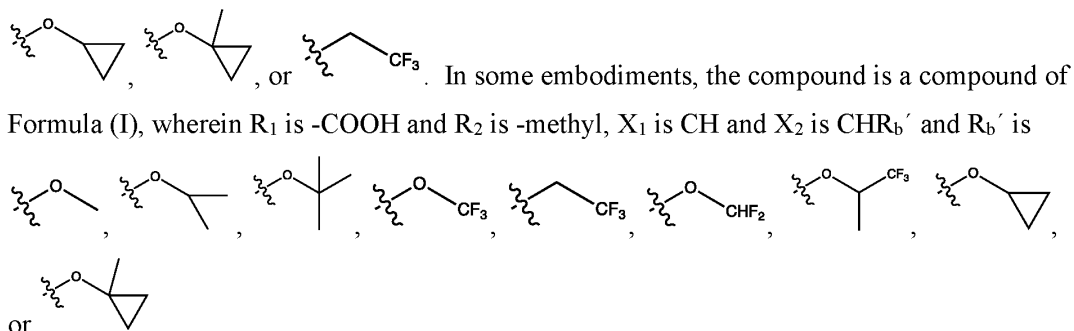
[00026] In some embodiments, the compound is a compound of Formula (I), wherein R₁ is -COOH. In some embodiments, the compound is a compound of Formula (I), wherein R₂ is -methyl. In some embodiments, the compound is a compound of Formula (I), wherein R₁ is -COOH and R₂ is -methyl.

[00027] In some embodiments, the compound is a compound of Formula (I), wherein X_1 is CH. In some embodiments, the compound is a compound of Formula (I), wherein X_2 is $\text{CHR}_{b'}$. In some embodiments, the compound is a compound of Formula (I), wherein X_1 is CH and X_2 is $\text{CHR}_{b'}$. In some embodiments, the compound is a compound of Formula (I), wherein X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is C_{1-4} alkyl, C_{1-4} alkyloxy, or C_{3-6} cycloalkyloxy, and each $R_{b'}$ is optionally substituted with one or more halogen or C_{1-4} alkyl. In some embodiments, the compound is a compound of Formula (I), wherein X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is C_{1-4} alkyl, C_{1-4} alkyloxy, or C_{3-6} cycloalkyloxy, and each $R_{b'}$ is optionally substituted with one or more fluoro. In some embodiments, the compound is a compound of Formula (I), wherein X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is C_{1-4} alkyl, C_{1-4} alkyloxy, or C_{3-6} cycloalkyloxy, and each $R_{b'}$ is optionally substituted with one or more fluoro.

[00028] In some embodiments, the compound is a compound of Formula (I), wherein R_1 is $-\text{COOH}$ and R_2 is $-\text{methyl}$, and X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is $-\text{O}-R_{b2'}$ or $-\text{CH}_2-R_{b2'}$, wherein $R_{b2'}$ is C_{1-4} alkyl or C_{3-6} cycloalkyl optionally substituted with one or more halogen or C_{1-4} alkyl. In some embodiments, the compound is a compound of Formula (I), wherein R_1 is $-\text{COOH}$ and R_2 is $-\text{methyl}$, X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is $-\text{O}-R_{b2'}$, wherein $R_{b2'}$ is C_{1-4} alkyl or cyclopropyl optionally substituted with one or more halogen or C_{1-4} alkyl. In some embodiments, the compound is a compound of Formula (I), wherein R_1 is $-\text{COOH}$ and R_2 is $-\text{methyl}$, X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is $-\text{O}-R_{b2'}$, wherein $R_{b2'}$ is C_{1-4} alkyl optionally substituted with one or more fluoro. In some embodiments, the compound is a compound of Formula (I), wherein R_1 is $-\text{COOH}$ and R_2 is $-\text{methyl}$, X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is $-\text{O}-R_{b2'}$, wherein $R_{b2'}$ is cyclopropyl optionally substituted with one or more C_{1-4} alkyl. In some embodiments, the compound is a compound of Formula (I), wherein R_1 is $-\text{COOH}$ and R_2 is $-\text{methyl}$, X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is $-\text{O}-R_{b2'}$, wherein $R_{b2'}$ is cyclopropyl optionally substituted with one or more methyl. In some embodiments, the compound is a compound of Formula (I), wherein X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is $-\text{CH}_2-R_{b2'}$, wherein $R_{b2'}$ is C_{1-4} alkyl or C_{3-6} cycloalkyl optionally substituted with one or more halogen or C_{1-4} alkyl. In some embodiments, the compound is a compound of Formula (I), wherein X_1 is CH and X_2 is $\text{CHR}_{b'}$ and $R_{b'}$ is $-\text{CH}_2-R_{b2'}$, wherein $R_{b2'}$ is C_{1-4} alkyl optionally substituted with one or more fluoro.

[00029] In some embodiments, the compound is a compound of Formula (I), wherein X_2 is



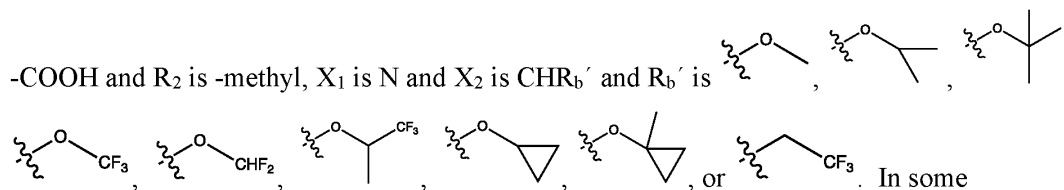


[00030] In some embodiments, the compound is a compound of Formula (I), wherein X₁ is CH. In some embodiments, the compound is a compound of Formula (I), wherein X₂ is CHR_{b'}. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is CH and X₂ is CHR_{b'}. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is CH and X₂ is CHR_{b'} and R_{b'} is C₁₋₄ alkyl, C₁₋₄alkyloxy, or C₃₋₆cycloalkyloxy, and each R_{b'} is optionally substituted with one or more halogen or C₁₋₄ alkyl. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is CH and X₂ is CHR_{b'} and R_{b'} is C₁₋₄ alkyl, C₁₋₄alkyloxy, or C₃₋₆cycloalkyloxy, and each R_{b'} is optionally substituted with one or more methyl or fluoro.

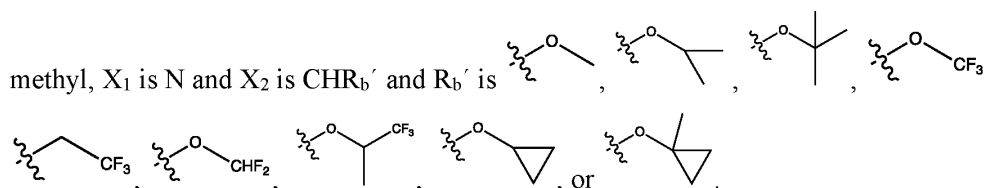
[00031] In some embodiments, the compound is a compound of Formula (I), wherein X₂ is NR_d. In some embodiments, the compound is a compound of Formula (I), wherein X₂ is NR_d and R_d is C₁₋₄ alkyl optionally substituted with one or more halogen. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is CH and X₂ is NR_d. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is CH and X₂ is NR_d and R_d is C₁₋₄ alkyl optionally substituted with one or more F. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is CH and X₂ is NR_d and R_d is -CH₂-CF₃.

[00032] In some embodiments, the compound is a compound of Formula (I), wherein X₁ is N. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is N, R₁ is -COOH and R₂ is -methyl. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is N and X₂ is CHR_{b'}. In some embodiments, the compound is a compound of Formula (I), wherein X₁ is N and X₂ is CHR_{b'} and R_{b'} is C₁₋₄ alkyl, C₁₋₄alkyloxy, or C₃₋₆cycloalkyloxy, and each R_{b'} is optionally substituted with one or more halogen or C₁₋₄ alkyl. In some embodiments, the compound is a compound of Formula (I), wherein R₁ is -COOH, R₂ is -methyl, X₁ is N and X₂ is CHR_{b'} and R_{b'} is C₁₋₄ alkyl, C₁₋₄alkyloxy, or C₃₋₆cycloalkyloxy, and each R_{b'} is optionally substituted with one or more fluoro.

[00033] In some embodiments, the compound is a compound of Formula (I), wherein R_1 is



In some embodiments, the compound is a compound of Formula (I), wherein R_1 is -COOH and R_2 is -



[00034] In some embodiments, the compound is a compound of Formula (I), wherein R_3 is halogen, or C_{1-4} alkyl optionally substituted with one or more halogen, and n is 0, 1 or 2. In some embodiments, the compound is a compound of Formula (I), wherein R_4 is halogen, or C_{1-4} alkyl optionally substituted with one or more halogen, and p is 0, 1 or 2. In some embodiments, the compound is a compound of Formula (I), wherein R_3 is halogen, or C_{1-4} alkyl optionally substituted with one or more halogen, n is 0, 1 or 2; R_4 is halogen, or C_{1-4} alkyl optionally substituted with one or more halogen, and p is 0, 1 or 2. In some embodiments, the compound is a compound of Formula (I), wherein R_3 is fluoro or chloro, or C_{1-4} alkyl optionally substituted with one or more fluoro, n is 0, 1 or 2; R_4 is fluoro or chloro, or C_{1-4} alkyl optionally substituted with one or more fluoro, and p is 0, 1 or 2. In some embodiments, the compound is a compound of Formula (I), wherein R_3 is fluoro or chloro, or methyl optionally substituted with one or more fluoro, n is 0, 1 or 2; R_4 is fluoro or chloro, or methyl optionally substituted with one or more fluoro, and p is 0, 1 or 2.

[00035] In some embodiments, the compound is a compound of Formula (I), wherein q is 0. In some embodiments, the compound is a compound of Formula (I), wherein m is 0. In some embodiments, the compound is a compound of Formula (I), wherein m is 0 and q is 0. In some embodiments, the compound is a compound of Formula (I), wherein R_1 is COOH, R_2 is methyl, m is 0 and q is 0.

[00036] In some embodiments, the compound is a compound of Formula (I), wherein q is 0, 1 or 2 and R_6 is halogen, or C_{1-5} alkyl optionally substituted with one or more halogen. In some embodiments, the compound is a compound of Formula (I), wherein m is 0, 1 or 2, and R_5 is halogen, or C_{1-4} alkyl optionally substituted with one or more halogen. In some embodiments,

the compound is a compound of Formula (I), wherein m is 0, 1 or 2 and q is 0, 1 or 2. In some embodiments, the compound is a compound of Formula (I), wherein R_1 is COOH, R_2 is methyl, R_5 is methyl optionally substituted with one or more fluoro; m is 0, 1 or 2; R_6 is methyl optionally substituted with one or more fluoro, and q is 0, 1 or 2.

[00037] In some embodiments, the compound is a compound of Formula (II), (III) or (IV), wherein Y_1 is N or CR_c ; and R_c is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen. In some embodiments, the compound is a compound of Formula (I), wherein Y_1 is N. In some embodiments, the compound is a compound of Formula (I), wherein Y_1 is CR_c ; and R_c is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

[00038] In some embodiments, the compound is a compound of Formula (II), (III) or (IV), wherein Y_2 is NR_d ; and R_d is H, halogen, C_{1-4} alkyl or 3-6 member heterocycloalkyl, wherein the C_{1-4} alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen. In some embodiments, the compound is a compound of Formula (I), wherein Y_2 is $CR_d'R_d''$; and R_d' and R_d'' are each independently H, halogen, or C_{1-4} alkyl, and each C_{1-4} alkyl is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4} alkyloxy. In some embodiments, the compound is a compound of Formula (I), wherein Y_1 is N and Y_2 is NR_d and R_d is H.

[00039] In some embodiments, the compound is a compound of Formula (II), (III) or (IV), wherein Y_1 is N and Y_2 is NR_d and R_d is 3-6 member heterocycloalkyl optionally substituted with one or more halogen, or C_{1-4} alkyl optionally substituted with one or more halogen. In some embodiments, the compound is a compound of Formula (I), wherein Y_1 is N and Y_2 is NR_d and R_d is 6-member heterocycloalkyl optionally substituted with one or more halogen or methyl optionally substituted with one or more halogen. In some embodiments, the compound is a compound of Formula (I), wherein Y_1 is N and Y_2 is NR_d and R_d is a 6-member heterocycloalkyl. In some embodiments, the compound is a compound of Formula (I), wherein Y_1 is N and X_2 is NR_d and R_d is tetrahydrofuran.

[00040] In some embodiments, the compound is a compound of Formula (II), (III) or (IV), wherein Y_1 is CH and Y_2 is NR_d and R_d is 3-6 member heterocycloalkyl optionally substituted with one or more halogen, or C_{1-4} alkyl optionally substituted with one or more halogen. In some embodiments, the compound is a compound of Formula (I), wherein Y_1 is CH and Y_2 is NR_d and R_d is 6-member heterocycloalkyl optionally substituted with one or more halogen or methyl optionally substituted with one or more halogen. In some embodiments, the compound

is a compound of Formula (I), wherein Y_1 is CH and Y_2 is NR_d and R_d is a 6-member heterocycloalkyl. In some embodiments, the compound is a compound of Formula (II), (III) or (IV), wherein Y_1 is CH and X_2 is NR_d and R_d is tetrahydrofuran.

[00041] In some embodiments, the compound is a compound of Formula (V), wherein

 and  are each independently a 6 member aryl or heteroaryl ring structure. In

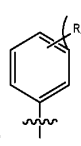
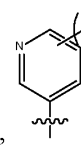
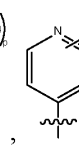
some embodiments, the compound is a compound of Formula (V), wherein  and  are each independently phenyl, pyridine or pyrimidine. In some embodiments, the compound

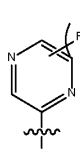
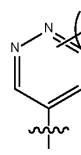
is a compound of Formula (V), wherein  and  are each independently phenyl, pyridine or pyrimidine. In some embodiments, the compound is a compound of Formula (V),

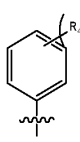
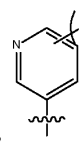
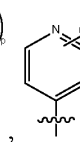
wherein  is phenyl and  is pyridine or pyrimidine. In some embodiments, the

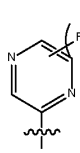
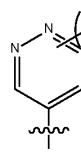
compound is a compound of Formula (V), wherein  is phenyl and  is pyridine.

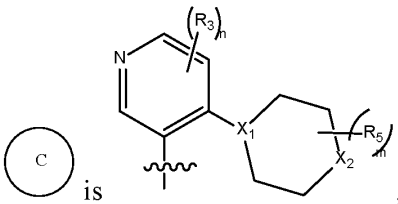
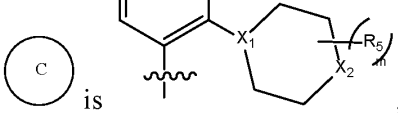
In some embodiments, the compound is a compound of Formula (V), wherein  is phenyl

and  is pyrimidine. In some embodiments,  is , , ,

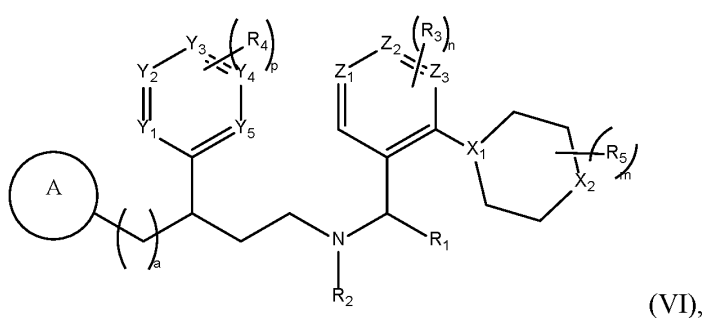
, or , wherein R_4 is as defined in Formula (I) or Formula (V) and  is

phenyl, pyridine or pyrimidine. In some embodiments,  is , , ,

, or , wherein R_4 is as defined in Formula (I) or Formula (V) and  is

phenyl. In some embodiments,  is , wherein R₃, X₁, X₂, R₅, n and m are as defined with respect to Formula (I) or Formula (V).

[00042] In some embodiments, the compound is a compound of Formula (VI), or a pharmaceutically acceptable salt thereof:



wherein , R₁, R₂, R₃, R₄, R₅, a, p, n and m are as defined above with respect to Formula (V) or Formula (I), and Y₁, Y₂, Y₃, Y₄, Y₅ and Z₁, Z₂ and Z₃ are each CH or N. In some

embodiments, the compound is a compound of Formula (VI), wherein , R₁, R₂, R₃, R₄, R₅, a, p, n and m are as defined above with respect to Formula (V) or Formula (I), and Y₁, Y₂, Y₃, Y₄, Y₅ and Z₁, Z₂ and Z₃ are each CH or N, provided that at least three of Y₁, Y₂, Y₃, Y₄, and Y₅ are CH and at least one of Z₁, Z₂ and Z₃ is CH.

Definitions

[00043] For convenience, before further description of the present invention, certain terms employed in the specification, examples and appended claims are collected here. These definitions should be read in light of the remainder of the disclosure and understood as by a person of skill in the art. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by a person of ordinary skill in the art.

[00044] In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

[00045] The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[00046] The phrase “and/or,” as used herein in the specification and in the claims, should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B”, when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[00047] As used herein in the specification and in the claims, “or” should be understood to have the same meaning as “and/or” as defined above. For example, when separating items in a list, “or” or “and/or” shall be interpreted as being inclusive, i.e., the inclusion of at least one, but also including more than one, of a number or list of elements, and, optionally, additional unlisted items. Only terms clearly indicated to the contrary, such as “only one of” or “exactly one of,” or, when used in the claims, “consisting of,” will refer to the inclusion of exactly one element of a number or list of elements. In general, the term “or” as used herein shall only be interpreted as indicating exclusive alternatives (i.e., “one or the other but not both”) when preceded by terms of exclusivity, such as “either,” “one of,” “only one of,” or “exactly one of.” “Consisting essentially of,” when used in the claims, shall have its ordinary meaning as used in the field of patent law.

[00048] As used herein in the specification and in the claims, the phrase “at least one,” in reference to a list of one or more elements, should be understood to mean at least one element selected from any one or more of the elements in the list of elements, but not necessarily including at least one of each and every element specifically listed within the list of elements and not excluding any combinations of elements in the list of elements. This definition also allows that elements may optionally be present other than the elements specifically identified within the list of elements to which the phrase “at least one” refers, whether related or

unrelated to those elements specifically identified. Thus, as a non-limiting example, “at least one of A and B” (or, equivalently, “at least one of A or B,” or, equivalently “at least one of A and/or B”) can refer, in one embodiment, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in another embodiment, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in yet another embodiment, to at least one, optionally including more than one, A, and at least one, optionally including more than one, B (and optionally including other elements); etc.

[00049] It should also be understood that, unless clearly indicated to the contrary, in any methods claimed herein that include more than one step or act, the order of the steps or acts of the method is not necessarily limited to the order in which the steps or acts of the method are recited.

[00050] In the claims, as well as in the specification above, all transitional phrases such as “comprising,” “including,” “carrying,” “having,” “containing,” “involving,” “holding,” “composed of,” and the like are to be understood to be open-ended, i.e., to mean including but not limited to. Only the transitional phrases “consisting of” and “consisting essentially of” shall be closed or semi-closed transitional phrases, respectively, as set forth in the United States Patent Office Manual of Patent Examining Procedures, Section 2111.03.

[00051] Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (d)-isomers, (l)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[00052] If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by

resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

[00053] Structures depicted herein are also meant to include compounds that differ only in the presence of one or more isotopically enriched atoms. For example, compounds produced by the replacement of a hydrogen with deuterium or tritium, or of a carbon with a ^{13}C - or ^{14}C -enriched carbon are within the scope of this invention.

[00054] The terms “ $\alpha\text{v}\beta 8$ ”, “avB8”, “avb8”, “alpha-v beta-8” and “alpha v beta 8” and the like as used herein all refer to $\alpha\text{v}\beta 8$.

[00055] The phrase “pharmaceutically acceptable excipient” or “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject chemical from one organ or portion of the body, to another organ or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation, not injurious to the patient, and substantially non-pyrogenic. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer’s solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

[00056] The term “pharmaceutically acceptable salts” refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride,

sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, and laurylsulphonate salts, and the like. (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66:1-19.)

[00057] In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared in situ during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

[00058] A "therapeutically effective amount" (or "effective amount") of a compound with respect to use in treatment, refers to an amount of the compound in a preparation which, when administered as part of a desired dosage regimen (to a mammal, preferably a human) alleviates a symptom, ameliorates a condition, or slows the onset of disease conditions according to clinically acceptable standards for the disorder or condition to be treated or the cosmetic purpose, e.g., at a reasonable benefit/risk ratio applicable to any medical treatment.

[00059] The term "prophylactic or therapeutic" treatment is art-recognized and includes administration to the host of one or more of the subject compositions. If it is administered prior to clinical manifestation of the unwanted condition (e.g., disease or other unwanted state of the host animal) then the treatment is prophylactic, (i.e., it protects the host against developing the unwanted condition), whereas if it is administered after manifestation of the unwanted condition, the treatment is therapeutic, (i.e., it is intended to diminish, ameliorate, or stabilize the existing unwanted condition or side effects thereof).

[00060] The term “patient” refers to a mammal in need of a particular treatment. In certain embodiments, a patient is a primate, canine, feline, or equine. In certain embodiments, a patient is a human.

[00061] Whenever a term (*e.g.*, alkyl or aryl) or either of their prefix roots (*e.g.*, alk- or ar-) appear in a name of a substituent the name is to be interpreted as including those limitations provided herein. For example, affixing the suffix “-ene” to a group indicates the group is a divalent moiety, *e.g.*, arylene is the divalent moiety of aryl, heteroarylene is the divalent moiety of heteroaryl, and heterocycloalkylene is the divalent moiety of heterocycloalkyl. Similarly, affixing the suffix “-oxy” to a group indicates the group is attached to the parent molecular structure through an oxygen atom (-O-) such as “alkyloxy,” “alkoxy” or “cycloalkoxy” as used herein.

[00062] An aliphatic chain comprises the classes of alkyl, alkenyl and alkynyl defined below. A straight aliphatic chain is limited to unbranched carbon chain moieties. As used herein, the term “aliphatic group” refers to a straight chain, branched-chain, or cyclic aliphatic hydrocarbon group and includes saturated and unsaturated aliphatic groups, such as an alkyl group, an alkenyl group, or an alkynyl group.

[00063] “Alkyl” refers to a fully saturated cyclic or acyclic, branched or unbranched carbon chain moiety having the number of carbon atoms specified, or 1 up to 30 carbon atoms if no specification is made. For example, alkyl of 1 to 8 carbon atoms refers to moieties such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, and octyl, and those moieties which are positional isomers of these moieties. Alkyl of 10 to 30 carbon atoms includes decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, eicosyl, heneicosyl, docosyl, tricosyl and tetracosyl. In certain embodiments, a straight chain or branched chain alkyl has 30 or fewer carbon atoms in its backbone (*e.g.*, C₁-C₃₀ for straight chains, C₃-C₃₀ for branched chains), and more preferably 20 or fewer. Alkyl groups may be substituted or unsubstituted. As used herein, “Me” and -CH₃ both refer to methyl.

[00064] As used herein, the term “alkylene” refers to an alkyl group having the specified number of carbons, for example from 2 to 12 carbon atoms, that contains two points of attachment to the rest of the compound on its longest carbon chain. Non-limiting examples of alkylene groups include methylene -(CH₂)-, ethylene -(CH₂CH₂)-, n-propylene -(CH₂CH₂CH₂)-, isopropylene -(CH₂CH(CH₃))-, and the like. Alkylene groups can be cyclic or

acyclic, branched or unbranched carbon chain moiety, and may be optionally substituted with one or more substituents.

[00065] "Cycloalkyl" means mono- or bicyclic or bridged or spirocyclic, or polycyclic saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Likewise, preferred cycloalkyls have from 3-10 carbon atoms in their ring structure, and more preferably have 3-6 carbons in the ring structure. Cycloalkyl groups may be substituted or unsubstituted. Exemplary cycloalkyl groups include cyclopropyl (C₃), cyclobutyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cycloheptyl (C₇), and cyclooctyl (C₈).

[00066] Unless the number of carbons is otherwise specified, "lower alkyl," as used herein, means an alkyl group, as defined above, but having from one to ten carbons, more preferably from one to six carbon atoms in its backbone structure such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and tert-butyl. Likewise, "lower alkenyl" and "lower alkynyl" have similar chain lengths. Throughout the application, preferred alkyl groups are lower alkyls. In certain embodiments, a substituent designated herein as alkyl is a lower alkyl.

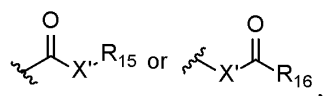
[00067] The term "aryl" as used herein includes 3- to 12-membered substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon (i.e., carbocyclic aryl) or where one or more atoms are heteroatoms (i.e., heteroaryl). Preferably, aryl groups include 5- to 12-membered rings, more preferably 6- to 10-membered rings. The term "aryl" also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Carbocyclic aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, and the like. Heteroaryl groups include substituted or unsubstituted aromatic 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like. Aryl and heteroaryl can be monocyclic, bicyclic, or polycyclic.

[00068] The term "halo", "halide", or "halogen" as used herein means halogen and includes, for example, and without being limited thereto, fluoro, chloro, bromo, iodo and the like, in both radioactive and non-radioactive forms. In a preferred embodiment, halo is selected from the group consisting of fluoro, chloro and bromo.

[00069] The terms “heterocyclyl” or “heterocyclic group” refer to 3- to 12-membered ring structures, more preferably 5- to 12-membered rings, more preferably 5- to 10-membered rings, whose ring structures include one to four heteroatoms. Heterocycles can be monocyclic, bicyclic, spirocyclic, or polycyclic. Heterocyclyl groups include, for example, thiophene, thianthrene, furan, pyran, isobenzofuran, chromene, xanthene, phenoxathiin, pyrrole, imidazole, pyrazole, isothiazole, isoxazole, pyridine, pyrazine, pyrimidine, pyridazine, indolizine, isoindole, indole, indazole, purine, quinolizine, isoquinoline, quinoline, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, carbazole, carboline, phenanthridine, acridine, pyrimidine, phenanthroline, phenazine, phenarsazine, phenothiazine, furazan, phenoxazine, pyrrolidine, oxolane, thiolane, oxazole, piperidine, piperazine, morpholine, lactones, lactams such as azetidinones and pyrrolidinones, sultams, sultones, and the like. The heterocyclic ring can be substituted at one or more positions with such substituents as described above, as for example, halogen, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, amino, nitro, sulfhydryl, imino, amido, phosphate, phosphonate, phosphinate, carbonyl, carboxyl, silyl, sulfamoyl, sulfinyl, ether, alkylthio, sulfonyl, ketone, aldehyde, ester, a heterocyclyl, an aromatic or heteroaromatic moiety, -CF₃, -CN, and the like.

[00070] The term “heterocycloalkyl” as used herein, is a non-aromatic heterocyclyl wherein at least one atom is a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus, and the remaining atoms are carbon. Examples of heterocycloalkyl groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazoliny, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinoliziny. The heterocycloalkyl group can be substituted or unsubstituted as recited, e.g., for heterocyclyls as described herein.

[00071] The term “carbonyl” is art-recognized and includes such moieties as can be represented by the formula:



wherein X' is a bond or represents an oxygen or a sulfur, and R₁₅ represents a hydrogen, an alkyl, an alkenyl, -(CH₂)_m-R₁₀ or a pharmaceutically acceptable salt, R₁₆ represents a hydrogen, an alkyl, an alkenyl or -(CH₂)_m-R₁₀, where m and R₁₀ are as defined above. Where X' is an oxygen and R₁₅ or R₁₆ is not hydrogen, the formula represents an "ester." Where X' is an oxygen, and R₁₅ is as defined above, the moiety is referred to herein as a carboxyl group, and particularly when R₁₅ is a hydrogen, the formula represents a "carboxylic acid". Where X' is an oxygen, and R₁₆ is a hydrogen, the formula represents a "formate." On the other hand, where X' is a bond, and R₁₅ is not hydrogen, the above formula represents a "ketone" group. Where X' is a bond, and R₁₅ is a hydrogen, the above formula represents an "aldehyde" group.

[00072] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those described herein above, and for example substituted with one or more substituents selected from alkyl, cycloalkyl, heterocycloalkyl, halogen, OH, OMe, C(H)F₂, C(F)H₂, CF₃, C(H)₂CF₃, SF₅, CHFCH₂amine, CH₂amine, and CN. The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of organic compounds. It will be understood that "substitution" or "substituted with" includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc.

[00073] As used herein, the term "nitro" means -NO₂; the term "halogen" designates -F, -Cl, -Br, or -I; the term "hydroxyl" means -OH; and the term "cyano" means -CN;.

[00074] As used herein, the definition of each expression, e.g., alkyl, m, n, etc., when it occurs more than once in any structure, is intended to be independent of its definition elsewhere in the same structure.

[00075] The term "prodrug" as used herein encompasses compounds that, under physiological conditions, are converted into therapeutically active agents. A common method

for making a prodrug is to include selected moieties that are hydrolyzed under physiological conditions to reveal the desired molecule. In other embodiments, the prodrug is converted by an enzymatic activity of the host animal. Accordingly, prodrugs include compounds that are transformed *in vivo* to yield a disclosed compound or any other pharmaceutically acceptable form of the compound. In embodiments, a prodrug may be inactive when administered to a subject but may be converted *in vivo* to an active compound, for example, by hydrolysis. See, e.g., Bundgaard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., "Pro-drugs as Novel Delivery Systems," *A.C.S. Symposium Series*, Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Prodrugs can typically be prepared using well known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed., 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elsevier, New York, 1985). The term "prodrug" is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a subject.

[00076] Prodrugs of compounds described herein may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to provide a compound described herein (i.e., the parent active compound). Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like. Other examples of prodrugs include compounds that comprise —NO, —NO₂, —ONO, or —ONO₂ moieties.

[00077] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

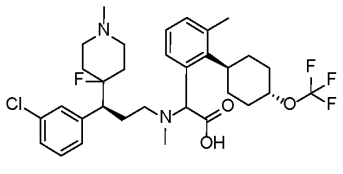
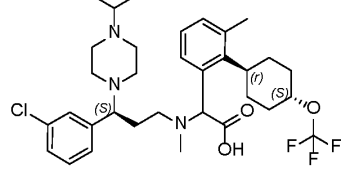
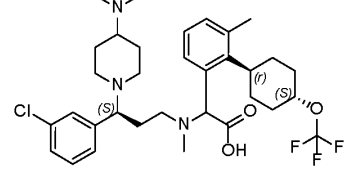
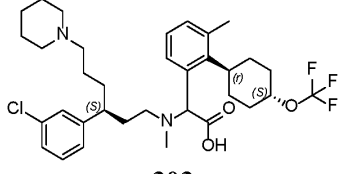
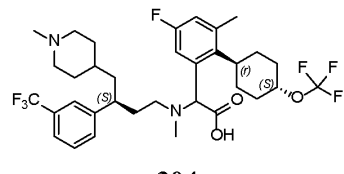
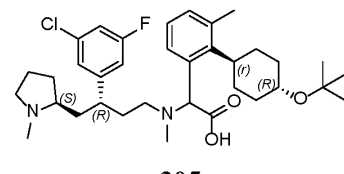
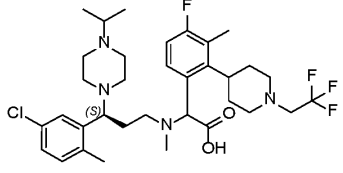
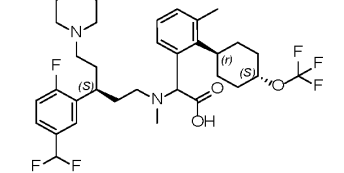
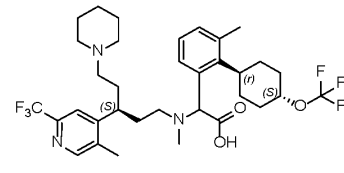
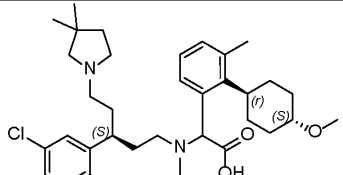
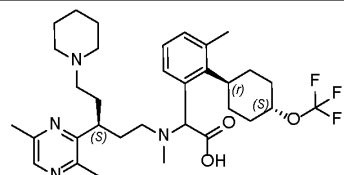
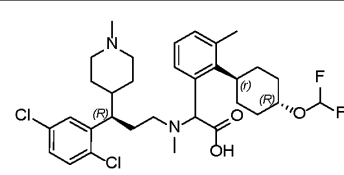
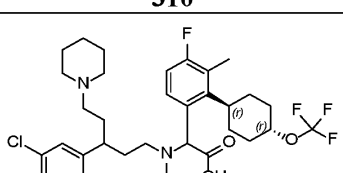
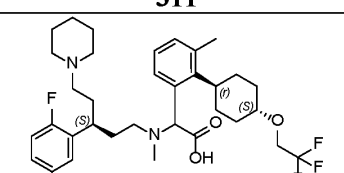
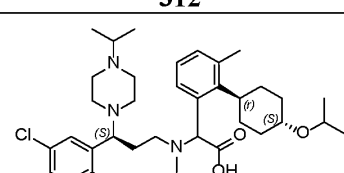
Exemplary Compounds of the Invention

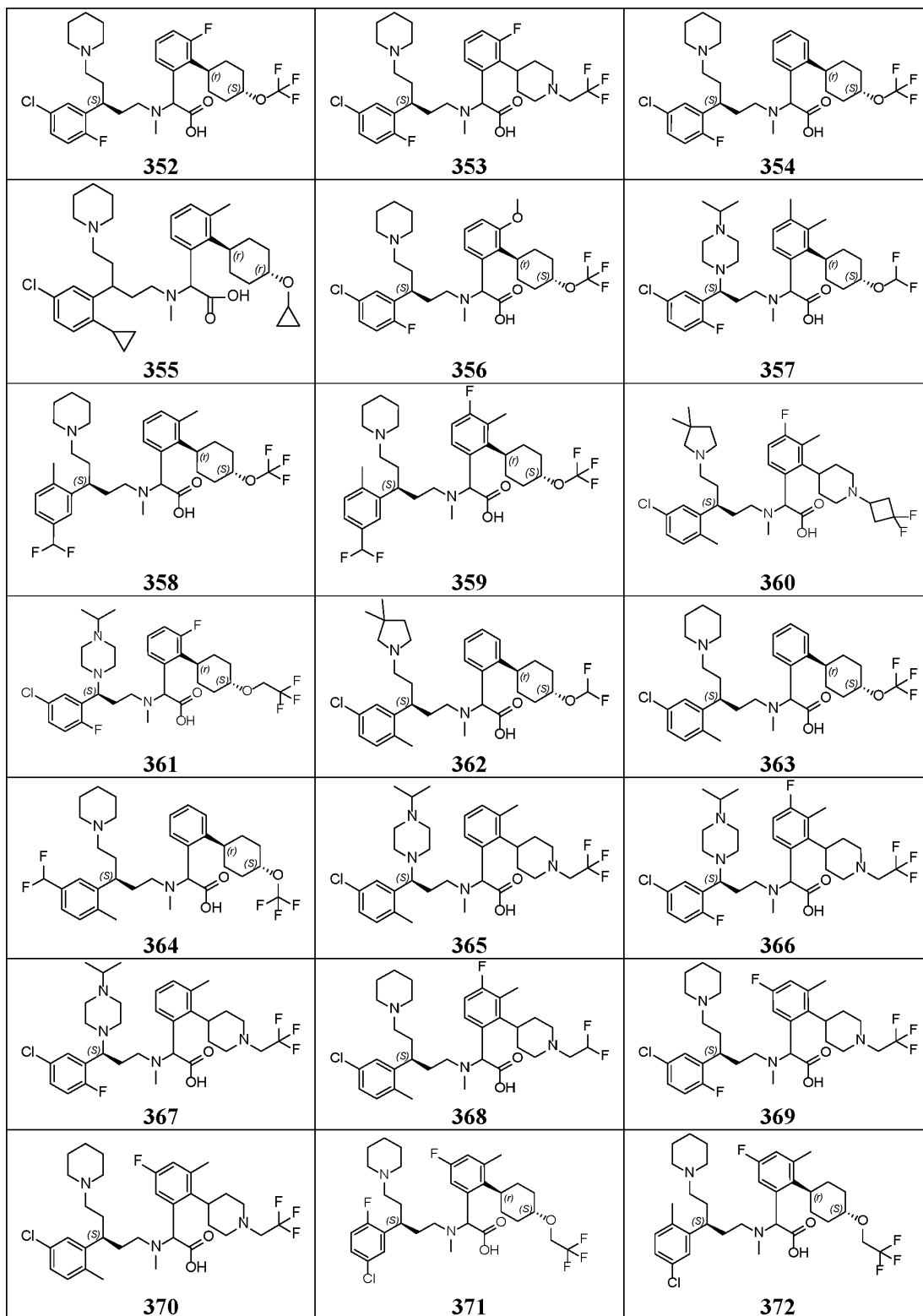
[00078] This disclosure relates to novel chemical compounds and methods useful for inhibiting $\alpha_v\beta_8$ integrin.

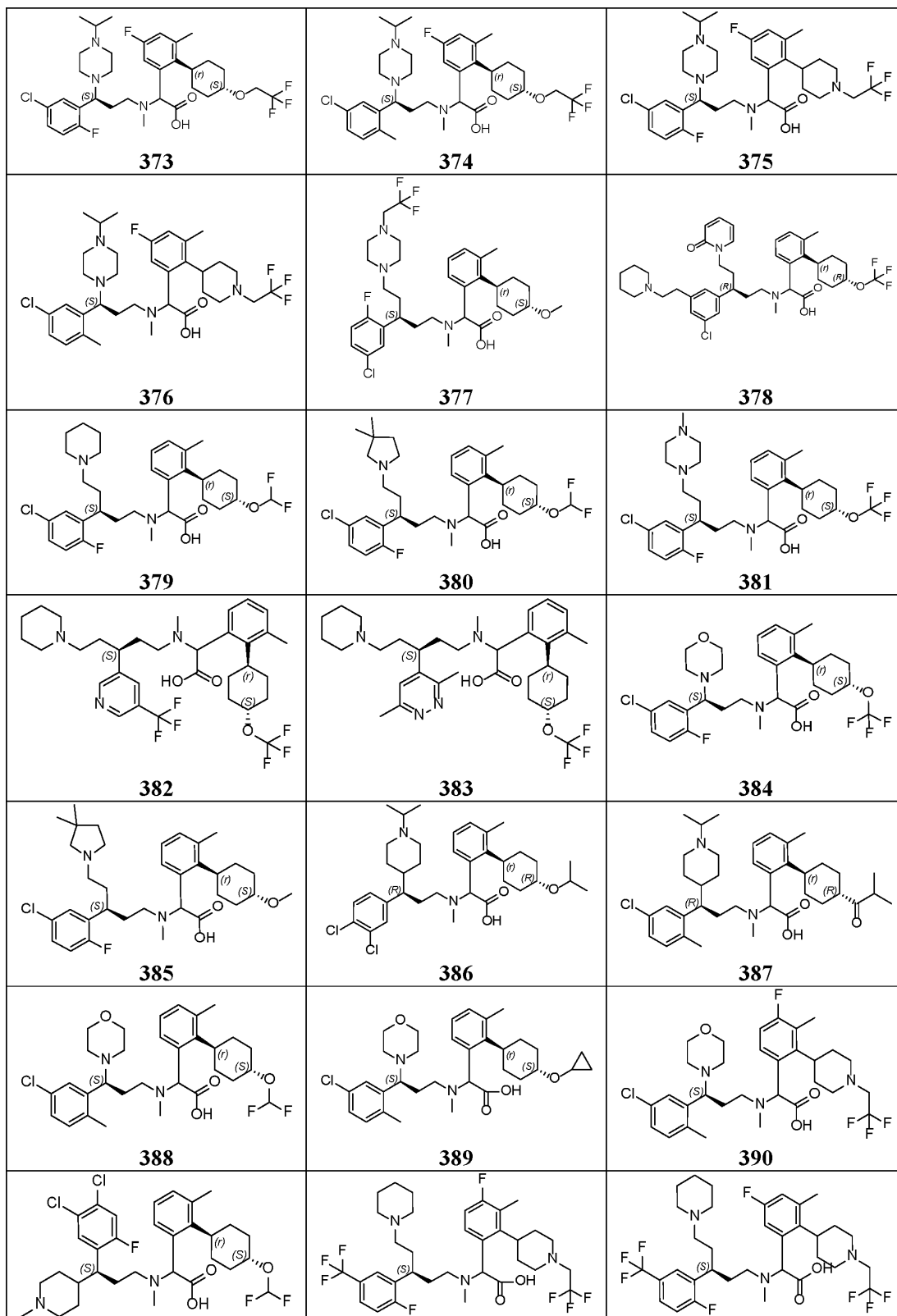
[00079] In some embodiments, the compound is a compound from Figure 1, Table 2, Table 3, or Table 4, or a pharmaceutically acceptable salt thereof.

[00080] In some embodiments, the compound is a compound from Table 2, or a pharmaceutically acceptable salt thereof.

Table 2. Additional Compound Table

 300	 301	 302
 303	 304	 305
 307	 308	 309
 310	 311	 312
 313	 350	 351





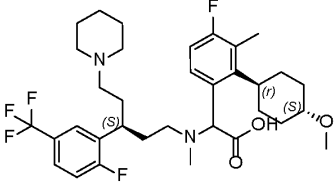
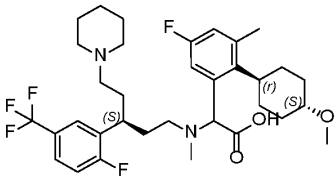
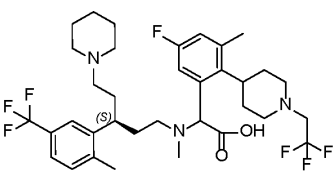
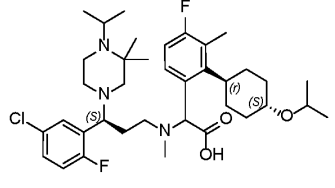
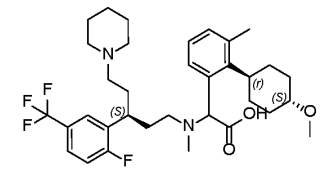
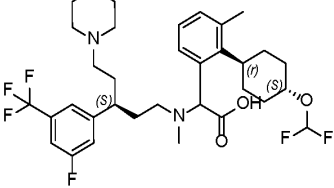
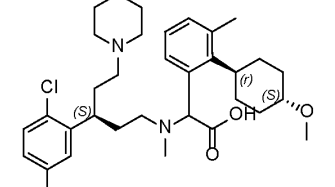
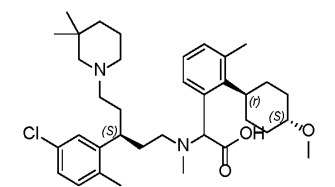
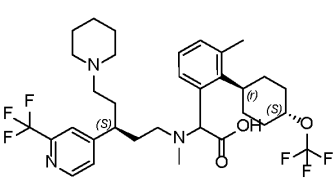
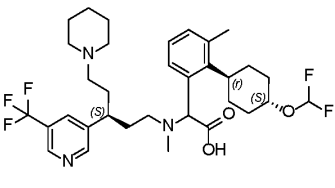
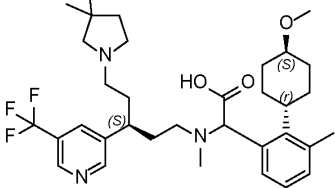
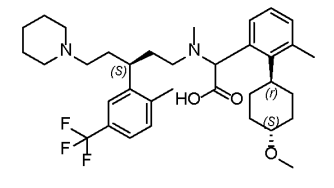
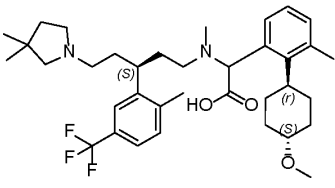
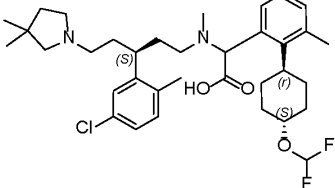
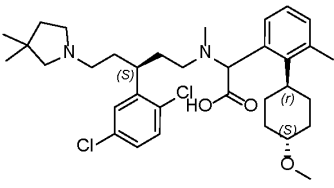
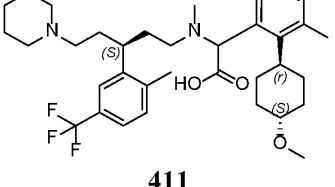
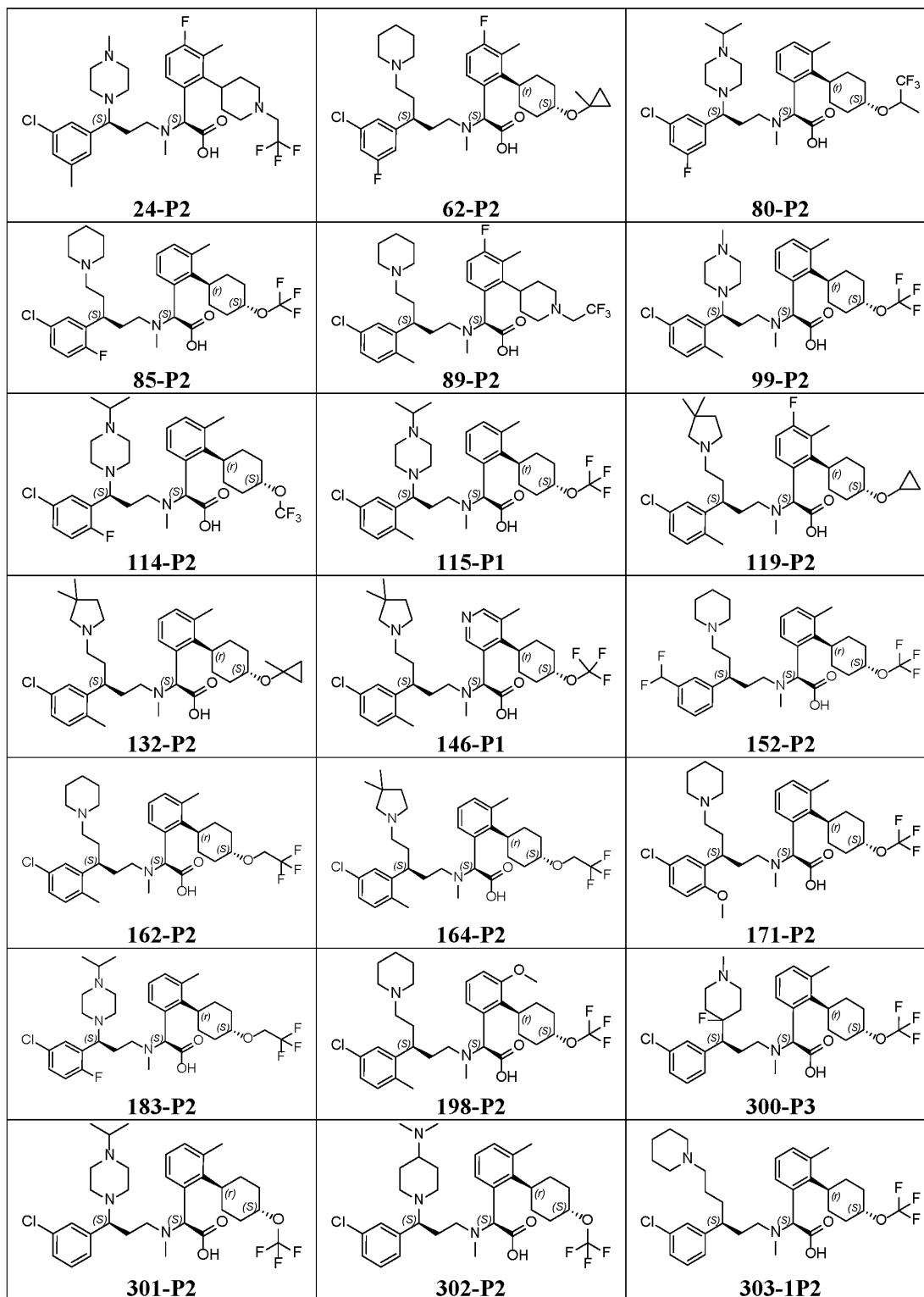
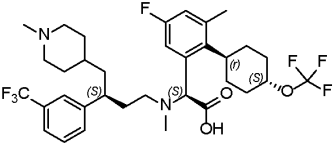
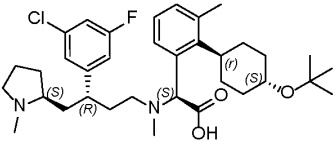
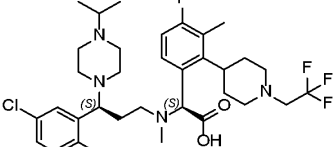
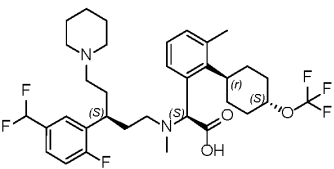
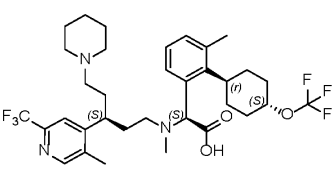
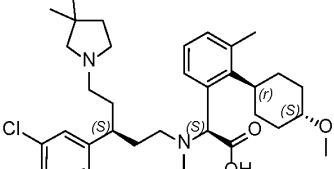
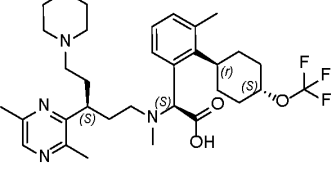
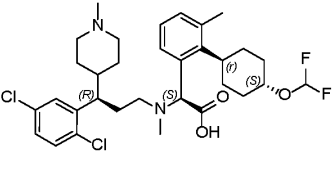
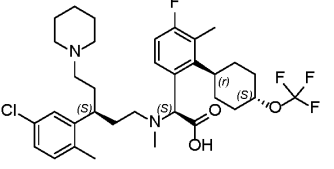
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 402	 403	 404
 405	 406	 407
 408	 409	 410
 411		

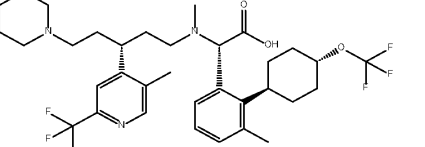
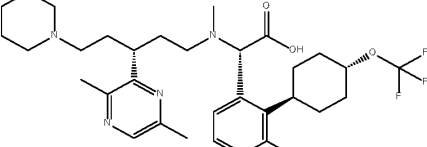
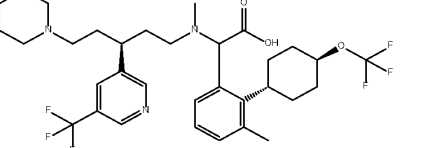
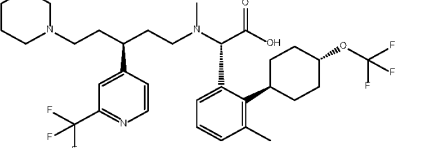
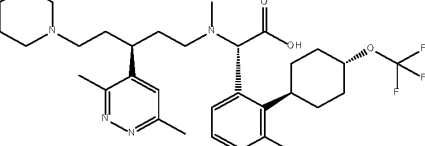
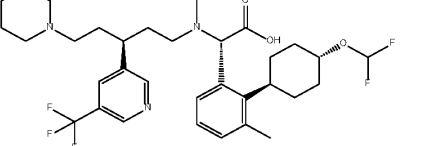
Table 3. Additional Compound Table

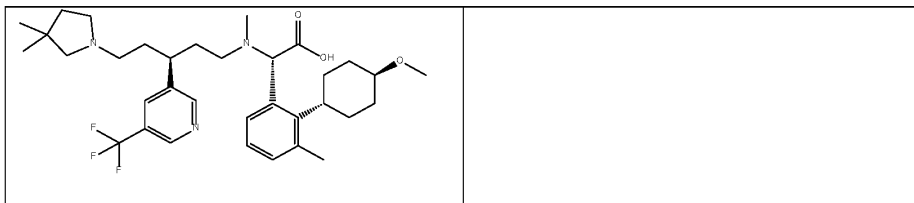


 304-P2	 305-2P1	 307-2P2
 308-1P2	 309-2P1	 310-1P2
 311-2P2	 312-2P2	 313-1P2

[00081] In some embodiments, the compound is a compound from Table 4, or a pharmaceutically acceptable salt thereof.

Table 4. Exemplary Compounds



[00082] Exemplary formulas and compounds are described herein. Also provided herein are exemplary embodiments of structural features which may be present in any formula described herein. Any exemplary embodiment of a structural feature may occur in combination with any other exemplary structural feature described herein. Further, and unless otherwise indicated herein, any description of a formula or compound also includes any pharmaceutically acceptable forms of the compound, including but not limited to any pharmaceutically acceptable salts, hydrates, solvates, isomers, polymorphs, prodrugs, and isotopically labeled derivatives of disclosed formulas and compounds.

Therapeutic Uses of a Compound of Formula (I)

[00083] The methods described herein may be applied to cell populations in vivo or ex vivo. “In vivo” means within a living individual, as within an animal or human. In this context, the methods described herein may be used therapeutically in an individual. “Ex vivo” means outside of a living individual. Examples of ex vivo cell populations include in vitro cell cultures and biological samples including fluid or tissue samples obtained from individuals.

[00084] Information gleaned from such use may be used for experimental purposes or in the clinic to set protocols for in vivo treatment. The selected compounds may be further characterized to examine the safety or tolerance dosage in human or non-human subjects. Such properties may be examined using commonly known methods to those skilled in the art.

[00085] In some embodiments, compounds described herein, or a pharmaceutically acceptable salt, stereoisomer, mixture of stereoisomers, tautomer, or deuterated analog thereof, may be used to treat subjects who have or are suspected of having disease states, disorders, and conditions (also collectively referred to as “indications”) responsive or believed to be responsive to the inhibition of $\alpha 4\beta 7$ integrin activity. In some embodiments, the compounds described herein may be used to inhibit the activity of $\alpha 4\beta 7$ integrin. In some embodiments, the compounds described herein may be used to inhibit excessive or destructive immune reactions or growth or a proliferation of a cell, such as a cancer cell, or inhibit immunosuppression.

[00086] In some embodiments, the present disclosure provides a compound described herein useful as an inhibitor of $\alpha 4\beta 7$ integrin. In some embodiments, the present disclosure provides a method of treating or preventing an inflammatory disease or condition comprising administering a compound described herein to a patient.

[00087] In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier.

[00088] In some embodiments, provided is a compound described herein useful for the treatment of an inflammatory disease or condition in a patient that is mediated, at least in part, by $\alpha 4\beta 7$ integrin.

[00089] Co-administration may also include administering component drugs e.g., one or more compounds described herein and one or more additional (e.g., a second, third, fourth or fifth) therapeutic agent(s). Such combination of one or more compounds described herein and one or more additional therapeutic agent(s) may be administered simultaneously or in sequence (one after the other) within a reasonable period of time of each administration (e.g., about 1 minute to 24 hours) depending on the pharmacokinetic and/or pharmacodynamics properties of each agent or the combination. Co-administration may also involve treatment with a fixed combination wherein agents of the treatment regimen are combinable in a fixed dosage or combined dosage medium e.g., solid, liquid or aerosol.

[00090] In some embodiments, a method of treating diseases or conditions mediated, at least in part, by $\alpha 4\beta 7$ integrin and/or diseases or symptoms that co-present, exacerbated, and/or triggered by the diseases or conditions mediated, at least in part, by $\alpha 4\beta 7$ integrin, e.g., an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction, comprises administering to a patient in need thereof an effective amount of a compound described herein optionally in combination with an additional agent (e.g., a second, third, fourth or fifth active agent) which can be useful for treating diseases or conditions mediated, at least in part, by $\alpha 4\beta 7$, an allergic disorder and/or an autoimmune and/or inflammatory disease, and/or an acute inflammatory reaction incident to or co-presenting with diseases or conditions mediated, at least in part, by $\alpha 4\beta 7$ integrin.

[00091] Treatment with the second, third, fourth or fifth active agent may be prior to, concomitant with, or following treatment with a compound described herein. In some

embodiments, a compound described herein is combined with another active agent in a single dosage form.

[00092] In embodiments, a subject is an adult subject.

Dosage Amounts and Frequency

[00093] In some embodiments, compounds of Formula (I) or any pharmaceutically acceptable salt thereof described herein is administered to a human patient in need thereof in an effective amount, such as, from about 25 mg to about 400 mg. In other embodiments, compounds of Formula (I) described herein are administered to a human patient in need thereof, in an effective amount, for example about 25 mg, about 50 mg, about 100 mg, about 150 mg, about 200 mg, or about 400 mg.

[00094] In embodiments, methods described herein comprise administration of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in an amount that is about 25 mg (e.g., administration of a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), or (V-A)) or Formula (VI), or a pharmaceutically acceptable salt thereof, in an amount that is about 25 mg).

[00095] In embodiments, a subject receives a dose of a compound of Formula (I) or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), or (V-A)) or Formula (VI), or a pharmaceutically acceptable salt thereof) once daily.

[00096] In embodiments, a subject receives a dose of a compound of Formula (I) or a pharmaceutically acceptable salt thereof (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), or (V-A)) or Formula (VI), or a pharmaceutically acceptable salt thereof) twice daily.

[00097] In embodiments, methods described herein comprise administration of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in an amount that is about 50 mg (e.g., administration of a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), or (V-A)) or Formula (VI), or a pharmaceutically acceptable salt thereof, in an amount that is about 50 mg).

[00098] In embodiments, methods described herein comprise administration of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in an amount that is about 100 mg (e.g., administration of a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V),

or (V-A)) or Formula (VI), or a pharmaceutically acceptable salt thereof, in an amount that is about 100 mg).

[00099] In embodiments, methods described herein comprise administration of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in an amount that is about 150 mg (e.g., administration of a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), or (V-A)) or Formula (VI), or a pharmaceutically acceptable salt thereof, in an amount that is about 150 mg).

[000100] In embodiments, methods described herein comprise administration of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in an amount that is about 200 mg (e.g., administration of a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), or (V-A)) or Formula (VI), or a pharmaceutically acceptable salt thereof, in an amount that is about 200 mg).

[000101] In embodiments, methods described herein comprise administration of a compound of Formula (I) or a pharmaceutically acceptable salt thereof in an amount that is about 400 mg (e.g., administration of a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), or (V-A)) or Formula (VI), or a pharmaceutically acceptable salt thereof, in an amount that is about 400 mg).

[000102] In embodiments, a method comprises administering to a subject in need thereof about 100 mg of a compound of Formula (I-A), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises once daily administration to a subject in need thereof about 100 mg of a compound of Formula (I-A), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises twice daily administration to a subject in need thereof about 100 mg of a compound of Formula (I-A), or a pharmaceutically acceptable salt thereof.

[000103] In embodiments, a method comprises administering to a subject in need thereof about 200 mg of a compound of Formula (I-A), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises once daily administration to a subject in need thereof about 200 mg of a compound of Formula (I-A), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises twice daily administration to a subject in need thereof about 200 mg of a compound of Formula (I-A), or a pharmaceutically acceptable salt thereof.

[000104] In embodiments, a method comprises administering to a subject in need thereof about 100 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A), or a

pharmaceutically acceptable salt thereof. In embodiments, a method comprises once daily administration to a subject in need thereof about 100 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises twice daily administration to a subject in need thereof about 100 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A), or a pharmaceutically acceptable salt thereof.

[000105] In embodiments, a method comprises administering to a subject in need thereof about 200 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises once daily administration to a subject in need thereof about 200 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises twice daily administration to a subject in need thereof about 200 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A), or a pharmaceutically acceptable salt thereof.

[000106] In embodiments, a method comprises administering to a subject in need thereof about 100 mg of a compound of Formula (VI), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises once daily administration to a subject in need thereof about 100 mg of a compound of Formula (VI), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises twice daily administration to a subject in need thereof about 100 mg of a compound of Formula (VI), or a pharmaceutically acceptable salt thereof.

[000107] In embodiments, a method comprises administering to a subject in need thereof about 200 mg of a compound of Formula (VI), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises once daily administration to a subject in need thereof about 200 mg of a compound of Formula (VI), or a pharmaceutically acceptable salt thereof. In embodiments, a method comprises twice daily administration to a subject in need thereof about 200 mg of a compound of Formula (VI), or a pharmaceutically acceptable salt thereof.

[000108] In some embodiments, administration of a compound of Formula (I) to a patient in need thereof results in a receptor occupancy (RO), indicated the percentage of $\alpha 4\beta 7$ bound by the compound at 12 hours after the dose is administered, of at least about 70%, about 85%, about 95%, or about 99%. In some embodiments, administration of a compound of Formula (I) to a patient in need thereof results in a receptor occupancy (RO), indicated the percentage of

$\alpha 4\beta 7$ bound by the compound at 24 hours after the dose is administered, of at least about 70%, about 85%, about 95%, or about 99%.

Integrin Mediated Disease

[000109] Diseases that are responsive to $\alpha 4\beta 7$ inhibition include autoimmune diseases, and chronic gastrointestinal and gastroesophageal inflammatory diseases. Inflammatory bowel disease (IBD), ulcerative colitis, Crohn's disease, gastroesophageal inflammatory disease, Eosinophilic Gastrointestinal Disorders (EGIDs), eosinophilic gastroenteritis, eosinophilic gastritis, eosinophilic duodenitis, and eosinophilic esophagitis (EoE) are examples of diseases that can be treated with a compound of Formula (I).

[000110] Methods of treating patients with diseases and conditions that are responsive to $\alpha 4\beta 7$ inhibition with a compound of Formula (I) minimizes off-target risk, because compounds of Formula (I) have been shown to be selective for $\alpha 4\beta 7$ inhibition over other integrins, such as $\alpha 4\beta 1$, which is implicated in the development of progressive multifocal leukoencephalopathy (PML). Compounds of Formula (I) also can be administered orally. In preclinical studies, the compound of Formula (VI) $\alpha 4\beta 7$ exhibited high potency and selectivity for $\alpha 4\beta 7$ integrin, good oral absorption, and pharmacokinetic properties suitable for doses regimens including twice daily dosing.

[000111] As further shown herein, methods of the invention can achieve significant therapeutic benefit for subjects having inflammatory bowel disease (e.g., ulcerative colitis or Crohn's disease).

[000112] Compound of Formula (I) are useful for the treatment of diseases or conditions mediated, at least in part, by $\alpha 4\beta 7$ integrin.

[000113] In additional embodiments, the methods are provided for alleviating a symptom of a disease or disorder mediated, at least in part, by $\alpha 4\beta 7$ integrin. In some embodiments, the methods include identifying a mammal having a symptom of a disease or disorder mediated, at least in part, by $\alpha 4\beta 7$ integrin, and providing to the mammal an amount of a compound as described herein effective to ameliorate (i.e., lessen the severity of) the symptom.

Treatment of Inflammatory Bowel Diseases

[000114] In some embodiments, the disease or condition mediated, at least in part, by $\alpha 4\beta 7$ integrin is inflammatory bowel disease (IBD).

[000115] The term “inflammatory bowel disease” or “IBD” as used herein is a collective term describing inflammatory disorders of the gastrointestinal tract, the most common forms of which are ulcerative colitis and Crohn’s disease. Other forms of IBD that can be treated with the presently disclosed compounds, compositions and methods include diversion colitis, ischemic colitis, infectious colitis, chemical colitis, microscopic colitis (including collagenous colitis and lymphocytic colitis), atypical colitis, pseudomembranous colitis, fulminant colitis, autistic enterocolitis, indeterminate colitis, Behcet’s disease, gastroduodenal CD, jejunoileitis, ileitis, ileocolitis, Crohn’s (granulomatous) colitis, irritable bowel syndrome, mucositis, radiation induced enteritis, short bowel syndrome, celiac disease, stomach ulcers, diverticulitis, pouchitis, proctitis, and chronic diarrhea.

[000116] Treating or preventing IBD also includes ameliorating or reducing one or more symptoms of IBD. As used herein, the term “symptoms of IBD” refers to detected symptoms such as abdominal pain, diarrhea, rectal bleeding, weight loss, fever, loss of appetite, and other more serious complications, such as dehydration, anemia and malnutrition. A number of such symptoms are subject to quantitative analysis (e.g. weight loss, fever, anemia, etc.). Some symptoms are readily determined from a blood test (e.g. anemia) or a test that detects the presence of blood (e.g. rectal bleeding). The term “wherein said symptoms are reduced” refers to a qualitative or quantitative reduction in detectable symptoms, including but not limited to a detectable impact on the rate of recovery from disease (e.g. rate of weight gain). The diagnosis is typically determined by way of an endoscopic observation of the mucosa, and pathologic examination of endoscopic biopsy specimens.

[000117] The course of IBD varies and is often associated with intermittent periods of disease remission and disease exacerbation. Various methods have been described for characterizing disease activity and severity of IBD as well as response to treatment in subjects having IBD. Treatment according to the present methods is generally applicable to a subject having IBD of any level or degree of disease activity.

[000118] Criteria useful for assessment of disease activity in subjects with ulcerative colitis can be found in, *e.g.*, Truelove et al., Br Med J 2:1041-1048 (1955).) Using these criteria, disease activity can be characterized in a subject having IBD as mild disease activity or severe disease activity. Subjects who do not meet all the criteria for severe disease activity, and who exceed the criteria for mild disease activity are classified as having moderate disease activity.

[000119] The presently disclosed treatment methods can also be applied at any point in the course of the disease. In some embodiments, the methods are applied to a subject having IBD during a time period of remission (i.e., inactive disease). In such embodiments, the present methods provide benefit by extending the time period of remission (e.g., extending the period of inactive disease) or by preventing, reducing, or delaying the onset of active disease. In other embodiments, methods may be applied to a subject having IBD during a period of active disease. Such methods provide benefit by reducing the duration of the period of active disease, reducing or ameliorating one or more symptoms of IBD, or treating IBD.

[000120] Measures for determining efficacy of treatment of IBD in clinical practice have been described and include, for example, the following: symptom control; fistula closure; extent of corticosteroid therapy required; and improvement in quality of life. Health-related quality of life (HRQL) can be assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ), which is extensively used in clinical practice to assess quality of life in a subject with IBD. (See Guyatt et al., *Gastroenterology* 96:804-810 (1989).) In some embodiments, the disease or condition is immune-mediated liver injury, disease or condition.

[000121] In embodiments, a subject has not previously received advanced therapy (AT) for treatment of a condition described herein (e.g., an inflammatory bowel disease such as ulcerative colitis or Crohn's disease) prior to any method comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof.

[000122] In embodiments, a subject has previously received advanced therapy (AT) for treatment of a condition described herein (e.g., an inflammatory bowel disease such as ulcerative colitis or Crohn's disease) prior to any method comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof. In embodiments, a subject was intolerant to a previously received advanced therapy. In embodiments, a subject was non-responsive to a previously received advanced therapy. In embodiments, a subject was inadequately responsive to a previously received advanced therapy.

[000123] Exemplary advanced therapies (ATs) include therapy comprising administration of immunomodulator therapy (e.g., azathioprine, 6-mercaptopurine, or methotrexate), a TNF blocker, one or more corticosteroids, natalizumab, and/or vedolizumab.

[000124] In embodiments, a subject has not previously received advanced therapy (AT) for treatment of a condition described herein (e.g., an inflammatory bowel disease such as ulcerative colitis or Crohn's disease) prior to any method comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof. Such subjects may also be referred to as treatment-naïve subjects.

[000125] In embodiments, a method comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof is a method of maintenance therapy for treating an inflammatory bowel disease (e.g., an inflammatory bowel disease such as ulcerative colitis or Crohn's disease). In embodiments, a method of maintenance therapy comprising administering a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof follows an initial method of induction therapy comprising administering a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof. In embodiments, a method of maintenance therapy immediately follows a method of induction therapy.

[000126] In embodiments, maintenance therapy comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof follows induction therapy comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof. In embodiments, periods of treatment described herein can be the sum of induction and maintenance therapy comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or any pharmaceutically acceptable salt thereof.

Ulcerative Colitis

[000127] In embodiments, a compound of Formula (I) (e.g., a compound of any one of Formulae (Ia), (Ib), and (Ic) such as a compound of Formula (VI)), or a pharmaceutically

acceptable salt thereof, can be used in methods to treat ulcerative colitis in a subject in need thereof.

[000128] In one aspect, the invention features a method of treating ulcerative colitis in a subject in need thereof. In embodiments, a method comprises administering a compound of Formula (I) (e.g., a compound of any one of Formulae (Ia), (Ib), and (Ic) such as a compound of Formula (VI)), or a pharmaceutically acceptable salt thereof, to the subject. In embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered in an amount of about 50-400 mg. In embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered once daily. In embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered twice daily.

[000129] In embodiments, a compound of Formula (I-A) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof. In embodiments, a compound of Formula (I-A) or a pharmaceutically acceptable salt thereof is administered in an amount of about 50-400 mg. In embodiments, a compound of Formula (I-A) or a pharmaceutically acceptable salt thereof is administered once daily (e.g., about 100 mg or about 200 mg once daily). In embodiments, a compound of Formula (I-A) or a pharmaceutically acceptable salt thereof is administered twice daily (e.g., about 100 mg or about 200 mg twice daily). In embodiments, about 100 mg of a compound of Formula (I-A) is administered twice daily. In embodiments, about 200 mg of a compound of Formula (I-A) is administered twice daily.

[000130] In embodiments, a compound of Formula (II-A), (III-A), (IV-A), or (V-A) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof. In embodiments, a compound of Formula (II-A), (III-A), (IV-A), or (V-A) or a pharmaceutically acceptable salt thereof is administered in an amount of about 50-400 mg. In embodiments, a compound of Formula (II-A), (III-A), (IV-A), or (V-A) or a pharmaceutically acceptable salt thereof is administered once daily (e.g., about 100 mg or about 200 mg once daily). In embodiments, a compound of Formula (II-A), (III-A), (IV-A), or (V-A) or a pharmaceutically acceptable salt thereof is administered twice daily (e.g., about 100 mg or about 200 mg twice daily). In embodiments, about 100 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A) is administered twice daily. In embodiments, about 200 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A) is administered twice daily.

[000131] In embodiments, a compound of Formula (VI) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof. In embodiments, a compound of Formula (VI) or a pharmaceutically acceptable salt thereof is administered in an amount of about 50-400 mg. In embodiments, a compound of Formula (VI) or a pharmaceutically acceptable salt thereof is administered once daily (e.g., about 100 mg or about 200 mg once daily). In embodiments, a compound of Formula (VI) or a pharmaceutically acceptable salt thereof is administered twice daily (e.g., about 100 mg or about 200 mg twice daily). In embodiments, about 100 mg of a compound of Formula (VI) is administered twice daily. In embodiments, about 200 mg of a compound of Formula (VI) is administered twice daily.

[000132] In embodiments, ulcerative colitis is moderate to severe ulcerative colitis. In embodiments, ulcerative colitis is moderate ulcerative colitis. In embodiments, ulcerative colitis is severe ulcerative colitis.

[000133] In embodiments, ulcerative colitis is moderately to severely active ulcerative colitis. In embodiments, ulcerative colitis is moderately active ulcerative colitis. In embodiments, ulcerative colitis is severely active ulcerative colitis.

[000134] In embodiments, a subject has a Mayo Endoscopy Score (MES) of 2. In embodiments, a subject has a Mayo Endoscopy Score (MES) of 3. In embodiments, a MES of 2 or 3 is determined prior to commencing any therapy comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or a pharmaceutically acceptable salt thereof. A subject's MES at time of commencing treatment according to methods described herein may also be referred to as a baseline MES.

[000135] Ulcerative colitis can be described according to the Mayo Clinic Score (MCS) for ulcerative colitis as described in **Table A**.

Table A. Mayo Clinic Score for Ulcerative Colitis

Component	Score	Description
Stool frequency	0	Normal number of stools for patient
	1	1-2 stools per day more than normal
	2	3-4 stools more than normal
	3	≥5 stools more than normal

Component	Score	Description
Rectal bleeding	0	No blood seen
	1	Streaks of blood with stool less than half the time
	2	Obvious blood with stool most of time
	3	Blood alone passes
Endoscopic Finding	0	Normal or inactive disease
	1	Mild disease
	2	Moderate disease
	3	Severe disease
Physician's global assessment	0	Normal
	1	Mild Disease
	2	Moderate Disease
	3	Severe Disease

[000136] In embodiments, a full Mayo Clinic Score (MCS) is used to describe the severity of disease, which comprises all four components of **Table A** and which ranges from 0-12.

[000137] In embodiments, a subject has a Mayo Clinic Score (MCS) of 6-12. In embodiments, a subject has a MCS of 6. In embodiments, a subject with ulcerative colitis has a MCS of 7. In embodiments, a subject has a MCS of 8. In embodiments, a subject has a MCS of 9. In embodiments, a subject has a MCS of 10. In embodiments, a subject has a MCS of 11. In embodiments, a subject has a MCS of 12. In embodiments, a MCS of 6-12 is determined prior to commencing any therapy comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or a pharmaceutically acceptable salt thereof. A subject's MCS at time of commencing treatment according to methods described herein may also be referred to as a baseline MCS.

[000138] In embodiments, a modified Mayo Clinic Score (mMCS) is used to describe the severity of disease, which comprises three components of **Table A** (stool frequency, rectal bleeding, and endoscopic finding) and which ranges from 0-9.

[000139] In embodiments, a subject has a modified Mayo Clinic Score (mMCS) of 5-9. In embodiments, a subject has a mMCS of 5. In embodiments, a subject has a mMCS of 6. In embodiments, a subject with ulcerative colitis has a mMCS of 7. In embodiments, a subject has a mMCS of 8. In embodiments, a subject has a mMCS of 9. In embodiments, a mMCS of 5-9 is determined prior to commencing any therapy comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or a pharmaceutically acceptable salt thereof. A subject's mMCS at time of commencing treatment according to methods described herein may also be referred to as a baseline mMCS.

[000140] In embodiments, the Robarts Histology Index (RHI) is used to describe severity of disease. The RHI is a histology index derived from the Geboes Score and is calculated by evaluating four histologic items, each on a scale from 0 to 3, and where each item is individually weighted in the RHI formula. The RHI can be calculated according to the below equation and ranges from 0 to 33. See also **Table B**.

$$\text{RHI} = (1 \times \text{chronic inflammatory infiltrate score}) + (2 \times \text{lamina propria neutrophils score}) + (3 \times \text{neutrophils in epithelium score}) + (5 \times \text{erosion or ulceration score})$$

Table B. Geboes score (GS) and the derived Robarts histopathological index (RHI)

Geboes score (GS)	Morphology		RHI
Grade 0: Architectural changes	0.0	No abnormality	0
	0.1	Mild abnormality	0
	0.2	Mild/moderate diffuse or multifocal abnormalities	0
	0.3	Severe diffuse or multifocal abnormalities	0
Grade 1: Chronic inflammatory infiltrate	1.0	No increase	0
	1.1	Mild but unequivocal increase	1
	1.2	Moderate increase	2
	1.3	Marked increase	3
	2A.0	No increase	0

Geboes score (GS)	Morphology		RHI
Grade 1: Chronic inflammatory infiltrate	2A.1	Mild but unequivocal increase	0
	2A.2	Moderate increase	0
	2A.3	Marked increase	0
Grade 2B: Neutrophils in lamina propria	2B.0	No increase	0
	2B. 1	Mild but unequivocal increase	2
	2B.2	Moderate increase	4
	2B. 3	Marked increase	6
Grade 3: Neutrophils in epithelium	3.0	None	0
	3.1	<5% crypts involved	3
	3.2	<50% crypts involved	6
	3.3	>50% crypts involved	9
Grade 4: Crypt destruction	4.0	None	0
	4.1	Probable-local excess of neutrophils in part of the crypts	0
	4.3	Probable-marked attenuation	0
	4.3	Unequivocal crypt destruction	0
Grade 5: Erosions and ulcerations	5.0	No erosion, ulceration or granulation tissue	0
	5.1	Recovering epithelium + adjacent inflammation	5
	5.2	Probable erosion – focally stippled	5
	5.3	Unequivocal erosion	10
	5.4	Ulcer or granulation tissue	15

[000141] In embodiments, a subject has a RHI that is ≥ 10 . In embodiments, a RHI that is ≥ 10 is determined prior to commencing any therapy comprising administration of a compound of Formula (I) (e.g., a compound of Formula (I), (II), (II-A), (III), (III-A), (IV), (IV-A), (V), (V-A) or (VI)) or a pharmaceutically acceptable salt thereof. A subject's RHI at time of commencing treatment according to methods described herein may also be referred to as a baseline RHI. Accordingly, in embodiments, a subject has a baseline RHI that is ≥ 10 (e.g., at least about 10-20, such as at least 10 or at least 20). In embodiments, methods described herein achieve a decrease in MCS (e.g., as assessed from a baseline MCS) of at least three points and/or a decrease of at least about 20, 25, or 30% (e.g., as assessed from a baseline MCS). In embodiments, methods described herein achieve a decrease in MCS (e.g., as assessed from a baseline MCS) of at least three points. In embodiments, methods described herein achieve a decrease of at least about 30% (e.g., as assessed from a baseline mMCS). In embodiments, a decrease in mMCS is assessed after about 6-52 weeks of therapy (e.g., as described herein such as after about 6, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 or 52 weeks of therapy). In embodiments, a decrease in MCS is assessed after about 6 or 12 weeks of therapy (e.g., as described herein). In embodiments, a decrease in MCS is assessed after induction therapy (e.g., as described herein). In embodiments, a decrease in MCS is accompanied by a decrease in the rectal bleeding subscore of at least one point and/or an absolute rectal bleeding subscore that is ≤ 1 .

[000142] In embodiments, methods described herein achieve a decrease in mMCS (e.g., as assessed from a baseline mMCS) of at least two points and/or a decrease of at least about 20, 25, or 30% (e.g., as assessed from a baseline mMCS). In embodiments, methods described herein achieve a decrease in mMCS (e.g., as assessed from a baseline mMCS) of at least two points. In embodiments, methods described herein achieve a decrease in mMCS (e.g., as assessed from a baseline mMCS) of at least three points. In embodiments, methods described herein achieve a decrease of at least about 30% (e.g., as assessed from a baseline mMCS). In embodiments, a decrease in mMCS is assessed after about 6-52 weeks of therapy (e.g., as described herein such as after about 6, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 or 52 weeks of therapy). In embodiments, a decrease in mMCS is assessed after about 6 or 12 weeks of therapy (e.g., as described herein). In embodiments, a decrease in mMCS is assessed after induction therapy (e.g., as described herein). In embodiments, a decrease in mMCS is accompanied by a decrease in the rectal bleeding subscore of at least one point and/or an absolute rectal bleeding subscore that is ≤ 1 .

[000143] In embodiments, methods described herein achieve a decrease in rectal bleeding. In embodiments, methods described herein achieve a decrease in the rectal bleeding subscore of the mMCS (e.g., a baseline mMCS). In embodiments, a method achieves a decrease of at least one point in the rectal bleeding subscore of the mMCS (e.g., a baseline mMCS). In embodiments, methods described herein achieve an absolute rectal bleeding subscore of the mMCS that is 0 or 1.

[000144] In embodiments, methods described herein achieve endoscopic improvement. In embodiments, endoscopic improvement is assessed by endoscopic appearance of the mucosa. In embodiments, methods described herein achieve a MES of ≤ 1 . In embodiments, methods described herein achieve a MES of 0. In embodiments, methods described herein achieve a MES of 1.

[000145] In embodiments, methods described herein achieve a decrease in RHI (e.g., as assessed from a baseline RHI). In embodiments, a decrease in RHI is at least a decrease of one point from a baseline RHI (e.g., a decrease of at least 1-7 points such as a decrease of at least 1, 2, 3, 4, 5, 6, or 7 points from a baseline RHI). In embodiments, a decrease in RHI is at least a decrease of seven points from a baseline RHI. In embodiments, a decrease in RHI is at least a decrease of at least about 20% from a baseline RHI (e.g., a decrease of at least about 20%, 25%, 30%, 35%, 40%, 45% or 50% from a baseline RHI).

[000146] In embodiments, methods described herein achieve an absolute RHI score that is ≤ 9 (e.g., an absolute RHI score that is $\leq 9, \leq 8, \leq 7, \leq 6, \leq 5, \leq 4$, or ≤ 3). In embodiments, methods described herein achieve an RHI score where subscores of lamina propria neutrophils and neutrophils is equal to 0 (e.g., with no ulcers or erosions).

[000147] In embodiments, methods described herein achieve an absolute RHI score that is ≤ 3 . In embodiments, methods described herein achieve an RHI score where subscores of lamina propria neutrophils and neutrophils is equal to 0 (e.g., with no ulcers or erosions).

[000148] In embodiments, methods described herein achieve mucosal healing. In embodiments, mucosal healing is characterized by a MES of 0 and/or a RHI ≤ 3 . In embodiments, a RHI ≤ 3 reflects subscores of 0 for lamina propria neutrophils score and neutrophils in the epithelium score and without ulcers or erosions. In embodiments, methods described herein achieve remission of disease.

[000149] In embodiments, methods described herein achieve an absolute rectal bleeding subscore of the mMCS that is 0, a stool frequency subscore of the mMCS that is 0 or 1; no individual subscore of the mMCS that is greater than 1; and/or a MES of 0; and/or a RHI ≤ 2 or ≤ 3 . In embodiments, a subject in remission has a MCS score of ≤ 2 and no subscore higher than 1.

[000150] In embodiments, methods described herein achieve an absolute rectal bleeding subscore of the mMCS that is 0.

[000151] In embodiments, methods described herein achieve a stool frequency subscore that is 0 or 1.

[000152] In embodiments, methods described herein achieve a MES of 0.

[000153] In embodiments, methods described herein achieve a RHI ≤ 2 or ≤ 3 .

[000154] In embodiments, methods described herein achieve a RHI ≤ 2 . In embodiments, a RHI ≤ 2 is with scores of 0 for lamina propria neutrophils score and neutrophils in the epithelium score, and without ulcers or erosions.

[000155] In embodiments, methods described herein achieve a RHI ≤ 3 . In embodiments, a RHI ≤ 3 is with scores of 0 for lamina propria neutrophils score and neutrophils in the epithelium score, and without ulcers or erosions.

[000156] In embodiments, a subject in remission has a MCS score of ≤ 2 and no subscore higher than 1.

Crohn's Disease

[000157] In embodiments, a compound of Formula (I) (e.g., a compound of any one of Formulae (Ia), (Ib), and (Ic) such as a compound of Formula (VI)), or a pharmaceutically acceptable salt thereof, can be used in methods to treat Crohn's disease in a subject in need thereof.

[000158] In one aspect, the invention features a method of treating Crohn's disease in a subject in need thereof. In embodiments, a method comprises administering a compound of Formula (I) (e.g., a compound of any one of Formulae (Ia), (Ib), and (Ic) such as a compound of Formula (VI)), or a pharmaceutically acceptable salt thereof, to the subject. In embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered in an

amount of about 50-400 mg. In embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered once daily. In embodiments, a compound of Formula (I) or a pharmaceutically acceptable salt thereof is administered twice daily.

[000159] In embodiments, a compound of Formula (I-A) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof. In embodiments, a compound of Formula (I-A) or a pharmaceutically acceptable salt thereof is administered in an amount of about 50-400 mg. In embodiments, a compound of Formula (I-A) or a pharmaceutically acceptable salt thereof is administered once daily (e.g., about 100 mg or about 200 mg once daily). In embodiments, a compound of Formula (I-A) or a pharmaceutically acceptable salt thereof is administered twice daily (e.g., about 100 mg or about 200 mg twice daily). In embodiments, about 100 mg of a compound of Formula (I-A) is administered twice daily. In embodiments, about 200 mg of a compound of Formula (I-A) is administered twice daily.

[000160] In embodiments, a compound of Formula (II-A), (III-A), (IV-A), or (V-A) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof. In embodiments, a compound of Formula (II-A), (III-A), (IV-A), or (V-A) or a pharmaceutically acceptable salt thereof is administered in an amount of about 50-400 mg. In embodiments, a compound of Formula (II-A), (III-A), (IV-A), or (V-A) or a pharmaceutically acceptable salt thereof is administered once daily (e.g., about 100 mg or about 200 mg once daily). In embodiments, a compound of Formula (II-A), (III-A), (IV-A), or (V-A) or a pharmaceutically acceptable salt thereof is administered twice daily (e.g., about 100 mg or about 200 mg twice daily). In embodiments, about 100 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A) is administered twice daily. In embodiments, about 200 mg of a compound of Formula (II-A), (III-A), (IV-A), or (V-A) is administered twice daily.

[000161] In embodiments, a compound of Formula (VI) or a pharmaceutically acceptable salt thereof is administered to a subject in need thereof. In embodiments, a compound of Formula (VI) or a pharmaceutically acceptable salt thereof is administered in an amount of about 50-400 mg. In embodiments, a compound of Formula (VI) or a pharmaceutically acceptable salt thereof is administered once daily (e.g., about 100 mg or about 200 mg once daily). In embodiments, a compound of Formula (VI) or a pharmaceutically acceptable salt thereof is administered twice daily (e.g., about 100 mg or about 200 mg twice daily). In

embodiments, about 100 mg of a compound of Formula (VI) is administered twice daily. In embodiments, about 200 mg of a compound of Formula (VI) is administered twice daily.

[000162] In embodiments, Crohn's disease is moderate to severe Crohn's disease. In embodiments, Crohn's disease is moderate Crohn's disease. In embodiments, Crohn's disease is severe ulcerative colitis.

[000163] In embodiments, Crohn's disease is moderately to severely active Crohn's disease. In embodiments, Crohn's disease is moderately active Crohn's disease. In embodiments, Crohn's disease is severely active Crohn's disease.

Exemplary Embodiments

[000164] The following examples are set forth to assist in understanding the invention and should not be construed as specifically limiting the invention described and claimed herein. Such variations of the invention, including the substitution of all equivalents now known or later developed, that would be within the purview of those skilled in the art, and changes in formulation or changes in experimental design, are to be considered to fall within the scope of the invention incorporated herein.

[000165] Certain examples below relate to methods for treating or preventing a disease responsive to an $\alpha 4\beta 7$ integrin inhibitor by administering a compound of formula (I), (Ia), (Ib), and/or (Ic) to a human in need of such treatment.

EXAMPLES

[000166] Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, polymers of the present invention may also be optically active. The present invention contemplates all such compounds, including cis- and trans-isomers, *R*- and *S*-enantiomers, diastereomers, (D)-isomers, (L)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are intended to be included in this invention.

[000167] If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

Examples

Abbreviations

Abbreviation	Chemical Name
Ac	acetyl
ACN	Acetonitrile
BINAP	(2,2'-bis(diphenylphosphino)-1,1'-binaphthyl)
Boc	tert-butyloxycarbonyl
Bu	butyl
CBS	N-cyclohexyl-2-benzothiazolesulfenamide
cod	cyclooctadiene
Cp	cyclopentadienyl
DAST	diethylaminosulfur trifluoride
dba	dibenzylideneacetone
DCM	dichloromethane
DCE	Dichloroethane
Dess-Martin, Dess-Martin periodinane	1,1,1-triacetoxy-1,1-dihydro-1,2-benzodioxo-3 (1 H)-one
DIAD	diisopropyl azodicarboxylate
DIEA	N,N-diisopropylethylamine

DIPEA	N,N-diisopropylethylamine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
dppf	1,1'-bis(diphenylphosphino)ferrocene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray ionization
Et	Ethyl
FA	Formic acid
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HMDS	Hexamethyldisilazyl
HOBt	Hydroxy benzotriazole
HPLC	High performance liquid chromatography
hr	hour
Hz	Hertz
iPr	Isopropyl
LAH	Lithium aluminum hydride
LDA	lithium diisopropyl amide
Me	Methyl
Ms	Methanesulfonyl
MS	Mass spectrometry
NBS	N-bromosuccinimide
NMR	Nuclear Magnetic Resonance
prep-HPLC	preparative high performance liquid chromatography
Qphos	pentaphenyl(di-tert-butylphosphino)ferrocene
Selectfluor	1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
RT	room temperature
SFC	supercritical fluid chromatography
t-Bu	tertiary-butyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin layer chromatography
TMS	trimethylsilyl
Xphos Pd G2	Chloro(2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl)[2-(2'-amino-1,1'-biphenyl)]palladium(II)

Analytical Methods, Materials, and Instrumentation

[000168] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Default methods, materials and instrumentation are listed below.

HNMR instrumental information:

[000169] Proton nuclear magnetic resonance (NMR) spectra were obtained on one of the following instruments:

[000170] BRUKER, AVANCE III 500MHZ, PROBHD 5 mm PABBO BB-, PULPROG zg30, TD 65536, NS 8, DS 0, SWH 10330.578 Hz, D1 1.00000000 sec, NUC1 1H, P1 13.72 usec, PL1W 13.34460926 W, SFO1 500.1330885 MHz

[000171] BRUKER, AVANCE III 400MHZ, PROBHD 5 mm PABBO BB/, PULPROG zg30, TD 65536, NS 8, DS 2, SWH 8223.685 Hz, D1 1.00000000 sec, SFO1 400.1324710 MHz, NUC1 1H, P1 15.00 usec, PL1W 11.00000000 W

[000172] Spectra are given in ppm (d) and coupling constants, J, are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard.

LCMS instrumental information and analysis method:

[000173] Compounds were analyzed using LC/MS conditions, with UV detector monitoring at 214 nm and 254 nm, and mass spectrometry scanning 110-1500 amu in ESI+ ionization mode.

[000174] LCMS A: column: XBridge C18, 4.6 X 50 mm, 3.5 µm; mobile phase: A water (10 mM ammonium hydrogen carbonate), B CH₃CN; gradient: 5%-95% B in 1.4 min, then 1.7 min hold; flow rate: 1.8 mL/min; oven temperature 45 °C.

[000175] LCMS B: column: Sunfire C18, 4.6 X 50 mm, 3.5 µm; mobile phase: A: water(0.1%FA) B: ACN(0.1%FA); gradient: 5%-95% B in 1.5 min, then 1.5 min hold; flow rate: 2 mL/min; oven temperature 50 °C.

[000176] LCMS C: column: Sunfire C18, 4.6 X 50 mm, 3.5 µm; mobile phase: A: water(0.01%TFA) B: ACN(0.01%TFA); gradient: 5%-95% B in 1.5 min, then 1.7 min hold; flow rate: 2 mL/min; oven temperature 50 °C.

[000177] LCMS D: column: Poroshell 120 EC-C18, 3.0 X 30 mm, 2.7 µm; mobile phase: A: water(0.01%TFA) B: ACN(0.01%TFA); gradient: 5%-95% B in 0.8 min, then 1.0 min hold; flow rate: 2 mL/min; oven temperature 50 °C.

Prep HPLC methods:

[000178] Crude samples were dissolved in MeOH and purified by prep HPLC using a Gilson 215 instrument, detection wavelength 214 nm:

[000179] Prep HPLC A: column: Xtimate Prep C18, 21.2 * 250 mm, 10 µm; mobile phase: A water (10 mM ammonium hydrogen carbonate), B CH₃CN; gradient elution as in text; flow rate: 20 mL/min.

[000180] Prep HPLC B: column: Boston pHlex ODS, 21.2 * 250 mm, 10 µm; mobile phase: A water (10 mM formic acid), B CH₃CN; gradient elution as in text; flow rate: 20 mL/min.

[000181] Prep HPLC C: column: XBridge OBD C18, 19 * 100 mm, 5 µm; mobile phase: A water, B CH₃CN; gradient elution as in text; flow rate: 20 mL/min.

Prep Chiral SFC Methods:

[000182] Racemic products were separated to individual enantiomers by chiral Prep SFC using an SFC-80 (Thar, Waters) instrument, detection wavelength 214 nm:

[000183] Prep chiral SFC A: column: (R,R)-Whelk-O1, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000184] Prep chiral SFC B: column: AD 20*250mm, 10 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000185] Prep chiral SFC C: column: AS 20*250mm, 10 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000186] Prep chiral SFC D: column: OD 20*250mm, 10 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000187] Prep chiral SFC E: column: Cellulose-SC 20*250mm, 10 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000188] Prep chiral SFC F: column: OZ 20*250mm, 10 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000189] Prep chiral SFC G: column: IC 20*250mm, 10 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000190] Prep chiral SFC H: column: (S,S)-Whelk-O1, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000191] Prep chiral SFC I: column: OX-H, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000192] Prep chiral SFC J: column: IG, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000193] Prep chiral SFC K: column: IH, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000194] Prep chiral SFC L: column: OJ, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000195] Prep chiral SFC M: column: Amylose-C Neo, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000196] Prep chiral SFC N: column: ID, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000197] Prep chiral SFC O: column: AY-H, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

[000198] Prep chiral SFC P: column: IK, 20*250mm, 5 µm (Daicel), column temperature: 35 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia)= 60/40, flow rate: 80 g/min, back pressure: 100 bar.

Prep Chiral HPLC Methods

[000199] Racemic products were separated into individual enantiomers by Prep chiral HPLC using an Gilson-281 (Thar, Waters) instrument (detection wavelength 214/254 nm):

[000200] Prep chiral HPLC A: Column: IE, 20*250mm, 10 µm (Daicel). Column temperature: 35 °C. Mobile phase: n-Hexane (0.1% DEA) /ethanol(0.1% DEA). Flow rate: 38 g/min. Back pressure: 100 bar.

[000201] Prep chiral HPLC B: Column: OJ-H, 20*250mm, 10 µm (Daicel). Column temperature: 35 °C. Mobile phase: n-Hexane (0.1% DEA) /ethanol(0.1% DEA). Flow rate: 38 g/min. Back pressure: 100 bar.

Analytical Chiral SFC Methods

[000202] Chiral products were analyzed by chiral SFC using an SFC-80 (Thar, Waters) instrument, detection wavelength 214 nm:

[000203] Chiral SFC A: column: (R,R)-Whelk-O1, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000204] Chiral SFC B: column: AD 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000205] Chiral SFC C: column: AS 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000206] Chiral SFC D: column: OD 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000207] Chiral SFC E: column: Cellulose-SC 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000208] Chiral SFC F: column: OZ 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000209] Chiral SFC G: column: IC 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO₂/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000210] Chiral SFC H: column: (S,S)-Whelk-O1, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000211] Chiral SFC I: column: OX-H, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000212] Chiral SFC J: column: IG, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000213] Chiral SFC K: column: IH, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000214] Chiral SFC L: column: OJ, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000215] Chiral SFC M: column: Amylose-C Neo, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000216] Chiral SFC N: column: ID, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000217] Chiral SFC O: column: AY, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

[000218] Chiral SFC P: column: IK, 4.6*100mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: CO2/methanol (0.2% methanol ammonia), isocratic elution as in text, flow rate: 4 g/min, back pressure: 120 bar.

Analytical Chiral HPLC Methods

[000219] Chiral HPLC A: column: OJ-H 4.6*250mm, 5 µm (Daicel), column temperature: 40 °C, mobile phase: n-Hexane (0.1% DEA) /ethanol(0.1% DEA), flow rate: 1 g/min

[000220] Chiral HPLC B: column: IE 4.6*250mm, 5 μ m (Daicel), column temperature: 40 °C, mobile phase: n-Hexane (0.1% DEA) /ethanol(0.1% DEA), flow rate: 1 g/min

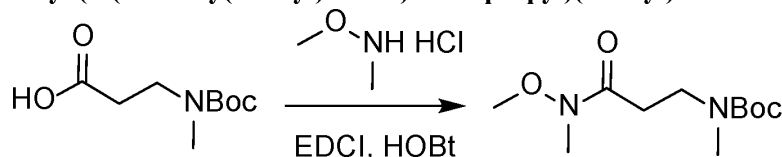
[000221] When chiral compounds are separated by HPLC or SFC, the absolute stereochemistry of the products is arbitrarily assigned. Unless otherwise noted, the first eluting peak from a separation is noted as P1, the second as P2, etc. In some cases, chiral intermediates have also been prepared and separated. In this case, 1P2 is used to denote a first eluting intermediate used to prepare a compound of the invention isolated as the second eluting peak, etc.

[000222] When isomers of compounds containing chiral centers were separated, the absolute stereochemistry of the products was not always determined. In some cases, stereochemistry was arbitrarily assigned in order to aid in the depiction of compounds and chemical schemes. Someone skilled in the art will recognize that if the stereochemistry of the starting materials different than shown arbitrarily, the stereochemistry of intermediates and final products may also be different than those drawn in any particular scheme or table.

Synthetic Schemes

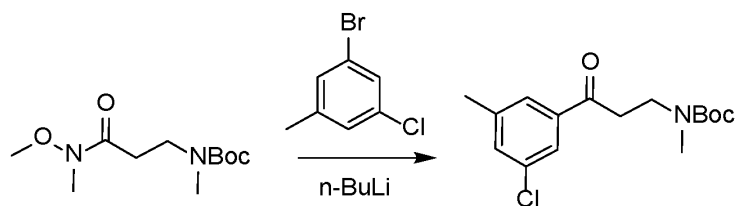
Example 1: Preparation of Compounds 24-P1 and 24-P2

Step 1: tert-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)(methyl)carbamate



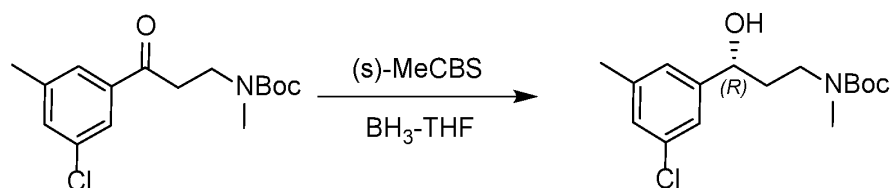
[000223] To a solution of 3-((tert-butoxycarbonyl)(methyl)amino)propanoic acid (15 g, 73.9 mmol, 1.0 eq.), N,O-dimethylhydroxylamine hydrochloride (7.6 g, 77.6 mmol, 1.1 eq.), 1-Hydroxybenzotriazole (10.0 g, 73.9 mmol, 1.0 eq.) and trimethylamine (16.4 g, 162.5 mmol, 2.2 eq.) in chloroform (100 ml) was added 1-Ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (15.6 g, 81.3 mmol, 1.1 eq.). The reaction was stirred at 50 °C for 1 hr, then diluted with water (100 mL) and extracted with dichloromethane (2 x 100 mL). The organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in *vacuo*. Crude residue was purified by silica gel column chromatography (95:5 dichloromethane: MeOH) to give tert-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)(methyl)carbamate as a yellow solid (13.6 g, 74.7%) (ESI 147.2 [M-Boc+H]⁺).

Step 2: tert-butyl (3-(3-chloro-5-methylphenyl)-3-oxopropyl)(methyl)carbamate



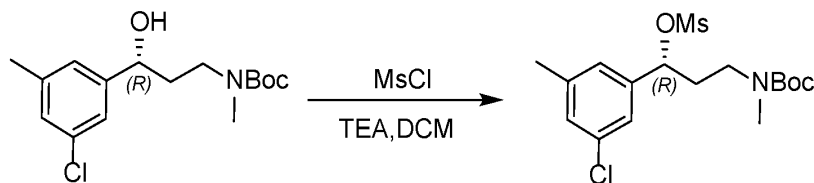
[000224] To a solution of 1-bromo-3-chloro-5-methylbenzene (13.6 g, 66.4 mmol, 1.2 eq.) in anhydrous THF (100 mL) at -78 °C was added n-BuLi (26.6 mL, 2.5 M in hexane, 66.4 mmol, 1.2 eq.) dropwise. The reaction was stirred at -78 °C for 30 min. A solution of tert-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)(methyl)carbamate (13.6 g, 55.3 mmol, 1.0 eq.) in tetrahydrofuran (50 mL) was then added. After stirring at -78 °C for another 1 hr., the reaction mixture was quenched with saturated NH₄Cl solution (100 mL) and extracted with EtOAc (2 x 100 mL). Combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (12:1 petroleum ether: EtOAc) to give tert-butyl (3-(3-chloro-5-methylphenyl)-3-oxopropyl)(methyl)carbamate as a yellow solid (9.5 g, 55.0%) (ESI 312.1 [M-Boc+H]⁺).

Step 3: tert-butyl (R)-(3-(3-chloro-5-methylphenyl)-3-hydroxypropyl)(methyl)carbamate



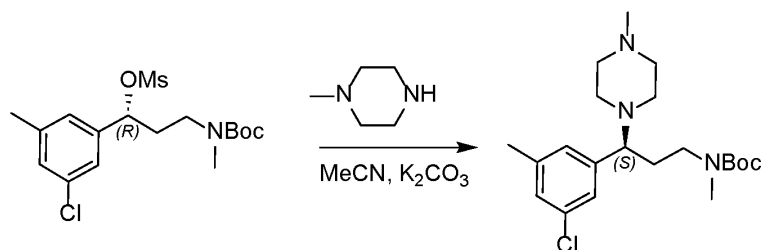
[000225] To a solution of tert-butyl (3-(3-chloro-5-methylphenyl)-3-oxopropyl)(methyl)carbamate (9.5 g, 30.4 mmol, 1.0 eq.) and (S)-3,3-Diphenyl-1-methylpyrrolidino[1,2-c]-1,3,2-oxazaborole (4.6 mL, 1 M in toluene, 4.6 mmol, 0.15 mmol) in anhydrous THF (100 mL) at -78 °C was added borane (1 M in THF, 35 mL, 35 mmol, 1.1 eq.) dropwise. The reaction was allowed to warm to 0 °C and stirred for 1 hr, quenched with methanol (10 mL) and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give tert-butyl (R)-(3-(3-chloro-5-methylphenyl)-3-hydroxypropyl)(methyl)carbamate as a yellow oil (8.1 g, 84.9%) (ESI 336.1 (M+Na)⁺).

Step 4: (R)-3-((tert-butoxycarbonyl)(methyl)amino)-1-(3-chloro-5-methylphenyl)propyl methanesulfonate



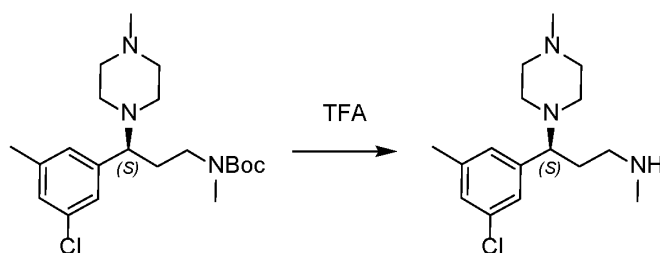
[000226] To a solution of tert-butyl (R)-3-(3-chloro-5-methylphenyl)-3-hydroxypropyl(methyl)carbamate (4.0 g, 12.8 mmol, 1.0 eq.) and trimethylamine (2.58 g, 25.6 mmol, 2.0 mmol) in dichloromethane (70 mL) at 0 °C was added methanesulfonyl chloride (1.46 g, 12.8 mmol, 1.0 eq.) dropwise. The reaction was stirred at 0 °C for 1 hr, quenched with saturated NaHCO₃ solution (100 mL) and extracted with EA (2 x 200 mL). Combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give (R)-3-((tert-butoxycarbonyl)(methyl)amino)-1-(3-chloro-5-methylphenyl)propyl methanesulfonate as a yellow oil (3.5 g, 2.6 mmol, crude) (ESI 196.1 (M-OMs-Boc)⁺). Crude product was used as is in the subsequent step.

Step 5: tert-butyl (S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl(methyl)carbamate



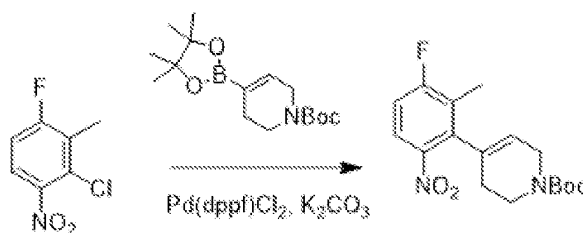
[000227] To a solution of (R)-3-((tert-butoxycarbonyl)(methyl)amino)-1-(3-chloro-5-methylphenyl)propyl methanesulfonate (3.5 g, 2.6 mmol, crude, 1.0 eq.) in acetonitrile (20 mL) was added 1-methylpiperazine (2.6 g, 26 mmol, 10.0 eq.) followed by K₂CO₃ (3.59 g, 26 mmol, 10.0 eq.). The reaction mixture was stirred at 80 °C for 1 hr, then diluted with water (200 mL) and extracted with EtOAc (2 x 100 mL). Combined organic layers were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (95:5 dichloromethane: MeOH) to give tert-butyl (S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl(methyl)carbamate as a yellow oil (420 mg, 40.8%) (ESI 396.2 [M+H]⁺).

Step 6: (S)-3-(3-chloro-5-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propan-1-amine



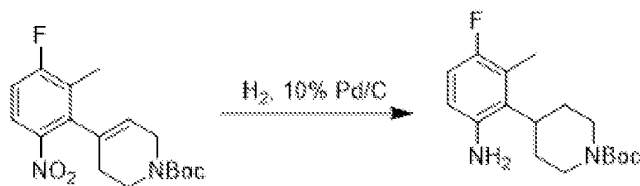
[000228] To a solution of tert-butyl (S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl(methyl)carbamate (420 mg, 1.1 mmol, 1.0 eq.) in dichloromethane (1 mL) was added trifluoroacetic acid (1 mL, 13.1 mmol, 11.9 eq.). The reaction mixture was stirred at RT for 30 min, then concentrated *in vacuo* to obtain (S)-3-(3-chloro-5-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propan-1-amine as a yellow oil (628 mg, 1.1 mmol, crude). (ESI 296.2 $[M+H]^+$). Crude product was used as is in the subsequent step.

Step 7: tert-butyl 4-(3-fluoro-2-methyl-6-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate



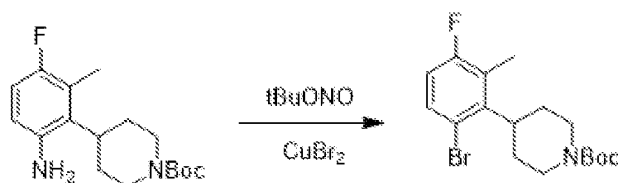
[000229] 2-chloro-4-fluoro-3-methyl-1-nitrobenzene (20 g, 105.5 mmol, 1.0 eq), tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (48.9 g, 158.3 mmol, 1.5 eq.), K_2CO_3 (43.7 g, 316.5 mmol, 3.0 eq) and $Pd(dppf)Cl_2$ (7.7 g, 10.55 mmol, 0.1 eq) were suspended in a mixture of dioxane (200 mL) and water (20 mL). Reaction was stirred overnight at 110 °C under N_2 atmosphere. Contents were then poured into 300 mL water and extracted with EtOAc (3 x 200 mL). Combined organic extracts were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (15:1 petroleum ether: EtOAc) to give tert-butyl 4-(3-fluoro-2-methyl-6-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate as a yellow solid (23.5 g, 66%) (ESI 281.1 $[M+H-tButyl]^+$).

Step 8: tert-butyl 4-(6-amino-3-fluoro-2-methylphenyl)piperidine-1-carboxylate



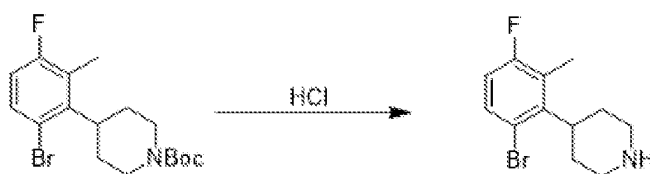
[000230] To a solution of tert-butyl 4-(3-fluoro-2-methyl-6-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (12 g, 29.8 mmol, 1.0 eq) in EtOH (150 mL) was added 10% Pd on carbon (3 g, 1.5 mmol, 0.025 eq.). Reaction was stirred at RT under H₂ atmosphere for 72 hr. Upon completion, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to give tert-butyl 4-(6-amino-3-fluoro-2-methylphenyl)piperidine-1-carboxylate as a brown oil (7.7 g, 70%) (ESI 283.1 [M+H-tButyl]⁺). Crude product was used directly in the subsequent step without further purification.

Step 9: tert-butyl 4-(6-bromo-3-fluoro-2-methylphenyl)piperidine-1-carboxylate



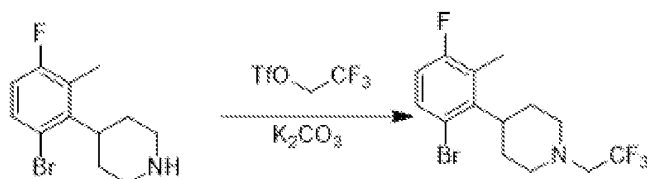
[000231] Tert-butyl 4-(6-amino-3-fluoro-2-methylphenyl)piperidine-1-carboxylate (12 g, 32.3 mmol, 1.0 eq) was dissolved in acetonitrile (100 mL). Tert-butyl nitrite (5 g, 48.45 mmol, 1.5 eq) was then added dropwise at -10°C, followed by the addition of CuBr₂ (5.4 g, 24.2 mmol, 0.75 eq) in acetonitrile (50 mL). After stirred at -10°C for 10min, the reaction mixture was allowed to warm to RT. Stirring was continued at RT for 6 hr. Reaction mixture was then diluted with dichloromethane (100 mL) and washed with brine (100 mL). Organic layer was separated, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (99:1 dichloromethane: MeOH) to give tert-butyl 4-(6-bromo-3-fluoro-2-methylphenyl)piperidine-1-carboxylate as a yellow oil (7.5 g, 52%) (ESI 316.1 [M+H-tButyl]⁺).

Step 10: 4-(6-bromo-3-fluoro-2-methylphenyl)piperidine hydrochloride



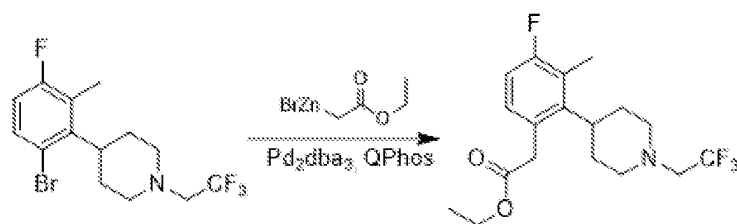
[000232] To a solution of tert-butyl 4-(6-bromo-3-fluoro-2-methylphenyl)piperidine-1-carboxylate (7.5 g, 20.2 mmol, 1.0 eq) in dichloromethane (10 mL) was added HCl in dioxane (4M, 20 ml, 80 mmol, 4.0 eq.). The mixture was stirred at RT for 1hr. Reaction was then concentrated *in vacuo* to give 4-(6-bromo-3-fluoro-2-methylphenyl)piperidine hydrochloride as a white solid (8.3 g, 26.2 mmol, crude) (ESI 272.1[M+H]⁺).

Step 11: 4-(6-bromo-3-fluoro-2-methylphenyl)-1-(2,2,2-trifluoroethyl)piperidine



[000233] To a solution of 4-(6-bromo-3-fluoro-2-methylphenyl)piperidine hydrochloride (8.3 g, 27 mmol, 1.0 eq) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (9.4 g, 40.5 mmol, 1.5 eq) in acetonitrile (100 ml) was added K₂CO₃ (11.2 g, 81 mmol, 3.0 eq). The reaction was stirred at 80°C for 3hr. After completion, the mixture was filtered and concentrated under reduced pressure. Crude residue was purified by silica gel column chromatography (99:1 dichloromethane: MeOH) to give 4-(6-bromo-3-fluoro-2-methylphenyl)-1-(2,2,2-trifluoroethyl)piperidine as a yellow oil (6 g, 52%) (ESI 354.1 [M+H]⁺).

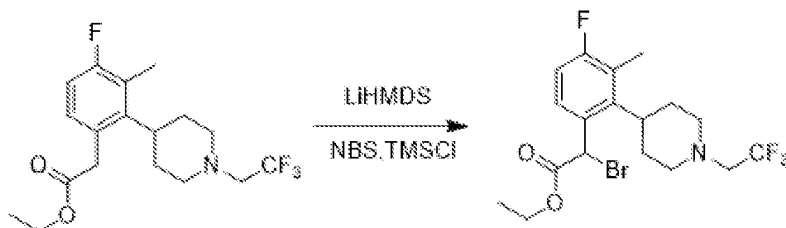
Step 12: ethyl 2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate



[000234] To a suspension of 4-(6-bromo-3-fluoro-2-methylphenyl)-1-(2,2,2-trifluoroethyl)piperidine (6 g, 17 mmol, 1.0 eq) in THF (50 mL) were added Pd₂(dba)₃ (1.56 g, 1.7 mmol, 0.1 eq) and Qphos (362.6 mg, 0.51 mmol, 0.03 eq). (2-ethoxy-2-oxoethyl)zinc(II) bromide solution (1M in THF, 51mL, 51 mmol, 3.0 eq.) was then added, and the reaction was stirred at 65 °C for 1 hr. under nitrogen. Contents were then poured into 50 mL saturated aqueous NH₄Cl solution and extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Crude

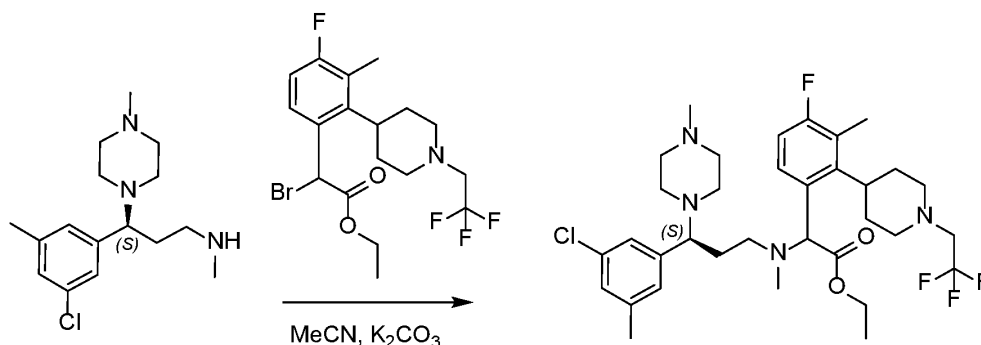
residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give ethyl 2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate as a colorless oil (4 g, 65%) (ESI 362.1 $[M+H]^+$).

Step 13: ethyl 2-bromo-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate



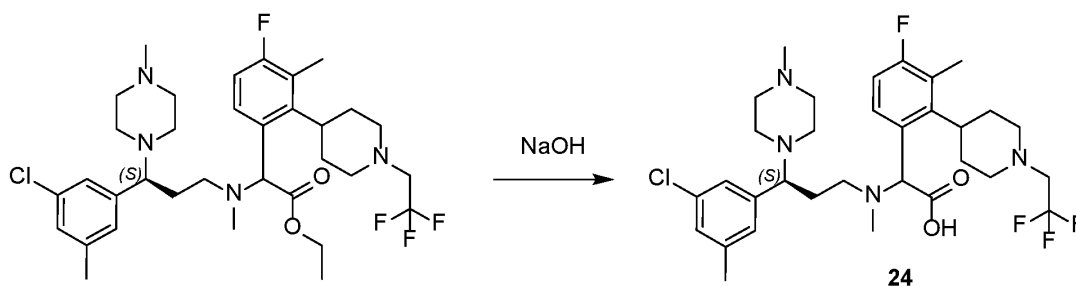
[000235] To a solution of ethyl 2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate (4.62 g, 12.8 mmol, 1.0 eq) in THF (60 mL) at -78°C , LiHMDS (1M in THF, 38 mL, 38 mmol, 3.0eq) was added dropwise. The reaction was stirred at -78°C for 0.5 hr. TMSCl (4.8mL, 38 mmol, 3.0 eq) was then added dropwise, and stirring was continued at -78°C for another 15min. A solution of NBS (5.7 g, 32 mmol, 2.5 eq) in THF (50 mL) was added dropwise. The reaction was stirred at -78°C for another 1 hr., then warmed to 0°C , quenched with saturated aqueous NH_4Cl solution (150 ml), and extracted with EtOAc (2×150 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate as a yellow solid (4.1 g, 73.2%) (ESI 440.1 $[M+H]^+$).

Step 14: ethyl 2-(((S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate



[000236] To a solution of (S)-3-(3-chloro-5-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propan-1-amine (314 mg, 0.53 mmol, crude, 1.0 eq.) in acetonitrile (5 mL) was added K_2CO_3 (512 mg, 3.71 mmol, 5.0 eq.). The mixture was stirred at RT for 15 min. Ethyl 2-bromo-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate (210 mg, 0.48 mmol, 0.9 eq.) was then added. Stirring was continued at 80 °C for another 1 hr, then filtered and concentrated under reduced pressure. Crude residue was purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methylamino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate as a yellow oil (260 mg, 82.7%) . (ESI 655.3 $[M+H]^+$).

Step 15: 2-(((S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methylamino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid (Compound 24)



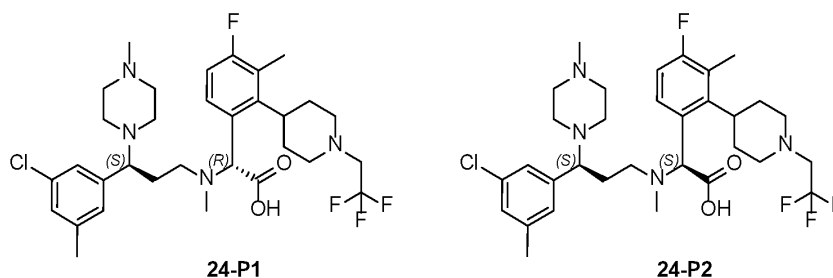
[000237] To a solution of ethyl 2-(((S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methylamino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate (260 mg, 0.4 mmol, 1.0 eq.) in ethanol (4.5 mL) and water (1.5 mL) was added NaOH (80 mg, 2.0 mmol, 5.0 eq.). The reaction was stirred at 80 °C for 16 hr. After completion, the reaction pH was adjusted to ~5 - 6 with 1N HCl. Solvents were removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH_3CN) to give

diastereomeric product **24** as white solid (200 mg, 80.0%). Diastereomers were further separated by prep chiral SFC A to give **24-P1** (66 mg) and **24-P2** (73 mg).

[000238] Compound 24-P1 LC/MS ESI 627.3 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.56 (s, 1H), 7.15 (s, 1H), 7.10 – 6.89 (m, 3H), 4.76 (s, 1H), 3.87 – 3.64 (m, 1H), 3.26 – 3.00 (m, 6H), 2.93 – 2.50 (m, 12H), 2.44 (s, 4H), 2.31 (d, $J = 16.1$ Hz, 9H), 1.98 – 1.50 (m, 4H).

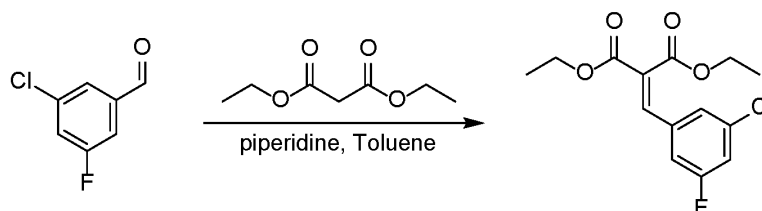
Compound 24-P2 LC/MS ESI 627.3 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.51 (d, $J = 6.5$ Hz, 1H), 7.23 – 6.80 (m, 4H), 4.75 (s, 1H), 3.55 – 3.38 (m, 1H), 3.27 – 2.99 (m, 6H), 2.98 – 2.67 (m, 6H), 2.66 – 2.49 (m, 6H), 2.45 (s, 4H), 2.30 (s, 8H), 2.18 – 2.06 (m, 1H), 1.92 – 1.38 (m, 4H).

[000239] 24-P1 and **24-P2** were assigned as (R)-2-(((S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid and (S)-2-(((S)-3-(3-chloro-5-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid, respectively.

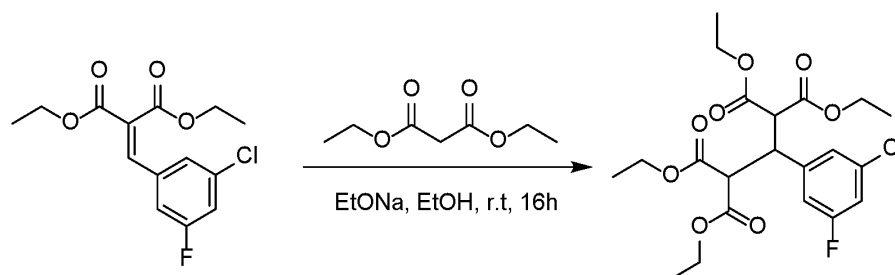


Example 2: Preparation of Compounds 62-P1 and 62-P2

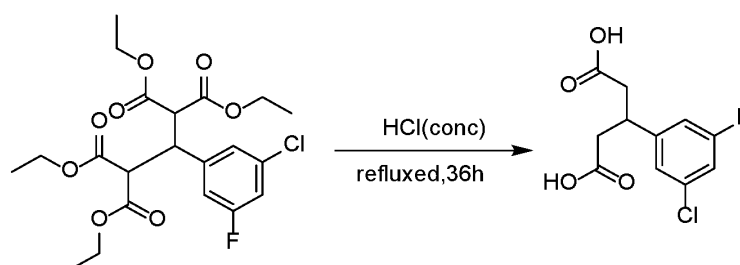
Step 1: diethyl 2-(3-chloro-5-fluorobenzylidene)malonate



[000240] A solution of 3-chloro-5-fluorobenzaldehyde (30.0 g, 0.19 mol), diethyl malonate (45.6 g, 0.29 mol) and piperidine (3.2 g, 38.0 mmol) in toluene (300 mL) was stirred at 110 °C for 16 hrs. The reaction mixture was concentrated under reduce pressure. The residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give diethyl 2-(3-chloro-5-fluorobenzylidene)malonate as colorless oil (51.1 g, 89 %) (ESI 301.0 $[M+H]^+$).

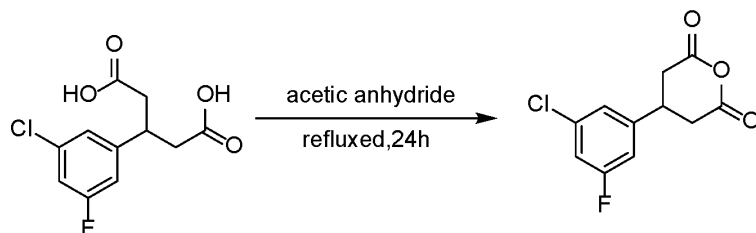
Step 2: tetraethyl 2-(3-chloro-5-fluorophenyl)propane-1,1,3,3-tetracarboxylate

[000241] To a solution of diethyl malonate (41.5 g, 0.3 mol) in EtOH(800 mL) was added EtONa(18.2 g, 0.26 mmol) and the reaction mixture was stirred at RT for 2hr. Then diethyl 2-(3-chloro-5-fluorobenzylidene) malonate (38.9 g, 0.13 mol) was added and stirred at RT for 16 hours. The reaction was concentrated under reduce pressure, diluted with saturated NH_4Cl , extracted with EtOAc. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to give tetraethyl 2-(3-chloro-5-fluorophenyl)propane-1,1,3,3-tetracarboxylate as colorless oil (60.1 g, 67 %) (ESI 461.1[M+H]⁺).

Step 3: 3-(3-chloro-5-fluorophenyl)pentanedioic acid

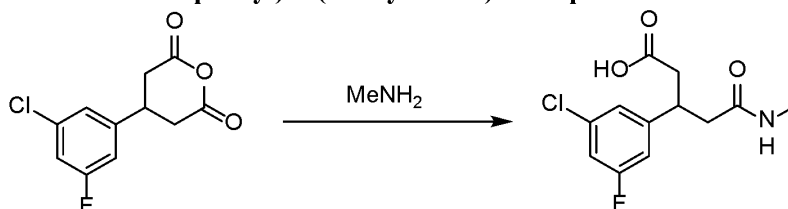
[000242] A mixture of tetraethyl 2-(3-chloro-5-fluorophenyl) propane-1,1,3,3-tetracarboxylate (180.0 g, 0.13 mol) in 36% aqueous HCl(700 mL) was stirred at 130 °C for 36 hours. The mixture was cooled and stirred at 0 °C for 1 hr. The solid formed was filtered and collected to give 3-(3-chloro-5-fluorophenyl) pentanedioic acid as a white solid (15.0 g, 63%) (ESI 283.0 [M+Na]⁺).

Step 4-(3-chloro-5-fluorophenyl)dihydro-2H-pyran-2,6(3H)-dione



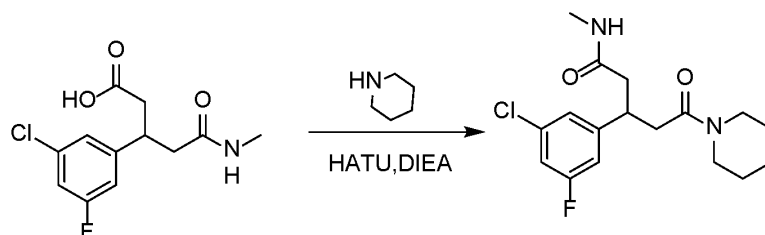
[000243] A solution of 3-(3-chloro-5-fluorophenyl) pentanedioic acid (15.0 g, 57.7 mmol) in acetic anhydride (50 mL) was stirred at 130 °C for 40 hr. The mixture was concentrated under reduced pressure. The residue was triturated with EtOAc (150 mL). The solid formed was filtered and collected to give 4-(3-chloro-5-fluorophenyl) dihydro-2H-pyran-2,6(3H)-dione as a white solid (14.0 g, 95%) (ESI 243.1 (M+H)⁺).

Step 5: 3-(3-chloro-5-fluorophenyl)-5-(methylamino)-5-oxopentanoic acid



[000244] To a solution of 4-(3-chloro-5-fluorophenyl)dihydro-2H-pyran-2,6(3H)-dione (13.0 g, 53.7 mmol) in THF (100mL) was added methylamine (2M in THF, 60mL, 120mmol) and the reaction was stirred at RT for 3hr. The reaction mixture was concentrated under reduce pressure and triturated with EtOAc(60 mL). The solid formed was filtered and collected to give 3-(3-chloro-5-fluorophenyl)-5-(methylamino)-5-oxopentanoic acid as white solid (6.6 g, 47%) (ESI 274.1 [M+H]⁺).

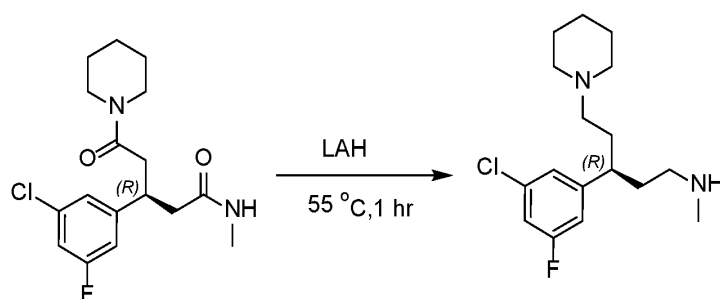
Step 6: 3-(3-chloro-5-fluorophenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide



[000245] To a solution of 3-(3-chloro-5-fluorophenyl)-5-(methylamino)-5-oxopentanoic acid (3.4 g, 12.4 mmol) in DCM (20 mL) was added piperidine (1.0 g, 12.4 mmol) and HATU(5.7 g, 14.9 mmol) followed by DIEPA(3.2 g, 24.8 mmol). The reaction was stirred at RT for 2 hr. After completion, the mixture was quenched with NH₄Cl solution (100 ml) and extracted with

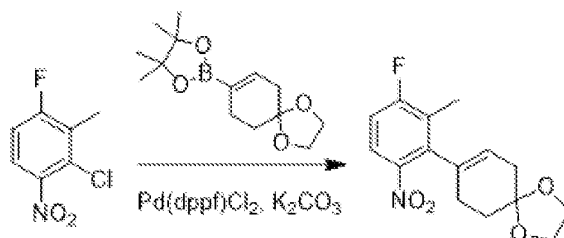
EtOAc (3x 100 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give racemic 3-(3-chloro-5-fluorophenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide as a colorless oil (3.0 g, 71%). Enantiomers were further separated by prep chiral SFC J to give the P1 fraction (R)-3-(3-chloro-5-fluorophenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide (1.3 g) and the P2 fraction (S)-3-(3-chloro-5-fluorophenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide (1.1 g) as white solids (ESI 341.2 $[\text{M}+\text{H}]^+$)

Step 7: (R)-3-(3-chloro-5-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine



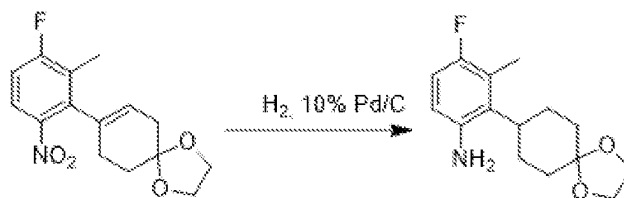
[000246] To a solution of (R)-3-(3-chloro-5-fluorophenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide (1.1 g, 3.2 mmol, 1.0 eq) in THF (20 mL) at RT was added LiAlH_4 (2M in THF, 5.0 mL, 9.7 mmol, 3.0 eq) dropwise and the reaction was stirred at 55 °C for 1 hr. After cooling to 0 °C, the reaction mixture was quenched with water (1 mL) dropwise and stirred at 0 °C for another 10 min. 15% aqueous NaOH (1 mL) and water (3 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT and stirred for another 15 min, then filtered and filtrate was concentrated *in vacuo* to give (R)-3-(3-chloro-5-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine as a white solid used directly in the next reaction (1 g, crude) (ESI 313.3 $[\text{M}+\text{H}]^+$).

Step 8: 8-(3-fluoro-2-methyl-6-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene



[000247] 2-chloro-4-fluoro-3-methylaniline (20 g, 105.5 mmol, 1.0 eq), 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (30.9 g, 116.1 mmol, 1.1 eq.), K_2CO_3 (29.2 g, 211.0 mmol, 2.0 eq) and $Pd(dppf)Cl_2$ (7.7 g, 10.55 mmol, 0.1 eq) were suspended in a mixture of dioxane (250 mL) and water (50 mL). The reaction was stirred at 110 °C overnight under nitrogen. After completion, water (300 mL) was added, and the mixture was extracted with EtOAc (3x 200 mL). Combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (6:1 petroleum ether: EtOAc) to give 8-(3-fluoro-2-methyl-6-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene as a yellow solid (27.0 g, 87%) (ESI 294.2 $[M+H]^+$).

Step 9: 4-fluoro-3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline



[000248] To a solution of 8-(3-fluoro-2-methyl-6-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (12 g, 41.0 mmol, 1.0 eq) in MeOH (200 mL) was added 10% Pd-C (12 g, 11.4mmol, 0.3 eq.). The reaction mixture was stirred at 60 °C under hydrogen atmosphere (1 atm, 3L) for 3 days. The reaction mixture was then filtered through a pad of Celite and concentrated *in vacuo*. Crude material was purified by silica gel column chromatography (5:1 petroleum ether: EtOAc) to give 4-fluoro-3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline as a yellow oil (7.1 g, 65%) (ESI 266.2 $[M+H]^+$).

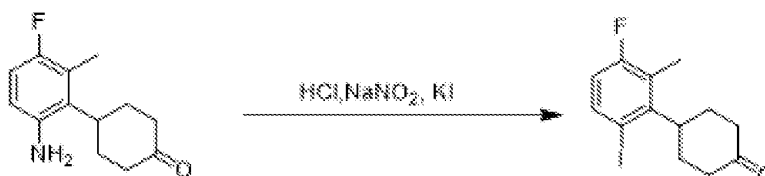
Step 10: 4-(6-amino-3-fluoro-2-methylphenyl)cyclohexan-1-one



[000249] To a solution of 4-fluoro-3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline (16.0 g, 60.3 mmol, 1.0 eq) in THF (300mL), 3M aqueous HCl (60.3 mL, 180.9 mmol, 3.0 eq) was added, and the contents were stirred at RT for 1 hr. The reaction mixture was then cooled to 0 °C, quenched with saturated aqueous $NaHCO_3$ solution (pH adjusted to ~9), and extracted with

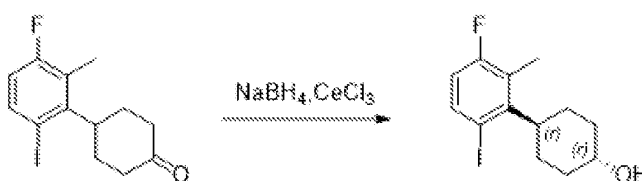
EtOAc (3x 200 mL). Combined organics were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give 4-(6-amino-3-fluoro-2-methylphenyl)cyclohexan-1-one as a yellow oil (13 g, 97%) (ESI 222.2 [M+H]⁺). Crude product was used directly in the next step.

Step 11: 4-(3-fluoro-6-iodo-2-methylphenyl)cyclohexan-1-one



[000250] To a solution of 4-(6-amino-3-fluoro-2-methylphenyl)cyclohexan-1-one (14 g, 63.3 mmol, 1.0 eq.) in THF (250 mL) at -35 °C was added aqueous HCl (6M, 26.4mL, 158.4 mmol, 2.5 eq). NaNO₂ (6.6 g in 30 mL water, 95mmol, 1.5 eq.) was then added dropwise over 15 mins. The reaction was stirred at -35 °C for 10 min. Aqueous KI solution (15.8g in 30 mL water, 95 mmol, 1.5 eq.) was then added portion wise into the mixture. Stirring was continued at -35 °C for 30 min. The reaction was allowed to warm to RT and stirred for another 1hr. Water (300 mL) and EtOAc (300 mL) were added into the reaction. Organic layer was separated, washed with saturated aqueous Na₂SO₃ (300 mL) and brine (300 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (15:1 petroleum ether: EtOAc) to give 4-(3-fluoro-6-iodo-2-methylphenyl)cyclohexan-1-one (7.5 g, 35.7%) (ESI 333.0 [M+H]⁺).

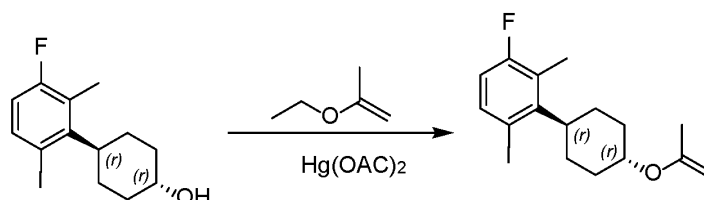
Step 12: (1r,4r)-4-(3-fluoro-6-iodo-2-methylphenyl)cyclohexan-1-ol



[000251] To a solution of 4-(3-fluoro-6-iodo-2-methylphenyl)cyclohexan-1-one (10 g, 30.1 mmol, 1.0 eq.) in THF (50 mL) and methanol (8 mL) at 0 °C was added CeCl₃ (8.9 g, 36.1 mmol, 1.2 eq.). NaBH₄ (1.4 g, 36.1 mmol, 1.2 eq.) was then added in portions. The mixture was stirred at 0 °C for 0.5 hr. The reaction was quenched with water (100 mL) at 0 °C and extracted with EtOAc (3 x 150 mL). Combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel

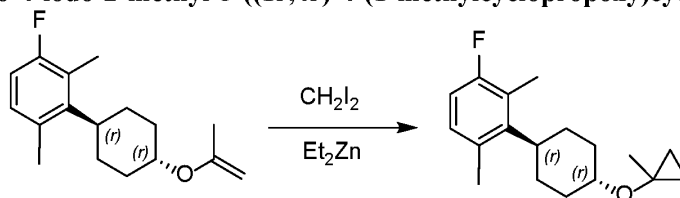
column chromatography (4:1 petroleum ether: EtOAc) to give (1*r*,4*r*)-4-(3-fluoro-6-iodo-2-methylphenyl)cyclohexan-1-ol as a white solid (8.3 g, 82.8%) (ESI 317.0 [M-OH]⁺).

Step 13: 1-fluoro-4-iodo-2-methyl-3-((1*r*,4*r*)-4-(prop-1-en-2-yloxy)cyclohexyl)benzene



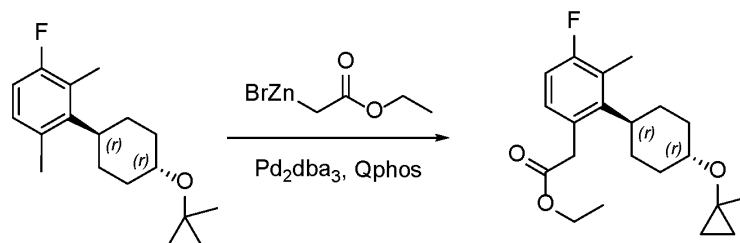
[000252] A mixture of (1*r*,4*r*)-4-(3-fluoro-6-iodo-2-methylphenyl)cyclohexan-1-ol (4.7 g, 14.1 mmol, 1.0 eq.), 2-ethoxyprop-1-ene (15 ml), Hg(OAc)₂ (1.3 g, 4.2 mmol, 0.3 eq.) at RT overnight under N₂ atmosphere. After completion, water (200 mL) was added and the mixture was extracted with dichloromethane (3 x 150 mL). Combined organics were washed with NaHCO₃ (100 ml) and brine (100 ml), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (98:1 petroleum ether: EtOAc) to give 1-fluoro-4-iodo-2-methyl-3-((1*r*,4*r*)-4-(prop-1-en-2-yloxy)cyclohexyl)benzene as a colorless oil (3.0 g, 56.7%)

Step 14: 1-fluoro-4-iodo-2-methyl-3-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)benzene



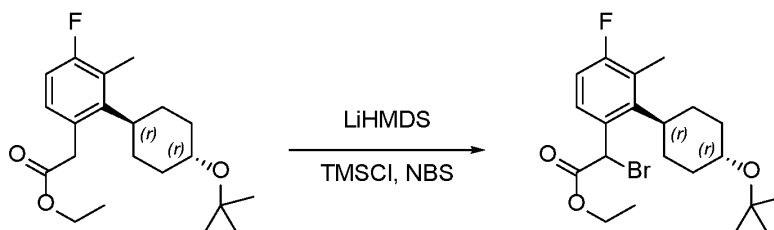
[000253] To a solution of 1-fluoro-4-iodo-2-methyl-3-((1*r*,4*r*)-4-(prop-1-en-2-yloxy)cyclohexyl)benzene (3.0 g, 8.0 mmol, 1.0 eq.) in dichloromethane (75 mL) at 0 °C was added Et₂Zn (32.0 ml, 32.0 mmol, 4.0 eq.). The mixture was stirred at 0 °C for 0.5 hr under N₂ atmosphere. CH₂I₂ (8.5 g, 32.0 mmol, 4.0 eq.) was then added dropwise into the mixture at 0 °C. The reaction was allowed to warm to room temperature and stirring was continued for 6 hr. Saturated aqueous NH₄Cl (150 mL) was added, and the mixture was extracted with dichloromethane (3 x 150 mL). Combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (95:1 petroleum ether: EtOAc) to give 1-fluoro-4-iodo-2-methyl-3-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)benzene as a colorless oil (1.3 g, 40%).

Step 15: ethyl 2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)-cyclohexyl)phenyl)acetate



[000254] To a suspension of 1-fluoro-4-iodo-2-methyl-3-((1*r*,4*r*)-4-(1-methylcyclopropoxy)-cyclohexyl)benzene (1.3 g, 3.3 mmol, 1.0 eq.) in tetrahydrofuran (12 mL) was added Pd_2dba_3 (82.0 mg, 0.09 mmol, 0.03 eq.) and QPhos (64 mg, 0.09 mmol, 0.03 eq.) followed by (2-ethoxy-2-oxoethyl)zinc(II) bromide (1M in THF, 8.2 mL, 8.2 mmol, 2.5 eq.). The mixture was stirred at 65 °C under N_2 atmosphere for 1 hr., then poured into 50 mL saturated aqueous NH_4Cl solution and extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated in *vacuo*. Crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give ethyl 2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate as a colorless oil (1.1 g, 90 %) (ESI 371.3 $[\text{M}+\text{Na}]^+$).

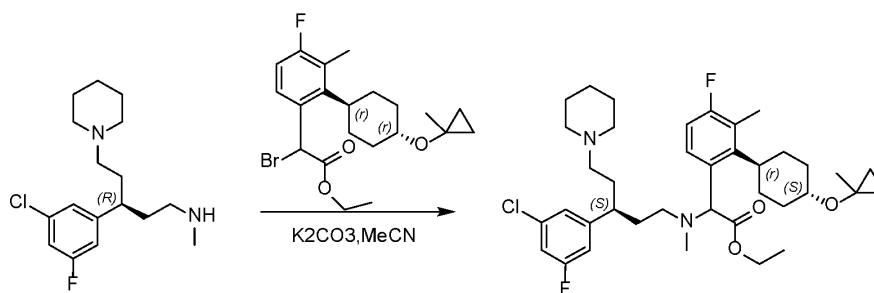
Step 16: ethyl 2-bromo-2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)-cyclohexyl)phenyl)acetate



[000255] To a solution of LiHMDS (1M in THF, 6.4 mL, 6.4 mmol, 2.0 eq.) at -78°C, ethyl 2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate (1.1 g, 3.2 mmol, 1.0 eq.) in tetrahydrofuran (20 mL) was added dropwise. The reaction was stirred at -78°C for 0.5 hr. TMSCl (698.0 mg, 6.4 mmol, 2.0 eq.) was then added dropwise, and stirring was continued at -78°C for another 15 min. A solution of NBS (1.14 g, 6.4 mmol, 2.0 eq.) in tetrahydrofuran (20 mL) was then added dropwise. The reaction was stirred at -78°C for

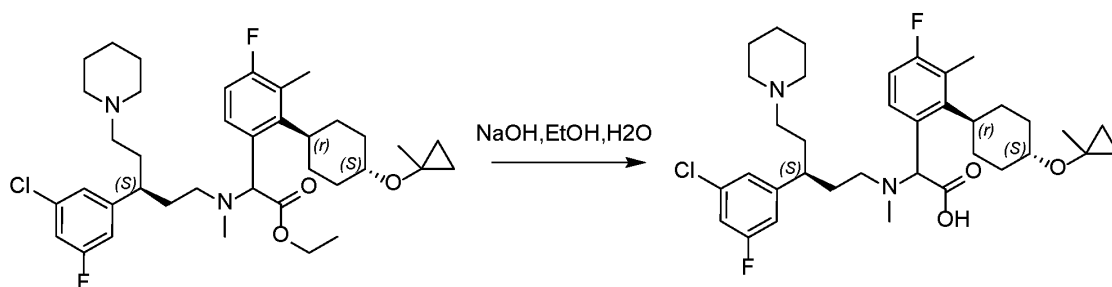
another 1 hr., then warmed to 0 °C, quenched with saturated aqueous NH₄Cl solution (100 ml) at 0°C, and extracted with EtOAc (3 x 150 ml). Combined organic layers were washed with brine (3 x 150 ml), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (19:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate as a colorless oil (3.72g, 90%) (ESI 449.0 [M+Na]⁺; 451.0 [M+2+Na]⁺).

Step 17: ethyl 2-(((S)-3-(3-chloro-5-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*S*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate



[000256] To a solution of (R)-3-(3-chloro-5-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (250 mg, 0.8 mmol, 1.0 eq.) in acetonitrile (5 mL) was added K₂CO₃ (331 mg, 2.4 mmol, 3.0 eq.). The mixture was stirred at RT for 15 min. Ethyl 2-bromo-2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate (340 mg, 0.8 mmol, 1.0 eq) was then added. Stirring was continued at 60 °C for another 3 hrs. After completion, the reaction mixture was filtered and concentrated under reduced pressure. Crude residue was purified by silica gel column chromatography (95:5 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(3-chloro-5-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*S*)-4-(1-methylcyclopropoxy)-cyclohexyl)phenyl)acetate as a yellow oil (200 mg, 38%) (ESI 659.3 [M+H]⁺).

Step 18: 2-(((S)-3-(3-chloro-5-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*S*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetic acid (Compounds 62-P1 and 62-P2)

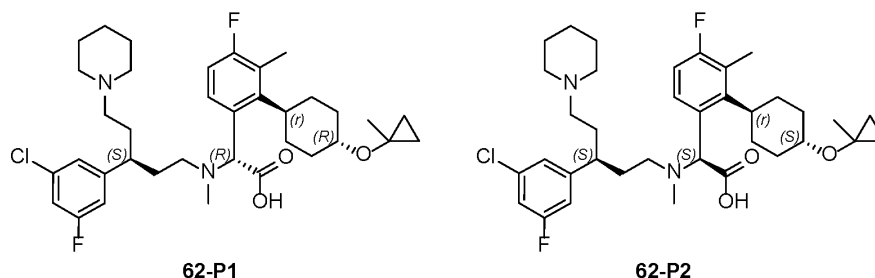


[000257] To a mixture of ethyl 2-(((S)-3-(3-chloro-5-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-((1R,4S)-4-(1-methylcyclopropoxy)cyclohexyl)-phenyl)acetate (200 mg, 0.3 mmol, 1.0 eq) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (36 mg, 0.9 mmol, 3.0 eq) and the reaction was stirred at 60 °C for 16 hrs. The reaction pH was adjusted to ~5 - 6 with 1N HCl. Solvents were removed *in vacuo*. Crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give **62-P1** (61.7 mg) and **62-P2** (67.0 mg) as white solids.

[000258] **Compound 62-P1** LC/MS 631.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.59 – 7.40 (m, 1H), 7.06 – 6.93 (m, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.59 (d, *J* = 69.1 Hz, 1H), 3.69 (s, 1H), 3.17 (d, *J* = 32.3 Hz, 1H), 2.59 (d, *J* = 39.3 Hz, 9H), 2.41 – 2.19 (m, 5H), 2.16 – 1.75 (m, 9H), 1.73 – 1.32 (m, 13H), 0.79 (t, *J* = 5.5 Hz, 2H), 0.44 (q, *J* = 4.7 Hz, 2H).

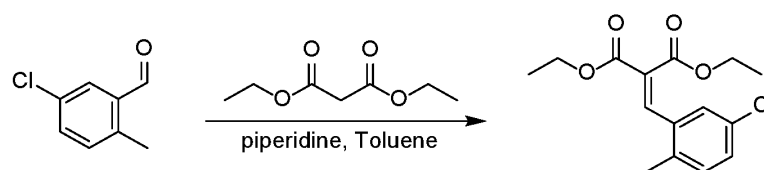
[000259] **Compound 62-P2** LC/MS ESI 631.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.72 – 7.38 (m, 1H), 7.14 – 6.77 (m, 4H), 4.53 (d, *J* = 106.8 Hz, 1H), 3.69 (s, 1H), 3.35 (s, 1H), 2.80 – 2.55 (m, 7H), 2.50 – 2.24 (m, 7H), 2.21 – 1.78 (m, 9H), 1.77 – 1.21 (m, 13H), 0.79 (s, 2H), 0.44 (q, *J* = 4.7 Hz, 2H).

[000260] **62-P1** and **62-P2** were assigned as (R)-2-(((S)-3-(3-chloro-5-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-((1R,4R)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetic acid and (S)-2-(((S)-3-(3-chloro-5-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-((1R,4S)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetic acid, respectively.



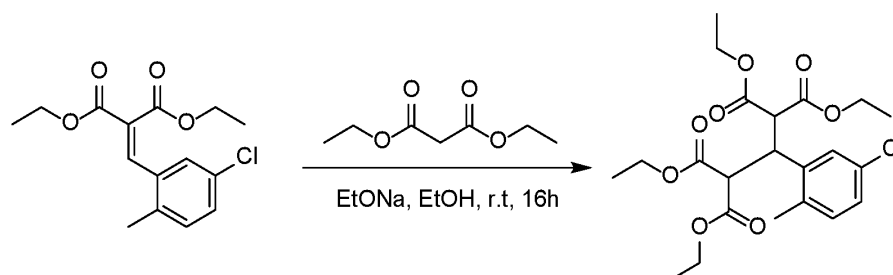
Example 3: Preparation of Compounds 89-P1 and 89-P2

Step 1: diethyl 2-(5-chloro-2-methylbenzylidene)malonate



[000261] A solution of 5-chloro-2-methylbenzaldehyde (100.0 g, 0.65 mol), diethyl malonate (155.8 g, 0.97 mol) and piperidine (8.3 g, 97.5 mmol) in toluene (300 mL) was stirred at 110 °C for 16 hr. The mixture was cooled to RT and concentrated under reduce pressure. The residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give diethyl 2-(5-chloro-2-methylbenzylidene)malonate as colorless oil (180 g, 93%) (ESI 297.3 [M+H]⁺).

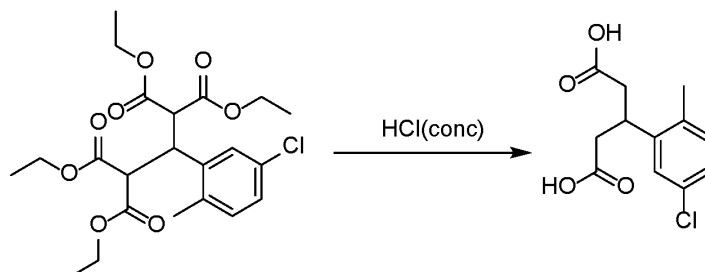
Step 2: tetraethyl 2-(5-chloro-2-methylphenyl)propane-1,1,3,3-tetracarboxylate



[000262] To a solution of diethyl malonate (194.6 g, 1.22 mol) in EtOH (400 mL) at RT was added EtONa (88.1 g, 1.3 mmol) and the mixture was stirred for 2 hr. Then diethyl 2-(5-chloro-2-methylbenzylidene)malonate (180 g, 0.61 mol) was added at RT and stirring was continued for another 16 hr. The reaction mixture was concentrated under reduce pressure. The residue was diluted with EtOAc (3 x 400 mL), washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to give tetraethyl 2-(5-chloro-2-

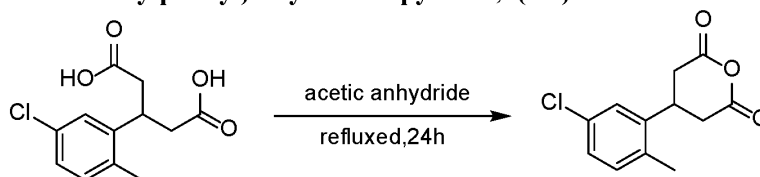
methylphenyl)propane-1,1,3,3-tetracarboxylate as colorless oil(180.0 g, 60%) (ESI 457.2[M+H]⁺).

Step 3: 3-(5-chloro-2-methylphenyl)pentanedioic acid



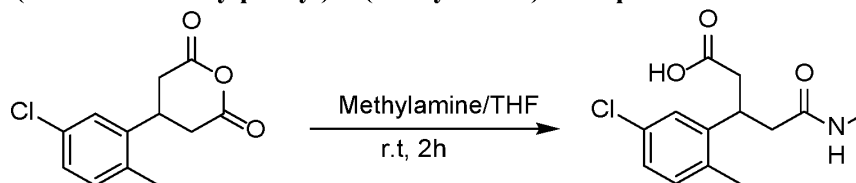
[000263] A mixture of tetraethyl 2-(5-chloro-2-methylphenyl)propane-1,1,3,3-tetracarboxylate (180.0 g, 0.39 mol) in 36% aqueous HCl (700 mL) was stirred at 130 °C for 36 hr. The mixture was cooled to 0 °C and stirred at 0 °C for 1 hr. The solid formed was filtered and collected to give 3-(5-chloro-2-methylphenyl)pentanedioic acid as a white solid without further purification (100.2 g, 99%) (ESI 279.0 [M+Na]⁺).

Step 4-(5-chloro-2-methylphenyl)dihydro-2H-pyran-2,6(3H)-dione



[000264] A solution of 3-(5-chloro-2-methylphenyl)pentanedioic acid (100.0 g, 0.39 mol) in acetic anhydride (400 mL) was stirred at 130 °C for 40 hr. The mixture was concentrated to dryness under reduce pressure, triturated with EtOAc(150 mL). The solid formed was filtered and collected to give 4-(5-chloro-2-methylphenyl)dihydro-2H-pyran-2,6(3H)-dione as a white solid(91.2 g, 97%) (ESI 239.1 [M+H]⁺).

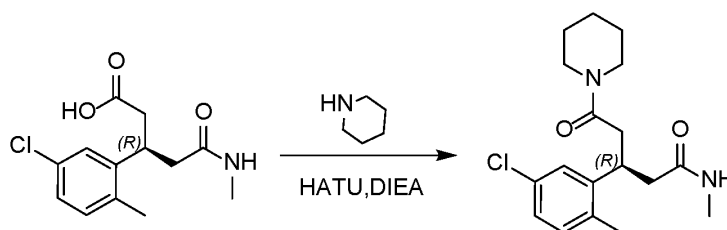
Step 5: 3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid



[000265] To a solution of 3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (91.2 g, 0.38 mol, 1.0 eq) in THF (300mL) was added methylamine (1M in THF, 1.15L, 1.15 mol, 3.0 eq) and the reaction was stirred at RT for 3hr. The reaction mixture was concentrated under reduce pressure and triturated with EtOAc(120 mL). The solid formed was

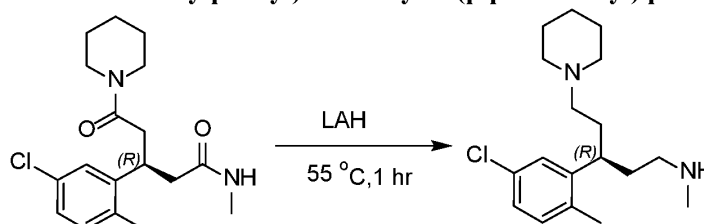
filtered and collected to give racemic 3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic as white solid (75.0 g, 73%). Enantiomers were further separated by prep chiral SFC K to give P1 fraction (R)-3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (31.0 g) and P2 fraction (S)-3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (31.0 g) as white solids (ESI 270.1 $[M+H]^+$).

Step 6: (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-oxo-5-(piperidin-1-yl) pentanamide



[000266] To a solution of (R)-3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (16.0 g, 59.4 mmol, 1.0 *eq*) and piperidine (5.0 g, 59.4 mmol, 1.0 *eq*) in DMF (60 mL) was added HATU (27.1 g, 71.3 mmol, 1.2 *eq*) followed by DIEPA (15.3 g, 118.9 mmol, 2.0 *eq*). The reaction was stirred at RT for 2 hr. After completion, the mixture was quenched with NH_4Cl solution (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (19:1 dichloromethane: MeOH) to give (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-oxo-5-(piperidin-1-yl) pentanamide as a colorless oil (16.3 g, 80%) (ESI 337.2 $[M+H]^+$).

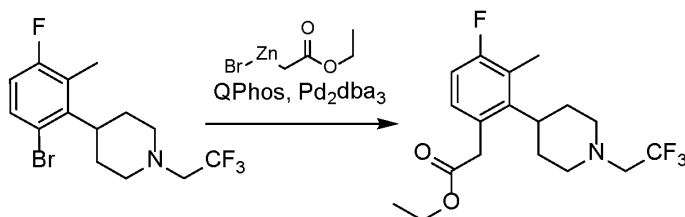
Step 7: (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-(piperidin-1-yl) pentan-1-amine



[000267] To a solution of (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-oxo-5-(piperidin-1-yl) pentanamide (16.3 g, 48.5 mmol, 1.0 *eq*) in THF (200 mL) at RT was added LiAlH_4 (58.2 mL, 145.5 mmol, 3.0 *eq*) dropwise and the reaction was stirred at 55 °C for 1 hr. After cooling to 0 °C, the reaction mixture was quenched with water (5.5 mL) dropwise and stirred at 0 °C for another 10 min. 15% aqueous NaOH (5.5 mL) and water (16.5 mL) were then added

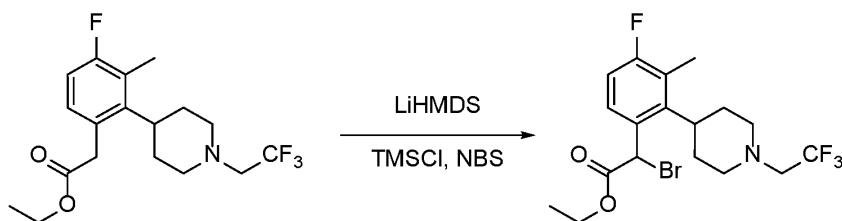
sequentially at 0 °C. The mixture was allowed to warm to RT and stirred for another 15 min, then filtered and filtrate was concentrated *in vacuo* to give (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine as a white solid used directly in the next reaction (13.1 g, 80%) (ESI 309.3 [M+H]⁺).

Step 8: ethyl 2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate



[000268] To a solution of 4-(6-bromo-3-fluoro-2-methylphenyl)-1-(2,2,2-trifluoroethyl) piperidine (6 g, 17 mmol, 1.0 eq), Pd2(dba)3 (1.56 g, 1.7 mmol, 0.1 eq) and Qphos (362.6 mg, 0.51 mmol, 0.03 eq) in THF (50 mL) under N₂ atmosphere was added (2-ethoxy-2-oxoethyl)zinc(II) bromide (51 mL, 1 mol/L, 51 mmol, 3.0 eq) and the mixture was heated to 80 °C for 1 hr. After completion, saturated aqueous NH₄Cl (100 mL) was added and the solution was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give ethyl 2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl) piperidin-4-yl) phenyl) acetate as a yellow oil (4.0 g, 65%) (ESI 362.1 [M+H]⁺).

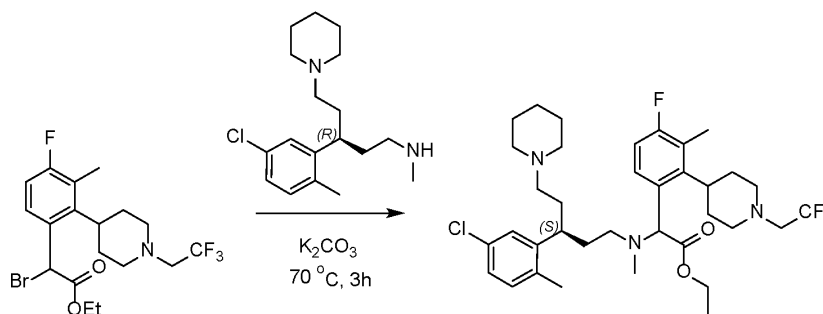
Step 9: ethyl 2-bromo-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl) piperidin-4-yl) phenyl) acetate



[000269] To a solution of LiHMDS (1M in THF, 110.8 mL, 110.8 mmol, 2.0 eq.) at -78 °C, ethyl 2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl) piperidin-4-yl) phenyl) acetate (20.0 g, 55.4 mmol, 1.0 eq.) in THF (80 mL) was added dropwise. The reaction was stirred at -78 °C for 0.5 hr. TMSCl (12.0 g, 110.8 mmol, 2.0 eq.) was then added dropwise, and stirring was continued at -78 °C for another 15 min. A solution of NBS (24.1 g, 110.8 mmol, 2.0 eq) in THF (200 mL) was then added dropwise. The reaction was stirred at -78 °C for another 1 hr., then

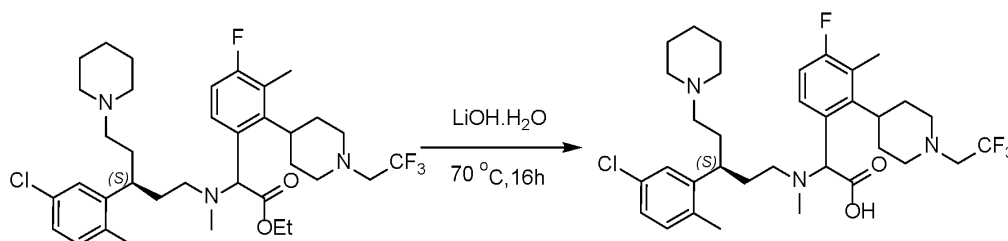
warmed to 0 °C, quenched with saturated aqueous NH₄Cl solution (200 ml) at 0 °C, and extracted with EtOAc (3 x 200 ml). Combined organic layers were washed with brine (3 x 150 ml), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl) piperidin-4-yl) phenyl) acetate (20.1 g, 82%) as a colorless oil, (ESI 440.1 [M+H]⁺).

Step 10: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate



[000270] To a solution of ethyl 2-bromo-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate (16.5 g, 37.5 mmol, 1 eq) and (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (13.1 g, 42.5 mmol, 1.1 eq) in CH₃CN (50 mL) was added K₂CO₃ (10.3 g, 75.0 mmol, 2.0 eq) at 70 °C for 4 hours. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate as a brown solid (16.0 g, 64%) (ESI 668.3 [M+H]⁺).

Step 11: 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid (Compounds 89-P1 and 89-P2)

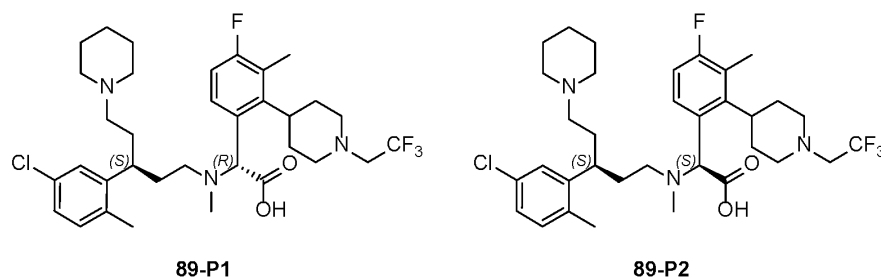


[000271] Ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate (16.0 g, 23.9 mmol, 1 eq) was treated with LiOH (5.0 g, 119.7 mmol, 5.0 eq) in EtOH (30 mL) and water (3 mL) at 70 °C for 16 hr. The reaction mixture was acidified to pH ~5-6 with 1N HCl. Solvents were removed *in vacuo*. The crude residue was purified by silica gel column chromatography (5:1 dichloromethane: MeOH) to give diastereomeric product **89** as white solid (13 g, 85%). Diastereomers were further separated by prep chiral SFC A to give **89-P1** (5.6 g) and **89-P2** (5.7 g) as white solids.

[000272] **Compound 89-P1** LC/MS ESI 640.3 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.44 (d, J = 7.0 Hz, 1H), 7.07 (d, J = 20.1 Hz, 3H), 6.83 (s, 1H), 4.39 (s, 1H), 3.30 (s, 1H), 3.15 – 3.00 (m, 4H), 2.91 – 2.43 (m, 12H), 2.39 – 2.06 (m, 10H), 2.06 – 1.74 (m, 4H), 1.47 (dd, J = 68.1, 34.3 Hz, 8H).

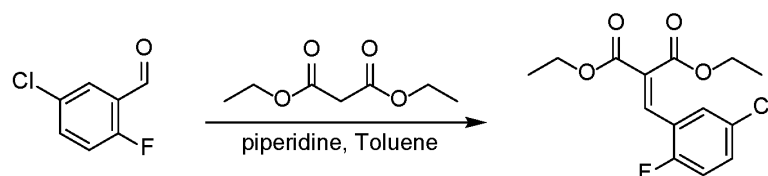
[000273] **Compound 89-P2** LC/MS ESI 640.3 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.49 (m, 1H), 7.30 – 7.01 (m, 3H), 6.84 (t, J = 8.4 Hz, 1H), 4.44 (s, 1H), 3.36 (s, 1H), 3.21 – 2.91 (m, 5H), 2.91 – 2.13 (m, 21H), 2.09 – 1.60 (m, 9H), 1.52 (s, 2H), 1.39 (d, J = 9.7 Hz, 1H).

[000274] **89-P1** and **89-P2** were assigned as (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid and (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid, respectively.



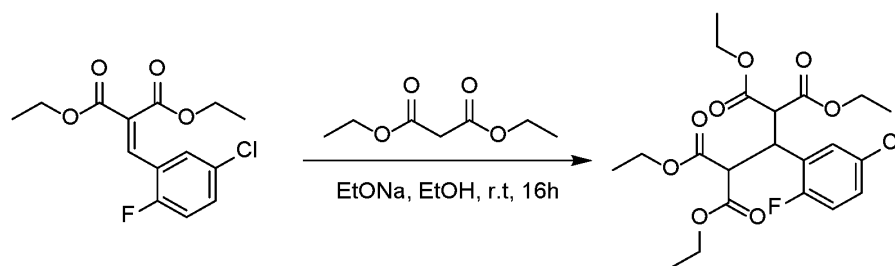
Example 4: Preparation of Compounds 85-P1 and 85-P2

Step 1: Diethyl 2-(5-chloro-2-fluorobenzylidene)malonate



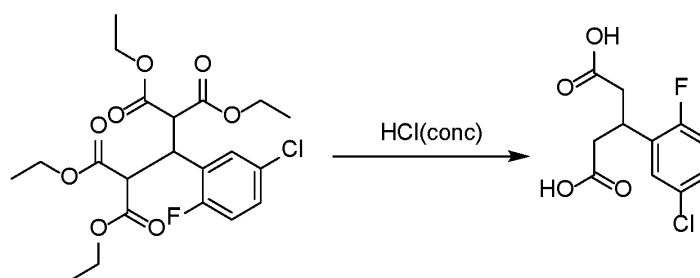
[000275] A solution of 5-chloro-2-fluorobenzaldehyde (75.0 g, 0.475 mol), diethyl malonate (152.0 g, 0.95 mol) and piperidine (6.0 g, 71.0 mmol) in toluene (200 mL) was stirred at 110 °C for 20 hr. The mixture was cooled to RT and concentrated under reduce pressure to give the crude product diethyl 2-(5-chloro-2-fluorobenzylidene)malonate (165 g, crude) as yellow oil. (ESI 301.0 $[M+H]^+$). Crude product was used directly in the next step.

Step 2: tetraethyl 2-(5-chloro-2-fluorophenyl)propane-1,1,3,3-tetracarboxylate

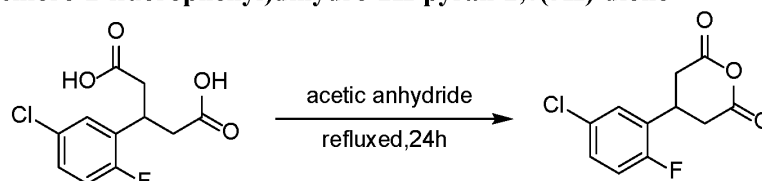


[000276] To a solution of diethyl malonate (176.0 g, 1.1 mol) in EtOH (2 L) at RT was added EtONa (113.0 g, 1.6 mol) and the mixture was stirred for 2hr. Then diethyl 2-(5-chloro-2-fluorobenzylidene)malonate (165.0 g, 0.55 mol) was added at RT and stirring was continued for another 16 hr. The reaction mixture was concentrated under reduce pressure. The residue was diluted with EtOAc (3 x 400 mL), washed with brine, dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to tetraethyl 2-(5-chloro-2-fluorophenyl)propane-1,1,3,3-tetracarboxylate (160.0 g, 2-step yield 63%) as yellow oil. (ESI 461.1 $[M+H]^+$).

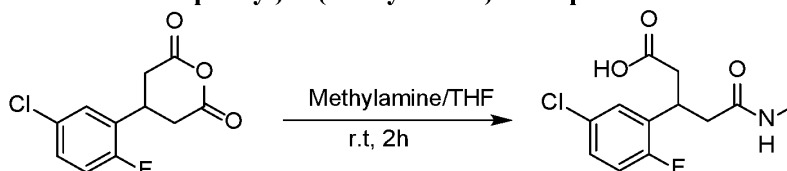
Step 3: 3-(5-chloro-2-fluorophenyl)pentanedioic acid



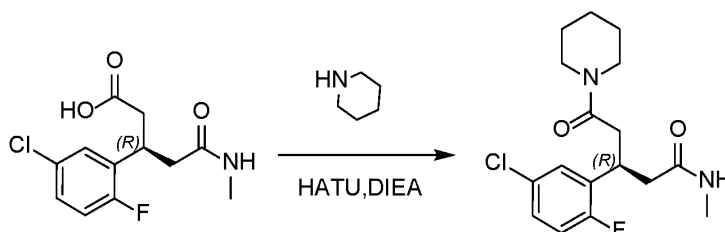
[000277] A mixture of tetraethyl tetraethyl 2-(5-chloro-2-fluorophenyl)propane-1,1,3,3-tetracarboxylate (80.0 g, 0.174 mol) in 36% aqueous HCl (200 mL) was stirred at 130 °C for 36 hr. The mixture was cooled to 0 °C and stirred at 0 °C for 1 hr. The solid formed was filtered and collected to give 3-(5-chloro-2-fluorophenyl)pentanedioic acid (40.0 g, 88%) without further purification. (ESI 283.0 $[M+Na]^+$).

Step 4: 4-(5-chloro-2-fluorophenyl)dihydro-2H-pyran-2,6(3H)-dione

[000278] A solution of 3-(5-chloro-2-fluorophenyl)pentanedioic acid (70.0 g, 270 mmol) in acetic anhydride (600 mL) was stirred at 130 °C for 40 hr. After cooling to 0 °C, the mixture was concentrated under reduce pressure, triturated with EtOAc (150 mL). The solid formed was filtered and collected to give 4-(5-chloro-2-fluorophenyl)dihydro-2H-pyran-2,6(3H)-dione as a white solid (59.1 g, 90%) (ESI 243.1 $[M+H]^+$).

Step 5: 3-(5-chloro-2-fluorophenyl)-5-(methylamino)-5-oxopentanoic acid

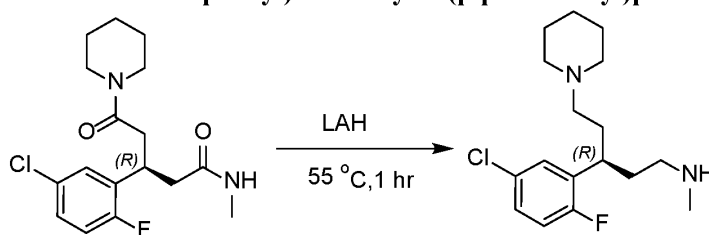
[000279] To a solution of 4-(5-chloro-2-fluorophenyl)dihydro-2H-pyran-2,6(3H)-dione (59.1 g, 243 mmol, 1.0 *eq*) in THF (300mL) was added methylamine (2M in THF, 364.5 mL, 729 mmol, 3.0 *eq*) and the reaction was stirred at RT for 3hr. The reaction mixture was concentrated under reduce pressure and triturated with EtOAc (120 mL). The solid formed was filtered and collected to give 3-(5-chloro-2-fluorophenyl)-5-(methylamino)-5-oxopentanoic acid (59.7 g, 90%) as white solid (ESI 274.0 $[M+H]^+$). Enantiomers were further separated by Prep chiral SFC K to give P1 fraction (R)-3-(5-chloro-2-fluorophenyl)-5-(methylamino)-5-oxopentanoic acid (28.2 g) and P2 fraction (S)-3-(5-chloro-2-fluorophenyl)-5-(methylamino)-5-oxopentanoic acid (26.0 g) as white solids.

Step 6: (R)-3-(5-chloro-2-fluorophenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide

[000280] A solution of (R)-3-(5-chloro-2-fluorophenyl)-5-(methylamino)-5-oxopentanoic acid (41.0 g, 150 mmol, 1.0 *eq*) in DCM (320 mL) was added piperidine (25.5 g, 300 mmol, 2.0 *eq*) and HATU (68.4 g, 180 mmol, 1.2 *eq*) followed by DIEA (38.7 g, 300 mmol, 2.0 *eq*).

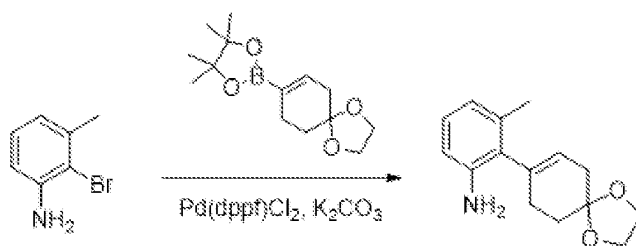
The reaction was stirred at RT for 2 hours. After completion, the mixture was quenched with NH_4Cl solution (1 L) and extracted with dichloromethane (3 x 200 ml). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (5:1 dichloromethane: MeOH) to give (R)-3-(5-chloro-2-fluorophenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide as a colorless oil (46.2 g, 90%) (ESI 341.1 $[\text{M}+\text{H}]^+$).

Step 7: (R)-3-(5-chloro-2-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine



[000281] To a solution of (R)-3-(5-chloro-2-fluorophenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide (46.2 g, 136 mmol, 1.0 *eq*) in THF (340 mL) at RT was added dropwise LiAlH_4 (2.5 M in THF, 206.7 mL, 516.8 mmol, 3.8 *eq*) and the reaction was stirred at 55 °C for 0.5 hour. After cooling to 0 °C, the reaction mixture was then quenched with water (19 mL) dropwise and stirred at 0 °C for another 10 min. 15% aqueous NaOH (19 mL) and water (57 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT and stirred for another 15 min, dried over Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (99: 0.1 MeOH: TEA) to give (R)-3-(5-chloro-2-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine as a colorless oil (13 g, 30%) (ESI 313.2 $[\text{M}+\text{H}]^+$).

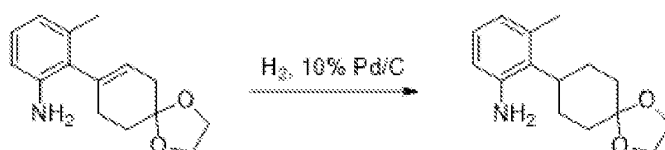
Step 8: 3-methyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)aniline



[000282] 2-bromo-3-methylaniline (50 g, 268.7 mmol, 1.0 *eq*), 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (75 g, 282.18 mmol, 1.05 *eq*), K_2CO_3 (63 g, 456.7 mmol, 1.7 *eq*) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (3.9 g, 5.37 mmol, 0.02 *eq*) were suspended in a mixture of dioxane (500 mL) and water (100 mL). The reaction was stirred overnight at 100 °C

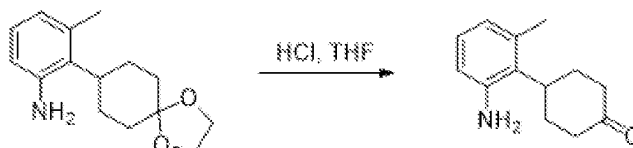
under N₂ atmosphere. Contents were poured into 300 mL water and extracted with EtOAc (3 x YY mL). Combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (6:1 petroleum ether: EtOAc) to give 3-methyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)aniline as a yellow solid (54 g, 81.8%) (ESI 246.3 [M+H]⁺).

Step 9: 3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline



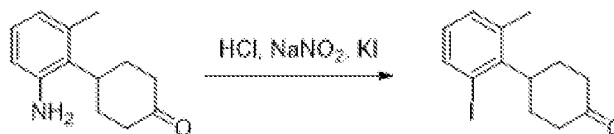
[000283] To a solution of 3-methyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)aniline (20 g, 81.3 mmol, 1.0 eq.) in EtOH (250 mL) was added 10% Pd/C (5.0 g, 2.2 mmol, 0.03 eq). The reaction mixture was stirred at 65 °C under H₂ atmosphere (1 atm, 3L) for 24 hr. Upon completion, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to give 3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline as a yellow oil (19.1 g, 95%) (ESI 248.3 [M+H]⁺). Crude product was used directly in the subsequent step without further purification.

Step 10: 4-(2-amino-6-methylphenyl)cyclohexan-1-one



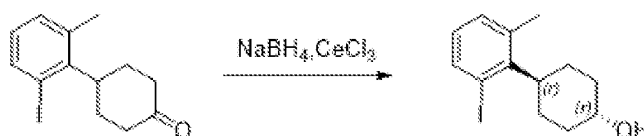
[000284] To a solution of 3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline (100 g, 403.2 mmol, 1.0 eq.) in THF (1L) was added 3M aqueous HCl (407 mL, 1.22 mol, 3 eq.). The reaction was stirred at RT for 1 hr. The reaction mixture was cooled to 0 °C, quenched with saturated aqueous NaHCO₃ solution (pH adjusted to ~8), and extracted with EtOAc (500 mL). The organic layer was washed with brine (500 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give 4-(2-amino-6-methylphenyl)cyclohexan-1-one as a yellow oil (72 g, 87.9%) (ESI 204.1 [M+H]⁺). Crude product was used directly in the next step.

Step 11: 4-(2-iodo-6-methylphenyl)cyclohexan-1-one



[000285] To a solution of 4-(2-amino-6-methylphenyl)cyclohexan-1-one (36 g, 90 % purity, 177.3 mmol, 1.0 eq.) in THF (250 mL) at -10 °C was added aqueous HCl (6M, 72 mL, 443.3 mmol, 2.5 eq.) followed by NaNO₂ (13.4 g in 30 mL water, 195.03 mmol, 1.1 eq.) dropwise over 15 mins. The reaction was stirred at -10 °C for another 30 min. KI solution (44.1 g in 30 mL water, 265.9 mmol, 1.5 eq.) was then added portion wise into the mixture. The reaction was allowed to warm to 0 °C and stirring was continued for 30 min. Water (300 mL) and EtOAc (300 mL) were added into the reaction. The organic layer was separated and washed with saturated aqueous Na₂SO₃ (300 mL) and brine (300 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel column chromatography (15:1 petroleum ether: EtOAc) to give the 4-(2-iodo-6-methylphenyl)cyclohexan-1-one as a white solid (12.2 g, 21.8%) (ESI 315.0 [M+H]⁺).

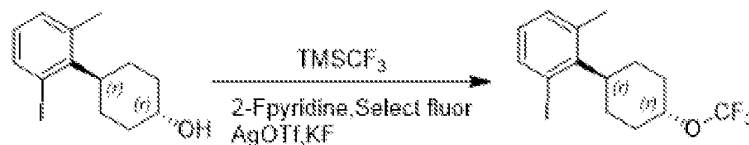
Step 12: (1r,4r)-4-(2-iodo-6-methylphenyl)cyclohexan-1-ol



[000286] To a solution of 4-(3-fluoro-6-iodo-2-methylphenyl)cyclohexan-1-one (10 g, 31.8 mmol, 1.0 eq.) in THF (50 mL) and MeOH (8 mL) at 0 °C was added CeCl₃ (9.4 g, 38.2 mmol, 1.2eq) followed by NaBH₄ (1.45 g, 38.2 mmol, 1.2 eq) in portions. The mixture was stirred at 0 °C for 0.5 hr. H₂O (100 mL) was slowly added at 0 °C, and the mixture was extracted with EtOAc (3 x 150 mL). Combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to give (1r,4r)-4-(2-iodo-6-methylphenyl)cyclohexan-1-ol as a white solid (8.4 g, 83.5%) (ESI 299.0 [M-OH]⁺).

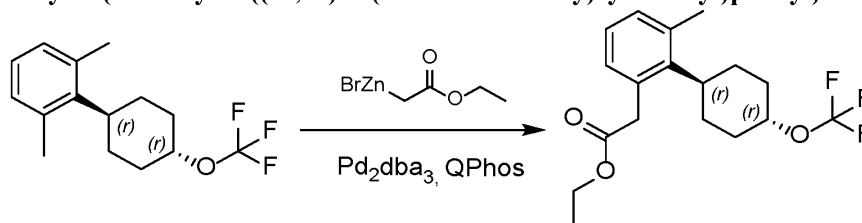
[000287] ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.15 – 6.96 (m, 1H), 6.72 (t, *J* = 7.7 Hz, 1H), 3.74 – 3.63 (m, 1H), 3.30 – 3.22 (m, 1H), 2.44 (s, 3H), 2.12 (d, *J* = 12.5 Hz, 2H), 1.96 (qd, *J* = 13.0, 3.1 Hz, 2H), 1.80 (d, *J* = 11.5 Hz, 2H), 1.47 (ddd, *J* = 23.7, 12.4, 3.6 Hz, 2H).

Step 13: 1-iodo-3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)benzene



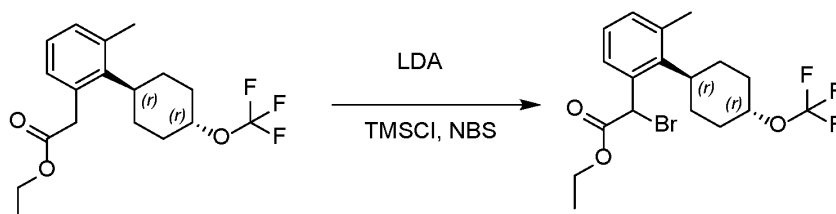
[000288] A solution of (1r,4r)-4-(2-iodo-6-methylphenyl)cyclohexan-1-ol (8.4 g, 26.6 mmol, 1.0 eq), Selectfluor (14.14 g, 39.9 mmol, 1.5 eq), KF (6.17 g, 106.4 mmol, 4.0 eq.) and AgOTf (20.5 g, 79.8 mmol, 3.0 eq.) in EtOAc (200 mL) was stirred at RT for 5 min under N₂ atmosphere. 2-fluoropyridine (7.75 g, 79.8 mmol, 3.0 eq.) and TMSCF₃ (11.4 g, 79.8 mmol, 3 eq.) were then added. The reaction was stirred at RT for 48 hr. After completion, the reaction mixture was filtered and concentrated under reduced pressure. Crude residue was purified by silica gel column chromatography (98:2 petroleum ether: EtOAc) to give 1-iodo-3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)benzene as a white solid (3.2g, 31.4%).

Step 14: ethyl 2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



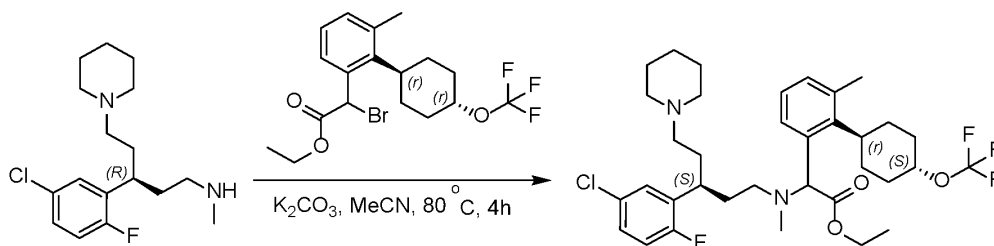
[000289] To a suspension of 1-iodo-3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)benzene (4.2 g, 10.9 mmol, 1.0 eq) in THF (30 mL) was added Pd₂dba₃ (100 mg, 0.11 mmol, 0.01 eq) and QPhos (154 mg, 0.22 mmol, 0.02 eq) followed by (2-ethoxy-2-oxoethyl)zinc(II) bromide (1M in THF, 32 mL, 32 mmol, 3.0 eq.). The mixture was stirred at 55 °C under N₂ atmosphere for 1 hr., then poured into 100 mL saturated aqueous NH₄Cl and extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in *vacuo*. Crude residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give ethyl 2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as a colorless oil (3.5 g, 93 %) (No Mass).

Step 15: ethyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000290] To a solution of Lithium diisopropylamide (2 M in THF, 15.1 mL, 30.3 mmol, 3.0 *eq*) at -78°C, ethyl 2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (3.5g, 10.1 mmol, 1.0 *eq*) in THF (60 ml) was added dropwise. The reaction was stirred at -78°C for 0.5 hr. TMSCl (5.39 g, 30.3 mmol, 3.0 *eq*) was then added dropwise, and stirring was continued at -78°C for another 15 min. A solution of NBS (5.36 g, 30.3 mmol, 3.0*eq*) in THF (100mL) was then added dropwise. The reaction was stirred at -78°C for another 1 hr., then warmed to 0 °C, quenched with saturated aqueous NH₄Cl solution (100 ml) at 0°C, and extracted with EtOAc (3 x 150 ml). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as yellow solid (3.2g, 75%) (ESI 445.0 [M+Na]⁺).

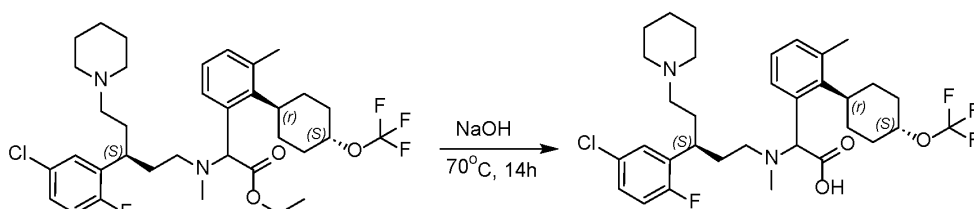
Step 16: ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000291] To a solution of (R)-3-(5-chloro-2-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (10.0 g, 31.2 mmol, 1.3 *eq*) in acetonitrile (150 mL), was added K₂CO₃ (9.9 g, 72 mmol, 3.0 *eq*). The mixture was stirred at RT for 15 min. The ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (10.1 g, 24.0 mmol, 1.0 *eq*) was added, the mixture continued stirred at 80 °C for 4 hr. After completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (5:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-

(trifluoromethoxy)cyclohexyl)phenyl)acetate as a yellow oil (12.4 g, 60.6%) (ESI 655.3 [M+H]⁺).

Step 17: 2-(((S)-3-(5-chloro-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid

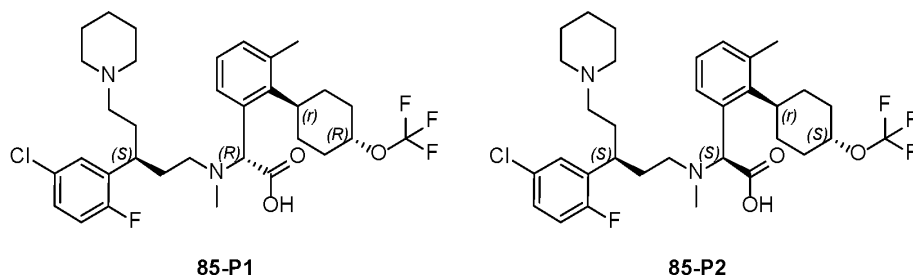


[000292] Ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (18.2 g, 27.7 mmol, 1.0 *eq*) was treated with NaOH (5.5 g, 138.5 mmol, 5.0 *eq*) in ethanol (120 mL) and water (40 mL) at 70 °C for 16 hr. The reaction mixture was acidified to pH ~5-6 with 1N HCl. Crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give the diastereomeric product **85** (15.0 g, 86.5%). Diastereomers were further separated by Prep chiral SFC A column to give products **85-P1** (5.4 g) and **85-P2** (4.99 g) as white solids.

[000293] **Compound 85-P1** LC/MS ESI 627.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.58 – 7.37 (m, 1H), 7.23 – 6.96 (m, 5H), 4.73 – 4.29 (m, 2H), 3.09 (d, *J* = 26.0 Hz, 1H), 2.86 (s, 1H), 2.58 (dd, *J* = 64.7, 49.7 Hz, 12H), 2.35 – 1.57 (m, 18H), 1.48 (s, 2H).

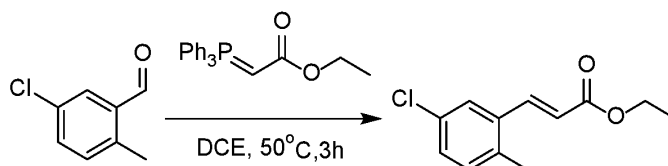
[000294] **Compound 85-P2** LC/MS ESI 627.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.52 (t, *J* = 68.3 Hz, 1H), 7.16 (d, *J* = 5.1 Hz, 2H), 7.08 – 6.90 (m, 3H), 4.40 (d, *J* = 55.3 Hz, 2H), 3.48 (s, 1H), 2.86 (s, 1H), 2.56 – 2.25 (m, 13H), 2.22 – 2.01 (m, 5H), 1.91 – 1.54 (m, 12H), 1.44 (s, 2H).

[000295] **85-P1** and **85-P2** were assigned as (R)-2-(((S)-3-(5-chloro-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetic acid and (S)-2-(((S)-3-(5-chloro-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetic acid, respectively.



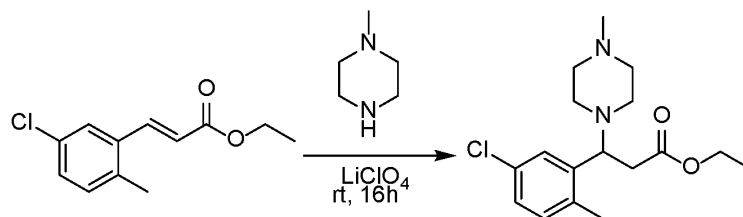
Example 5: Preparation of Compounds 99-P1 and 99-P2

Step 1: ethyl (E)-3-(5-chloro-2-methylphenyl)acrylate

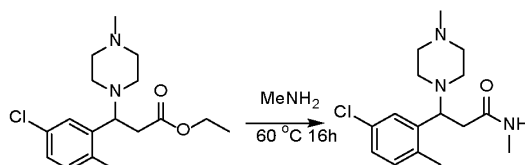


[000296] To a solution of 5-chloro-2-methylbenzaldehyde (5.0 g, 32.5 mmol, 1.0 eq) in DCE (50 mL) was added ethyl 2-(triphenylphosphoranylidene)acetate (12.5 g, 35.7 mmol, 1.1 eq). The reaction was heated to 50 °C under N₂ atmosphere for 3hr. After completion, the reaction was concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl (E)-3-(5-chloro-2-methylphenyl)acrylate as a colorless oil (7.0 g, 96.3 %) (ESI 225.1 [M+H]⁺).

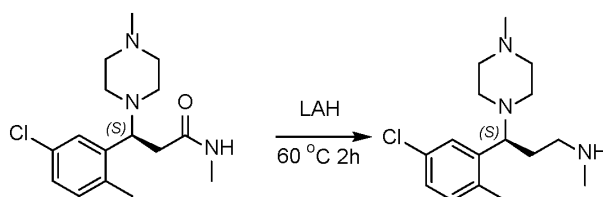
Step 2: ethyl 3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propanoate



[000297] To a solution of ethyl (E)-3-(5-chloro-2-methylphenyl)acrylate (3.5 g, 15.6 mmol, 1.0 eq) in 1-methylpiperazine (15 mL) was added LiClO₄ (3.3 g, 31.2 mmol, 2.0 eq). The reaction was stirred at room temperature for 16hr. Then the mixture was diluted with EtOAc (100 mL), washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give ethyl 3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propanoate as a white solid (3.0 g, 59.4 %) (ESI 325.1 [M+H]⁺).

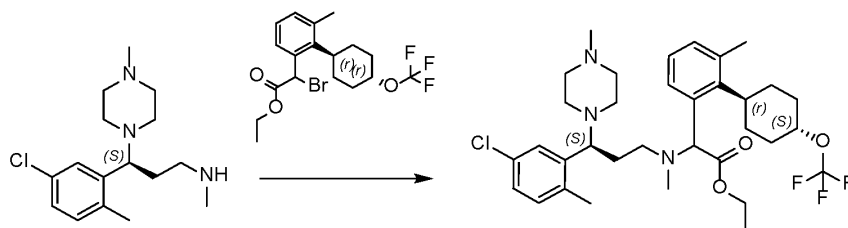
Step 3: 3-(5-chloro-2-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propanamide

[000298] A solution of ethyl 3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propanoate (3.0 g, 9.3 mmol, 1.0 eq) in MeNH₂ solution (1M in MeOH, 40 ml, 40 mmol, 4.0 eq) was heated to 60°C for 16 hr. The reaction was concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (10:1 dichloromethane: MeOH) to give 3-(5-chloro-2-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propanamide as a white solid (1.5 g, 52.4%). Enantiomers were further separated by prep chiral SFC F to give amide P1 (0.7 g) and amide P2 (0.7 g) (ESI 310.1 [M+H]⁺).

Step 4: (S)-3-(5-chloro-2-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propan-1-amine

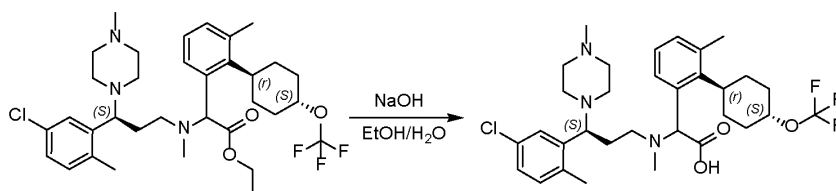
[000299] To a solution of P2 amide (S)-3-(5-chloro-2-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propanamide (700 mg, 2.27 mmol, 1.0 eq) in THF (9 mL) was added LAH (2.3 mL, 5.66 mmol, 2.5 eq) at 0°C and stirred at 60°C for 2 hr. The reaction was quenched with water (1.0 mL) dropwise, NaOH (1.0 mL, 15% in water) and water (3.0 mL) and stirred at 0°C for 15 min, dried over anhydrous Na₂SO₄, filtrated and the filtrate was concentrated *in vacuo* to give (S)-3-(5-chloro-2-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propan-1-amine (600 mg, yield: 90.1%) as a yellow oil (ESI 296.1 (M+H)⁺). Crude product was used directly in the subsequent step without further purification.

Step 5: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1R,4R)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetate



[000300] To a solution of (S)-3-(5-chloro-2-methylphenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propan-1-amine (148mg, 0.5 mmol) and ethyl 2-bromo-2-(3-methyl-2-((1R,4R)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (211 mg, 0.5 mmol) in acetonitrile (5 mL) was added DIEA (200 mg, 1.5 mmol, 3.0 eq). The reaction mixture was stirred at 70 °C for 3 hr, then filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1R,4R)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate as a yellow liquid (223 mg, 70.1%). (ESI 638.2 [M+H]⁺).

Step 6: 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1R,4R)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



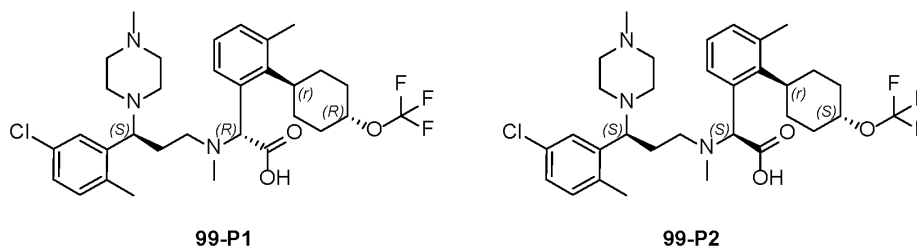
[000301] To a solution of 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1R,4R)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (212 mg, 0.33 mmol, 1.0 eq.) in ethanol (3 mL) and water (1 mL) was added NaOH (67 mg, 1.7 mmol, 5.0 eq.). The reaction was stirred at 80 °C for 16 hr. After completion, the reaction pH was adjusted to ~ 6 - 7 with 1N HCl. Solvents were removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give diastereomeric product **99** as white solid (130 mg, 71.5%). Diastereomers were further separated by prep chiral SFC A to give **99-P1** (52.9 mg) and **99-P2** (44.3 mg).

[000302] **Compound 99-P1** LC/MS ESI 610.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.52 (d, J = 36.9 Hz, 1H), 7.31 – 7.03 (m, 5H), 4.85 – 4.68 (m, 1H), 4.59 – 4.35 (m, 1H), 4.05

(s, 1H), 3.18 (s, 1H), 2.57 (s, 10H), 2.50 (s, 3H), 2.42 (d, J = 12.3 Hz, 3H), 2.37 – 2.24 (m, 7H), 2.15 (dd, J = 43.6, 9.3 Hz, 3H), 2.00 – 1.58 (m, 6H).

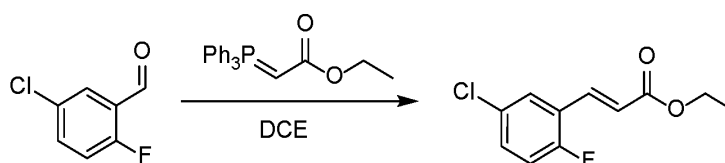
[000303] **Compound 99-P2** LC/MS ESI 610.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.50 (dd, J = 47.5, 7.0 Hz, 1H), 7.19 (m, 5H), 4.88 – 4.76 (m, 1H), 4.37 (s, 1H), 3.68 (s, 1H), 3.24 – 3.12 (m, 1H), 3.03 – 2.55 (m, 10H), 2.52 (s, 3H), 2.37 (dd, J = 32.4, 23.5 Hz, 6H), 2.29 – 2.02 (m, 7H), 1.78 (m, 6H).

[000304] **99-P1** and **99-P2** were assigned as (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1R,4R)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid and (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-methylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1R,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid, respectively.



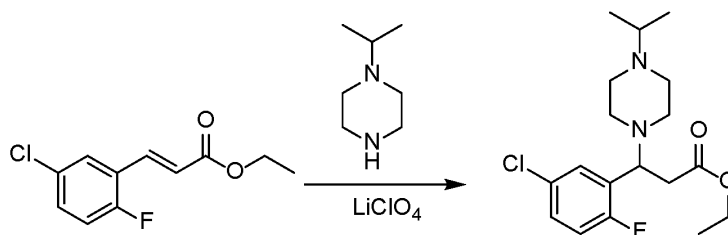
Example 6: Preparation of Compounds 114-P1 and 114-P2

Step 1: ethyl (E)-3-(5-chloro-2-fluorophenyl)acrylate



[000305] A solution of 5-chloro-2-fluorobenzaldehyde (125 g, 791 mmol, 1.0 eq.) and ethyl 2-(triphenylphosphanylidene)acetate (330 g, 949 mmol, 1.2 eq) in DCE (1L) was stirred at RT for 3 hours. After completion, the reaction was concentrated *in vacuo*. The residue was diluted with petroleum ether (1L). The reaction was filtered to remove triphenylphosphine oxide. The filtrate was concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl (E)-3-(5-chloro-2-fluorophenyl)acrylate as a yellow oil (152 g, 84%) (ESI 229.6[M+H]⁺).

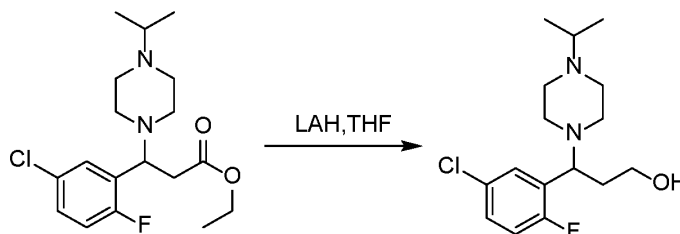
Step 2: ethyl 3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propanoate



[000306] To a solution of ethyl (E)-3-(5-chloro-2-fluorophenyl)acrylate (152g, 667 mmol, 1.0 eq) in 1-isopropylpiperazine (106 g, 1000 mmol, 1.5 eq) was added LiClO₄

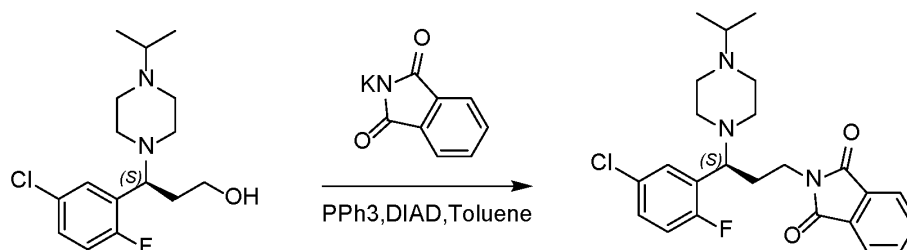
(128 g, 1000 mmol, 1.5 eq.). The reaction was stirred at 60 °C for 16 hours. The reaction mixture was poured into water (1000 mL) and extracted with EtOAc (2000 mL). Combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (97:3 dichloromethane: MeOH) to give tertethyl 3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propanoate as a yellow solid (160g, 67%) (ESI 357.8 [M+H]⁺).

Step 3: 3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propan-1-ol



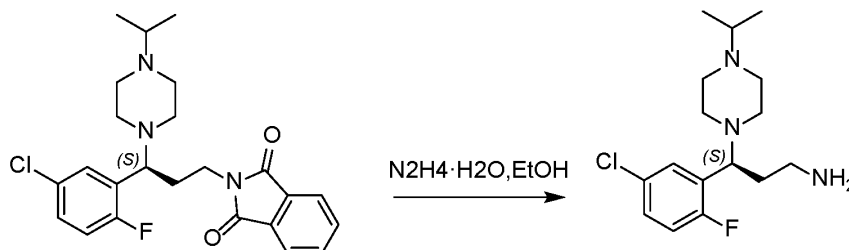
[000307] To a solution of tertethyl 3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propanoate (160 g, 449mmol, 1.0 eq.) in THF (1000 mL) at 0 °C was added LAH (674 mL, 674 mmol, 1.5 eq) under N₂. The reaction was stirred at 0 °C for 1 hr. After completion, the reaction mixture was quenched with water (25.5 mL) dropwise and stirred at 0 °C for another 10 min. 15% aqueous NaOH (25.5 mL) and water (76 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT and stirred for another 15 min, dried over Na₂SO₄, filtered and the filtrate was concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (80:20 petroleum ether: EtOAc) to give 3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propan-1-ol as a yellow oil (140 g, 99%). Enantiomers were further separated by prep chiral SFC B to give P1 fraction (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propan-1-ol (60 g) and P2 fraction (R)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propan-1-ol as a yellow oil (55 g).

Step 4: (S)-2-(3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)isoindoline-1,3-dione



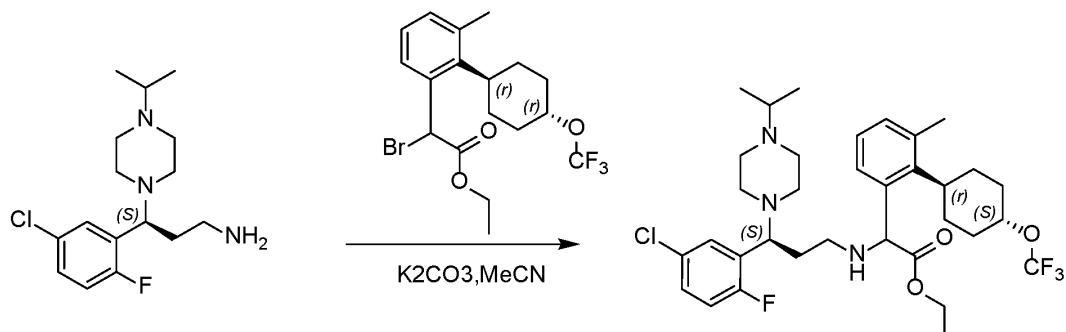
[000308] To a solution of (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propan-1-ol (28 g, 89 mmol, 1.0 eq) and isoindoline-1,3-dione (17 g, 116 mmol, 1.3 eq) in Toluene (300 mL) at 0 °C was added triphenylphosphine (30 g, 116 mmol, 1.3 eq) followed by diethyl azodicarboxylate (23 g, 116 mmol, 1.3 eq). The reaction was stirred at RT for 3 hrs. The reaction was filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give (S)-2-(3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)isoindoline-1,3-dione as a yellow oil (33 g, 85 %) (ESI 444.9 [M+H]⁺).

Step 5: (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propan-1-amine



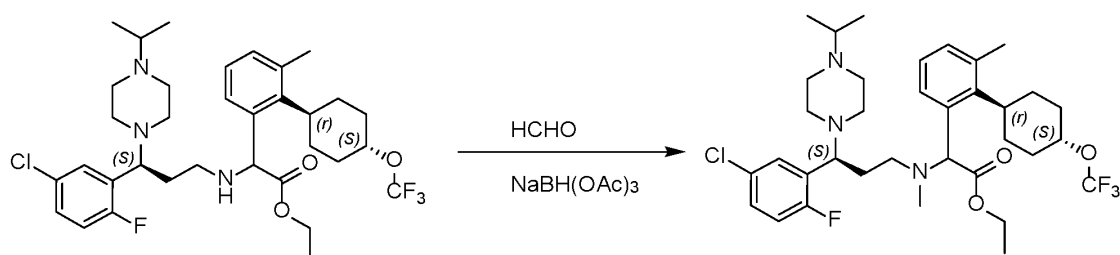
[000309] To a solution of (S)-2-(3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)isoindoline-1,3-dione (33 g, 74 mmol, 1.0 eq) in EtOH (800 mL) at RT was added 98% hydrazine hydrate (19 g, 372 mmol, 5 eq). The reaction mixture was warmed to 80 °C and stirred for 1 hr. After completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (80:20 dichloromethane: MeOH) to give (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propan-1-amine as a yellow oil (23 g, 99%) (ESI 314.8 [M+H]⁺).

Step 6: ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000310] To a solution of (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propan-1-amine (13 g, 42 mmol, 1.0 eq.) in acetonitrile (150 mL) was added K_2CO_3 (17 g, 125 mmol, 3.0 eq.). The mixture was stirred at RT for 15 min. Ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (17 g, 42 mmol, 1.0 eq) was then added. Stirring was continued at 60 °C for another 16 hrs. After completion, the reaction mixture was filtered and concentrated under reduced pressure. Crude residue was purified by silica gel column chromatography (9:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate as a yellow oil (16 g, 59%) (ESI 656.2 $[M+H]^+$).

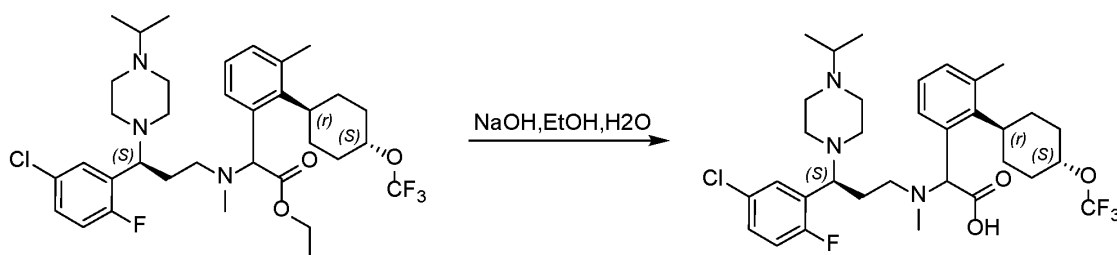
Step 7: 2 ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate



[000311] To a solution of ethyl (S)-2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (16 g, 25 mmol, 1.0 eq.) in MeOH (140 mL) was added 33% aqueous HCHO (10 g, 100 mmol, 5.0 eq.). The reaction was stirred at RT for 1 hr. $NaBH(OAc)_3$ (11 g, 50 mmol, 2.0 eq.) was then added, and stirring was continued at RT for another 3 hrs. After completion, the reaction mixture was poured into water (300 mL) and

extracted with dichloromethane (3 x 200 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (95:5 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as colorless oil (14 g, 86%) (ESI 670.2 [M+H]⁺).

Step 8: 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid

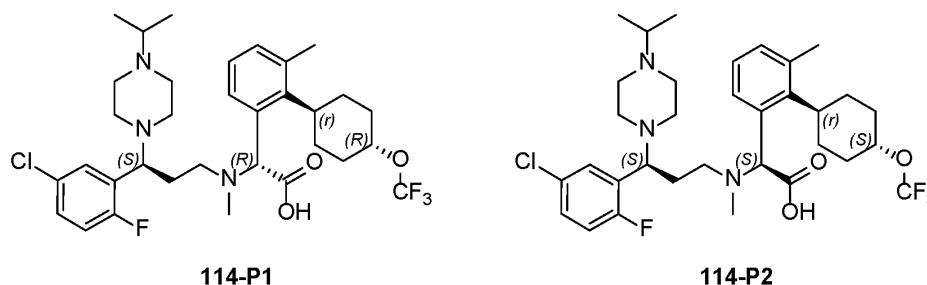


[000312] To a mixture of ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (14 g, 21 mmol, 1.0 eq) in EtOH (100 mL) and H₂O (20 mL) was added NaOH (2.5 g, 63 mmol, 3.0 eq) and stirred at 60 °C for 16 hrs. The reaction pH was adjusted to ~5 - 6 with 1N HCl. Solvents were removed *in vacuo*. Crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give diastereomeric product **114** as a white solid (10 g, 75%). Diastereomers were further separated by prep chiral SFC A to give **114-P1** (4.0 g) and **114-P2** (3.98g).

[000313] **Compound 114-P1** LC/MS 642.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.66 – 7.52 (m, 1H), 7.36 (s, 2H), 7.21 (d, *J* = 40.1 Hz, 3H), 4.47 (d, *J* = 62.4 Hz, 3H), 3.48 (s, 1H), 3.13 (s, 1H), 2.97 – 2.48 (m, 13H), 2.43 (s, 2H), 2.34 – 2.07 (m, 5H), 2.03 – 1.53 (m, 6H), 1.06 (d, *J* = 5.6 Hz, 6H).

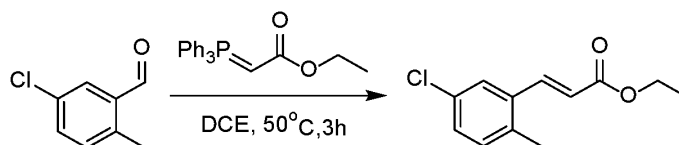
[000314] **Compound 114-P2** LC/MS ESI 642.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.71 – 7.43 (m, 1H), 7.38 – 6.96 (m, 5H), 4.90 (s, 1H), 4.83 – 4.27 (m, 2H), 3.82 (s, 1H), 3.49 – 3.33 (m, 1H), 2.71 (d, *J* = 78.6 Hz, 9H), 2.48 (s, 5H), 2.41 (s, 2H), 2.31 – 1.54 (m, 10H), 1.04 (d, *J* = 6.3 Hz, 6H).

[000315] 114-P1 and 114-P2 were assigned as (R)-2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid and (S)-2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid, respectively.



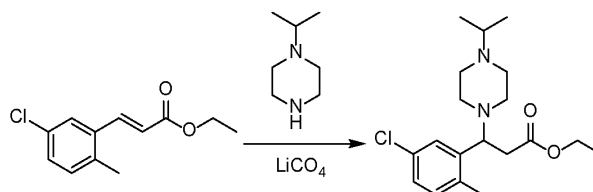
Example 7: Preparation of Compounds 115-P1 and 115-P2

Step 1: ethyl (E)-3-(5-chloro-2-methylphenyl)acrylate



[000316] A mixture of 5-chloro-2-methylbenzaldehyde (5.0 g, 32.3 mmol, 1.0 eq.) and ethyl 2-(triphenyl-15-phosphaneylidene)acetate (11.8 g, 33.9 mmol, 1.05 eq.) in 1,2-dichloroethane (100 mL) was stirred at 50°C for 3 hr. The reaction mixture was concentrated in *vacuo*. Crude residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give ethyl (E)-3-(5-chloro-2-methylphenyl)acrylate (7.0 g, 96 %) (ESI 225.1 (M+H)⁺).

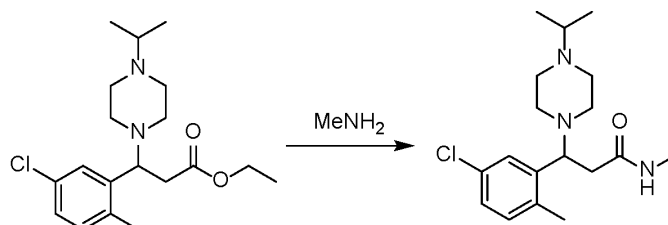
Step 2: ethyl 3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propanoate



[000317] To a solution of ethyl (E)-3-(5-chloro-2-methylphenyl)acrylate (11.5 g, 51.2 mmol, 1.0 eq.) in 1-isopropylpiperazine (50 mL) was added LiCO₄ (11.8 g, 102.4 mmol, 2.0 eq.) and stirred at RT for 3 days. The mixture was poured into 200 mL water and extracted with EtOAc (3 x 100 mL). Combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in *vacuo*. Crude residue was purified by silica gel column chromatography

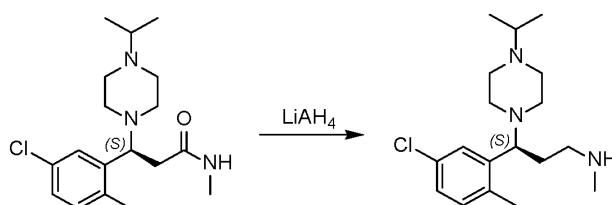
(3:1 petroleum ether: EtOAc) to give ethyl 3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propanoate (8.7 g, 48 %) (ESI 353.2 (M+H)⁺).

Step 3: 3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropanamide



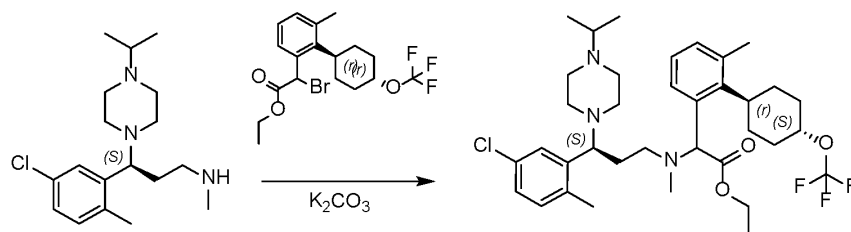
[000318] A mixture of ethyl 3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propanoate (8.4 g, 23.8 mmol) in MeNH₂ solution (1M in MeOH, 300 mL) was stirred RT for 3 days. The reaction mixture was concentrated in *vacuo*. The residue was purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give racemic product as white solid (7.0 g, 87%). Enantiomers were further separated by prep chiral SFC F to give amide P1 (2.9 g) and amide P2 (2.8 g).

Step 4: (S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine



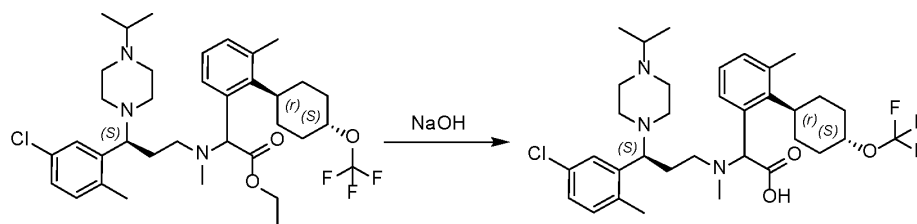
[000319] To a solution of (S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropanamide (2.8 g, 8.3 mmol, 1.0 eq.) P2 in THF (10 mL) was added LiAlH₄ (2.5M in THF, 10 mL, 24.9 mmol, 3.0 eq.). The reaction was stirred at 60 °C for 1hr. The mixture was cooled to 0°C. NaSO₄·10H₂O was added slowly and the mixture was stirred for 10 mins, filtered through a pad of Celite and the filtrate was concentrated in *vacuo* to give (S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine (2.1 g, 6.48 mmol, crude). (ESI 324.3 [M+H]⁺). Crude product was used directly in the subsequent step without further purification.

Step 5: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate



[000320] To a solution of (S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine (200 mg, 0.62 mmol) and ethyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (261 mg, 0.62 mmol) in acetonitrile (5 mL) was added K_2CO_3 (257 mg, 1.9 mmol, 3.0 eq). The reaction mixture was stirred at 70 °C for 3 hr, then filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as a yellow liquid (210 mg, 50%)(ESI 666.2 [M+H]⁺).

Step 6: 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)-(methylamino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid

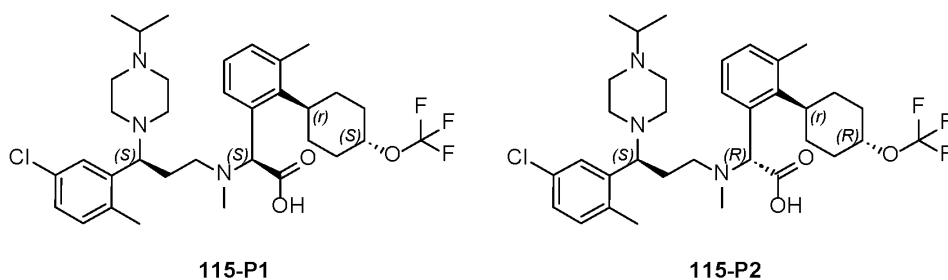


[000321] To a solution of ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (210 mg, 0.31 mmol, 1.0 eq.) in ethanol (3 mL) and water (1 mL) was added NaOH (60 mg, 1.5 mmol, 5.0 eq.). The reaction was stirred at 80 °C for 16 hr. After completion, the reaction pH was adjusted to ~ 6 - 7 with 1N HCl. Solvents were removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH_3CN) to give diastereomeric product **115** as white solid (160 mg, 81.0%). Diastereomers were further separated by prep chiral SFC H to give **115-P1** (31.0 mg) and **115-P2** (41.0 mg).

[000322] **Compound 115-P1** LC/MS ESI 638.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.53 (dd, J = 58.5, 6.9 Hz, 1H), 7.30 – 6.84 (m, 5H), 4.79 – 4.13 (m, 2H), 3.59 (s, 1H), 3.26 – 3.03 (m, 1H), 2.98 – 2.02 (m, 24H), 1.98 – 1.48 (m, 6H), 1.11 (d, J = 5.2 Hz, 6H).

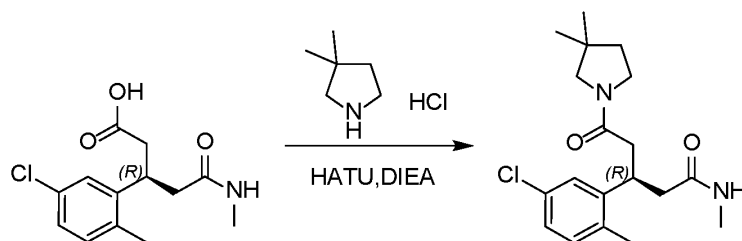
[000323] Compound **115-P2** LC/MS ESI 638.2 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.57 (dd, $J = 58.5, 6.9$ Hz, 1H), 7.39 – 6.91 (m, 5H), 4.87 – 4.22 (m, 2H), 3.67 (s, 1H), 3.38 – 3.15 (m, 1H), 3.09 – 2.15 (m, 24H), 2.08 – 1.64 (m, 6H), 1.19 (d, $J = 5.2$ Hz, 6H).

[000324] **115-P1** and **115-P2** were assigned as (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid and (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid, respectively.



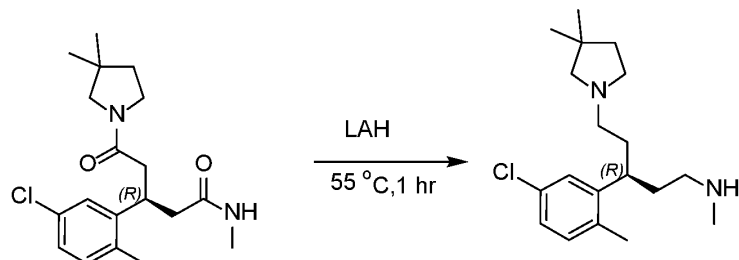
Example 8: Preparation of Compounds 119-P1 and 119-P2

Step 1: (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methyl-5-oxopentanamide



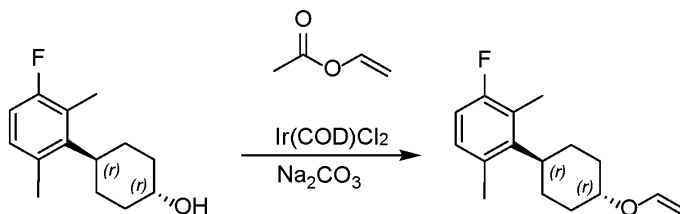
[000325] To a solution of (R)-3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (15.0 g, 55.7 mmol, 1.0 *eq*) and 3,3-dimethylpyrrolidine (5.5 g, 55.7 mmol, 1.0 *eq*) in DMF (60 mL) was added HATU (25.4 g, 66.8 mmol, 1.2 *eq*) followed by DIEA (14.4 g, 111.4 mmol, 2.0 *eq*). The reaction was stirred at RT for 2 hours. After completion, the mixture was quenched with NH_4Cl solution (100 mL) and extracted with EtOAc (3 x 150 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo*, purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methyl-5-oxopentanamide as a colorless oil (16.6 g, 85%) (ESI 351.1 $[M+H]^+$).

Step 2: (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine



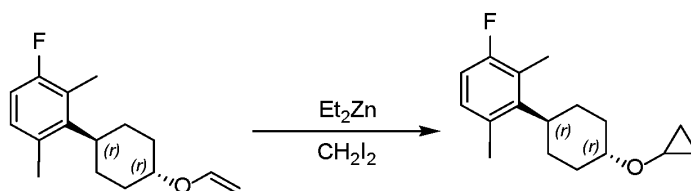
[000326] To a solution of (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-oxo-5-(piperidin-1-yl) pentanamide (16.6 g, 47.4 mmol, 1.0 *eq*) in THF (200 mL) at RT was added LiAlH₄ (56.9 mL, 142.3 mmol, 3.0 *eq*) dropwise and the reaction was stirred at 55 °C for 1 hour. After cooling to 0 °C, the reaction mixture was then quenched with water (5.5 mL) dropwise and stirred at 0 °C for another 10 min. 15% aqueous NaOH (5.5 mL) and water (16.5 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT and stirred for another 15 min, dried over Na₂SO₄, filtered and the filtrate was concentrated in *vacuo* to give (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine as a white solid used directly in next reaction (13.1 g, 85%) (ESI 323.3 [M+H]⁺).

Step 3: 1-fluoro-4-iodo-2-methyl-3-((1*r*,4*r*)-4-(vinylloxy)cyclohexyl)benzene



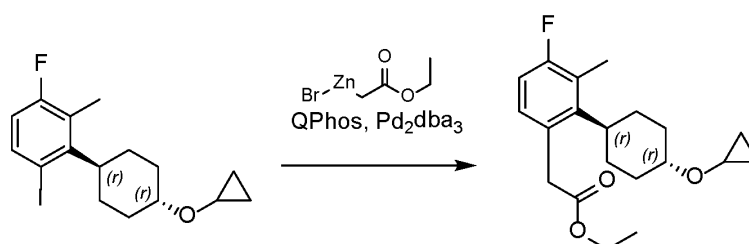
[000327] To a solution of (1*r*,4*r*)-4-(3-fluoro-6-iodo-2-methylphenyl)cyclohexan-1-ol (50.1 g, 150.0 mmol, 1.0 *eq*), Na₂CO₃ (15.9 g, 150.0 mmol, 1.0 *eq*) and chloro-1,5-cyclooctadiene iridium (I) dimer (4.04 mg, 6.0 mmol, 0.04 *eq*) in Toluene (400 mL) under N₂ atmosphere was added vinyl acetate (38.7 g, 450 mmol, 3.0 *eq*) and the mixture was stirred at 100 °C for 16 hours. After completion, water (2 L) was added and the solution was extracted with EtOAc (3 x 800 mL). The combined organic layers were washed with brine (1 L), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (9 : 1 petroleum ether: EtOAc) to give 1-fluoro-4-iodo-2-methyl-3-((1*r*,4*r*)-4-(vinylloxy)cyclohexyl)benzene as a yellow oil (27.0 g, 50%) e

Step 4: 2-((1*r*,4*r*)-4-cyclopropoxycyclohexyl)-4-fluoro-1-iodo-3-methylbenzene



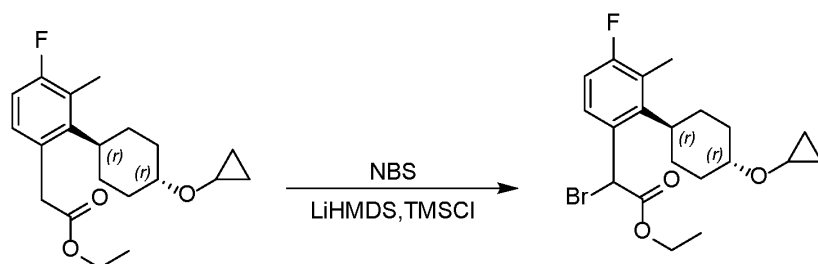
[000328] To a solution of 1-fluoro-4-iodo-2-methyl-3-((1r,4r)-4-(vinylloxy)cyclohexyl)benzene (27.0 g, 75.0 mmol, 1.0 *eq*) in dichloromethane (250 mL) at 0 °C was added Et₂Zn (36.9 g, 300.0 mmol, 4.0 *eq*) dropwise. The reaction was stirred at 0 °C for 0.5 hr. The CH₂I₂ (10.4 g, 300.0 mmol, 4.0 *eq*) was added dropwise, warmed to room temperature and stirring was continued for another 6 hr. The reaction was quenched with saturated NH₄Cl solution (1.5 L) slowly, extracted with dichloromethane (3 x 600 mL). The combined organic phases were washed with brine (900 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate concentrated *in vacuo*. The residue was purified by silica gel column chromatography (10: 1 petroleum ether: EtOAc) to give 2-((1r,4r)-4-cyclopropoxycyclohexyl)-4-fluoro-1-iodo-3-methylbenzene as a colorless oil (20.2 g, 72%).

Step 5: ethyl 2-(2-((1r,4r)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate



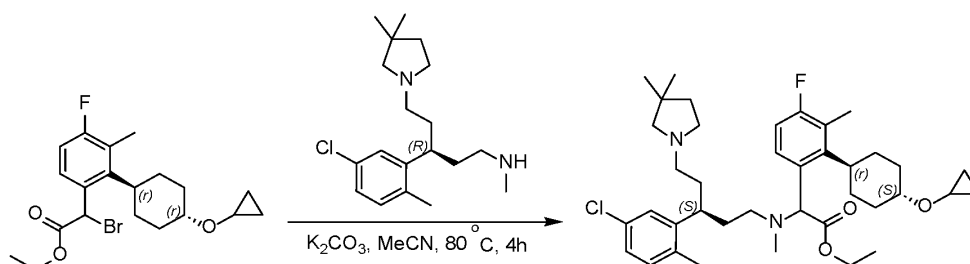
[000329] To a solution of 2-((1r,4r)-4-cyclopropoxycyclohexyl)-4-fluoro-1-iodo-3-methylbenzene (20.2 g, 54 mmol, 1.0 *eq*), Pd₂(dba)₃ (990 mg, 1.08 mmol, 0.02 *eq*) and QPhos (792 mg, 1.08 mmol, 0.02 *eq*) in tetrahydrofuran (100 mL) under N₂ atmosphere was added (2-ethoxy-2-oxoethyl)zinc(II) bromide (162 mL, mol/L, 162 mmol, 3.0 *eq*) and the mixture was heated to 65 °C for 1 hr. After completion, saturated NH₄Cl aqueous solution (500 mL) was added and the solution was extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (15: 1 petroleum ether: EtOAc) to give ethyl 2-(2-((1r,4r)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate as a colorless oil (17.0 g, 72%) (ESI 357.1 [M+Na]⁺).

Step 6: ethyl 2-bromo-2-(2-((1r,4r)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate



[000330] To a solution of LiHMDS (1M in THF, 102.0 ml, 102.0 mmol, 2.0 *eq*) at -78°C, ethyl 2-(2-((1r,4r)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate (17.0 g, 51.0 mmol, 1.0 *eq*) in tetrahydrofuran (150 ml) was added dropwise. The reaction was stirred at -78°C for 0.5 hr. TMSCl (11.1g, 102.0 mmol, 2.0 *eq*) was then added dropwise, and stirring was continued at -78°C for another 15 min. A solution of NBS (20.2 g, 102.0 mmol, 2.0 *eq*) in tetrahydrofuran (150 mL) was then added dropwise. The reaction was stirred at -78°C for another 1 hr., then warmed to 0 °C, quenched with saturated aqueous NH₄Cl solution (1.1 L) at 0°C, extracted with EtOAc (3 x 600 ml). Combined organic layers were washed with brine (500 ml x 3), dried over Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (19:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(2-((1r,4r)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate as a yellow oil (19.0 g, 90.2%) (ESI 435.0 [M+Na]⁺).

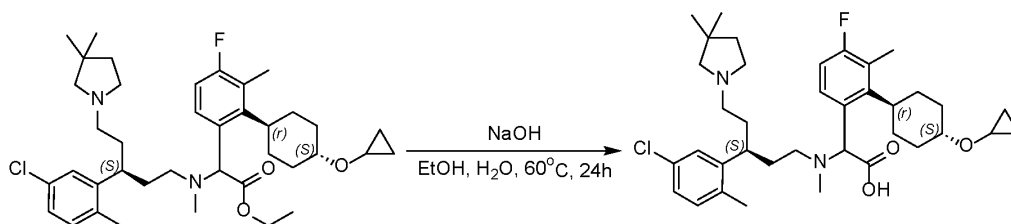
Step 7: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(2-((1r,4S)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate



[000331] To a solution of (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine (10.0 g, 31.0 mmol, crude) in acetonitrile (150 mL), was added K₂CO₃ (12.42 g, 90 mmol, 3.0 *eq*). The mixture was stirred at RT for 15 min. The ethyl 2-bromo-2-(2-((1r,4r)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate (12.36 g, 30.0 mmol, 1.0 *eq*) was added. Stirring was continued at 80 °C for another 4 hr. After completion, the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The

residue was purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(2-((1*r*,4*S*)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate as a yellow oil (14.1 g, 71.7%) (ESI 655.3 [M+H]⁺).

Step 8: 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(2-((1*r*,4*S*)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetic acid (Compound 119)



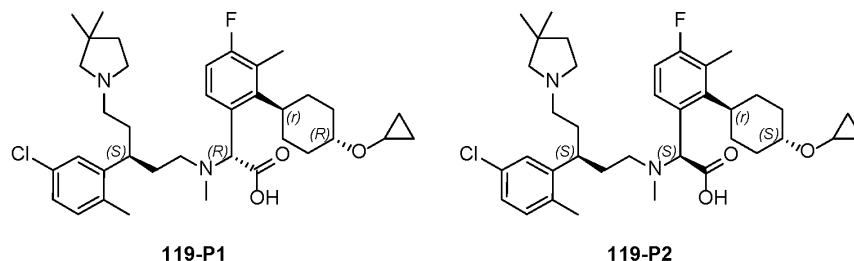
[000332] Ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(2-((1*r*,4*S*)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetate (14.1 g, 21.5 mmol, 1.0 *eq*) was treated with NaOH (3.44 g, 86.0 mmol, 4.0 *eq*) in ethanol (120 mL) and water (40 mL) at 60 °C for 24 hr. The reaction mixture was acidified to pH ~5-6 with 1N HCl. Solvents were removed *in vacuo*. Crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give the diastereomeric product **119** as white solid (10.6 g, 78.6%). Diastereomers were further separated by Prep chiral SFC P to give products **119-P1** (4.3 g) and **119-P2** (4.1 g) as white solids.

[000333] **Compound 119-P1** LC/MS ESI 627.4 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.53 (dd, *J* = 65.0, 56.6 Hz, 1H), 7.08 – 6.93 (m, 3H), 6.73 (t, *J* = 9.0 Hz, 1H), 4.30 – 4.08 (m, 1H), 3.69 – 3.38 (m, 3H), 2.85 – 2.74 (m, 1H), 2.52 (dd, *J* = 11.2, 6.7 Hz, 2H), 2.40 – 2.07 (m, 17H), 1.98 (dd, *J* = 24.8, 11.8 Hz, 2H), 1.82 – 1.63 (m, 4H), 1.55 (t, *J* = 6.9 Hz, 3H), 1.49 – 1.29 (m, 3H), 1.11 – 0.98 (m, 6H), 0.59 – 0.43 (m, 4H).

[000334] **Compound 119-P2** LC/MS ESI 627.4 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.57 (d, *J* = 106.9 Hz, 1H), 7.24 – 7.03 (m, 3H), 6.85 (dt, *J* = 33.2, 8.7 Hz, 1H), 4.52 (d, *J* = 85.4 Hz, 1H), 3.66 – 3.32 (m, 3H), 3.05 (dd, *J* = 26.6, 19.1 Hz, 3H), 2.83 – 2.28 (m, 12H), 2.24 – 1.98 (m, 8H), 1.94 – 1.69 (m, 6H), 1.59 – 1.30 (m, 3H), 1.10 (s, 6H), 0.64 – 0.43 (m, 4H).

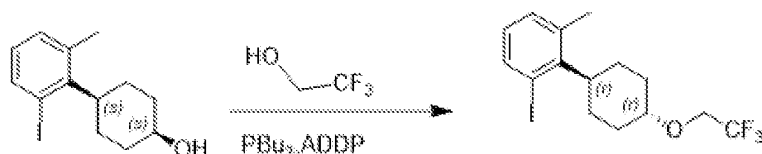
[000335] **119-P1** and **119-P2** were assigned as (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(2-((1*r*,4*R*)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetic acid and (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-

dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(2-((1*r*,4*S*)-4-cyclopropoxycyclohexyl)-4-fluoro-3-methylphenyl)acetic acid, respectively.



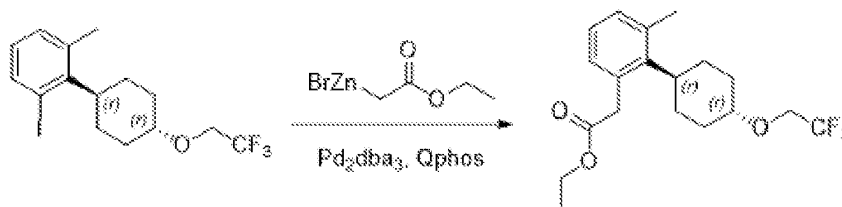
Example 9: Preparation Compounds 162-P1 and 162-P2

Step 1: 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)benzene



[000336] To a solution of (1*s*,4*s*)-4-(2-iodo-6-methylphenyl)cyclohexan-1-ol (4.4 g, 13.9 mmol, 1.0 eq) and ADDP (7.0 g, 27.8 mmol, 2.0 eq) in toluene (70 mL) at 0°C, PBu₃ (5.6 g, 27.8 mmol, 2.0 eq.) was added dropwise. The reaction was stirred at 0°C for 10 min. 2,2,2-trifluoroethan-1-ol (13.9 g, 139.0 mmol, 10.0 eq.) was then added dropwise. The reaction was heated at 70°C for 16 hr. The reaction was poured into water (60 mL) and extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with brine (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)benzene as a colorless oil (1.25 g, 26%) (ESI 421.0 [M+Na]⁺).

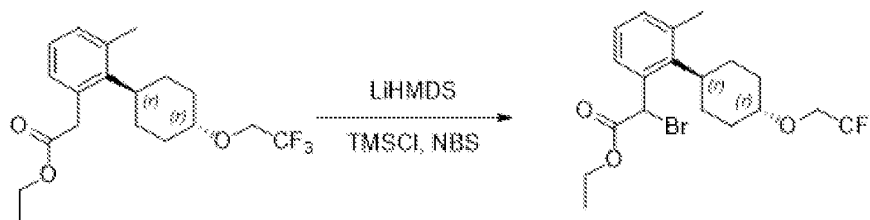
Step 2: ethyl 2-(3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate



[000337] To a suspension of 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)benzene (1.25 g, 3.1 mmol, 1.0 eq.) in THF (10 mL) was added Pd₂dba₃ (140 mg, 0.16 mmol, 0.05 eq.) and QPhos (88 mg, 0.12 mmol, 0.04 eq.) followed by

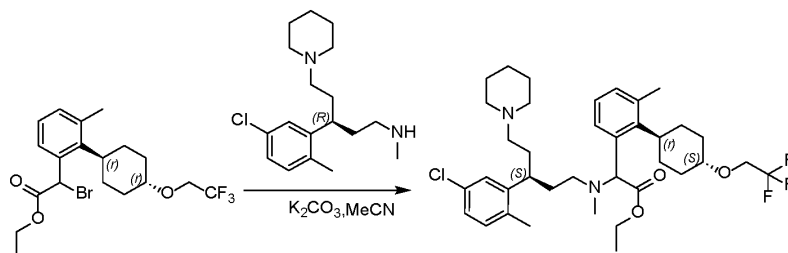
(2-ethoxy-2-oxoethyl)zinc(II) bromide (1M in THF, 15.5 mL, 15.5 mmol, 5.0 eq.). The mixture was stirred at 65 °C under N₂ atmosphere for 1 hr., then poured into 50 mL saturated aqueous NH₄Cl solution and extracted with EtOAc (3 x 50 mL). Combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give ethyl 2-(3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl) phenyl)acetate as a colorless oil (540 mg, 45%) (ESI 381.0 [M+Na]⁺).

Step 3: ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl) phenyl)acetate



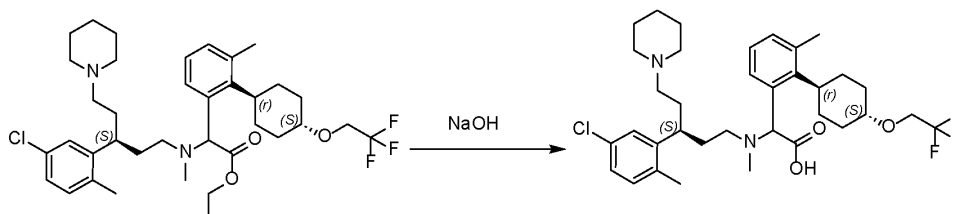
[000338] To a solution of LiHMDS (1M in THF, 2.3 ml, 2.3 mmol, 1.5 eq.) at -78°C, ethyl 2-(3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate (540 mg, 1.5 mmol, 1.0 eq.) in THF (10 ml) was added dropwise. The reaction was stirred at -78°C for 0.5 hr. TMSCl (240 mg, 2.3 mmol, 1.5 eq.) was then added dropwise, and stirring was continued at -78°C for another 15 min. A solution of NBS (400 mg, 2.3 mmol, 1.5 eq) in THF (10mL) was then added dropwise. The reaction was stirred at -78°C for another 1 hr., then warmed to 0 °C, quenched with saturated aqueous NH₄Cl solution (50 ml) at 0°C, and extracted with EtOAc (3 x 50 ml). Combined organic layers were washed with brine (3 x 50 ml), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (10:1 PE: EA) to give ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate as a colorless oil (440 mg, 68%) (ESI 459.1 [M+Na]⁺).

Step 4: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl) phenyl)acetate



[000339] To a solution of ethyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate (220 mg, 0.5 mmol, 1.0 eq.) in acetonitrile (6 mL) was added K_2CO_3 (210 mg, 1.5 mmol, 3.0 eq.) followed by (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (200 mg, 0.65 mmol, 1.3 eq.). The mixture was stirred at 70 °C for 3 hr. After completion, the reaction mixture was filtered and concentrated under reduced pressure. Crude residue was purified by silica gel column chromatography (9:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate as a yellow oil (250 mg, 75%) (ESI 665.3 $[M+H]^+$).

Step 5: 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetic acid



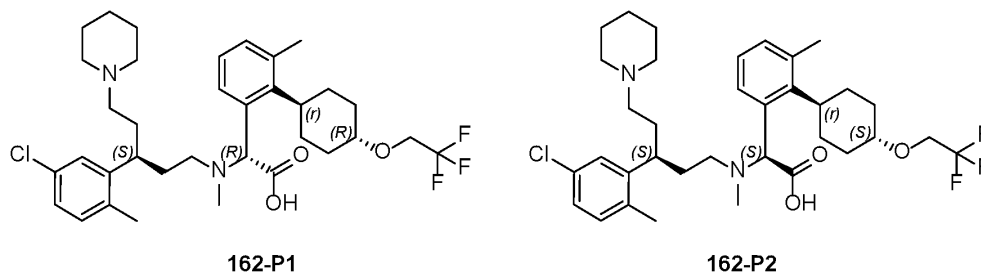
[000340] To a solution of ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate (250 mg, 0.38 mmol, 1.0 eq.) in ethanol (3 mL) and water (1 mL) was added NaOH (150 mg, 3.8 mmol, 10.0 eq.). The reaction was stirred at 60 °C for 16 hr. After completion, the reaction pH was adjusted to ~ 6 - 7 with 1N HCl. Solvents were removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH_3CN) to give diastereomeric product **162** as white solid (160 mg, 64%). Diastereomers were further separated by prep chiral SFC A to give **162-P1** (66 mg) and **162-P2** (68 mg).

[000341] **Compound 162-P1** LC/MS ESI 637.2 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.65 – 7.34 (m, 1H), 7.21 – 6.80 (m, 5H), 4.64 (d, J = 33.6 Hz, 1H), 4.02 – 3.84 (m, 2H), 3.68 –

3.45 (m, 1H), 3.25 – 2.96 (m, 1H), 2.93 – 2.55 (m, 5H), 2.54 – 2.29 (m, 9H), 2.23 – 1.71 (m, 13H), 1.66 – 1.52 (m, 5H), 1.51 – 1.31 (m, 4H). RT (cSFC, (R,R)WHELK-O1): 1.54 min

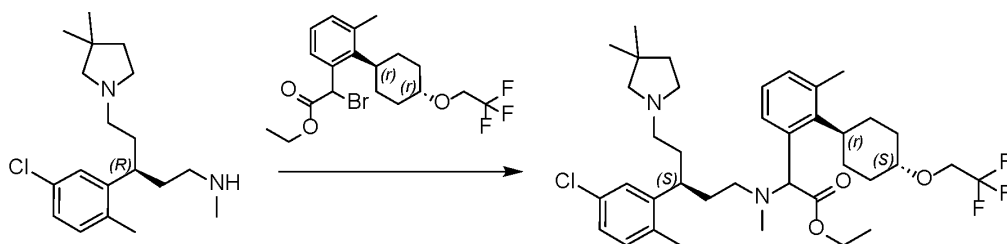
[000342] **Compound 162-P2** LC/MS ESI 637.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.64 – 7.39 (m, 1H), 7.32 – 6.96 (m, 5H), 4.64 (d, J = 56.7 Hz, 1H), 4.11 – 3.77 (m, 2H), 3.72 – 3.42 (m, 1H), 3.29 – 2.90 (m, 2H), 2.86 – 2.41 (m, 12H), 2.39 – 2.24 (m, 2H), 2.21 – 1.76 (m, 12H), 1.70 – 1.59 (m, 4H), 1.58 – 1.32 (m, 5H). RT (cSFC, (R,R)WHELK-O1): 1.89 min.

[000343] **162-P1** and **162-P2** were assigned as (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*R*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetic acid and (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetic acid, respectively.



Example 10: Preparation of Compounds 164-P1 and 164-P2)

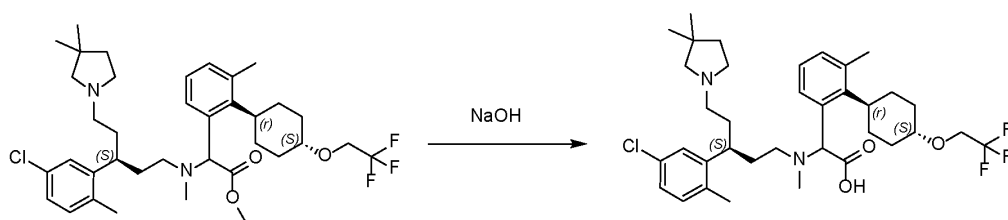
Step 1: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)-(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate



[000344] To a solution of (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine (218 mg, 0.5 mmol) and ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate (196 mg, 0.5 mmol) in acetonitrile (5 mL) was added DIEA (200 mg, 1.5 mmol, 3.0 eq). The reaction mixture was stirred at 70 °C for 3 hr, then filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (20:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-

chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate as a yellow liquid (200 mg, 0.29 mmol, 49.1%). (ESI 679.2 [M+H]⁺).

Step 2: 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)-(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetic acid

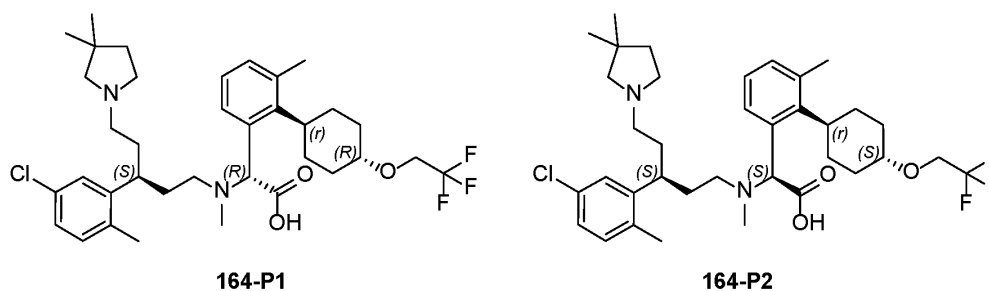


[000345] To a solution of ethyl 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate (200 mg, 0.30 mmol, 1.0 eq.) in ethanol (3 mL) and water (1 mL) was added NaOH (72 mg, 1.8 mmol, 6.0 eq.). The reaction was stirred at 80 °C for 16 hr. After completion, the reaction pH was adjusted to ~ 6 - 7 with 1N HCl. Solvents were removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give **164-P1** (44.2 mg) and **164-P2** (50.5 mg) as white solids.

[000346] **Compound 164-P1** LC/MS ESI 651.1 ¹H NMR (400 MHz, MeOD) δ 7.46 (dd, *J* = 44.3, 5.9 Hz, 1H), 7.06 (m, 5H), 4.65 (d, *J* = 32.3 Hz, 1H), 4.04 – 3.89 (m, 2H), 3.51 (t, *J* = 11.6 Hz, 1H), 3.13 (m, 1H), 2.84 (d, *J* = 49.9 Hz, 4H), 2.63 (d, *J* = 17.5 Hz, 3H), 2.54 – 2.37 (m, 6H), 2.32 (s, 2H), 2.23 – 1.71 (m, 12H), 1.65 (t, *J* = 7.0 Hz, 2H), 1.58 – 1.31 (m, 3H), 1.11 (d, *J* = 21.1 Hz, 6H).

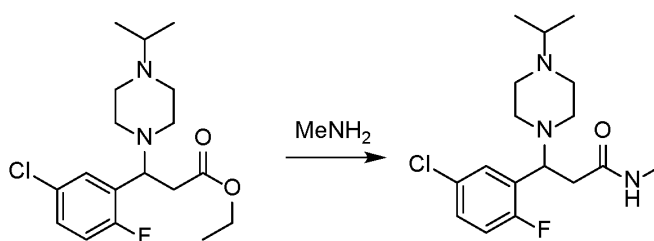
[000347] **Compound 164-P2** LC/MS ESI 651.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.53 (dd, *J* = 77.8, 5.8 Hz, 1H), 7.10 (m, 5H), 4.61 (d, *J* = 57.7 Hz, 1H), 3.96 (m, 2H), 3.54 (dd, *J* = 26.8, 15.7 Hz, 1H), 3.08 – 2.80 (m, 3H), 2.61 (d, *J* = 11.2 Hz, 4H), 2.56 – 2.30 (m, 8H), 2.25 – 1.73 (m, 13H), 1.67 (dd, *J* = 14.2, 7.0 Hz, 2H), 1.58 – 1.31 (m, 3H), 1.09 (s, 6H).

[000348] **164-P1** and **164-P2** were assigned as (*R*)-2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*R*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetic acid and (*S*)-2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetic acid, respectively.



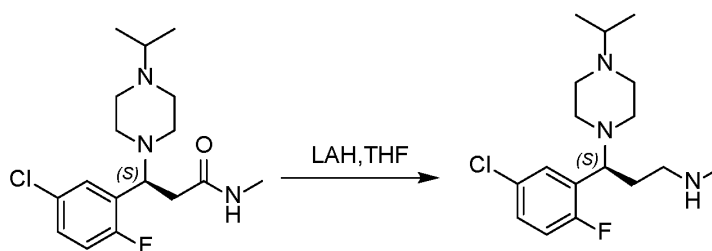
Example 11: Preparation of Compounds 183-P1 and 183-P2

Step 1: 3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropanamide



[000349] A solution of 3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropanamide (27 g, 75.8 mmol, 1.0 eq.) in methylamine (33% in methanol, 35.6 g, 379mmol, 5.0 eq) was stirred at 60°C for 16 hr. The reaction was concentrated *in vacuo*. Crude residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to give 3-(5-chloro-2-fluorophenyl)-N-methyl-3-(4-methylpiperazin-1-yl)propanamide (22 g, 85%). 10g enantiomers was further separated by prep chiral SFC C to give amide P1 (4.2 g) and amide P2 (4.2 g) as yellow oil (ESI 342.1 [M+H]⁺).

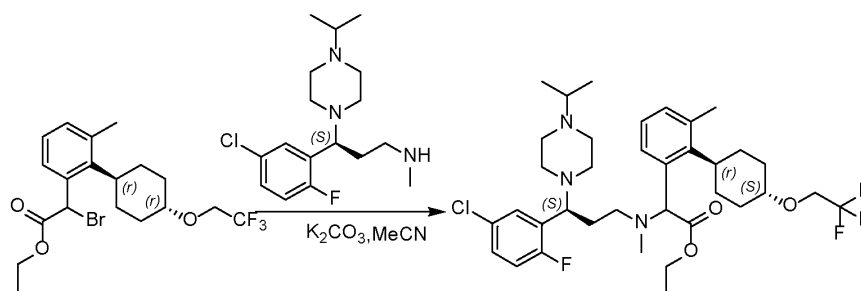
Step 2: (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine



[000350] To a solution of (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropanamide (4.2 g, 12.3mmol, 1.0 eq.) in THF (50 mL) at 0 °C was added LAH (37 mL, 37.0 mmol, 3 eq) under N₂. The reaction was stirred at 60 °C for 20 min under N₂. The reaction was quenched with water(1.4 mL) dropwise. NaOH(1.4 mL, 15% in water) and

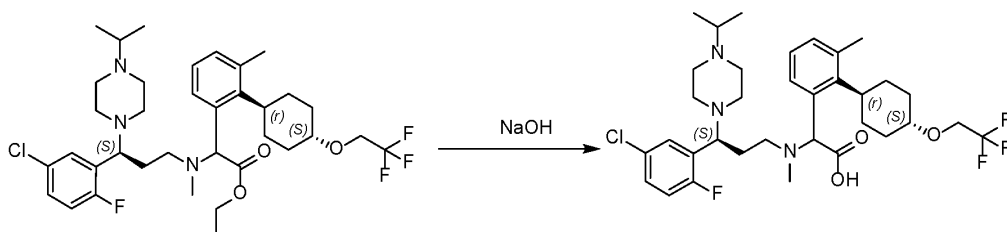
water (4.2 mL) and stirred at 0°C for 15 min, dried over anhydrous Na₂SO₄, filtrated and the filtrate was concentrated *in vacuo*. Crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine as a colorless oil (560 mg, 14%).

Step 3: ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)-(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy) cyclohexyl)phenyl)acetate



[000351] To a solution of ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetate (200 mg, 0.46 mmol, 1.0 eq.) in acetonitrile (6 mL) was added K₂CO₃ (190 mg, 1.38 mmol, 3.0 eq.) and (S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine (200 mg, 0.6 mmol, 1.3 eq.). The mixture was stirred at 70°C for 3 hr. After completion, the reaction mixture was filtered and concentrated under reduced pressure. Crude residue was purified by silica gel column chromatography (9:1 dichloromethane: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)-(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy) cyclohexyl)phenyl)acetate as a yellow oil (190 mg, 62%) (ESI 684.3 [M+H]⁺).

Step 4: 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)-(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl) phenyl)acetic acid (Compound 183)

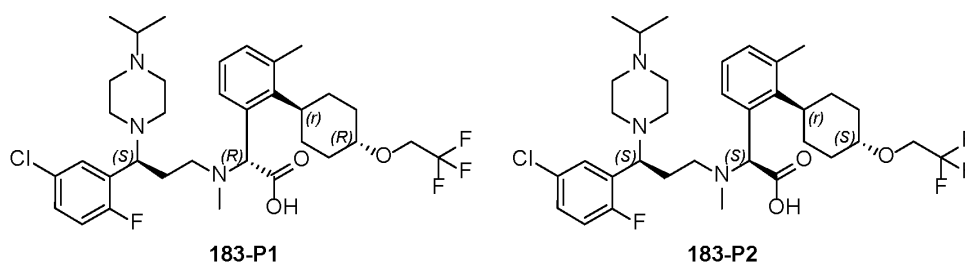


[000352] To a solution of ethyl 2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy) cyclohexyl)phenyl)acetate (190 mg, 0.28 mmol, 1.0 eq.) in ethanol (3 mL) and water (1 mL) was added NaOH (110 mg, 2.8 mmol, 10.0 eq.). The reaction was stirred at 60 °C for 16 hr. After completion, the reaction pH was adjusted to ~ 6 - 7 with 1N HCl. Solvents were removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give diastereomeric product **183** as white solid (100 mg, 53%). Diastereomers were further separated by prep chiral SFC A to give **183-P1** (42 mg) and **183-P2** (42 mg).

[000353] **Compound 183-P1** LC/MS ESI 656.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.65 – 7.50 (m, 1H), 7.46 – 7.05 (m, 5H), 4.89 (s, 1H), 4.33 (s, 1H), 4.12 – 3.89 (m, 2H), 3.83 – 3.50 (m, 2H), 3.28 – 3.08 (m, 2H), 2.98 – 2.34 (m, 15H), 2.30 – 1.82 (m, 7H), 1.79 – 1.35 (m, 3H), 1.20 – 0.99 (m, 6H). RT (chiral SFC A): 1.28 min

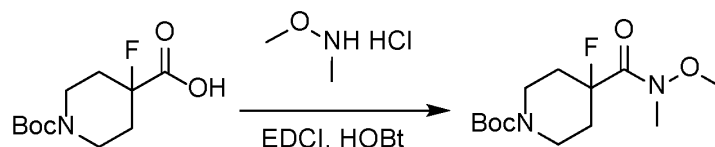
[000354] **Compound 183-P2** LC/MS ESI 656.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.70 – 7.44 (m, 1H), 7.41 – 6.99 (m, 5H), 4.89 (s, 1H), 4.80 (s, 1H), 4.09 – 3.83 (m, 3H), 3.74 – 3.51 (m, 1H), 3.30 – 3.15 (m, 2H), 3.08 – 2.30 (m, 17H), 2.31 – 2.12 (m, 3H), 2.11 – 1.69 (m, 4H), 1.63 – 1.39 (m, 2H), 1.20 – 1.00 (m, 6H). RT (chiral SFC A): 1.80 min

[000355] **183-P1** and **183-P2** were assigned as (R)-2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*R*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetic acid and (S)-2-(((S)-3-(5-chloro-2-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(2,2,2-trifluoroethoxy)cyclohexyl)phenyl)acetic acid, respectively.



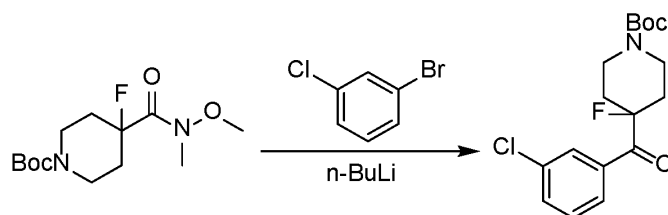
Example 12: Preparation of Compound 300-P3

Step 1: tert-butyl 4-fluoro-4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate



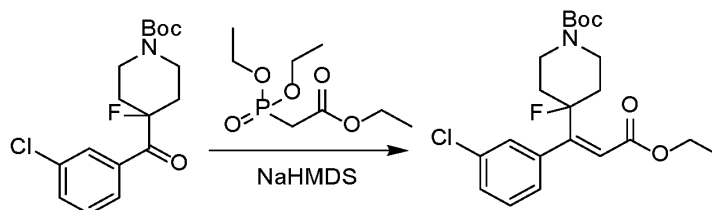
[000356] To a solution of 1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carboxylic acid (10 g, 40.4 mmol, 1.0 eq.), *N,O*-dimethylhydroxylamine hydrochloride (4.7 g, 48.5 mmol, 1.2 eq.), HOBT (6.6 g, 48.5 mmol, 1.2 eq.) and TEA (12.3 g, 121.2 mmol, 3.0 eq.) in DCM (100 ml) was added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (8.5 g, 44.5 mmol, 1.1 eq.). The reaction mixture was allowed to stir at RT for 1 hr, diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (5:1 petroleum ether: EtOAc) to give tert-butyl 4-fluoro-4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate as a colorless oil (9.1 g, 77%) (ESI 235.3 [M-tBu+H]⁺).

Step 2: tert-butyl 4-(3-chlorobenzoyl)-4-fluoropiperidine-1-carboxylate



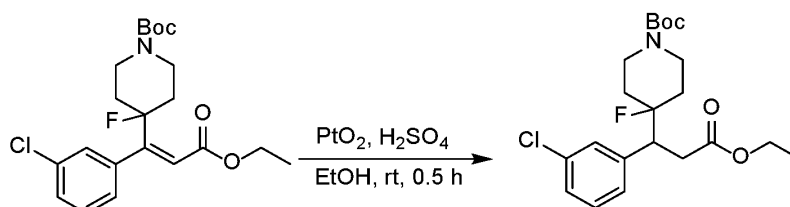
[000357] To a solution of 1-bromo-3-chloro-5-methylbenzene (6.6 g, 34.4 mmol, 1.1 eq.) in anhydrous THF (100 mL) at -78 °C was added n-BuLi (2.5 M in hexane, 10.4 mL, 26.1 mmol, 1.2 eq.). The reaction mixture was allowed to stir at -78 °C for 30 min. A solution of tert-butyl 4-fluoro-4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate (9.1 g, 31.3 mmol, 1.0 eq.) in THF (20 mL) was then added. The reaction was allowed to continue to stir at -78 °C for another 1 hr. The reaction was quenched by the addition of saturated aqueous NH₄Cl (100 mL) and extracted with EtOAc (2 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give tert-butyl 4-(3-chlorobenzoyl)-4-fluoropiperidine-1-carboxylate as a colorless oil (9.0 g, 84.0 %) (ESI 286.1 [M-tBu+H]⁺).

Step 3: tert-butyl (Z)-4-(1-(3-chlorophenyl)-3-ethoxy-3-oxoprop-1-en-1-yl)-4-fluoropiperidine-1-carboxylate



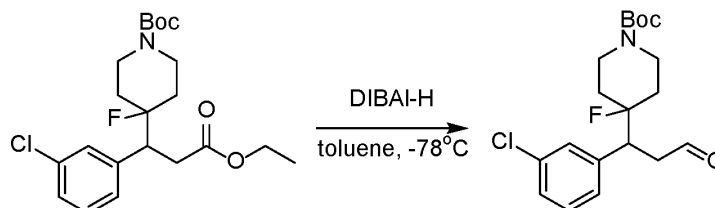
[000358] To a solution of ethyl 2-(diethoxyphosphoryl)acetate (7.8 g, 35.1 mmol, 1.5 eq) in anhydrous THF (50 mL) at 0 °C was added NaHMDS (1.0 M in THF, 35.1 mL, 35.1 mmol, 1.5 eq) dropwise. The reaction mixture was allowed to stir at RT for 0.5 hr. A solution of tert-butyl ((1r,3r)-3-(3-chlorophenyl)-3-(2-oxoethyl)cyclobutyl)(methyl)carbamate (8.0 g, 23.4 mmol, 1.0 eq) in THF (25 mL) was then added. The reaction was allowed to continue to stir at 45 °C for another 16 hrs, quenched by the addition of saturated aqueous NH₄Cl (80 mL) and extracted with EtOAc (3 x 100 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give tert-butyl (Z)-4-(1-(3-chlorophenyl)-3-ethoxy-3-oxoprop-1-en-1-yl)-4-fluoropiperidine-1-carboxylate as a white solid (6.2 g, 64%) (ESI 434.1 [M + Na]⁺).

Step 4: tert-butyl 4-(1-(3-chlorophenyl)-3-ethoxy-3-oxopropyl)-4-fluoropiperidine-1-carboxylate



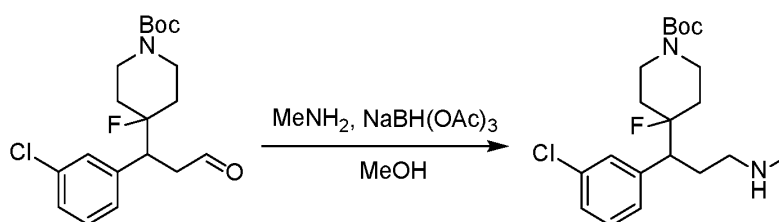
[000359] To a solution of tert-butyl (Z)-4-(1-(3-chlorophenyl)-3-ethoxy-3-oxoprop-1-en-1-yl)-4-fluoropiperidine-1-carboxylate (3.2 g, 7.77 mmol, 1.0 eq.) in EtOH (100 mL) were added PtO₂ (108 mg, 0.39 mmol, 0.05 eq.) and concentrated H₂SO₄ (0.05 mL). The reaction mixture was allowed to stir at RT under an atmosphere of H₂ (1 atm, 3L) for 30 mins. Upon completion, the reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give tert-butyl 4-(1-(3-chlorophenyl)-3-ethoxy-3-oxopropyl)-4-fluoropiperidine-1-carboxylate as a white solid (3.0 g, 93%) (ESI 436.3 [M + Na]⁺).

Step 5: tert-butyl 4-(1-(3-chlorophenyl)-3-oxopropyl)-4-fluoropiperidine-1-carboxylate



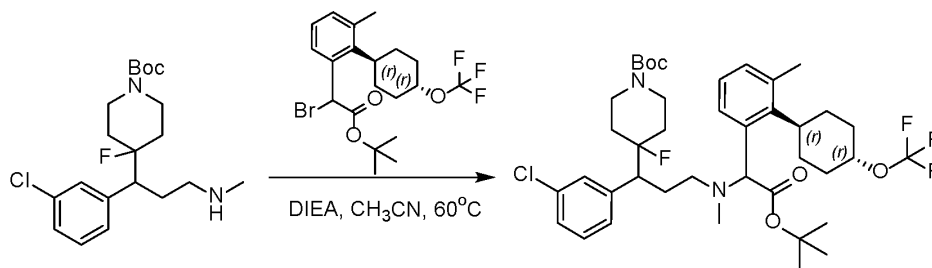
[000360] To a solution of tert-butyl 4-(1-(3-chlorophenyl)-3-ethoxy-3-oxopropyl)-4-fluoropiperidine-1-carboxylate (3.0 g, 7.25 mmol, 1.0 eq.) in anhydrous toluene (50 ml) was added DIBAL-H (1M in toluene, 10.88 ml, 10.88 mmol, 1.5 eq.) at -78°C . The reaction mixture was allowed to stir at -78°C for 2 hrs. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 ml) and extracted with EtOAc (3 x 50 ml). The organic solutions were combined, washed with brine (3 x 20 ml), dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to give tert-butyl 4-(1-(3-chlorophenyl)-3-oxopropyl)-4-fluoropiperidine-1-carboxylate as a colorless oil (crude, 2.0 g, 74%) (ESI 392.1 $[\text{M}+\text{Na}]^+$). The crude product was used directly in the subsequent step without further purification.

Step 6: tert-butyl 4-(1-(3-chlorophenyl)-3-(methylamino)propyl)-4-fluoropiperidine-1-carboxylate



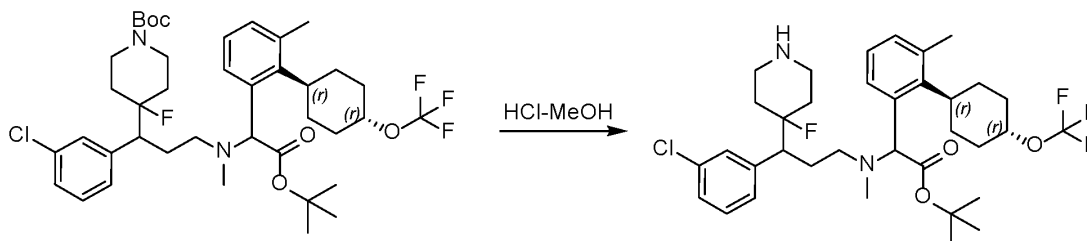
[000361] To a solution of tert-butyl 4-(1-(3-chlorophenyl)-3-oxopropyl)-4-fluoropiperidine-1-carboxylate (2.0 g, 5.41 mmol, 1.0 eq.) in MeOH (100 mL) was added methanamine hydrochloride (1.8 g, 27.05 mmol, 5.0 eq.). The reaction mixture was allowed to stir at RT for 1 hr. $\text{NaBH}(\text{OAc})_3$ (3.4 g, 16.23 mmol, 3.0 eq.) was then added. The reaction was allowed to continue to stir at RT for another 16 hrs and then concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give tert-butyl 4-(1-(3-chlorophenyl)-3-(methylamino)propyl)-4-fluoropiperidine-1-carboxylate as a colorless oil (750 mg, 36%) (ESI 385.4 $[\text{M}+\text{H}]^+$).

Step 7: tert-butyl 4-(3-((2-(tert-butoxy)-1-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)-cyclohexyl)phenyl)-2-oxoethyl)(methyl)amino)-1-(3-chlorophenyl)propyl)-4-fluoropiperidine-1-carboxylate



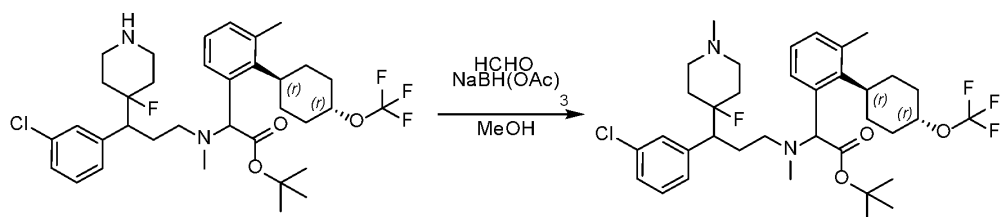
[000362] To a solution of tert-butyl 4-(1-(3-chlorophenyl)-3-(methylamino)propyl)-4-fluoropiperidine-1-carboxylate (380 mg 0.99 mmol, 1.0 eq) in ACN (20 mL) was added DIPEA (384 mg, 2.97 mmol, 3.0 eq.) and tert-butyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (491 mg, 1.09 mmol, 1.1 eq.). The mixture was allowed to stir at 60 °C for 20 hr. The reaction mixture was filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give tert-butyl 4-(3-((2-(tert-butoxy)-1-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)-2-oxoethyl)(methylamino)-1-(3-chlorophenyl)propyl)-4-fluoropiperidine-1-carboxylate as a colorless oil (350 mg, 47%) (ESI 755.6 [M+H]⁺).

Step 8: tert-butyl 2-((3-(3-chlorophenyl)-3-(4-fluoropiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



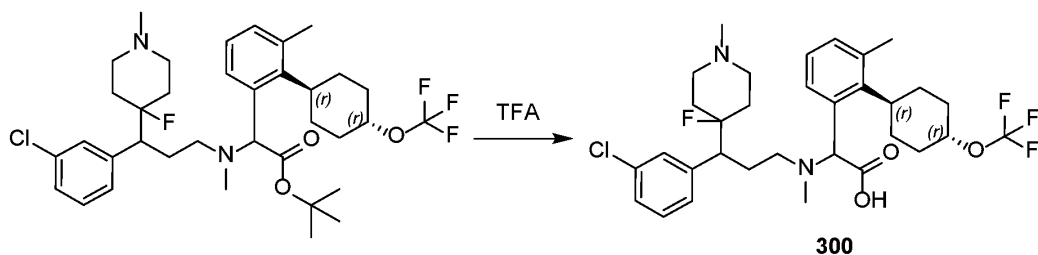
[000363] Tert-butyl 4-(3-((2-(tert-butoxy)-1-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)-phenyl)-2-oxoethyl)(methylamino)-1-(3-chlorophenyl)propyl)-4-fluoropiperidine-1-carboxylate (350 mg, 0.46 mmol, 1.0 eq) in dioxane (6 mL) was treated with HCl-MeOH (4M, 5 mL, 20mmol, 43.0 eq). The reaction mixture was allowed to stir at RT for 2 hr and concentrated *in vacuo* to obtain tert-butyl 2-((3-(3-chlorophenyl)-3-(4-fluoropiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate hydrochloride as a colorless oil (300 mg, 0.46 mmol, crude) (ESI 655.3 [M+H]⁺). The crude product was used directly in the subsequent step.

Step 9: tert-butyl 2-((3-(3-chlorophenyl)-3-(4-fluoro-1-methylpiperidin-4-yl)propyl)-(methylamino)-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000364] To a solution of tert-butyl 2-((3-(3-chlorophenyl)-3-(4-fluoropiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (300 mg, 0.46 mmol, 1.0 eq.) in MeOH (20 mL) was added 33% aqueous HCHO (4 mL, 42 mmol, 96.0eq). The reaction mixture was allowed to stir at RT for 1 hr. NaBH(OAc)₃ (195 mg, 0.92 mmol, 2.0 eq.) was then added and the reaction was allowed to continue to stir at RT for another 20 hr. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give tert-butyl 2-((3-(3-chlorophenyl)-3-(4-fluoro-1-methylpiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as colorless oil (280 mg, 91%) (ESI 669.3 [M+H]⁺).

Step 10: 2-((3-(3-chlorophenyl)-3-(4-fluoro-1-methylpiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



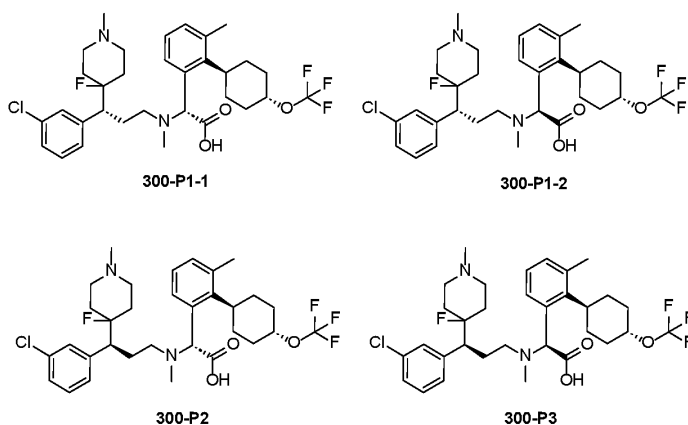
[000365] To a solution of tert-butyl 2-((3-(3-chlorophenyl)-3-(4-fluoro-1-methylpiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (280 mg, 0.42 mmol, 1.0 eq) in DCM (1 mL) was added TFA (5mL, 79 mmol, 189.0 eq). The reaction mixture was allowed to stir overnight at RT. Solvent was removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give a mixture of isomeric compounds **300** as a white solid (200 mg, 78%). Isomers were further separated by prep chiral SFC I to give **300-P1-1** (16.7 mg), **300-P1-2** (16.7 mg), **300-P2** (16.5 mg) and **300-P3** (30.0 mg) as white solids.

[000366] **300-P1-1**, assigned as (R)-2-(((R)-3-(3-chlorophenyl)-3-(4-fluoro-1-methylpiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 613.2 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.58 – 6.95 (m, 7H), 4.85 – 4.77 (m, 1H), 4.55 – 4.30 (m, 1H), 3.16 – 2.60 (m, 7H), 2.53 – 1.94 (m, 16H), 1.92 – 1.30 (m, 8H).

[000367] **300-P1-2**, assigned as (S)-2-(((R)-3-(3-chlorophenyl)-3-(4-fluoro-1-methylpiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 613.3 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.58 – 6.88 (m, 7H), 4.83 – 4.75 (m, 1H), 4.55 – 4.30 (m, 1H), 3.20 – 2.55 (m, 8H), 2.58 – 1.95 (m, 16H), 1.95 – 1.34 (m, 7H).

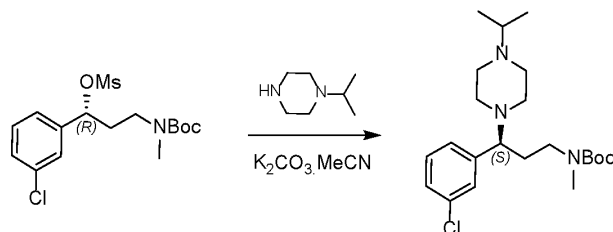
[000368] **300-P2**, assigned as (R)-2-(((S)-3-(3-chlorophenyl)-3-(4-fluoro-1-methylpiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 613.3 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.59 – 6.86 (m, 7H), 4.86 – 4.74 (m, 1H), 4.55 – 4.30 (m, 1H), 3.22 – 3.03 (m, 1H), 3.00 – 2.58 (m, 6H), 2.54 – 1.98 (m, 16H), 1.98 – 1.37 (m, 8H).

[000369] **300-P3**, assigned as (S)-2-(((S)-3-(3-chlorophenyl)-3-(4-fluoro-1-methylpiperidin-4-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 613.3 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 8.51 (s, 0.52H), 7.75 – 6.39 (m, 7H), 4.78 – 4.69 (m, 1H), 4.54 – 4.31 (m, 1H), 3.26 – 2.96 (m, 3H), 2.90 – 1.99 (m, 21H), 1.94 – 1.26 (m, 7H).



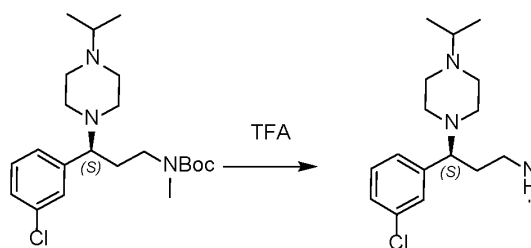
Example 13: Preparation of Compound 301-P2

Step 1: tert-butyl (S)-(3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)-carbamate



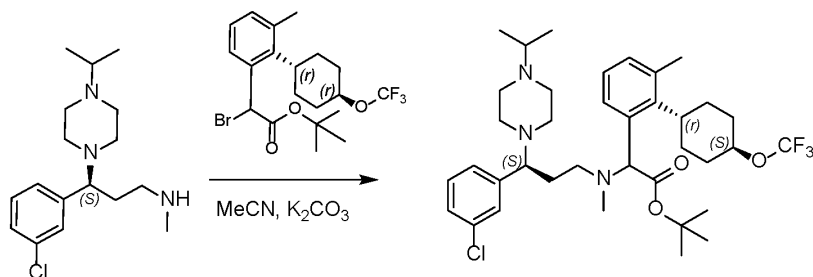
[000370] To a solution of 1-isopropylpiperazine (678 mg 5.3 mmol, 1.0 *eq*) in ACN (10 mL) was added K₂CO₃ (2.2 g, 15.9 mmol, 3.0 *eq*) and (R)-3-((tert-butoxycarbonyl)(methyl)amino)-1-(3-chlorophenyl)propyl methanesulfonate (2 g, 5.3 mmol, 1.0 *eq*). The reaction mixture was allowed to stir at 80 °C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give tert-butyl (S)-3-(3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)carbamate as a yellow oil (300 mg, 14%) (ESI 410.2 [M+H]⁺).

Step 2: (S)-3-(3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine



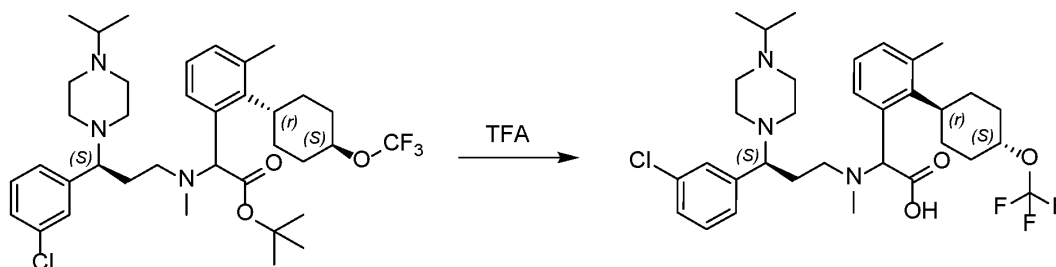
[000371] To a solution of tert-butyl (S)-3-(3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)carbamate (300 mg, 0.73 mmol, 1.0 *eq*) in DCM (2 mL) was added TFA (1 mL, 13.5 mmol, 18.5 *eq*). The reaction mixture was allowed to stir at RT for 2 hr and concentrated *in vacuo* to obtain (S)-3-(3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine as a yellow oil (180 mg, 0.58 mmol, crude) (ESI 310.2 [M+H]⁺). The crude product was used directly in the subsequent step.

Step 3: tert-butyl 2-(((S)-3-(3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000372] To a solution of (S)-3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine (180 mg 0.58 mmol, crude) in ACN (10 mL) was added K_2CO_3 (240 mg, 1.74 mmol, 5.0 *eq.*). The mixture was allowed to stir at RT for 15 min. Tert-butyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (262 mg, 0.58 mmol, 1.0 *eq.*) was then added. The reaction was allowed to continue to stir at 80 °C for another 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue purified by silica gel column chromatography (9:1 DCM: MeOH) to give tert-butyl 2-(((S)-3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as a yellow oil (220 mg, 55%) (ESI 680.4[M+H]⁺).

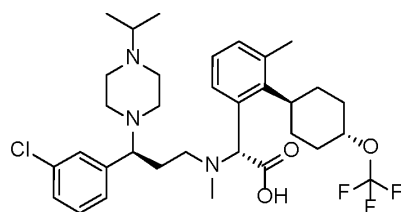
Step 4: 2-(((S)-3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



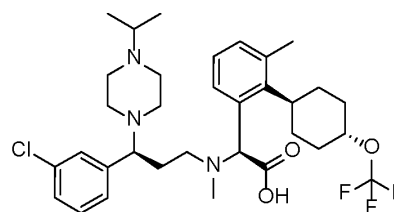
[000373] To a solution of tert-butyl 2-(((S)-3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (220 mg, 0.32 mmol, 1.0 *eq.*) in DCM (1 mL) was added TFA (3 mL, 39 mmol, 122.0 *eq.*). The reaction mixture was allowed to stir overnight at RT. Solvent was removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH_3CN) to give a mixture of stereoisomeric compounds **301** as a white solid (160 mg, 80%). Isomers were further separated by prep chiral SFC A to give **301-P1** (65 mg) and **301-P2** (82 mg) as a white solids.

[000374] **301-P1**, assigned as (R)-2-(((S)-3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 634.2 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.64-7.51 (m, 1H), 7.45-7.09 (m, 6H), 5.08-4.91 (m, 1H), 4.60-4.32 (m, 1H), 4.20-3.75 (m, 1H), 3.70-3.40 (m, 1H), 3.23-2.98 (m, 2H), 2.90-2.40 (m, 15H), 2.38-2.13 (m, 4H), 2.10-1.55 (m, 6H), 1.34-0.96 (m, 6H).

[000375] **301-P2**, assigned as (S)-2-(((S)-3-(3-chlorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 634.2 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.61-7.43 (m, 1H), 7.40-7.03 (m, 6H), 5.02-4.89 (m, 1H), 4.62-4.30 (m, 1H), 3.65-3.42 (m, 1H), 3.25-3.10 (m, 1H), 3.08-2.40 (m, 17H), 2.38-2.12 (m, 4H), 2.09-1.58 (m, 6H), 1.33-0.94 (m, 6H).



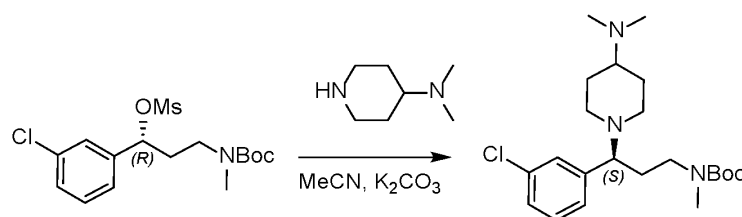
301-P1



301-P2

Example 14: Preparation of Compound 302-P2

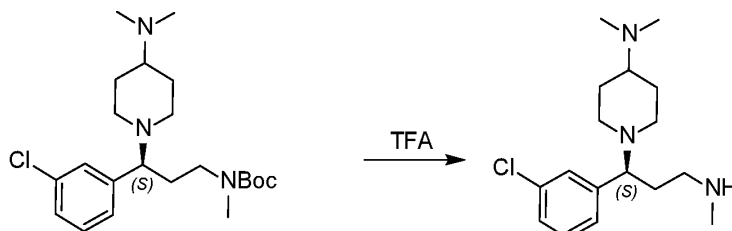
Step 1: tert-butyl (S)-3-(3-(3-chlorophenyl)-3-(4-(dimethylamino)piperidin-1-yl)propyl)(methyl)carbamate



[000376] To a solution of (R)-3-((tert-butoxycarbonyl)(methylamino)-1-(3-chlorophenyl)propyl) methanesulfonate (3.5 g, 9.26 mmol, 1.0 eq.) in ACN (30 mL) was added K_2CO_3 (3.83 g, 27.78 mmol, 3.3 eq.) and *N,N*-dimethylpiperidin-4-amine (1.19 g, 9.26 mmol, 1.0 eq.). The reaction mixture was allowed to stir at 80 °C for 16 hr., filtered and filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (15:1 DCM: MeOH) to give tert-butyl (S)-3-(3-(3-chlorophenyl)-3-(4-

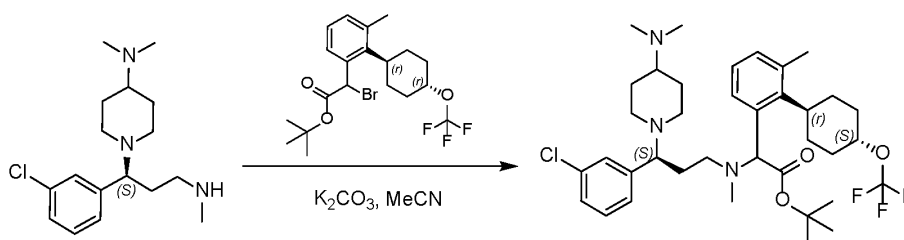
(dimethylamino)piperidin-1-yl)propyl)(methyl)carbamate as a yellow oil (490.0 mg, 12.9%) (ESI 410.3 $[M+H]^+$).

Step 2: (S)-1-(1-(3-chlorophenyl)-3-(methylamino)propyl)-N,N-dimethylpiperidin-4-amine



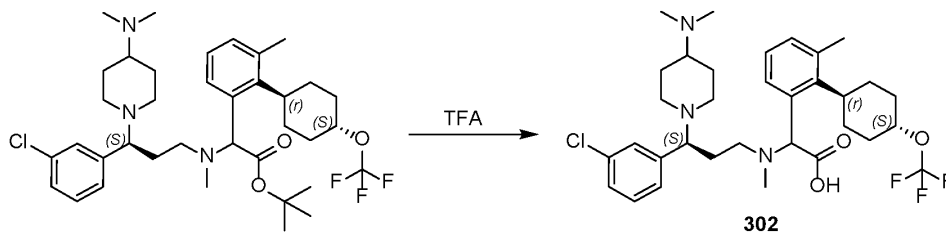
[000377] To a solution of tert-butyl (S)-3-(3-(3-chlorophenyl)-3-(4-(dimethylamino)piperidin-1-yl)propyl)(methyl)carbamate (490 mg, 1.2 mmol, 1.0 *eq*) in DCM (2 mL) was added TFA (1 mL, 13.5 mmol, 11.3 *eq*). The reaction mixture was allowed to stir at RT for 2 hr. and concentrated *in vacuo* to obtain (S)-1-(1-(3-chlorophenyl)-3-(methylamino)propyl)-N,N-dimethylpiperidin-4-amine as a yellow oil (420 mg, 1.35 mmol, crude) (ESI 310.3 $[M+H]^+$). The crude product was used directly in the subsequent step.

Step 3: tert-butyl 2-(((S)-3-(3-chlorophenyl)-3-(4-(dimethylamino)piperidin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000378] To a solution of (S)-1-(1-(3-chlorophenyl)-3-(methylamino)propyl)-N,N-dimethylpiperidin-4-amine (210 mg 0.67 mmol, crude) in ACN (10 mL) was added K_2CO_3 (427 mg, 3.1 mmol, 5.0 *eq*). The mixture was allowed to stir at RT for 15 min. Tert-butyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (302 mg, 0.67 mmol, 1.0 *eq*) was then added. The reaction was allowed to continue to stir at 80 °C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give tert-butyl 2-(((S)-3-(3-chlorophenyl)-3-(4-(dimethylamino)piperidin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as a yellow oil (220 mg, 39.5%) (ESI 680.3 $[M+H]^+$).

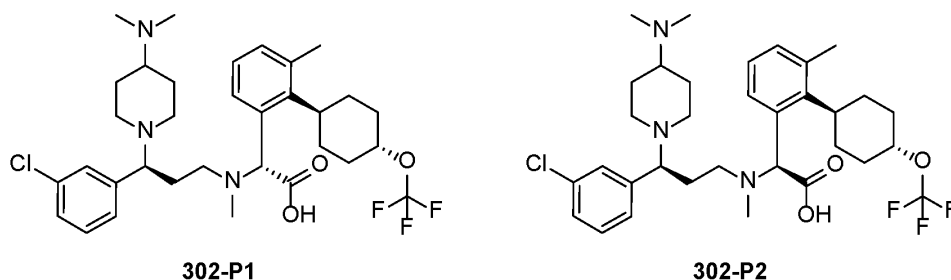
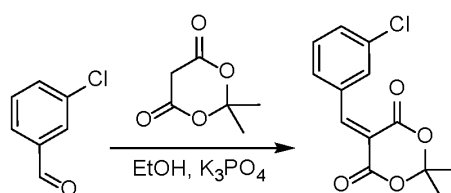
Step 4: 2-(((S)-3-(3-chlorophenyl)-3-(4-(dimethylamino)piperidin-1-yl)propyl)(methyl)-amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



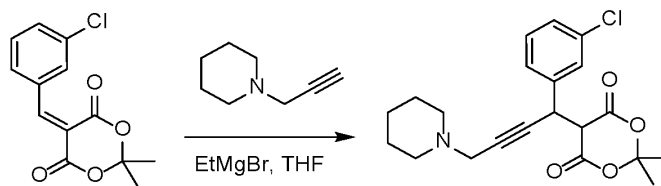
[000379] To a mixture of ethyl 2-(((1*S*,3*R*)-3-(3-chlorophenyl)-3-(2-(piperidin-1-yl)ethyl)cyclobutyl)(methyl)amino)-2-(4-fluoro-1-((1*r*,4*R*)-4-methoxycyclohexyl)-3-methyl-1*H*-indazol-7-yl)acetate (180.0 mg, 0.26 mmol, 1.0 eq) in DCM (1 mL) was added TFA (3 mL, 39 mmol, 150.0 eq). The reaction mixture was allowed to stir overnight at RT. Solvent was removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give a mixture of stereoisomeric compounds **302** as a white solid (110.0 mg, 62%). Stereoisomers were further separated by prep chiral HPLC A to give **302-P1** (30.3 mg) and **302-P2** (25.2 mg) as a white solids.

[000380] **302-P1**, assigned as (R)-2-(((S)-3-(3-chlorophenyl)-3-(4-(dimethylamino)piperidin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 623.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.59 – 7.48 (m, 1H), 7.40 – 7.09 (m, 6H), 4.70 (s, 1H), 4.45 (d, J = 51.0 Hz, 1H), 4.06 (s, 1H), 3.48 – 3.34 (m, 2H), 3.27 – 2.85 (m, 3H), 2.67 (s, 1H), 2.53 – 2.09 (m, 18H), 2.00 – 1.66 (m, 9H), 1.48 (d, J = 12.2 Hz, 1H).

[000381] **302-P2**, assigned as (S)-2-(((S)-3-(3-chlorophenyl)-3-(4-(dimethylamino)piperidin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 623.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.62 – 7.45 (m, 1H), 7.38 – 7.05 (m, 6H), 4.73 (s, 1H), 4.47 (d, J = 79.9 Hz, 1H), 3.59 – 3.48 (m, 1H), 3.33 (s, 1H), 3.06 (ddd, J = 105.0, 59.7, 37.4 Hz, 7H), 2.58 – 2.03 (m, 16H), 1.99 – 1.55 (m, 10H), 1.51 (dd, J = 28.6, 17.5 Hz, 4H).

**Example 15: Preparation of Compound 303-1P2****Step 1: 5-(3-chlorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione**

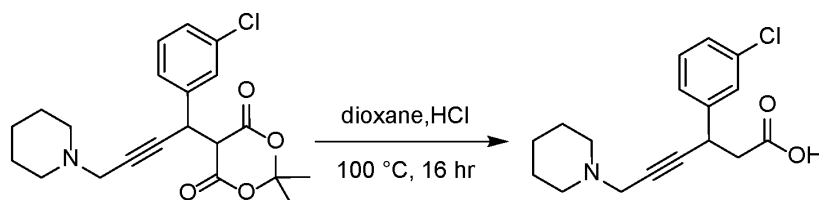
[000382] To a solution of 3-chlorobenzaldehyde (20.0 g, 142.3 mmol, 1.0 eq) and 2,2-dimethyl-1,3-dioxane-4,6-dione (20.52 g, 142.3 mmol, 1.0 eq) in EtOH (500 mL) was added K_3PO_4 (6.0 g, 28.5 mmol, 0.2 eq). The reaction mixture was allowed to stir overnight at RT, then concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (3:1 petroleum ether: EtOAc) to give 5-(3-chlorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione as a yellow solid. (15.0 g, 39.6%). 1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.04 (d, $J = 1.7$ Hz, 1H), 7.87 (d, $J = 7.8$ Hz, 1H), 7.52 (dd, $J = 8.1, 0.8$ Hz, 1H), 7.42 (dd, $J = 9.1, 6.8$ Hz, 1H), 1.82 (s, 6H).

Step 2: 5-(1-(3-chlorophenyl)-4-(piperidin-1-yl)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione

[000383] To a solution of 1-(prop-2-yn-1-yl)piperidine (5.0 g, 40.6 mmol, 1.2 eq.) in anhydrous THF (100 mL) at 0 °C was added ethylmagnesium bromide (1 M in THF, 40.6 mL, 40.6 mmol, 1.2 eq.) dropwise. The reaction mixture was allowed to stir at 0 °C for 30 min. The resulting solution was added slowly into a solution of 5-(3-chlorobenzylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (9.0 g, 33.8 mmol, 1.0 eq.) at 0 °C. The reaction was allowed to continue to stir at 0 °C for another 1 hr. The reaction was quenched by the addition of

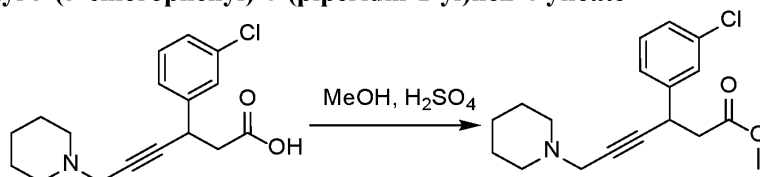
saturated aqueous NH_4Cl (200 mL). The solid which formed was filtered, collected and washed with EtOAc (100 mL) to give 5-(1-(3-chlorophenyl)-4-(piperidin-1-yl)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione as a yellow solid (7.1 g, 53.9%) (ESI 390.1 $[\text{M}+\text{H}]^+$).

Step 3: 3-(3-chlorophenyl)-6-(piperidin-1-yl)hex-4-ynoic acid



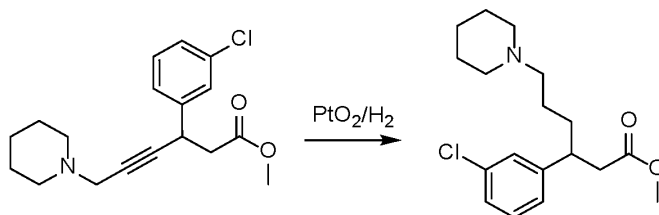
[000384] To a solution of 5-(1-(3-chlorophenyl)-4-(piperidin-1-yl)but-2-yn-1-yl)-2,2-dimethyl-1,3-dioxane-4,6-dione (7.1 g, 18.2 mmol, 1.0 *eq*) in dioxane (75 mL) was added 36% aqueous HCl (25 mL, 300 mmol, 16.5 *eq*). The reaction mixture was allowed to stir at 100 °C for 16 hr. and concentrated *in vacuo* to obtain 3-(3-chlorophenyl)-6-(piperidin-1-yl)hex-4-ynoic acid as a yellow oil (4.0 g, 13.1 mmol, crude) (ESI 306.1 $[\text{M}+\text{H}]^+$). The crude product was used directly in the subsequent step.

Step 4: methyl 3-(3-chlorophenyl)-6-(piperidin-1-yl)hex-4-ynoate



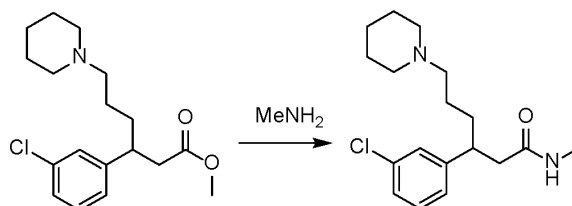
[000385] To a solution of 3-(3-chlorophenyl)-6-(piperidin-1-yl)hex-4-ynoic acid (6 g, 13.1 mmol, 1.0 *eq*) in methanol (80 mL) was added H_2SO_4 (0.5 mL, 9 mmol, 0.69 *eq*) dropwise at 0 °C. The mixture was allowed to stir at 65 °C for 1 hr. The reaction mixture was concentrated under reduced pressure and diluted with EtOAc (200 mL). The organic solution was washed with saturated aqueous NaHCO_3 (200 mL) and brine (200 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (25:1 DCM: MeOH) to give ethyl methyl 3-(3-chlorophenyl)-6-(piperidin-1-yl)hex-4-ynoate as a yellow oil (3.2 g, 76.3%) (ESI 320.1 $[\text{M}+\text{H}]^+$).

Step 5: methyl 3-(3-chlorophenyl)-6-(piperidin-1-yl)hexanoate



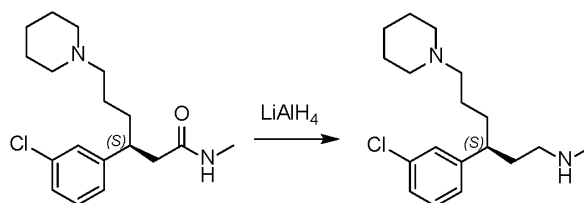
[000386] To a solution of ethyl methyl 3-(3-chlorophenyl)-6-(piperidin-1-yl)hex-4-ynoate (2.8 g, 8.75 mmol, 1.0 eq.) in methanol (32 mL) was added PtO_2 (100 mg, 0.44 mmol, 0.05 eq.). The reaction mixture was allowed to stir at RT under an atmosphere of H_2 (1 atm) for 2 hr. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (25:1 DCM: MeOH) to give methyl 3-(3-chlorophenyl)-6-(piperidin-1-yl)hexanoate as a yellow oil (1.5 g, 52.9%) (ESI 320.1 $[\text{M}+\text{H}]^+$).

Step 6: 3-(3-chlorophenyl)-N-methyl-6-(piperidin-1-yl)hexanamide



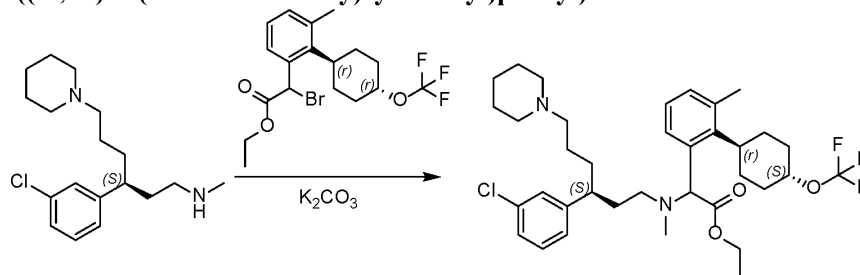
[000387] To a solution of methyl 3-(3-chlorophenyl)-6-(piperidin-1-yl)hexanoate (1.5 g, 4.6 mmol, 1.0 eq) in MeOH (10mL) was added methylamine (4M in THF, 20mL, 80mmol, 17.4 eq) and the reaction mixture was allowed to stir at RT for 16 hr. The reaction mixture was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (10:1 DCM: MeOH) to give racemic product 3-(3-chlorophenyl)-N-methyl-6-(piperidin-1-yl)hexanamide (1.1 g, 74.0%) (ESI 323.2 $[\text{M}+\text{H}]^+$). Enantiomers were separated by prep chiral SFC J to give two compounds. Peak 1 (400 mg), assigned as (S)-3-(3-chlorophenyl)-N-methyl-6-(piperidin-1-yl)hexanamide, and Peak 2 (300 mg), assigned as (R)-3-(3-chlorophenyl)-N-methyl-6-(piperidin-1-yl)hexanamide.

Step 7: (S)-3-(3-chlorophenyl)-N-methyl-6-(piperidin-1-yl)hexan-1-amine



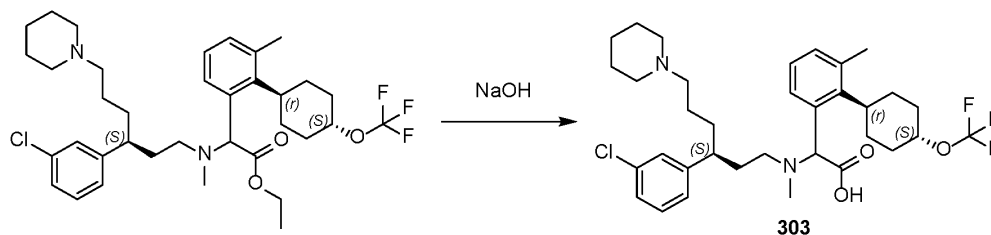
[000388] To a solution of assigned (S)-3-(3-chlorophenyl)-N-methyl-6-(piperidin-1-yl)hexanamide (peak 1 from Step 6, 400 mg, 1.24 mmol, 1.0 *eq*) in THF (8 mL) at RT was added LAH (2.5M in THF, 1.5 mL, 3.72 mmol, 3.0 *eq*) dropwise and the reaction mixture was allowed to stir at 65 °C for 1 hr. After cooling to 0 °C, the reaction was quenched carefully with water (0.15 mL) and allowed to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.15 mL) and water (0.45 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT and stirred for another 15 min. The mixture was dried over Na₂SO₄, filtered and filtrate was concentrated in *vacuo* to give assigned (S)-3-(3-chlorophenyl)-N-methyl-6-(piperidin-1-yl)hexan-1-amine as a colorless oil used directly in next reaction (300 mg, crude, 78.2%) (ESI 309.2 [M+H]⁺).

Step 8: ethyl 2-(((S)-3-(3-chlorophenyl)-6-(piperidin-1-yl)hexyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000389] To a solution of assigned (S)-3-(3-chlorophenyl)-N-methyl-6-(piperidin-1-yl)hexan-1-amine (150 mg, 0.49 mmol, crude) in ACN (5 mL) were added K₂CO₃ (338 mg, 2.45 mmol, 5.0 *eq.*) and ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetate (207 mg, 0.49 mmol, 1.0 *eq*). The reaction mixture was allowed to stir at 80 °C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((S)-3-(3-chlorophenyl)-6-(piperidin-1-yl)hexyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as a yellow oil (170 mg, 53.3%) (ESI 651.3 [M+H]⁺).

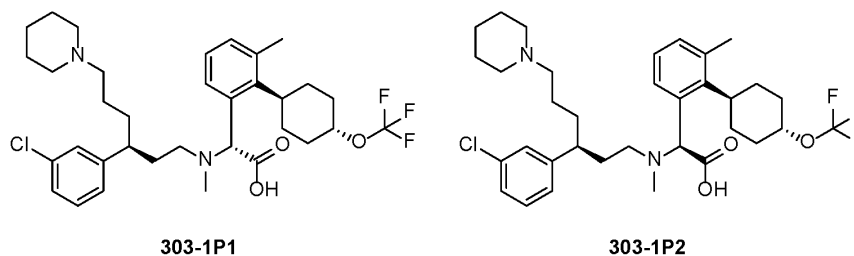
Step 9: 2-(((S)-3-(3-chlorophenyl)-6-(piperidin-1-yl)hexyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



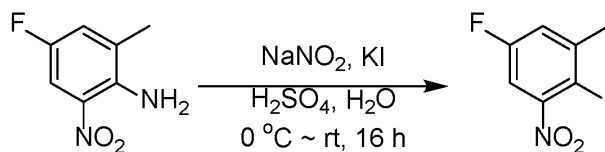
[000390] To a mixture of assigned ethyl 2-(((S)-3-(3-chlorophenyl)-6-(piperidin-1-yl)hexyl)(methyl)amino)-2-(3-methyl-2-((1R,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (170 mg, 0.26 mmol, 1.0 eq) in EtOH (4 mL) and H₂O (1 mL) was added NaOH (52 mg, 1.3 mmol, 5.0 eq). The reaction mixture was allowed to stir at 80 °C for 16 hr. and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give a mixture of stereoisomeric compounds **303** as a white solid (110 mg, 67.6%). The stereoisomers were further separated by prep chiral SFC A to give **303-1P1** (40 mg) and **303-1P2** (40 mg).

[000391] **303-1P1**, assigned as (R)-2-(((S)-3-(3-chlorophenyl)-6-(piperidin-1-yl)hexyl)(methyl)amino)-2-(3-methyl-2-((1R,4R)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 623.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.58 – 7.38 (m, 1H), 7.31 – 6.89 (m, 6H), 4.70 – 4.21 (m, 2H), 3.21 – 2.92 (m, 1H), 2.85 – 2.47 (m, 10H), 2.44 (s, 4H), 2.34 (s, 1H), 2.26 – 1.91 (m, 5H), 1.90 – 1.66 (m, 4H), 1.66 – 1.53 (m, 7H), 1.49 (s, 3H), 1.34 – 1.27 (m, 1H).

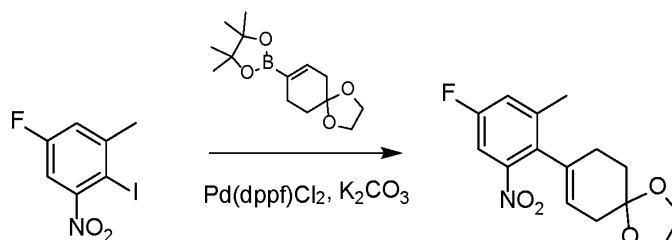
[000392] **303-1P2**, assigned as (S)-2-(((S)-3-(3-chlorophenyl)-6-(piperidin-1-yl)hexyl)(methyl)amino)-2-(3-methyl-2-((1R,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 623.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.68 – 7.36 (m, 1H), 7.32 – 6.85 (m, 6H), 4.62 – 4.26 (m, 2H), 3.13 (s, 1H), 2.87 – 2.53 (m, 9H), 2.54 – 2.42 (m, 5H), 2.39 (s, 1H), 2.24 – 2.08 (m, 3H), 2.06 – 1.72 (m, 5H), 1.72 – 1.55 (m, 7H), 1.54 – 1.36 (m, 4H), 1.35 – 1.23 (m, 1H).



Example 16: Preparation of Compound 304-P2

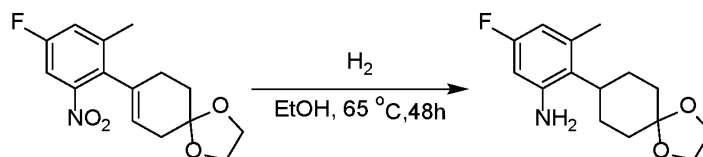
Step 1: 5-fluoro-2-iodo-1-methyl-3-nitrobenzene

[000393] To a solution of 4-fluoro-2-methyl-6-nitroaniline (21.7 g, 127.6 mmol, 1.0 eq.) in THF (250 mL) at $-10\text{ }^\circ\text{C}$ was added aqueous HCl (6M, 53 mL, 319 mmol, 2.5 eq.) and aqueous NaNO_2 (9.7 g in 30 mL water, 140.36 mmol, 1.1 eq.) over 15 mins. The reaction mixture was allowed to stir at $-10\text{ }^\circ\text{C}$ for another 30 min. Aqueous KI (31.8 g in 30 mL water, 191.4 mmol, 1.5 eq.) was then added portionwise into the mixture. The reaction was allowed to warm to $0\text{ }^\circ\text{C}$ and allowed to stir for 30 min. Water (300 mL) and EtOAc (300 mL) were added into the reaction. The organic solution was separated and washed with saturated aqueous Na_2SO_3 (300 mL) and brine (300 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (15:1 petroleum ether: EtOAc) to give 5-fluoro-2-iodo-1-methyl-3-nitrobenzene as a white solid (10.2 g, 28.4%) (ESI 282.0 $[\text{M}+\text{H}]^+$).

Step 2: 8-(4-fluoro-2-methyl-6-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene

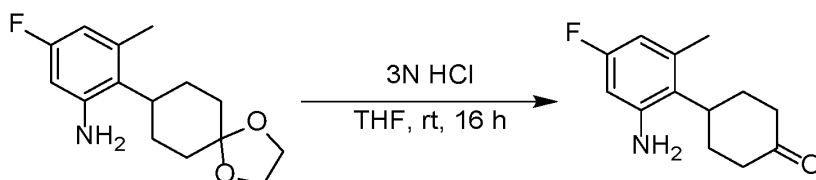
[000394] 5-fluoro-2-iodo-1-methyl-3-nitrobenzene (10.2 g, 36.30 mmol, 1.0 eq.), 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (10.1 g, 38.11 mmol, 1.05 eq.), K_2CO_3 (8.5 g, 61.71 mmol, 1.7 eq) and Pd(dppf)Cl_2 (530 mg, 0.73 mmol, 0.02 eq.) were suspended in a mixture of dioxane (100 mL) and water (50 mL). The reaction mixture was allowed to stir overnight at $100\text{ }^\circ\text{C}$ under an atmosphere of N_2 . The mixture was poured into 150 mL water and extracted with EtOAc (3 x 150 mL). The organic solutions were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (6:1 petroleum ether: EtOAc) to give 8-(4-fluoro-2-methyl-6-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene as a yellow solid (8.3 g, 78.0%) (ESI 294.3 $[\text{M}+\text{H}]^+$).

Step 3: 5-fluoro-3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline



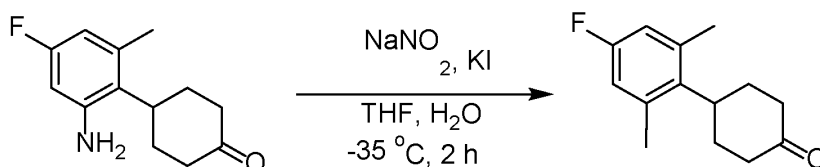
[000395] To a solution of 8-(4-fluoro-2-methyl-6-nitrophenyl)-1,4-dioxaspiro[4.5]dec-7-ene (8.3 g, 28.32 mmol, 1.0 eq.) in EtOH (100 mL) was added 10% Pd/C (1.9 g, 0.85 mmol, 0.03 eq). The reaction mixture was allowed to stir at 65 °C under an atmosphere of H₂ (1 atm, 3L) for 24 hr. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to give 5-fluoro-3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline as a yellow oil (5.3 g, 19.9 mmol, crude) (ESI 266.3 [M+H]⁺). The crude product was used directly in the subsequent step without further purification.

Step 4: 4-(2-amino-4-fluoro-6-methylphenyl)cyclohexan-1-one



[000396] To a solution of 5-fluoro-3-methyl-2-(1,4-dioxaspiro[4.5]decan-8-yl)aniline (4.6 g, 17.35 mmol, 1.0 eq.) in THF (100 mL) was added 3M aqueous HCl (17 mL, 52.05 mmol, 3.0 eq.). The reaction mixture was allowed to stir at RT for 1 hr. The reaction mixture was cooled to 0 °C, quenched by the addition of saturated aqueous NaHCO₃ solution (pH adjusted to ~8), and extracted with EtOAc (100 mL). The organic solution was separated, washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give 4-(2-amino-4-fluoro-6-methylphenyl)-cyclohexan-1-one as a yellow oil (3.7 g, 16.74 mmol, crude) (ESI 222.1 [M+H]⁺). The crude product was used directly in the next step.

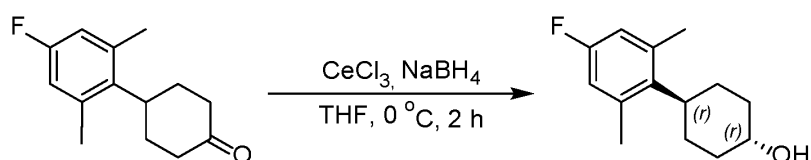
Step 5: 4-(4-fluoro-2-iodo-6-methylphenyl)cyclohexan-1-one



[000397] To a solution of 4-(2-amino-4-fluoro-6-methylphenyl)cyclohexan-1-one (3.7 g, 16.74 mmol, 1.0 eq.) in THF (20 mL) at -10 °C was added aqueous HCl (6M, 7 mL, 41.8 mmol, 2.5 eq.) followed by aqueous NaNO₂ (1.3 g in 3 mL water, 18.41 mmol, 1.1 eq.) dropwise over 15 mins. The reaction mixture was allowed to stir at -10 °C for another 30 min.

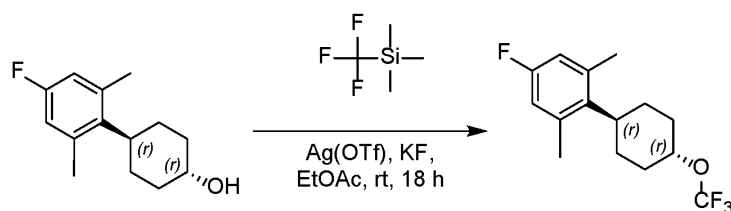
Aqueous KI (4.1 g in 3 mL water, 25.11 mmol, 1.5 eq.) was then added portionwise into the mixture. The reaction was allowed to warm to 0 °C and the reaction mixture was allowed to continue to stir for 30 min. Water (100 mL) and EtOAc (100 mL) were added into the reaction. The organic solution was separated, washed with saturated aqueous Na₂SO₃ (100 mL) and brine (100 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (15:1 petroleum ether: EtOAc) to give 4-(4-fluoro-2-iodo-6-methylphenyl)cyclohexan-1-one as a white solid (2.5 g, 44.9%) (ESI 333.0 [M+H]⁺).

Step 6: (1r,4r)-4-(4-fluoro-2-iodo-6-methylphenyl)cyclohexan-1-ol



[000398] To a solution of 4-(4-fluoro-2-iodo-6-methylphenyl)cyclohexan-1-one (2.5 g, 7.53 mmol, 1.0 eq.) in THF (25 mL) and MeOH (4 mL) at 0 °C was added CeCl₃ (2.2 g, 9.03 mmol, 1.2eq) followed by NaBH₄ (343 mg, 9.03 mmol, 1.2 eq) in portions. The mixture was allowed to stir at 0 °C for 0.5 hr. H₂O (50 mL) was slowly added at 0 °C, and the mixture was extracted with EtOAc (3 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to give assigned (1r,4r)-4-(4-fluoro-2-iodo-6-methylphenyl)cyclohexan-1-ol as a white solid (1.2 g, 47.7%) (ESI 317.0 [M-OH]⁺).

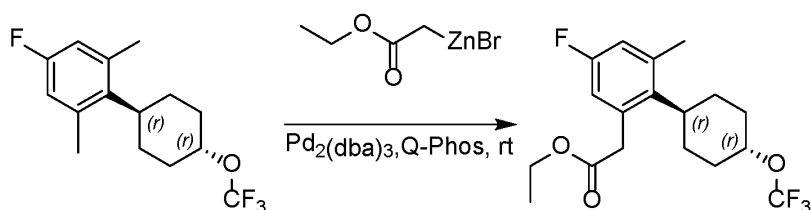
Step 7: 5-fluoro-1-iodo-3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)benzene



[000399] A mixture of assigned (1r,4r)-4-(4-fluoro-2-iodo-6-methylphenyl)-cyclohexan-1-ol (1.2 g, 3.6 mmol, 1.0 eq), Selectfluor (1.91 g, 5.4 mmol, 1.5 eq), KF (838 mg, 14.4 mmol, 4 eq) and AgOTf (2.76 g, 10.8 mmol, 3.0 eq) in EtOAc (20 mL) were allowed to stir at RT for 5 min under an atmosphere of N₂. 2-fluoropyridine (1050 mg, 10.8 mmol, 3 eq) and TMSCF₃ (1.5 g, 10.8 mmol, 3 eq) were then added. The reaction mixture was allowed to stir at RT for

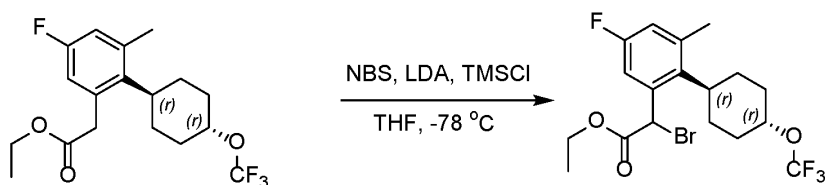
48 hr. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (97:3 petroleum ether: EtOAc) to give assigned 5-fluoro-1-iodo-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)-cyclohexyl)benzene as a white solid (680 mg, 46 %) (ESI 403.0 [M+H]⁺).

Step 8: ethyl 2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000400] To a solution of assigned 5-fluoro-1-iodo-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)benzene (680 mg, 1.68 mmol, 1.0 eq), Pd₂(dba)₃ (76 mg, 0.062 mmol, 0.05 eq) and Qphos (60 mg, 0.084 mmol, 0.05 eq) in THF (20 ml) under an atmosphere of N₂ was added (2-ethoxy-2-oxoethyl)zinc(II) bromide (1M in THF, 5.04 mL, 5.04 mmol, 3.0 eq) and the mixture was allowed to stir at 80°C for 1hr. Saturated aqueous NH₄Cl (20 mL) was added, and the solution was extracted with EtOAc (20 mL x 3). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give ethyl 2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate as a yellow oil (550 mg, 90%) (ESI 363.2(M+H)⁺).

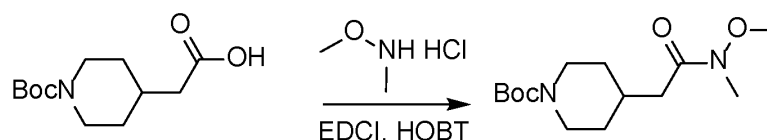
Step 9: ethyl 2-bromo-2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate



[000401] To a solution of LiHMDS (1M in THF, 3.5 mL, 3.50 mmol, 2.3 eq.) at -78°C, assigned ethyl 2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetate (550 mg, 1.52 mmol, 1.0 eq.) in THF (10 mL) was added dropwise. The reaction mixture was allowed to stir at -78°C for 0.5 hr. TMSCl (380 mg, 3.50 mmol, 2.3 eq.) was then added dropwise, and the reaction was allowed to continue to stir at -78°C for another 15 min. A

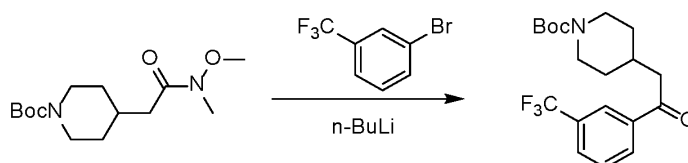
solution of NBS (270 mg, 1.52 mmol, 2.3 eq) in THF (5 mL) was then added dropwise. The reaction mixture was allowed to stir at -78°C for another 1 hr., then warmed to 0°C , quenched by the addition of saturated aqueous NH_4Cl (20 ml), and extracted with EtOAc (3 x 20 ml). The organic solutions were combined, washed with brine (3 x 20 ml), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate as a colorless oil (300mg, 44 %)(ESI $442.2[\text{M}+\text{H}]^+$).

Step 10: tert-butyl 4-(2-(methoxy(methyl)amino)-2-oxoethyl)piperidine-1-carboxylate



[000402] To a solution of 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid (10 g, 41.1 mmol, 1.0 eq.), *N,O*-dimethylhydroxylamine hydrochloride (4.4 g, 45.2 mmol, 1.1 eq.), HOBT (5.5 g, 41.1 mmol, 1.0 eq.) and TEA (5.3 g, 90.42 mmol, 2.2 eq.) in DCM (100 ml) were added 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (8.7 g, 45.2 mmol, 1.1 eq.). The reaction mixture was allowed to stir at 50°C for 1 hr, then diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (95:5 DCM: MeOH) to give tert-butyl 4-(2-(methoxy(methyl)-amino)-2-oxoethyl)piperidine-1-carboxylate as a yellow solid (9.1 g, 77.4%) (ESI $187.4 [\text{M}-\text{Boc}+\text{H}]^+$).

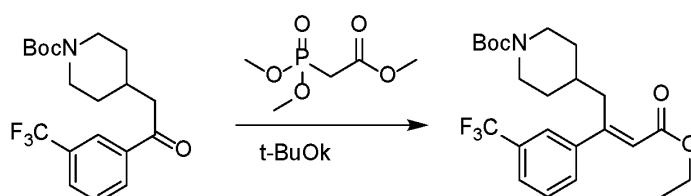
Step 11: tert-butyl 4-(2-oxo-2-(3-(trifluoromethyl) phenyl) ethyl) piperidine-1-carboxylate



[000403] To a solution of 1-bromo-3-(trifluoromethyl)benzene (8.6 g, 38.2 mmol, 1.2 eq.) in anhydrous THF (100 mL) at -78°C was added *n*-BuLi (2.5 M in hexane, 15.2 mL, 38.2 mmol, 1.2 eq.). The reaction mixture was allowed to stir at -78°C for 30 min. A solution of tert-butyl 4-(2-(methoxy(methyl)amino)-2-oxoethyl)piperidine-1-carboxylate (9.1 g, 31.8 mmol, 1.0 eq.)

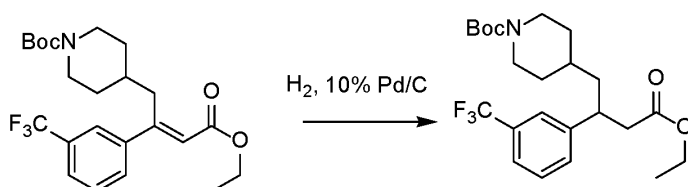
in THF (50 mL) was then added. The reaction was allowed to continue to stir at -78 °C for another 1 hr. The reaction was quenched by the addition of saturated aqueous NH₄Cl (100 mL) and extracted with EtOAc (2 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (12:1 petroleum ether: EtOAc) to give tert-butyl 4-(2-oxo-2-(3-(trifluoromethyl) phenyl) ethyl) piperidine-1-carboxylate as a yellow solid (5.1 g, 43.2%) (ESI 272.4 [M-Boc+H]⁺).

Step 12: tert-butyl (E)-4-(4-ethoxy-4-oxo-2-(3-(trifluoromethyl)phenyl)but-2-en-1-yl)piperidine-1-carboxylate



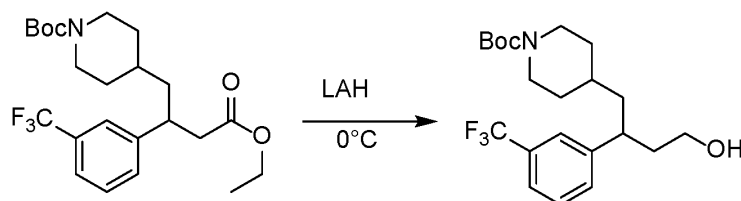
[000404] To a solution of methyl 2-(dimethoxyphosphoryl)acetate (3.05 g, 16.4 mmol, 1.2 eq) in anhydrous THF (10 mL) at 0 °C was added t-BuOK (1.8 g, 16.4 mmol, 1.2 eq). The reaction mixture was allowed to stir at 0 °C for 30 min. A solution of tert-butyl 4-(2-oxo-2-(3-(trifluoromethyl) phenyl) ethyl) piperidine-1-carboxylate (5.1 g, 13.7 mmol, 1.0 eq) in THF (10 mL) was then added. The reaction was allowed to continue to stir at 0 °C for another 12 hr, quenched by the addition of saturated aqueous NH₄Cl (20 mL) and extracted with EtOAc (3 x 20 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give tert-butyl (E)-4-(4-ethoxy-4-oxo-2-(3-(trifluoromethyl)phenyl)but-2-en-1-yl)piperidine-1-carboxylate as a yellow oil (3.5 g, 58%) (ESI 442.1 [M+H]⁺).

Step 13: tert-butyl 4-(4-ethoxy-4-oxo-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate



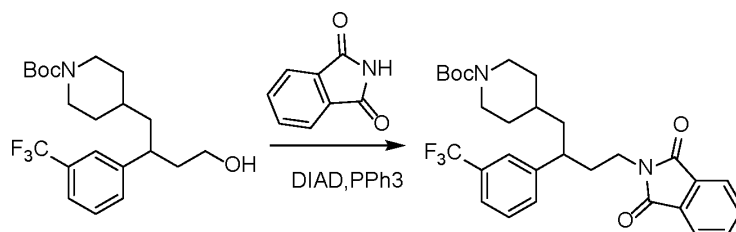
[000405] To a solution of tert-butyl (E)-4-(4-ethoxy-4-oxo-2-(3-(trifluoromethyl)phenyl)but-2-en-1-yl)piperidine-1-carboxylate (3.5 g, 7.9 mmol, 1.0 eq.) in EtOH (25 mL) was added 10% Pd/C (500mg, 0.24 mmol, 0.03 eq). The reaction mixture was allowed to stir at 65 °C under an atmosphere of H₂ (1 atm, 3L) for 24 hr. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated in *vacuo* to give tert-butyl 4-(4-ethoxy-4-oxo-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate as a yellow oil (3.3 g, 7.4 mmol, crude) (ESI 444.3 [M+H]⁺). The crude product was used directly in the subsequent step without further purification.

Step 14: tert-butyl 4-(4-hydroxy-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate



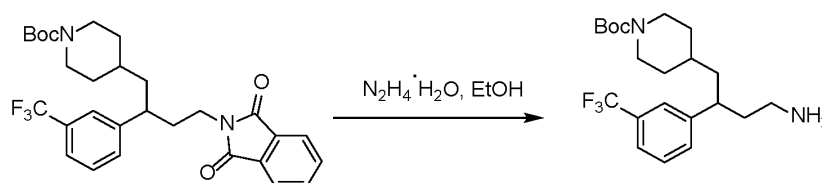
[000406] To a solution of tert-butyl 4-(4-ethoxy-4-oxo-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate (3.3 g, 7.4 mmol, 1.0 eq.) in THF (20 ml) at 0 °C was added LAH (1M in THF, 18.5 mL, 18.5 mmol, 2.5 eq.). The reaction mixture was allowed to stir at 0 °C for 1 hr and quenched by the addition of water (0.1 mL). The reaction was allowed to continue to stir at 0 °C for 10 min. 15% aqueous NaOH (0.1 mL) and water (0.2 mL) were then added sequentially at 0 °C. The reaction mixture was allowed to warm to RT and stirred for another 15 min. The mixture was dried over Na₂SO₄, filtered and concentrated in *vacuo* to give tert-butyl 4-(4-hydroxy-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate as a crude colorless oil (3.1 g, 7.7 mmol, crude) (ESI 402.0 [M+H]⁺). The crude product was used directly in the subsequent step without further purification.

Step 15: tert-butyl 4-(4-(1,3-dioxoisindolin-2-yl)-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate



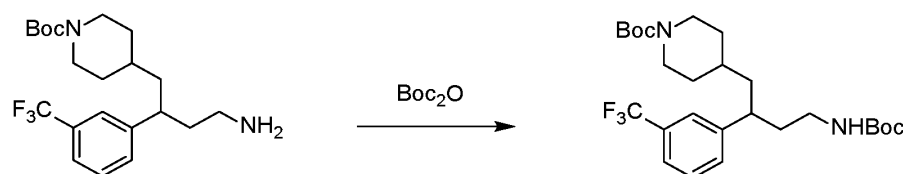
[000407] To a solution of tert-butyl 4-(4-hydroxy-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate (3.1 g, 7.7 mmol, 1.0 eq) and isoindoline-1,3-dione (1.5 g, 10.01 mmol, 1.3 eq) in toluene (30 mL) at 0 °C were added triphenylphosphine (2.6 g, 10.01 mmol, 1.3 eq) and diisopropyl azodicarboxylate (2.0 g, 10.01 mmol, 1.3 eq). The reaction mixture was allowed to stir at RT for 3 hr, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give tert-butyl 4-(4-(1,3-dioxoisindolin-2-yl)-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate as a yellow oil (2.9 g, 71 %) (ESI 531.9 [M+H]⁺).

Step 16: tert-butyl 4-(4-amino-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate



[000408] A solution of tert-butyl 4-(4-(1,3-dioxoisindolin-2-yl)-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate (2.9 g, 5.47 mmol, 1.0 eq) and 98% N₂H₄·H₂O (547 mg, 10.94 mmol, 2 eq) in EtOH (10 mL) was allowed to stir at 70 °C for 1 hr. The reaction mixture was filtered and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give tert-butyl 4-(4-amino-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate as yellow oil (2 g, 91%) (ESI 401.0 [M+H]⁺).

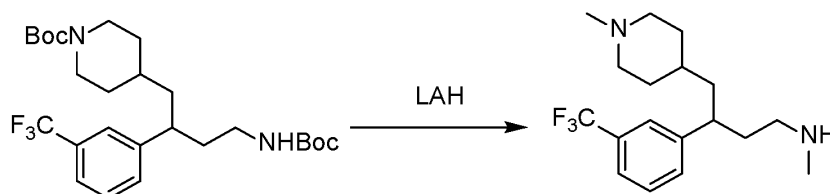
Step 17: tert-butyl 4-(4-((tert-butoxycarbonyl)amino)-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate



[000409] To a solution of tert-butyl 4-(4-amino-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate (2 g, 5.0 mmol, 1.0 eq) and TEA (1.5 g, 15.0 mmol, 3.0 eq) in DCM (30 mL) was added di-tert-butyl dicarbonate (1.6 g, 7.5 mmol, 1.5 eq). The reaction mixture was allowed to stir at RT for 2 hr. The reaction mixture was concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to give tert-butyl 4-(4-((tert-

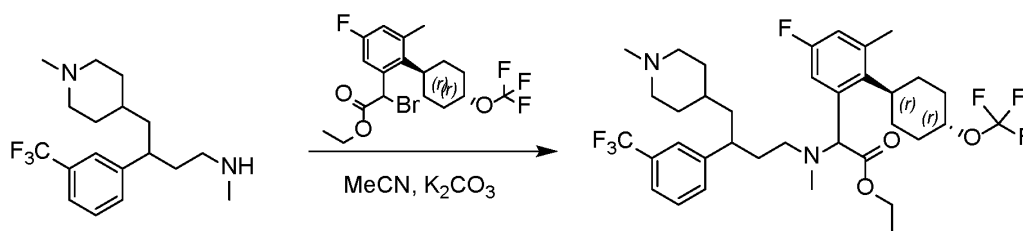
butoxycarbonyl)amino)-2-(3-(trifluoromethyl)phenyl)butyl)piperidine-1-carboxylate as a white solid (2.1 g, 84%) (ESI 523.1 $[M+Na]^+$).

Step 18: N-methyl-4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)butan-1-amine



[000410] To a solution of tert-butyl 4-(4-((tert-butoxycarbonyl)amino)-2-(3-(trifluoromethyl)-phenyl)butyl)piperidine-1-carboxylate (2.1 g, 4.2 mmol, 1.0 *eq*) in THF (30 mL) at RT was added LAH (3M in THF, 4.2 mL, 12.6 mmol, 3.0 *eq*) and the reaction mixture was allowed to stir at 70 °C for 1 hr. After cooling to 0 °C, the reaction was quenched carefully by the addition of water (0.5 mL) and was allowed to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.5 mL) and water (1.5 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT and stir for another 15 min. The mixture was dried over Na₂SO₄, filtered and concentrated *in vacuo* to give N-methyl-4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)butan-1-amine as a white solid. The crude solid was used directly in next reaction (1 g, 72%) (ESI 329.3 $[M+H]^+$).

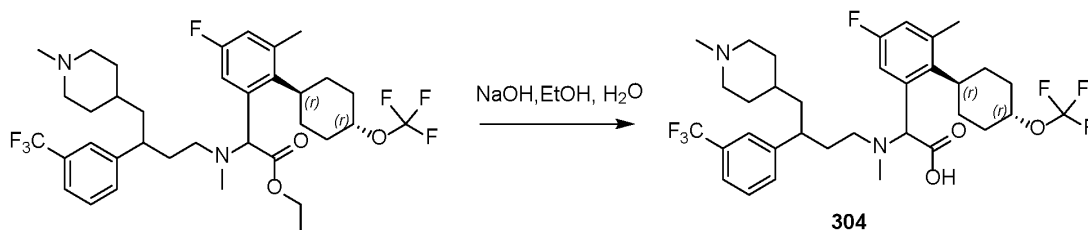
Step 19: ethyl 2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)-2-(methyl(4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)butyl)amino)acetate



[000411] To a solution of N-methyl-4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl) butan-1-amine (500 mg 1.52 mmol, crude) in ACN (10 mL) was added K₂CO₃ (1 g, 7.6 mmol, 5.0 *eq*). The mixture was allowed to stir at RT for 15 min. ethyl 2-bromo-2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (668 mg, 1.52 mmol, 1.0 *eq*) was then added. The reaction was allowed to continue to stir at 80 °C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(5-

fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)-2-(methyl(4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)butyl)amino)acetate as a yellow oil (550 mg, 52%) (ESI 689.3 $[M+H]^+$).

Step 20: 2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)-2-(methyl(4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)butyl)amino)acetic acid



[000412] To a solution of ethyl 2-(5-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)-2-(methyl(4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)-phenyl)butyl)amino)acetate (550 mg, 0.80 mmol, 1.0 eq) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (160 mg, 4.0 mmol, 5.0 eq). The reaction mixture was allowed to stir at 80 °C for 1 hr. and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give a stereoisomeric mixture of compounds **304** as a white solid (480 mg, 90%). Stereoisomers were further separated by prep chiral SFC A to give **304-P1A** (94.4 mg), **304-P1B** (78.2 mg), **304-P2** (85.5 mg) and **304-P3** (120.5 mg).

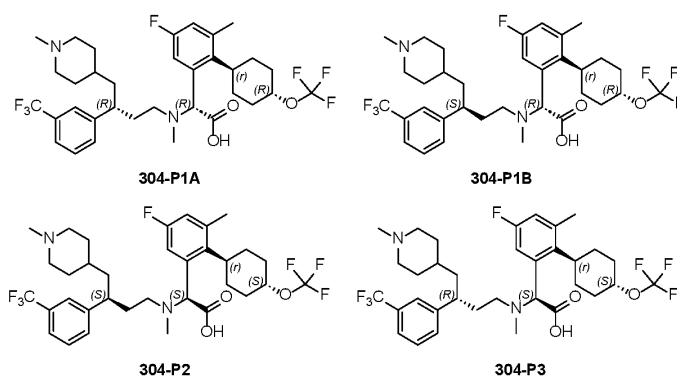
[000413] **304-P1A**, assigned as (R)-2-(5-fluoro-3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)-2-(methyl((R)-4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)butyl)amino)acetic acid. LC/MS ESI 661.2 $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ 7.50 – 7.23 (m, 5H), 6.81 - 6.78 (m, 1H), 4.68 – 4.48 (m, 1H), 4.37 – 4.31 (m, 1H), 3.33 - 2.80 (m, 5H), 2.58 – 2.22 (m, 12H), 2.2 – 1.92 (m, 6H), 1.82 - 1.57 (m, 7H), 1.38 – 1.20 (m, 4H).

[000414] **304-P1B**, assigned as (R)-2-(5-fluoro-3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)-2-(methyl((S)-4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)butyl)amino)acetic acid. LC/MS ESI 661.3 $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ 7.53 – 7.26 (m, 5H), 6.83 – 6.81 (m, 1H), 4.67-4.51 (m, 1H), 4.38 – 4.32 (m, 1H), 3.33 – 2.79 (m, 5H), 2.71 – 2.39 (m, 12H), 2.14 -1.87 (m, 6H) 1.82 – 1.54 (m, 7H), 1.35 - 1.20(m, 4H).

[000415] **304-P2**, assigned as (S)-2-(5-fluoro-3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)-2-(methyl((S)-4-(1-methylpiperidin-4-yl)-3-(3-

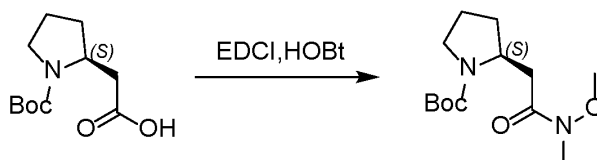
(trifluoromethyl)phenyl)butyl)amino)acetic acid. LC/MS ESI 661.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.52 – 7.25 (m, 5H), 6.95 – 6.81 (m, 1H), 4.66 – 4.48 (m, 1H), 4.37 – 4.37 (m, 1H), 3.21 – 2.67 (m, 5H), 2.62 – 2.38 (m, 12H), 2.16 – 1.91 (m, 6H), 1.86 – 1.53 (m, 7H), 1.39 – 1.19 (n, 4H).

[000416] **304-P3**, assigned as (S)-2-(5-fluoro-3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)-2-(methyl((R)-4-(1-methylpiperidin-4-yl)-3-(3-(trifluoromethyl)phenyl)butyl)amino)acetic acid. LC/MS ESI 661.2 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.50 – 7.23 (m, 5H), 6.86 – 6.75 (m, 1H), 4.62 – 4.46 (m, 1H), 4.36 – 4.31 (m, 1H), 3.32 – 2.66 (m, 5H), 2.56 – 2.31 (m, 12H), 2.21 – 1.86 (m, 6H), 1.92 – 1.57 (m, 7H), 1.39 – 1.18 (m, 4H).

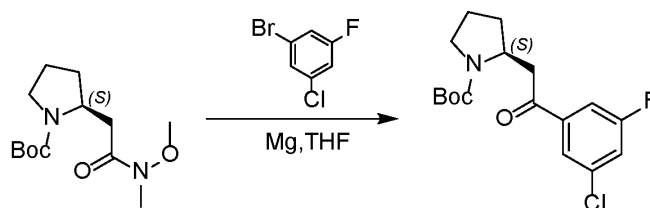


Example 17: Preparation of Compound 305-2P1

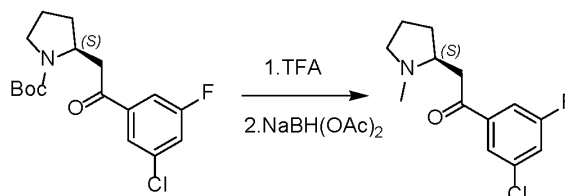
Step 1: tert-butyl (S)-2-(2-(methoxy(methyl)amino)-2-oxoethyl)pyrrolidine-1-carboxylate



[000417] To a solution of (S)-2-(1-(tert-butoxycarbonyl)pyrrolidin-2-yl)acetic acid (10 g, 43.6 mmol, 1.0 eq.), N,O-dimethylhydroxylamine hydrochloride (5.0 g, 52.4 mmol, 1.2 eq.), HOBt (7.1 g, 52.4 mmol, 1.2 eq.) and DIEA (8.0 g, 87.2 mmol, 2.0 eq.) in DCM (100 ml) was added EDCI (10.0 g, 52.4 mmol, 1.2 eq.). The reaction was allowed to stir at RT for 16 hr, then diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography (20:1 dichloromethane: methanol) to give tert-butyl (S)-2-(2-(methoxy(methyl)amino)-2-oxoethyl)pyrrolidine-1-carboxylate as a yellow solid (10.0 g, 85.1%) (ESI 273.3 $[M+H]^+$).

Step 2: tert-butyl (S)-2-(2-(3-chloro-5-fluorophenyl)-2-oxoethyl)pyrrolidine-1-carboxylate

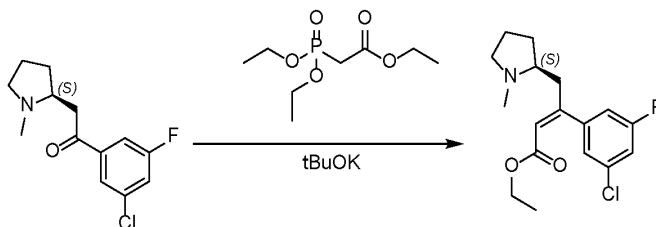
[000418] To a solution of 1-bromo-3-chloro-5-fluorobenzene (6.0 g, 28.6 mmol, 1.3 eq) in THF (20 mL) were added magnesium (792.0 mg, 33.0 mmol, 1.5 eq) and 1,2-dibromoethane (810 mg, 4.4 mmol, 0.2eq). The mixture was allowed to stir at 60 °C for 1 hr. After cooling to RT, the mixture was added dropwise into a solution of tert-butyl (S)-2-(2-(methoxy(methyl)amino)-2-oxoethyl)pyrrolidine-1-carboxylate (6.0 g, 22.0 mmol, 1.0 eq) in THF (60 mL) at 0 °C. The reaction mixture was then allowed to warm to RT and stirred for 1 hr. The mixture was diluted with saturated NH₄Cl (200 mL) and extracted with DCM (2 × 200 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (95:5 DCM: MeOH) to give tert-butyl (S)-2-(2-(3-chloro-5-fluorophenyl)-2-oxoethyl)pyrrolidine-1-carboxylate as a colorless oil (4.3 g, 57.2 mmol, 84.6%)(ESI 364.1 [M+Na]⁺).

Step 3: (S)-1-(3-chloro-5-fluorophenyl)-2-(1-methylpyrrolidin-2-yl)ethan-1-one

[000419] To a solution of tert-butyl (S)-2-(2-(3-chloro-5-fluorophenyl)-2-oxoethyl)pyrrolidine-1-carboxylate (4.3 g, 12.6 mmol, 1.0 eq) in DCM (5 mL) was added TFA (5 mL, 65.0 mmol, 5.1 eq.). The reaction mixture was allowed to stir at RT for 2 hr and then concentrated. The residue was dissolved in MeOH (140 mL) and 33% aqueous HCHO (6.0 g, 63 mmol, 5.0 eq.) was added to the solution. The mixture was allowed to stir at RT for 1 hr. NaBH(OAc)₃ (5.3 g, 25.2 mmol, 2.0 eq.) was then added, and the reaction was allowed to continue to stir at RT for another 3 hr. The reaction mixture was poured into water (300 mL) and extracted with DCM (3 × 200 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (95:5 DCM: MeOH) to give (S)-1-(3-chloro-5-

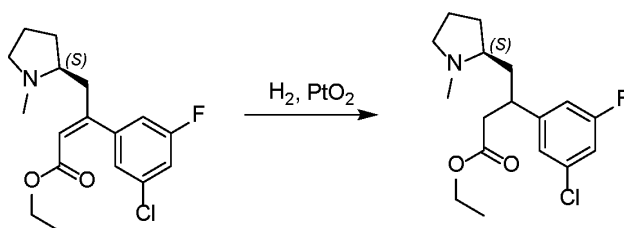
fluorophenyl)-2-(1-methylpyrrolidin-2-yl)ethan-1-one as colorless oil (2.9 g, 83%) (ESI 256.2 [M+H]⁺).

Step 4: ethyl (S,Z)-3-(3-chloro-5-fluorophenyl)-4-(1-methylpyrrolidin-2-yl)but-2-enoate



[000420] To a solution of ethyl 2-(diethoxyphosphoryl)acetate (6.1 g, 27.4 mmol, 2.5 eq) in anhydrous THF (120 mL) at RT was added t-BuOK (3.1 g, 27.4 mmol, 2.5 eq). The reaction mixture was allowed to stir at RT for 2 h. A solution of (S)-1-(3-chloro-5-fluorophenyl)-2-(1-methylpyrrolidin-2-yl)ethan-1-one (3.0 g, 11.7 mmol, 1.0 eq) in THF (20 mL) was then added. The reaction was allowed to continue to stir for another 12 hr. The reaction was then quenched by the addition of saturated aqueous NH₄Cl (100 mL) and extracted with EtOAc (3 x 100 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (20:1 DCM: MeOH) to give ethyl (S,Z)-3-(3-chloro-5-fluorophenyl)-4-(1-methylpyrrolidin-2-yl)but-2-enoate as a yellow oil (2.2 g, 50.1%) (ESI 326.1 [M+H]⁺).

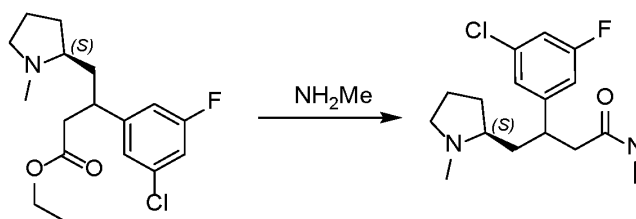
Step 5: ethyl 3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butanoate



[000421] To a solution of ethyl (S,Z)-3-(3-chloro-5-fluorophenyl)-4-(1-methylpyrrolidin-2-yl)but-2-enoate (2.2 g, 6.8 mmol, 1.0 eq) in MeOH (35 mL) at RT was added PtO₂ (227 mg, 1.0 mmol, 0.15eq). The reaction mixture was allowed to stir at RT under an atmosphere of H₂ (1 atm, 3L) for 2 hr. The contents were then filtered through a pad of celite and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (25:1 DCM: MeOH) to give ethyl 3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butanoate as a pale brown solid (1.3 g, 51.3%) (ESI 328.2 [M+H]⁺).

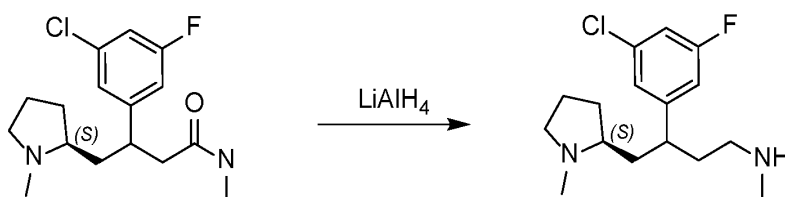
Step 6: 3-(3-chloro-5-fluorophenyl)-1-(methyl-12-azaneyl)-4-((S)-1-methylpyrrolidin-2-

yl)butan-1-one



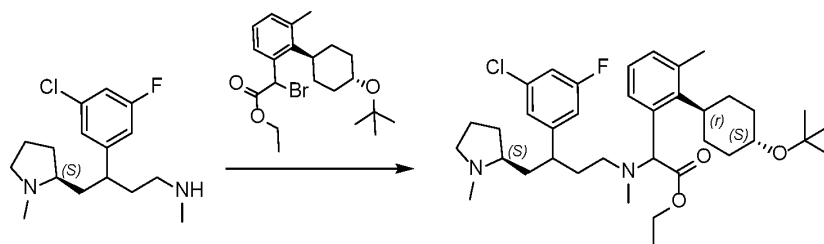
[000422] A solution of ethyl 3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butanoate (1.3 g, 4.0 mmol, 1.0 eq) in MeNH₂ (1M in MeOH, 15 mL, 15.0 mmol, 3.7 eq) was allowed to stir at 55 °C for 2 hr. The mixture was then cooled to RT and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (25:1 DCM: MeOH) to give 3-(3-chloro-5-fluorophenyl)-1-(methyl-12-azaneyl)-4-((S)-1-methylpyrrolidin-2-yl)butan-1-one as a colorless oil (1.0 g, 81.2 %) (ESI 312.2 [M+H]⁺).

Step 7: 3-(3-chloro-5-fluorophenyl)-N-methyl-4-((S)-1-methylpyrrolidin-2-yl)butan-1-amine



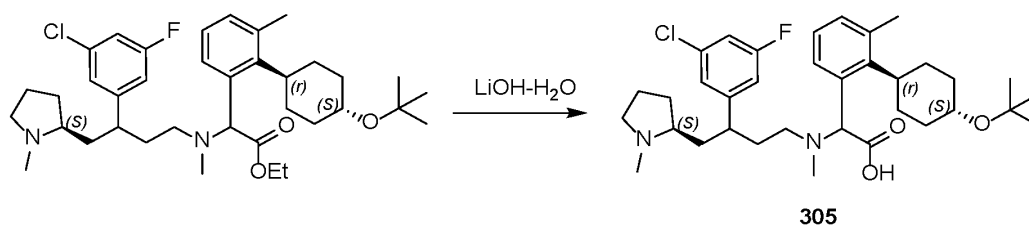
[000423] To a solution of 3-(3-chloro-5-fluorophenyl)-1-(methyl-12-azaneyl)-4-((S)-1-methylpyrrolidin-2-yl)butan-1-one (800 mg, 2.6 mmol, 1.0 eq) in THF (20 mL) at RT was added LAH (3.5M in THF, 1.5 mL, 3.8 mmol, 1.5 eq). The reaction mixture was allowed to stir at RT for 2 hr. After cooling to 0 °C, the reaction mixture was then quenched carefully by the addition of water (0.2 mL) and allowed to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.2 mL) and water (0.6 mL) were then added sequentially at 0 °C. The mixture was then allowed to warm to RT and stir for another 15 min, dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 3-(3-chloro-5-fluorophenyl)-N-methyl-4-((S)-1-methylpyrrolidin-2-yl)butan-1-amine (400 mg, 52.6%) as a white solid. (ESI 299.1 [M+H]⁺) The crude solid was used directly in the next step.

Step 8: ethyl 2-(2-((1R,4S)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)-2-((3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butyl)(methyl)amino)acetate



[000424] To a solution of 3-(3-chloro-5-fluorophenyl)-N-methyl-4-((S)-1-methylpyrrolidin-2-yl)butan-1-amine (200 mg 0.67 mmol, crude) in ACN (8 mL) was added K_2CO_3 (277 mg, 2.0 mmol, 3.0 *eq.*). The mixture was allowed to stir at RT for 15 min. ethyl 2-bromo-2-(2-((1r,4r)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)acetate (275 mg, 0.67 mmol, 1.0 *eq.*) was then added. The reaction was allowed to continue to stir at 80 °C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(2-((1r,4S)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)-2-((3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butyl)(methyl)amino)acetate as a yellow oil (240 mg, 56.7%) (ESI 629.3 $[M+H]^+$).

Step 9: 2-(2-((1r,4S)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)-2-((3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butyl)(methyl)amino)acetic acid



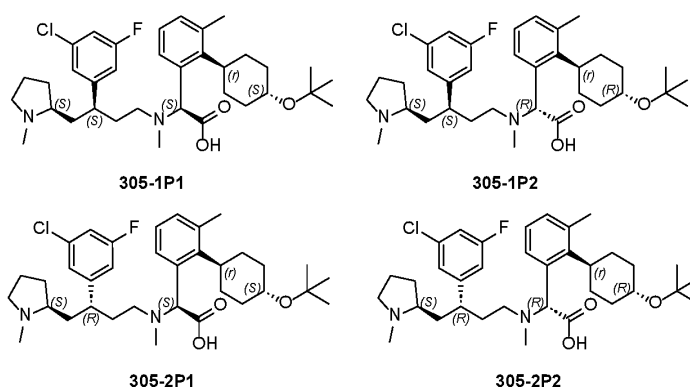
[000425] To a solution of ethyl 2-(2-((1r,4S)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)-2-((3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butyl)(methyl)amino)acetate (240 mg, 0.38 mmol, 1.0 *eq.*) in EtOH (3 mL) and H_2O (1 mL) was added LiOH- H_2O (80 mg, 1.91 mmol, 5.0 *eq.*). The reaction mixture was allowed to stir at RT for 16 hr. The reaction pH was adjusted to ~ 6 - 7 with 2N HCl. Solvents were removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH_3CN) to give **305-1** (85mg, 37%) and **305-2** (90mg, 39%) as a white solids. **305-1** was further separated by prep chiral SFC A to give **305-1P1** (21 mg) and **305-1P2** (15 mg). **305-2** was further separated by prep chiral HPLC A to give **305-2P1** (28 mg) and **305-2P2** (12 mg).

[000426] 305-1P1, assigned as (S)-2-(2-((1*r*,4*S*)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)-2-(((S)-3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butyl)(methyl)amino)acetic acid. LC/MS ESI 601.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.50-7.37 (m, 1H), 7.13-6.98 (m, 4H), 6.84-6.82 (m, 1H), 4.74-4.62 (m, 1H), 3.59-3.54 (m, 1H), 3.20-2.95 (m, 2H), 2.66-2.32 (m, 14H), 2.78-2.15 (m, 11H), 1.21-1.70 (m, 14H).

[000427] 305-1P2, assigned as (R)-2-(2-((1*r*,4*R*)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)-2-(((S)-3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butyl)(methyl)amino)acetic acid. LC/MS ESI 601.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.52-7.37 (m, 1H), 7.11-6.98 (m, 4H), 6.84-6.82 (m, 1H), 4.74-4.61 (m, 1H), 3.59-3.54 (m, 1H), 3.20-2.95 (m, 2H), 2.66-2.32 (m, 14H), 2.78-2.15 (m, 11H), 1.21-1.70 (m, 5H), 1.40 (s, 9H).

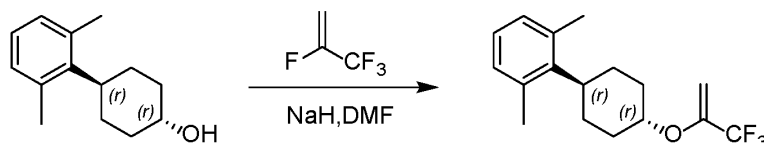
[000428] 305-2P1, assigned as (S)-2-(2-((1*r*,4*S*)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)-2-(((R)-3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butyl)(methyl)amino)acetic acid. LC/MS ESI 601.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.50-7.48 (m, 1H), 7.21-6.86 (m, 5H), 4.74-4.61 (m, 1H), 3.60-3.53 (m, 1H), 3.30-3.21 (m, 2H), 2.74-2.49 (m, 11H), 2.43-2.32 (m, 2H), 2.19-1.79 (m, 11H), 1.21-1.70 (m, 15H).

[000429] 305-2P2, assigned as (R)-2-(2-((1*r*,4*R*)-4-(tert-butoxy)cyclohexyl)-3-methylphenyl)-2-(((R)-3-(3-chloro-5-fluorophenyl)-4-((S)-1-methylpyrrolidin-2-yl)butyl)(methyl)amino)acetic acid. LC/MS ESI 601.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.50-7.38 (m, 1H), 7.11-6.98 (m, 4H), 6.84-6.82 (m, 1H), 4.77-4.61 (m, 1H), 3.66-3.31 (m, 1H), 3.16-2.99 (m, 2H), 2.66-2.31 (m, 14H), 2.12-1.77 (m, 11H), 1.52-1.24 (m, 14H).



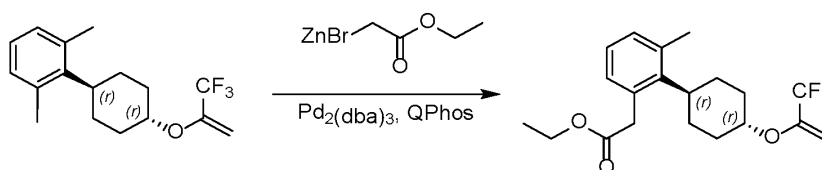
Example 18: Preparation of Compound 80-P2

Step 1: 1-iodo-3-methyl-2-((1*r*,4*r*)-4-((3,3,3-trifluoroprop-1-en-2-yl)oxy)cyclohexyl)benzene



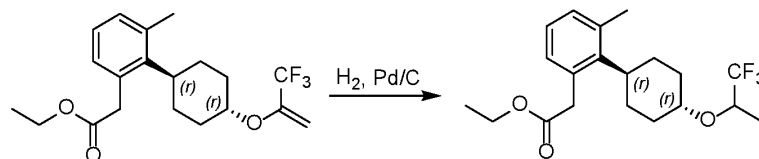
[000430] To a solution of (1r,4r)-4-(2-iodo-6-methylphenyl)cyclohexan-1-ol (1 g, 3.2 mmol, 1.0 eq) in DMF (10mL) at 0 °C was added sodium hydride (506 mg, 12.7 mmol, 4.0 eq, 60% in mineral oil). The reaction mixture was allowed to stir at 0 °C for 0.5 hr. 2,3,3,3-tetrafluoroprop-1-ene (1atm, 2L) was then added and the reaction was allowed to warm to RT. The reaction was allowed to continue to stir for another 5 hr. The reaction was then quenched by the addition of cold saturated aqueous NH₄Cl (100 mL) and extracted with EtOAc (3 x 60 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give 1-iodo-3-methyl-2-((1r,4r)-4-((3,3,3-trifluoroprop-1-en-2-yl)oxy)cyclohexyl)benzene as a white solid (500mg, 38.5 %).

Step 2: ethyl 2-(3-methyl-2-((1r,4r)-4-((3,3,3-trifluoroprop-1-en-2-yl)oxy)cyclohexyl)phenyl)acetate



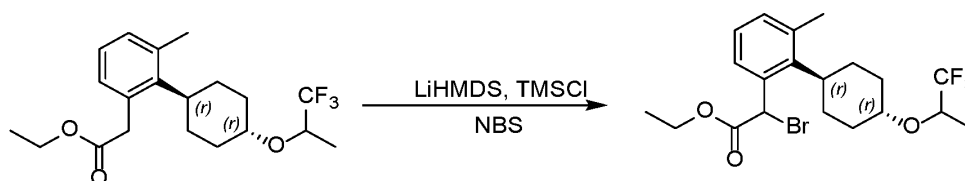
[000431] To a suspension of 1-iodo-3-methyl-2-((1r,4r)-4-((3,3,3-trifluoroprop-1-en-2-yl)oxy)cyclohexyl)benzene (1.0 g, 2.4 mmol, 1.0 eq) in THF (15 mL) was added Pd₂dba₃ (45.0 mg, 0.07 mmol, 0.03 eq) and QPhos (34 mg, 0.07 mmol, 0.03 eq). (2-ethoxy-2-oxoethyl)zinc(II) bromide (1M in THF, 7.2 mL, 7.2 mmol, 3.0 eq) was then added and the mixture was allowed to stir at 50 °C under an atmosphere of N₂ for 0.5 hr. The reaction mixture was poured into saturated aqueous NH₄Cl solution (50 mL) and extracted with EtOAc (3 x 50 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (95:5 petroleum ether: EtOAc) to give ethyl 2-(3-methyl-2-((1r,4r)-4-((3,3,3-trifluoroprop-1-en-2-yl)oxy)cyclohexyl)phenyl)acetate as a brown oil (0.78 g, 92 %) (ESI 393.3 [M+Na]⁺).

Step 3: ethyl 2-(3-methyl-2-((1r,4r)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetate



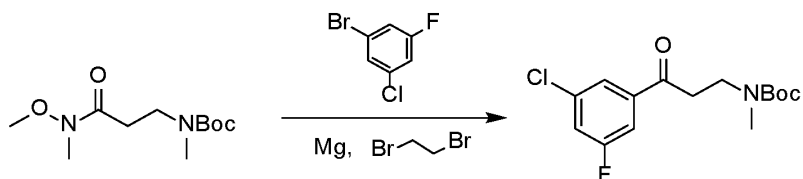
[000432] To a solution of ethyl 2-(3-methyl-2-((1r,4r)-4-((3,3,3-trifluoroprop-1-en-2-yl)oxy)cyclohexyl)phenyl)acetate (0.78 g, 2.11 mmol, 1.0 eq) in MeOH (10 mL) was added 10% Pd/C (260 mg, 0.11 mmol, 0.05 eq). The reaction mixture was allowed to stir at RT under an atmosphere of H₂ (1 atm, 3L) for 3 hr. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to give ethyl 2-(3-methyl-2-((1r,4r)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetate as a yellow oil (0.75 g, 97 %) (ESI 395.1 [M+Na]⁺). The crude product was used directly in the subsequent step without further purification.

Step 4: ethyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)-phenyl)acetate



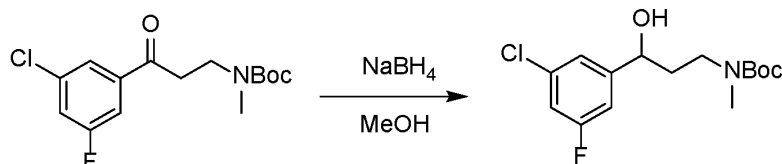
[000433] To a solution of LiHMDS (1M in THF, 4 mL, 4.0 mmol, 2.0 eq) at -78°C, ethyl 2-(3-methyl-2-((1r,4r)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetate (750 mg, 2.0 mmol, 1.0 eq) in THF (10 mL) was added dropwise. The reaction mixture was allowed to stir at -78°C for 0.5 hr. TMSCl (440.0 mg, 4.0 mmol, 2.0 eq) was added dropwise and the reaction was allowed to continue to stir at -78°C for 15 min. A solution of NBS (720 mg, 4.0 mmol, 2.0 eq) in THF (10 mL) was added. The reaction mixture was allowed to stir at -78°C for another 2 hr., warmed to 0 °C, quenched by the addition of saturated aqueous NH₄Cl solution (50 mL), and extracted with EtOAc (3 x 50 mL). The organic solutions were combined, washed with brine (3 x 50 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (90:10 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetate as a colorless oil (800 mg, 95%) (ESI 473.0 [M+Na]⁺).

Step 5: tert-butyl (3-(3-chloro-5-fluorophenyl)-3-oxopropyl)(methyl)carbamate



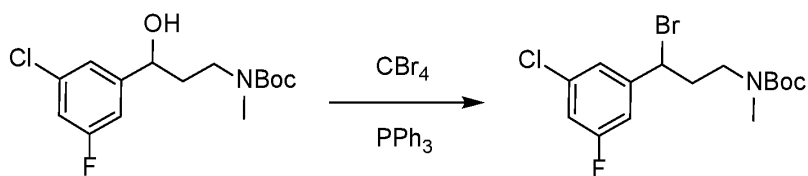
[000434] To a suspension of Mg (970 mg, 39.8 mmol, 1.4 eq) in THF (40 mL) was added 1-bromo-3-chloro-5-fluorobenzene (7.14g, 34.1 mmol, 1.2 eq) dropwise. The mixture was allowed to stir at 60 °C for 1 h. The reaction mixture was cooled to 0 °C and added dropwise into a solution of tert-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)(methyl)carbamate (7 g, 28.4 mmol, 1.0 eq) in THF (40 mL). The reaction mixture was allowed to stir at 0 °C for 2 hr., quenched by the addition of saturated aqueous NH₄Cl solution (200 mL) and extracted with EtOAc (3 x 200 mL). The organic solutions were combined, washed with brine (3 x 200 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (94:6 petroleum ether: EtOAc) to give tert-butyl (3-(3-chloro-5-fluorophenyl)-3-oxopropyl)(methyl)-carbamate as a yellow oil (4.0 g, 98%) (ESI 260.1 [M-tBu+H]⁺).

Step 6: tert-butyl (3-(3-chloro-5-fluorophenyl)-3-hydroxypropyl)(methyl)carbamate



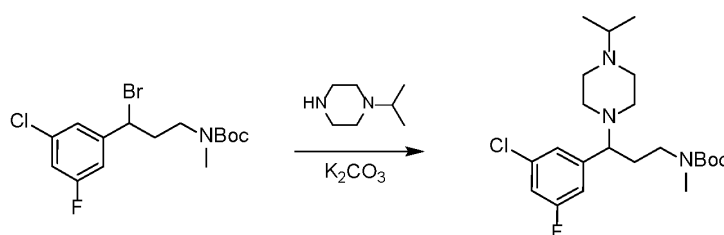
[000435] To a solution of tert-butyl (3-(3-chloro-5-fluorophenyl)-3-oxopropyl)(methyl)carbamate (2.5 g, 7.9 mmol, 1.0 eq) in MeOH (25 mL) at 0 °C was added NaBH₄ (898.6 mg, 23.7 mmol, 3.0 eq) in portions. The mixture was allowed to stir at RT for 2 hr. Water (100 mL) was slowly added at 0 °C, and the mixture was extracted with EtOAc (3 x 150 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (92:8 DCM: MeOH) to give tert-butyl (3-(3-chloro-5-fluorophenyl)-3-hydroxypropyl)(methyl)carbamate (2.3 g, 91%) (ESI 340.0 [M+Na]⁺).

Step 7: tert-butyl (3-bromo-3-(3-chloro-5-fluorophenyl)propyl)(methyl)carbamate



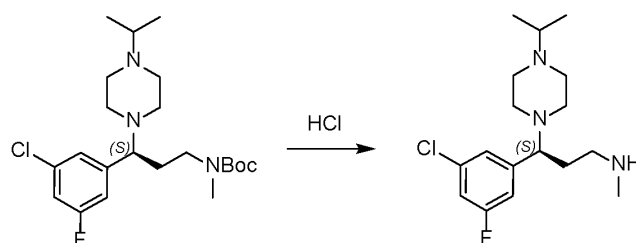
[000436] To a solution of tert-butyl (3-(3-chloro-5-fluorophenyl)-3-hydroxypropyl)(methyl)carbamate (2.3 g, 7.24 mmol, 1.0 eq) in DCM (25 mL) was added CBr_4 (3.6 g, 10.9 mmol, 1.5 eq) and PPh_3 (2.8 g, 10.9 mmol, 1.5 eq). The mixture was allowed to stir at RT for 2 hr and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (93:7 petroleum ether: EtOAc) to give tert-butyl (3-bromo-3-(3-chloro-5-fluorophenyl)propyl)(methyl)carbamate (1.8 g, 85%) (ESI 324.0 $[\text{M}+\text{tBu}+\text{H}]^+$).

Step 8: tert-butyl (3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)carbamate



[000437] Tert-butyl (3-bromo-3-(3-chloro-5-fluorophenyl)propyl)(methyl)carbamate (950.0 mg, 2.5 mmol, 1.0 eq), 1-isopropylpiperazine (478.0 mg, 2.74 mmol, 1.5 eq) and K_2CO_3 (1.1 g, 7.5 mmol, 3.0 eq) were dissolved in MeCN (10 mL). The mixture was allowed to stir at 60 °C for 3 hr and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (95:5 DCM: MeOH) to give racemic tert-butyl (3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)carbamate (930 mg, 88%) (ESI 428.3 $[\text{M}+\text{H}]^+$). Isomers were further separated by prep chiral SFC I to give peak 1, assigned as tert-butyl (R)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)carbamate (420 mg), and peak 2, assigned as tert-butyl (S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)carbamate (390 mg), as a white solids.

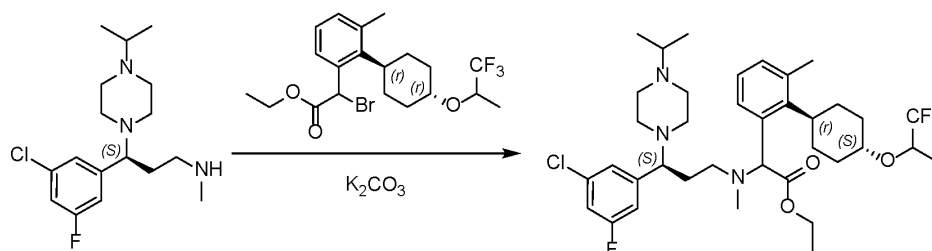
Step 9: (S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine



[000438] To a solution of tert-butyl (S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)carbamate (390.0 mg, 0.9 mmol, 1.0 eq) in DCM (5

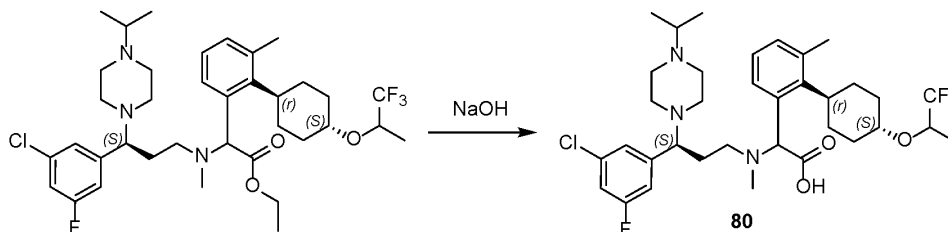
mL) was added HCl (4M in dioxane, 2.5mL, 9.9 mmol, 10.0 eq). The mixture was allowed to stir at RT for 2 hr and then concentrated *in vacuo* to give (S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine (280 mg, 95%) (ESI 328.3 [M+H]⁺). The crude product was used directly in the subsequent step without further purification.

Step 10: ethyl 2-(((S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetate



[000439] A mixture of (S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine (280.0 mg, 0.85 mmol, 1.0 eq), ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetate (385.0 mg, 0.85 mmol, 1.0 eq) and K₂CO₃ (355.0 mg, 2.56 mmol, 3.0 eq) in MeCN (3 mL) was allowed to stir at 60 °C for 8 hr. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (92:8 DCM: MeOH) to give ethyl 2-(((S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetate (320 mg, 94%) (ESI 698.3 [M+H]⁺).

Step 11: Preparation of 2-(((S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetic acid



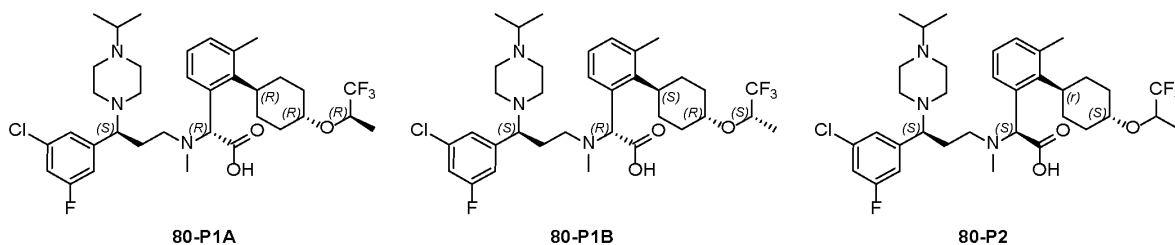
[000440] To a solution of ethyl 2-(((S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetate (280 mg, 0.40 mmol, 1.0 eq) in EtOH (3 mL) and H₂O (1

mL) was added NaOH (80 mg, 2 mmol, 5.0 eq). The reaction mixture was allowed to stir at 70 °C for 8 hr. The pH of the mixture was adjusted to ~ 6 - 7 with 2N HCl. Solvents were removed in vacuo. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give a mixture of stereoisomeric compounds **80** as a white solid (240 mg, 89%). The stereoisomers were further separated by prep chiral SFC A to give **80-P1** (100 mg) and **80-P2** (72 mg). **80-P1** was further separated by prep chiral SFC J to give **80-P1A** (31 mg) and **80-P1B** (35 mg).

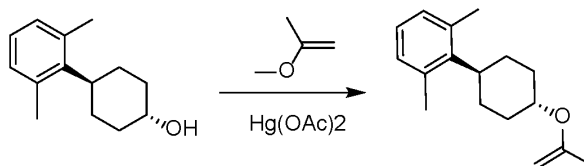
[000441] **80-P1A**, assigned as (R)-2-(((S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1R,4R)-4-(((R)-1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 670.2 ¹H NMR (400 MHz, CD₃OD) δ 7.59-7.53 (m, 1H), 7.26-7.00 (m, 5H), 4.92 (s, 1H), 4.14-4.07 (m, 1H), 3.70-3.61 (m, 2H), 3.26-3.18 (m, 1H), 2.69-2.36 (m, 15H), 2.23-2.12 (m, 4H), 2.08-1.80 (m, 3H), 1.73-1.69 (m, 1H), 1.63-1.40 (m, 3H), 1.30 (d, J = 6.6 Hz, 4H), 1.06 (d, J = 5.4 Hz, 6H).

[000442] **80-P1B**, assigned as (R)-2-(((S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1S,4R)-4-(((S)-1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 670.2 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.59-7.53 (m, 1H), 7.26-7.02 (m, 5H), 4.92 (s, 1H), 4.13-4.07 (m, 1H), 3.70-3.59 (m, 2H), 3.23-3.18 (m, 1H), 2.70-2.41 (m, 15H), 2.34-2.04 (m, 4H), 1.92-1.87 (m, 3H), 1.73-1.70 (m, 1H), 1.58-1.42 (m, 3H), 1.30 (d, J = 6.4 Hz, 4H), 1.06 (d, J = 5.6 Hz, 6H).

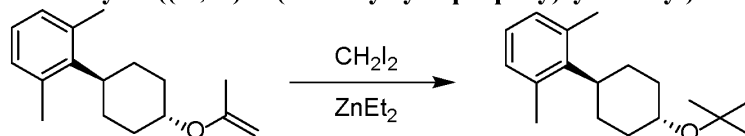
[000443] **80-P2**, assigned as (2S)-2-(((S)-3-(3-chloro-5-fluorophenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-((1,1,1-trifluoropropan-2-yl)oxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 670.2 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.56-7.47 (m, 1H), 7.29-6.93 (m, 5H), 4.93 (s, 1H), 4.13-4.08 (m, 1H), 3.74-3.71 (m, 1H), 3.61-3.48 (m, 2H), 3.20-3.16 (m, 1H), 3.05-2.80 (m, 10H), 2.52 (s, 3H), 2.42 (s, 1H), 2.22-2.02 (m, 4H), 1.91-1.85 (m, 4H), 1.71-1.42 (m, 3H), 1.30 (d, J = 6.8 Hz, 4H), 1.12 (d, J = 5.6 Hz, 6H).



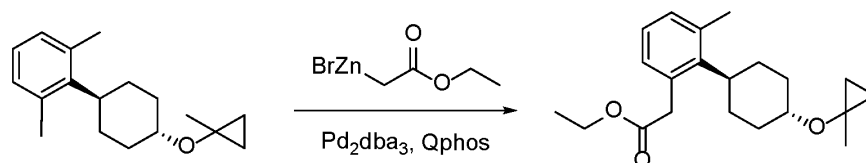
Example 19: Preparation of Compound 132-P2

Step 1: 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(prop-1-en-2-yloxy)cyclohexyl)benzene

[000444] A mixture of (1*r*,4*r*)-4-(2-iodo-6-methylphenyl)cyclohexan-1-ol (4.0 g, 12.6 mmol, 1.0 eq.) and Hg(OAc)₂ (1.2 g, 3.8 mmol, 0.3 eq.) in 2-methoxyprop-1-ene (30 ml) was allowed to stir at RT overnight under an atmosphere of N₂. Water (200 mL) was added, and the mixture was extracted with DCM (3 x 150 mL). The organic solutions were combined, washed sequentially with NaHCO₃ (100 ml) and brine (100 ml), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (19:1 petroleum ether: EtOAc) to give 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(prop-1-en-2-yloxy)cyclohexyl)benzene as a colorless oil (2.2 g, 50.3%).

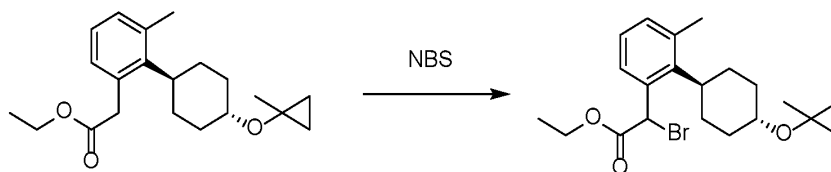
Step 2: 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)benzene

[000445] To a solution of 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(prop-1-en-2-yloxy)cyclohexyl)benzene (2.2 g, 6.2 mmol, 1.0 eq.) in DCM (40 mL) at 0 °C was added Et₂Zn (24.7 ml, 24.7 mmol, 4.0 eq.). The mixture was allowed to stir at 0 °C for 0.5 hr under an atmosphere of N₂. CH₂I₂ (6.6 g, 24.7 mmol, 4.0 eq.) was added dropwise into the mixture at 0 °C. The reaction was allowed to warm to RT and then allowed to continue to stir for 6 hr. Saturated aqueous NH₄Cl (150 mL) was added, and the mixture was extracted with DCM (3 x 150 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (95:1 petroleum ether: EtOAc) to give 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclo-propoxy)cyclohexyl)benzene as a colorless oil (1.1 g, 47.8 %).

Step 3: ethyl 2-(3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate

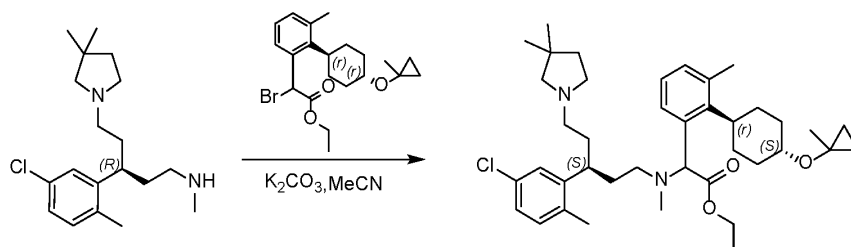
[000446] To a suspension of 1-iodo-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)-cyclohexyl)benzene (1.1 g, 3.0 mmol, 1.0 eq.) in THF (12 mL) was added Pd₂dba₃ (82.0 mg, 0.09 mmol, 0.03 eq.) and QPhos (64 mg, 0.09 mmol, 0.03 eq.). (2-ethoxy-2-oxoethyl)zinc(II) bromide (1M in THF, 7.4 mL, 7.4 mmol, 2.5 eq.) was then added and the mixture was allowed to stir at 65 °C under an atmosphere of N₂ for 1 hr.. Contents were then poured into 50 mL saturated aqueous NH₄Cl solution and extracted with EtOAc (3 x 100 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give ethyl 2-(3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate as a colorless oil (1.0 g, 94 %) (ESI 353.3 [M+Na]⁺).

Step 4: ethyl 2-bromo-2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate



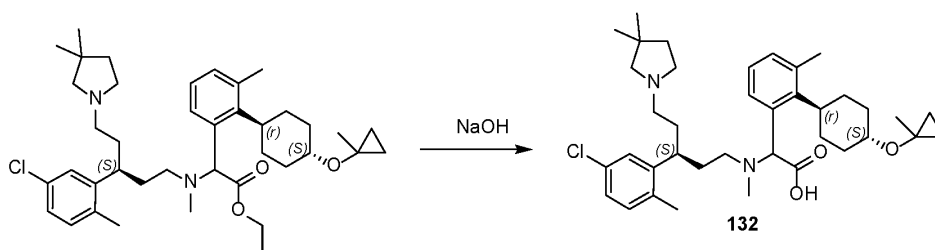
[000447] To a solution of LiHMDS (1M in THF, 6.0 mL, 6.0 mmol, 2.0 eq.) at -78°C, ethyl 2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate (1.0 g, 3.0 mmol, 1.0 eq.) in THF (20 mL) was added dropwise. The reaction mixture was allowed to stir at -78°C for 0.5 hr. TMSCl (648.0 mg, 6.0 mmol, 2.0 eq.) was then added dropwise, and The reaction was allowed to continue to stir at -78°C for another 15 min. A solution of NBS (1.07 g, 6.0 mmol, 2.0 eq.) in THF (20mL) was then added dropwise. The reaction mixture was allowed to stir at -78 °C for another 1 hr., warmed to 0 °C, quenched by the addition of saturated aqueous NH₄Cl solution (100 mL), and extracted with EtOAc (3 x 150 mL). The organic solutions were combined, washed with brine (3 x 150 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate as a colorless oil (1.1 g, 75%) (ESI 431.0 [M+Na]⁺; 433.0 [M+2+Na]⁺).

Step 5: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate



[000448] To a solution of (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine (200 mg 0.62 mmol, crude) in ACN (10 mL) was added K_2CO_3 (427 mg, 3.1 mmol, 5.0 *eq.*). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-(1-methylcyclopropoxy)-cyclohexyl)phenyl)acetate (253 mg, 0.62 mmol, 1.0 *eq.*) was then added. The reaction was allowed to continue to stir at 80 °C for another 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetate as a yellow oil (250 mg, 62%) (ESI 651.4 $[M+H]^+$).

Step 6: 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl) amino)-2-(3-methyl-2-((1r,4S)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetic acid

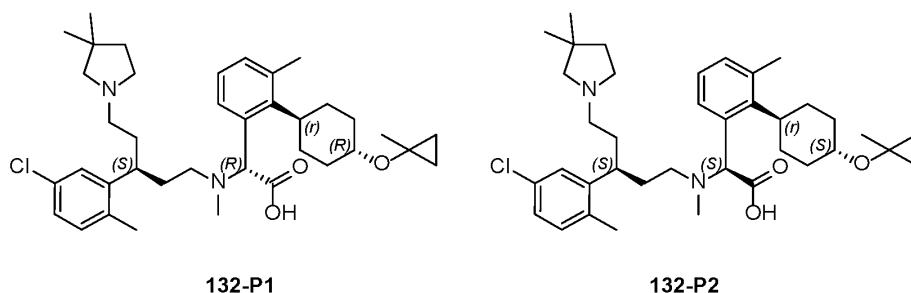


[000449] To a solution of ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl) acetate (250 mg, 0.38 mmol, 1.0 *eq.*) in EtOH (5 mL) and H_2O (1 mL) was added NaOH (76 mg, 1.9 mmol, 5.0 *eq.*). The reaction mixture was allowed to stir at 80 °C for 1 hr. and concentrated *in vacuo*. The crude residue was purified by

prep HPLC A (30 - 70% CH₃CN) to give a stereoisomeric product mixture **132** as a white solid (140 mg, 58%). Diastereomers were further separated by prep chiral SFC A to give **132-P1** (45 mg) and **132-P2** (61 mg).

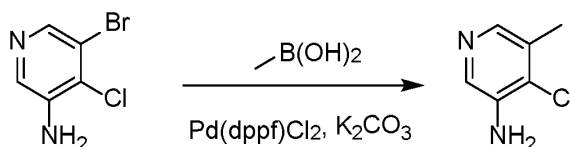
[000450] **132-P1**, assigned as (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*R*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 623.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.59 – 7.36 (m, 1H), 7.13 – 6.95 (m, 5H), 4.55 (d, *J* = 62.2 Hz, 1H), 3.68-3.61 (m, 1H), 3.24 (s, 1H), 2.93 – 2.53 (m, 5H), 2.52 – 2.14 (m, 13H), 1.87-1.79 (m, 8H), 1.64 – 1.49 (m, 3H), 1.45 – 1.26 (m, 6H), 1.06 (s, 6H), 0.84 – 0.72 (m, 2H), 0.43 (q, *J* = 4.4 Hz, 2H).

[000451] **132-P2**, assigned as (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(1-methylcyclopropoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 623.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.67 – 7.40 (m, 1H), 7.30 – 7.00 (m, 5H), 4.67 (d, *J* = 65.5 Hz, 1H), 3.72 (d, *J* = 41.4 Hz, 1H), 3.13 (s, 1H), 3.03 – 2.80 (m, 3H), 2.70 – 2.32 (m, 12H), 2.18 – 1.64 (m, 14H), 1.52 – 1.27 (m, 6H), 1.09 (s, 6H), 0.79 (s, 2H), 0.52 – 0.38 (m, 2H).



Example 20: Preparation of Compound 146-P1

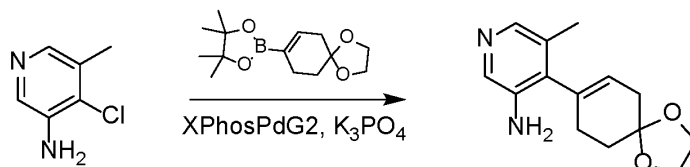
Step 1: 4-chloro-5-methylpyridin-3-amine



[000452] 2-bromo-3-methylaniline (25 g, 120.5 mmol, 1.0 eq.), methylboronic acid (18.0 g, 301.3 mmol, 2.5 eq.), K₂CO₃ (41.6 g, 301.3 mmol, 2.5 eq) and Pd(dppf)Cl₂ (5.29 g, 7.23 mmol, 0.06 eq.) were suspended in dioxane (300 mL) and water (50 mL). The reaction mixture was allowed to stir overnight at 100 °C under an atmosphere of N₂. The reaction mixture was poured into 300 mL water and extracted with EtOAc (3 x 200 mL). The organic solutions were

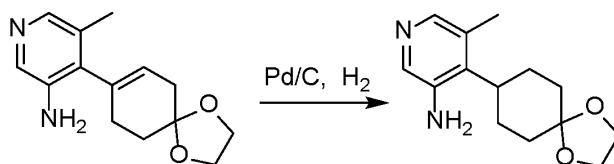
combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (1:1 petroleum ether: EtOAc) to give 4-chloro-5-methylpyridin-3-amine as a yellow solid (9.6 g, 55.9%) (ESI 143.0 [M+H]⁺).

Step 2: 5-methyl-4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)pyridin-3-amine



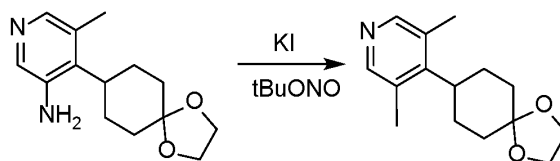
[000453] 4-chloro-5-methylpyridin-3-amine (9.6 g, 67.3 mmol, 1.0 eq.), 4,4,5,5-tetramethyl-2-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)-1,3,2-dioxaborolane (18.8 g, 70.7 mmol, 1.05 eq.), K₃PO₃ (18.6 g, 134.6 mmol, 2 eq) and XPhosPdG2 (2.1 g, 2.69 mmol, 0.04 eq.) were suspended in dioxane (100 mL) and water (20 mL). The reaction mixture was allowed to stir overnight at 100 °C under an atmosphere of N₂. The mixture was poured into 200 mL water and extracted with EtOAc (3 x 100 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (1:1 petroleum ether: EtOAc) to give 5-methyl-4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)pyridin-3-amine as a brown solid (13.1 g, 79.0%) (ESI 247.1 [M+H]⁺).

Step 3: 5-methyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-amine



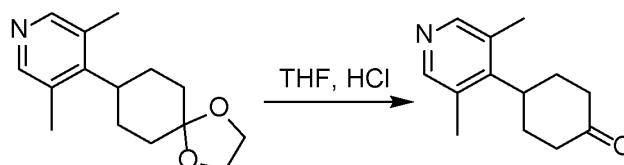
[000454] To a solution of 5-methyl-4-(1,4-dioxaspiro[4.5]dec-7-en-8-yl)pyridin-3-amine (13.1 g, 53.2 mmol, 1.0 eq.) in EtOH (200 mL) was added 10% Pd/C (5.64 g, 2.66 mmol, 0.05 eq). The reaction mixture was allowed to stir at 65 °C under an atmosphere of H₂ (1 atm, 3L) for 24 hr. The reaction mixture was filtered through a pad of Celite and concentrated *in vacuo* to give 5-methyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-amine as a yellow solid (11.1 g, 84.0%) (ESI 249.2 [M+H]⁺). The crude product was used directly in the subsequent step without further purification.

Step 4: 3-iodo-5-methyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)pyridine



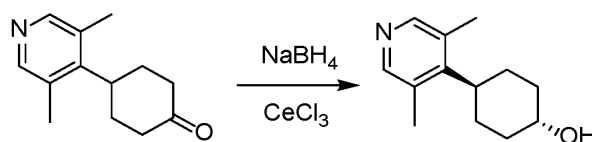
[000455] To a solution of 5-methyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)pyridin-3-amine (11.1 g, 44.7 mmol, 1.0 eq.) in ACN (150 mL) was added KI (22.3 g, 134.1 mmol, 3 eq.) and tert-butyl nitrite (23.0 g, 223.5 mmol, 5 eq.) at 0 °C. The mixture was heated at 40 °C for 2 days. The mixture was poured into 300 mL saturated aqueous Na₂SO₃ and extracted with EtOAc (3 x 100 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (1:1 petroleum ether: EtOAc) to give 3-iodo-5-methyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)pyridine as a yellow solid (7.1 g, 44.2%) (ESI 360.0 [M+H]⁺).

Step 5: 4-(3-iodo-5-methylpyridin-4-yl)cyclohexan-1-one



[000456] To a solution of 3-iodo-5-methyl-4-(1,4-dioxaspiro[4.5]decan-8-yl)pyridine (7.1 g, 19.8 mmol, 1.0 eq.) in THF (80 mL) was added 3M aqueous HCl (19.8 mL, 59.4 mmol, 3.0 eq.). The reaction mixture was allowed to stir at RT for 1 hr, cooled to 0 °C, quenched by the addition of saturated aqueous NaHCO₃ (pH adjusted to ~8), and extracted with EtOAc (2 x 200 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give 4-(3-iodo-5-methylpyridin-4-yl)cyclohexan-1-one as a yellow oil (6.2 g, 13.9 mmol, crude) (ESI 316.0 [M+H]⁺). The crude product was used directly in the next step.

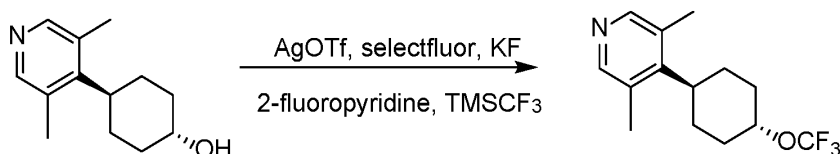
Step 6: (1*r*,4*r*)-4-(3-iodo-5-methylpyridin-4-yl)cyclohexan-1-ol



[000457] To a solution of 4-(3-iodo-5-methylpyridin-4-yl)cyclohexan-1-one (6.2 g, 13.9 mmol, crude, 1.0 eq.) in MeOH (60 mL) at 0 °C was added CeCl₃ (4.1 g, 16.7 mmol, 1.2eq). NaBH₄ (635 mg, 16.7 mmol, 1.2 eq) was then added portionwise. The mixture was allowed to stir at 0 °C for 0.5 hr. Water (100 mL) was slowly added at 0 °C, and the mixture was extracted

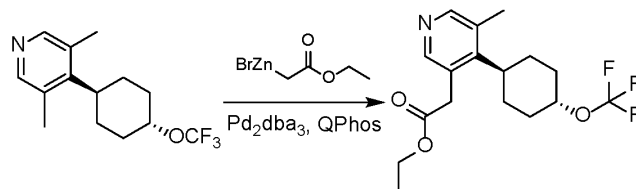
with EtOAc (3 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by HPLC A (30 - 60% ACN) to give (1*r*,4*r*)-4-(3-iodo-5-methylpyridin-4-yl)cyclohexan-1-ol as a white solid (2.5 g, 56.7%) (ESI 318.0 [M-OH]⁺).

Step 7: 3-iodo-5-methyl-4-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)pyridine



[000458] To a solution of (1*r*,4*r*)-4-(3-iodo-5-methylpyridin-4-yl)cyclohexan-1-ol (2.3 g, 7.26 mmol, 1.0 eq), Selectfluor (3.86 g, 10.9 mmol, 1.5 eq), KF (1.68 g, 29.0 mmol, 4.0 eq) and AgOTf (5.6 g, 21.8 mmol, 3.0 eq) in EtOAc (80 mL) was allowed to stir at RT for 5 min under an atmosphere of N₂. 2-fluoropyridine (2.1 g, 21.8 mmol, 3 eq) and TMSCF₃ (3.1 g, 21.8 mmol, 3 eq) were then added. The reaction mixture was allowed to stir at RT for 48 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (2:1 petroleum ether: EtOAc) to give 3-iodo-5-methyl-4-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)pyridine as a yellow oil (280 mg, 10%) (ESI 386.0 [M+H]⁺).

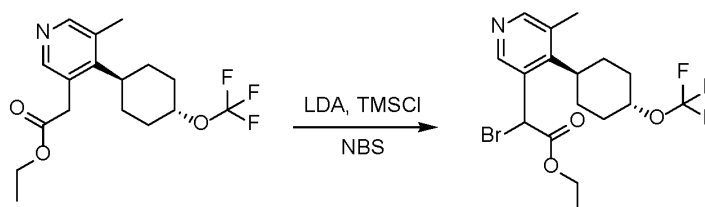
Step 8: ethyl 2-(5-methyl-4-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)pyridin-3-yl)acetate



[000459] To a suspension of 3-iodo-5-methyl-4-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)pyridine (280 mg, 0.73 mmol, 1.0 eq.), QPhos (16 mg, 0.022 mmol, 0.03 eq.) and Pd₂dba₃ (10 mg, 0.011 mmol, 0.015 eq) in THF (5 mL) was added (2-ethoxy-2-oxoethyl)zinc(II) bromide (1 M in THF, 2.9 mL, 2.9 mmol, 4.0 eq.). The reaction mixture was allowed to stir at 65 °C under an atmosphere of N₂ for 1 hr. The reaction mixture was poured into saturated aqueous NH₄Cl (50 mL) and extracted with EtOAc (2 x 50 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (2:1 petroleum ether: EtOAc) to give ethyl

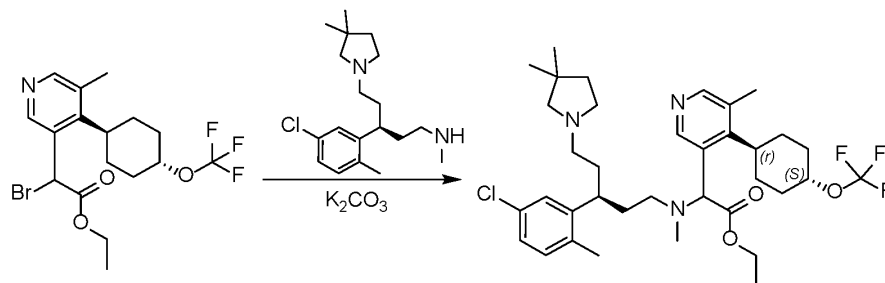
2-(5-methyl-4-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)pyridin-3-yl)acetate as a yellow oil (180 mg, 71.4%). (ESI 346.2 [M+H]⁺).

Step 9: ethyl 2-bromo-2-(5-methyl-4-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)pyridin-3-yl)acetate



[000460] To a solution of ethyl 2-(5-methyl-4-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)pyridin-3-yl)acetate (180 mg, 0.52 mmol, 1.0 eq) in THF (5 ml) at -78°C was added LDA (2M in THF and hexane, 0.65 mL, 1.3 mmol, 2.5 eq). The reaction mixture was allowed to stir at -78°C for 0.5 h. TMSCl (141 mg, 1.3 mmol, 2.5 eq) was added dropwise at -78°C and the reaction was allowed to continue to stir at -78°C for 15 min. A solution of NBS (184 mg, 1.04 mmol, 2.0 eq) in THF (2 mL) was added. The reaction mixture was allowed to stir at -78°C for 1 h. The reaction was quenched by the addition of saturated aqueous NH₄Cl (50 ml) and extracted with EtOAc (2 × 50 ml). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (2:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(5-methyl-4-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)pyridin-3-yl)acetate as a yellow solid (160 mg, 72.6%). (ESI 424.1 (M+H)⁺).

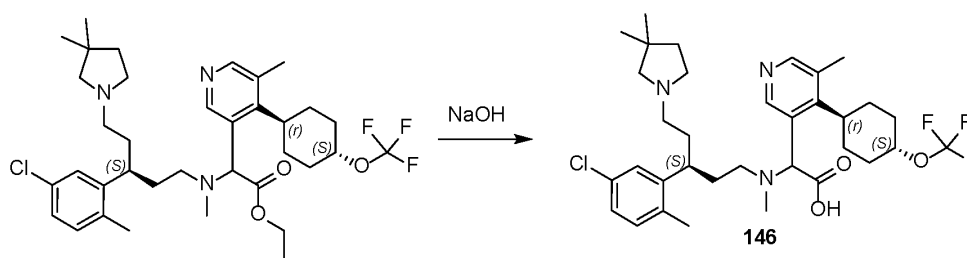
Step 10: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(5-methyl-4-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)pyridin-3-yl)acetate



[000461] To a solution of (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine (123 mg, 0.38 mmol, 1.0 eq) in ACN (5 mL) was added K₂CO₃ (262

mg, 1.9 mmol, 5.0 *eq.*) and ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (160 mg, 0.38 mmol, 1.0 *eq.*). The reaction mixture was allowed to stir at 80 °C for 1 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(5-methyl-4-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)pyridin-3-yl)acetate as a yellow oil (150 mg, 59.2%) (ESI 666.4 $[M+H]^+$).

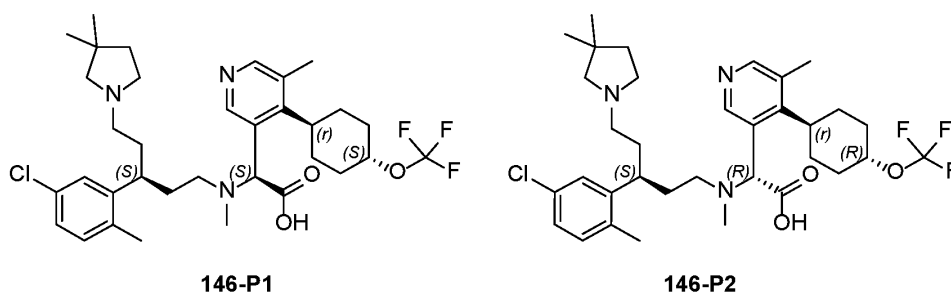
Step 11: 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(5-methyl-4-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)pyridin-3-yl)acetic acid



[000462] To a mixture of ethyl 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(5-methyl-4-((1*r*,4*S*)-4-(trifluoromethoxy)-cyclohexyl)pyridin-3-yl)acetate (150 mg, 0.23 mmol, 1.0 *eq.*) in EtOH (4 mL) and H₂O (1 mL) was added NaOH (46 mg, 1.15 mmol, 5.0 *eq.*). The mixture was allowed to stir at 80 °C for 16 hr and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give stereoisomeric mixture of compounds **146** as a white solid (100 mg, 69.7%). The stereoisomers were further separated by prep chiral SFC D to give **146-P1** (32 mg) and **416-P2** (30 mg).

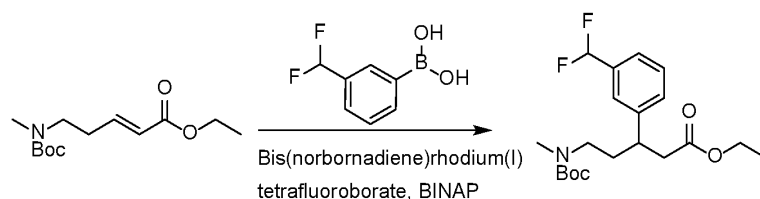
[000463] **146-P1**, assigned as (*S*)-2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(5-methyl-4-((1*r*,4*S*)-4-(trifluoromethoxy)-cyclohexyl)pyridin-3-yl)acetic acid. LC/MS ESI 638.3 $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ 9.31 – 8.48 (m, 1H), 8.33 – 7.75 (m, 1H), 7.49 – 6.89 (m, 3H), 4.56 – 4.15 (m, 2H), 3.61 (s, 1H), 3.36 (s, 1H), 3.27 – 3.17 (m, 1H), 3.12 – 2.93 (m, 3H), 2.84 – 2.66 (m, 2H), 2.56 – 2.32 (m, 4H), 2.32 – 2.20 (m, 5H), 2.21 – 1.99 (m, 7H), 1.99 – 1.89 (m, 1H), 1.89 – 1.53 (m, 8H), 1.15 (s, 6H).

[000464] **146-P2**, assigned as (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(5-methyl-4-((1*r*,4*R*)-4-(trifluoromethoxy)-cyclohexyl)pyridin-3-yl)acetic acid. LC/MS ESI 638.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 8.99 – 8.47 (m, 1H), 8.24 – 7.91 (m, 1H), 7.23 – 6.86 (m, 3H), 4.27 (d, $J = 55.6$ Hz, 2H), 3.48 (s, 1H), 3.27 (s, 2H), 3.07 – 2.86 (m, 4H), 2.70 (t, $J = 9.6$ Hz, 1H), 2.49 – 2.27 (m, 7H), 2.26 – 2.09 (m, 6H), 2.08 – 1.85 (m, 5H), 1.81 (t, $J = 7.4$ Hz, 2H), 1.77 – 1.49 (m, 5H), 1.13 (s, 6H).

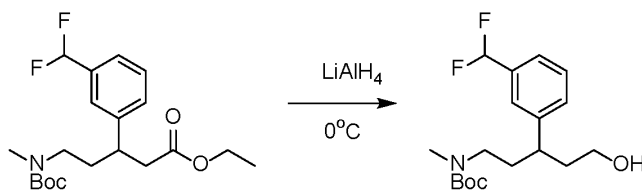


Example 21: Preparation of Compound 152-P2

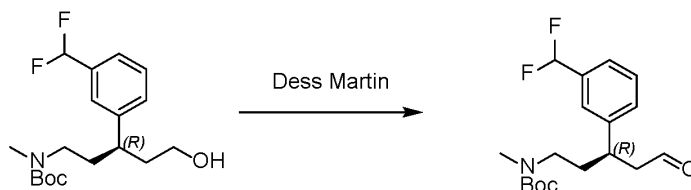
Step 1: ethyl 5-((tert-butoxycarbonyl)(methylamino)-3-(3-(difluoromethyl)phenyl)-pentanoate



[000465] To a solution of (3-(difluoromethyl)phenyl)boronic acid (5.2 g, 30.0 mmol, 2.5 eq.), bis(norbornadiene)rhodium(I) tetrafluoroborate (360 mg, 1.0 mmol, 0.08 eq.), ethyl (E)-5-((tert-butoxycarbonyl)(methylamino)pent-2-enoate (3.0 g, 12.0 mmol, 1 eq.) and BINAP (750 mg, 1.2 mmol, 0.1 eq.) in dioxane (50 mL) was added a solution of KOH (1.0 g, 18.0 mmol, 1.5 eq.) in H_2O (7 mL) under a nitrogen atmosphere. The reaction mixture was allowed to stir at RT for 6 hr. The reaction mixture was poured into 200 mL of water and extracted with EtOAc (3 x 400 mL). The organic solutions were combined, washed with brine (2 x 100 mL), dried over anhydrous Na_2SO_4 , filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column (7:1 petroleum ether: EtOAc) to give ethyl 5-((tert-butoxycarbonyl)(methylamino)-3-(3-(difluoromethyl)phenyl)pentanoate (3.0 g, 67%) (ESI 286.2 $[M-Boc+H]^+$).

Step 2: : tert-butyl (3-(3-(difluoromethyl)phenyl)-5-hydroxypentyl)(methyl)carbamate

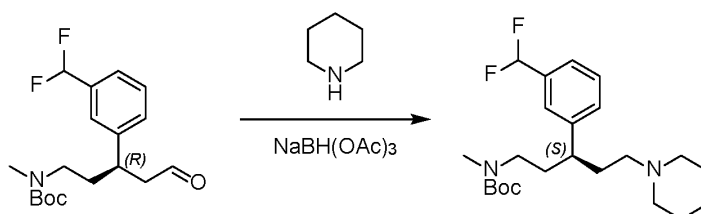
[000466] To a solution of ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-(3-(difluoromethyl)phenyl)pentanoate (3.0 g, 8.0 mmol, 1.0 eq) in THF (30 mL) at 0 °C was added lithium aluminum hydride (2.5M in THF, 4.0 mL, 10.0 mmol, 1.3 eq). The reaction mixture was allowed to stir at 0 °C for 1 hr and quenched by the addition of water (0.4 mL). The mixture was allowed to continue to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.4 mL) and water (1.2 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT. The mixture was allowed to continue to stir for another 15 min. The reaction mixture was then dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (7:2 petroleum ether: EtOAc) to give tert-butyl (3-(3-(difluoromethyl)phenyl)-5-hydroxypentyl)(methyl)carbamate (1.0 g, 37%)(ESI 344.2 [M+H]⁺). Enantiomers were separated by prep chiral SFC J to give peak 1, tert-butyl (S)-3-(3-(difluoromethyl)phenyl)-5-hydroxypentyl(methyl)carbamate (200mg), and peak 2, tert-butyl (R)-3-(3-(difluoromethyl)phenyl)-5-hydroxypentyl(methyl)carbamate (325mg), as a white solids (ESI 362.2 [M+H]⁺).

Step 3: tert-butyl (R)-3-(3-(difluoromethyl)phenyl)-5-oxopentyl(methyl)carbamate

[000467] To a solution of tert-butyl (R)-3-(3-(difluoromethyl)phenyl)-5-hydroxypentyl(methyl)carbamate (230 mg, 0.67 mmol, 1.0 eq.) in DCM (6 mL) was added Dess-Martin periodinane (370 mg, 0.87 mmol, 1.3 eq.) at 0 °C. The reaction was then allowed to warm to RT and to stir for 1 hr. The reaction mixture was diluted with saturated aqueous Na₂SO₃ (50 mL) and extracted with DCM (3 x 50 mL). The organic solutions were combined, washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to obtain tert-butyl (R)-3-(3-(difluoromethyl)phenyl)-5-oxopentyl(methyl)carbamate (230

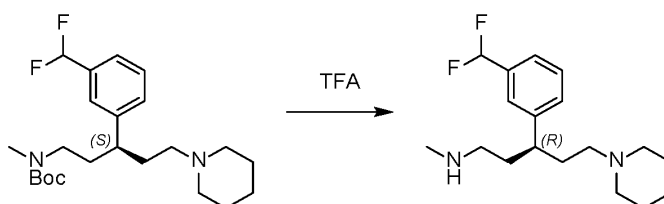
mg, 100%)(ESI 364.0 ($[M+Na]^+$). The crude product was used without purification in the subsequent step.

Step 4: tert-butyl (S)-(3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methyl)-carbamate



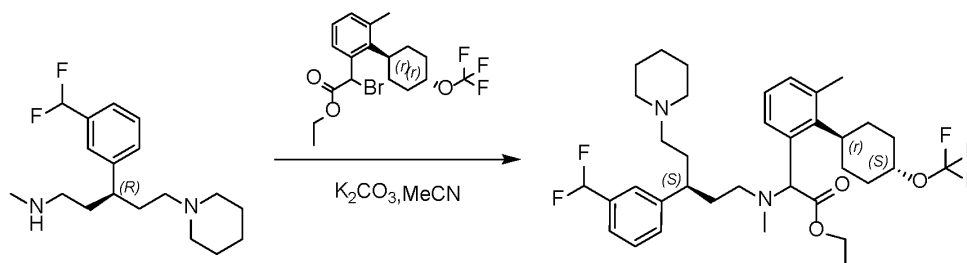
[000468] To a solution of tert-butyl (R)-(3-(3-(difluoromethyl)phenyl)-5-oxopentyl)(methyl)carbamate (230 mg, 0.67 mmol, 1.0 eq.) in dichloroethane (6 mL) was added piperidine (85 mg, 1.0 mmol, 1.5 eq.). The reaction mixture was allowed to stir at RT for 1 hr. $NaBH(OAc)_3$ (285 mg, 1.34 mmol, 2.0 eq.) was then added into the reaction. The reaction mixture was allowed to continue to stir at RT for another 2 hr. The reaction mixture was then poured into water (50 mL) and extracted with DCM (3 x 50 mL). The organic solutions were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 DCM: methanol) to give tert-butyl (S)-(3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methyl)carbamate as yellow oil (160 mg, 60%) (ESI 411.2 $[M+H]^+$).

Step 5: (R)-3-(3-(difluoromethyl)phenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine



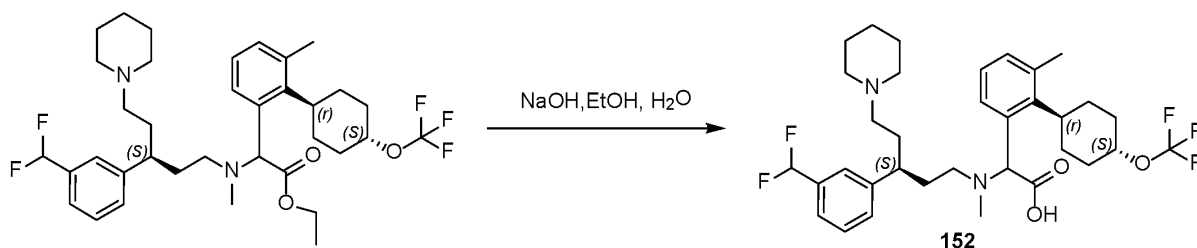
[000469] To a solution of tert-butyl (S)-(3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methyl)carbamate (160 mg, 0.4 mmol, 1.0 eq.) in DCM (2 mL) was added TFA (0.2 mL, 2.8 mmol, 7.0 eq.). The reaction mixture was allowed to stir at RT for 2 hr. and concentrated *in vacuo* to obtain (R)-3-(3-(difluoromethyl)phenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine as a colorless oil (160 mg 0.4 mmol, crude). (ESI 311.3 $[M+H]^+$). The crude product was used without purification in the next step.

Step 6: ethyl 2-(((S)-3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000470] To a solution of (R)-3-(3-(difluoromethyl)phenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (160 mg, 0.4 mmol) in ACN (10 mL) was added K_2CO_3 (276 mg, 2.0 mmol, 5.0 *eq.*). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (169 mg, 0.4 mmol, 1.0 *eq.*) was then added. The reaction mixture was allowed to continue to stir at 80 °C for another 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((S)-3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (190 mg, 59 %) (ESI 653.4 $[M+H]^+$).

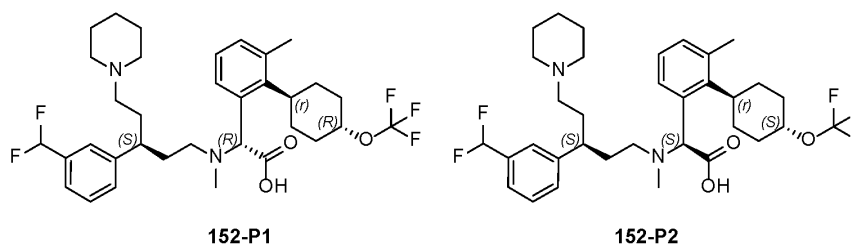
Step 7: 2-(((S)-3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



[000471] To a solution of ethyl 2-(((S)-3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (190 mg, 0.29 mmol, 1.0 *eq.*) in EtOH (5 mL) and H_2O (1 mL) was added NaOH (58 mg, 1.5 mmol, 5.0 *eq.*) and the mixture was allowed to stir at 80 °C for 1 hr. The reaction was concentrated *in vacuo* and the residue was purified by prep HPLC A (30 - 70% CH_3CN) to give **152** as a mixture of stereoisomers (160 mg, 88%). The stereoisomers were further separated by prep chiral SFC A to give **152-P1** (65.1 mg) **152-P2** (69.7 mg).

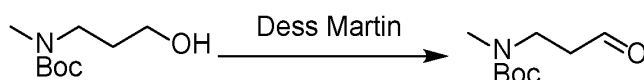
[000472] **152-P1**, assigned as (R)-2-(((S)-3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 625.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.63 – 6.91 (m, 7H), 6.84 – 6.54 (m, 1H), 4.78 – 4.15 (m, 2H), 3.26 – 3.00 (m, 1H), 2.99 – 2.44 (m, 10H), 2.44 (s, 3H), 2.32 (s, 1H), 2.27 – 1.64 (m, 11H), 1.70 – 1.05 (m, 8H).

[000473] **152-P2**, assigned as (S)-2-(((S)-3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 625.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.75 – 6.92 (m, 7H), 6.86 – 6.57 (m, 1H), 4.75 – 4.23 (m, 2H), 2.98 – 2.53 (m, 8H), 2.52 – 2.39 (m, 6H), 2.39 – 2.24 (m, 2H), 2.22 – 1.71 (m, 10H), 1.70 – 1.55 (m, 6H), 1.54 – 1.40 (m, 2H).



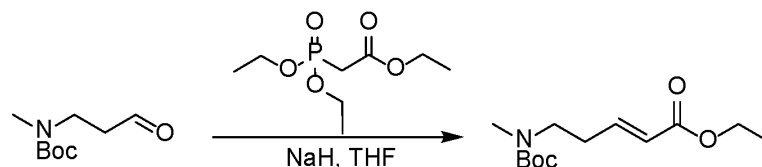
Example 22: Preparation of Compound 171-P2

Step 1: tert-butyl methyl(3-oxopropyl)carbamate



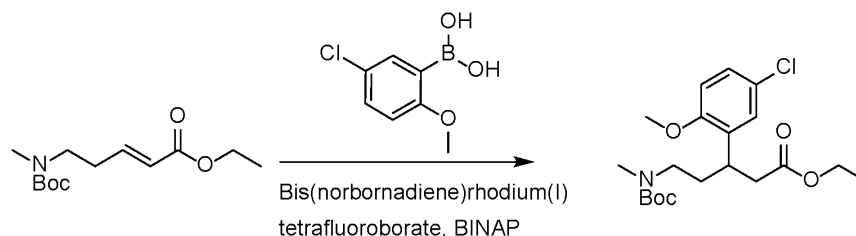
[000474] To a solution of tert-butyl (3-hydroxypropyl)(methyl)carbamate (50 g, 264.6 mmol, 1.0 eq.) in DCM (1 L) was added Dess-Martin periodinane (118 g, 278 mmol, 1.05 eq.) at 0 °C. The reaction mixture was then warmed to RT and stirred for 30 minutes. The reaction was quenched by the addition of saturated aqueous Na₂SO₃ (800 mL) and extracted with DCM (2 x 500 mL). The organic solutions were combined, washed with saturated Na₂CO₃ solution (2 x 800 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give tert-butyl methyl(3-oxopropyl)carbamate as a yellow oil (44 g, 213.9 mmol) (ESI 210 [M+Na]⁺). The crude product was used without purification in the subsequent step.

Step 2: ethyl (E)-5-((tert-butoxycarbonyl)(methyl)amino)pent-2-enoate



[000475] To a solution of NaH (60% in oil, 11.1 g, 278 mmol, 1.3 eq.) in THF (500 mL) was added ethyl 2-(diethoxyphosphoryl)acetate (57.5 g, 256.7 mmol, 1.2 eq.) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 30 minutes. A solution of tert-butyl methyl(3-oxopropyl)carbamate (44 g, 213.9 mmol, 1.0 eq.) in THF (200 mL) was then added over 5 min. The mixture was allowed to warm to RT and stirred for 30 min. The reaction was then quenched by the addition of saturated aqueous NH₄Cl solution (400 mL) and extracted with EtOAc (2 x 400 mL). The organic solutions were combined, washed with brine (400 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (12:1 petroleum ether: EtOAc) to give ethyl (E)-5-((tert-butoxycarbonyl)(methyl)amino)pent-2-enoate as a yellow oil (27.5 g, 41.6%) (ESI 158.2 (M-Boc+H)⁺).

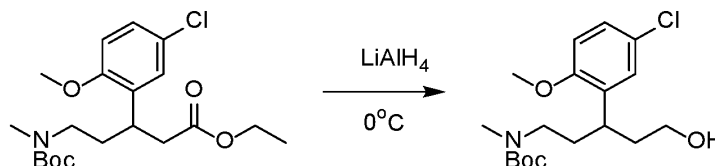
Step 3: ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-methoxyphenyl)pentanoate



[000476] To a solution of (5-chloro-2-methoxyphenyl)boronic acid (5.6 g, 30.0 mmol, 2.5 eq.), bis(norbornadiene)rhodium(I) tetrafluoroborate (360 mg, 1.0 mmol, 0.08 eq.), ethyl (E)-5-((tert-butoxycarbonyl)(methyl)amino)pent-2-enoate (3.0 g, 12.0 mmol, 1.0 eq.) and BINAP (750 mg, 1.2 mmol, 0.1 eq.) in dioxane (50 mL) was added a solution of KOH (1.0 g, 18.0 mmol, 1.5 eq.) in H₂O (7 mL). The reaction mixture was allowed to stir at RT for 6 hr under nitrogen atmosphere. The reaction mixture was then poured into 200 mL water and extracted with EtOAc (3 x 400 mL). The organic solutions were combined, washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column (7:1 petroleum ether: EtOAc) to give ethyl 5-((tert-

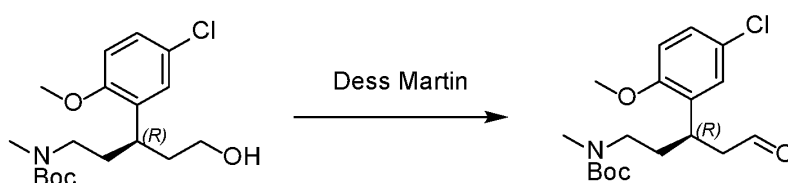
butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-methoxyphenyl)pentanoate (3.2 g, 68%) (ESI 300.2 [M-Boc+H]⁺).

Step 4: tert-butyl (3-(5-chloro-2-methoxyphenyl)-5-hydroxypentyl)(methyl)carbamate



[000477] To a solution of ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-(5-chloro-2-methoxyphenyl)pentanoate (3.2 g, 8.0 mmol, 1.0 eq) in THF (30 mL) at 0 °C was added lithium aluminum hydride (2.5 M in THF, 4.0 mL, 10.0 mmol, 1.3 eq). The reaction mixture was allowed to stir at 0 °C for 1 hr and quenched by the addition of water (0.4 mL). The reaction was allowed to continue to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.4 mL) and water (1.2 mL) were sequentially added, and the mixture was allowed to warm to RT. After another 15 min, the mixture was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (7:2 petroleum ether: EtOAc) to give tert-butyl (3-(5-chloro-2-methoxyphenyl)-5-hydroxypentyl)(methyl)carbamate (1.2 g, 42%). Stereoisomers were separated by prep chiral SFC J to give peak 1, tert-butyl (S)-3-(5-chloro-2-methoxyphenyl)-5-hydroxypentyl(methyl)carbamate (400 mg), and peak 2, tert-butyl (R)-3-(5-chloro-2-methoxyphenyl)-5-hydroxypentyl(methyl)carbamate (410 mg), as a white solids (ESI 358.2 [M+H]⁺).

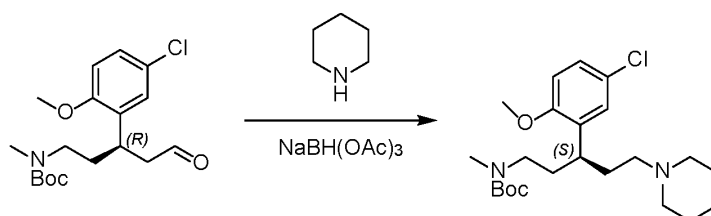
Step 5: tert-butyl (R)-3-(5-chloro-2-methoxyphenyl)-5-oxopentyl(methyl)carbamate



[000478] To a solution of tert-butyl (R)-3-(5-chloro-2-methoxyphenyl)-5-hydroxypentyl(methyl)carbamate (240 mg, 0.67 mmol, 1.0 eq.) in DCM (6 mL) was added Dess-Martin periodinane (370 mg, 0.87 mmol, 1.3 eq.) at 0 °C. The reaction was then allowed to warm to RT and stir for 1 hr. The mixture was diluted with saturated aqueous Na₂SO₃ (50 mL) and extracted with DCM (3 x 50 mL). The organic solutions were combined, washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to obtain tert-butyl (R)-3-(5-chloro-2-methoxyphenyl)-5-oxopentyl(methyl)carbamate (240 mg, 100%)(ESI

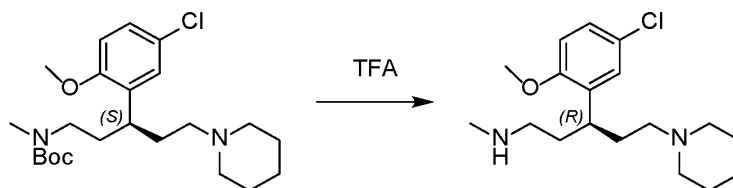
378.0 ($[M+Na]^+$). The crude product was used in the subsequent step without further purification.

Step 6: tert-butyl (S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl(methyl)-carbamate



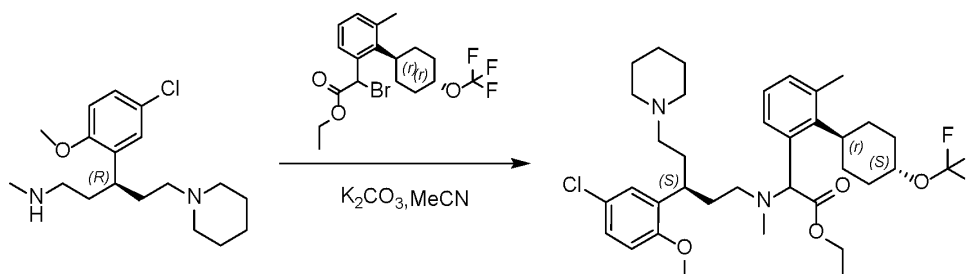
[000479] To a solution of tert-butyl (R)-3-(5-chloro-2-methoxyphenyl)-5-oxopentyl(methyl)carbamate (240 mg, 0.67 mmol, 1.0 eq.) in dichloroethane (6 mL) was added piperidine (85 mg, 1.0 mmol, 1.5 eq.). The reaction mixture was allowed to stir at RT for 1 hr. $NaBH(OAc)_3$ (285 mg, 1.34 mmol, 2.0 eq.) was then added into the reaction. The reaction was allowed to continue to stir at RT for 2 hr. The reaction mixture was then poured into water (50 mL) and extracted with DCM (3 x 50 mL). The organic solutions were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 DCM: methanol) to give tert-butyl (S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl(methyl)carbamate as a yellow oil (170 mg, 60%) ($ESI\ 425.2\ [M+H]^+$).

Step 7: (R)-3-(5-chloro-2-methoxyphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine



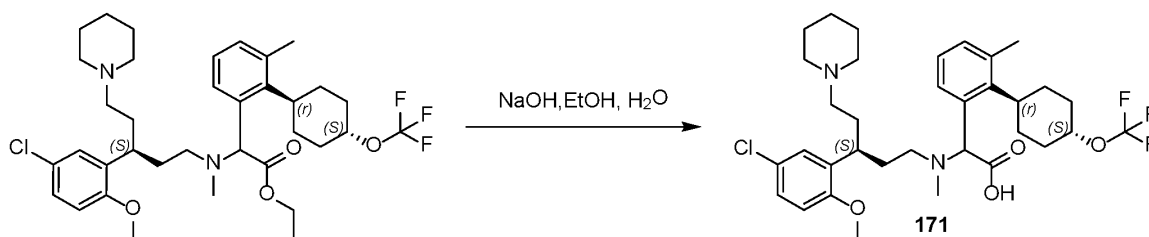
[000480] To a solution of tert-butyl (S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl(methyl)carbamate (170 mg, 0.4 mmol, 1.0 eq.) in DCM (2 mL) was added TFA (0.2 mL, 2.8 mmol, 7.0 eq.). The reaction mixture was allowed to stir at RT for 2 hr. and concentrated *in vacuo* to give (R)-3-(5-chloro-2-methoxyphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine as a colorless oil (130 mg 0.4 mmol, crude). ($ESI\ 325.2\ [M+H]^+$). The crude product was used without purification in the subsequent step.

Step 8: ethyl 2-(((S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000481] To a solution of (R)-3-(5-chloro-2-methoxyphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (130 mg 0.4 mmol, crude) in ACN (10 mL) was added K_2CO_3 (276 mg, 2.0 mmol, 5.0 eq.). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (169 mg, 0.4 mmol, 1.0 eq) was then added. The reaction was allowed to continue to stir at 80 °C for another 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl)-(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (190 mg, 71 %) (ESI 667.3 $[M+H]^+$).

Step 9: 2-(((S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid

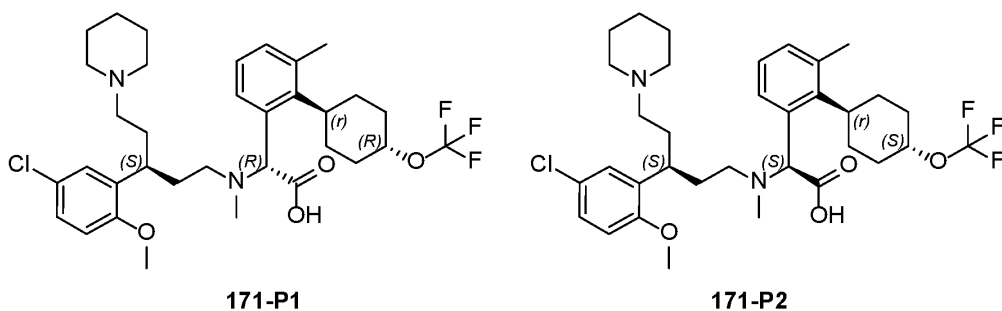


[000482] To a mixture of ethyl 2-(((S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (190 mg, 0.29 mmol, 1.0 eq) in EtOH (5 mL) and H_2O (1 mL) was added NaOH (58 mg, 1.5 mmol, 5.0 eq). The reaction mixture was allowed to stir at 80 °C for 1 hr and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH_3CN) to give the mixture of stereoisomers **171** as a white solid (160 mg, 88%). The

stereoisomers were separated by prep chiral SFC A to give **171-P1** (52.8 mg) and **171-P2** (47.2 mg) as a white solids.

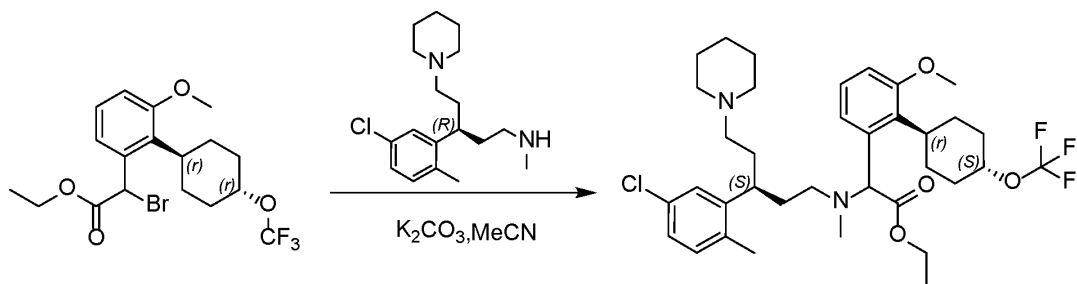
[000483] **171-P1**, assigned as (R)-2-(((S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 639.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.62 – 7.31 (m, 1H), 7.25 – 6.93 (m, 4H), 6.84 (d, 1H), 4.71 – 4.27 (m, 2H), 3.70 (s, 3H), 3.25 – 3.03 (m, 1H), 3.00 – 2.84 (m, 1H), 2.81 – 2.29 (m, 13H), 2.25 – 1.84 (m, 9H), 1.82 – 1.36 (m, 10H).

[000484] **171-P2**, assigned as (S)-2-(((S)-3-(5-chloro-2-methoxyphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 639.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.72 – 7.36 (m, 1H), 7.33 – 6.99 (m, 4H), 6.99 – 6.81 (m, 1H), 4.75 – 4.25 (m, 2H), 3.73 (s, 3H), 3.19 – 2.95 (m, 1H), 2.88 – 2.25 (m, 14H), 2.24 – 1.82 (m, 9H), 1.82 – 1.00 (m, 10H).



Example 23: Preparation of Compound 198-P2

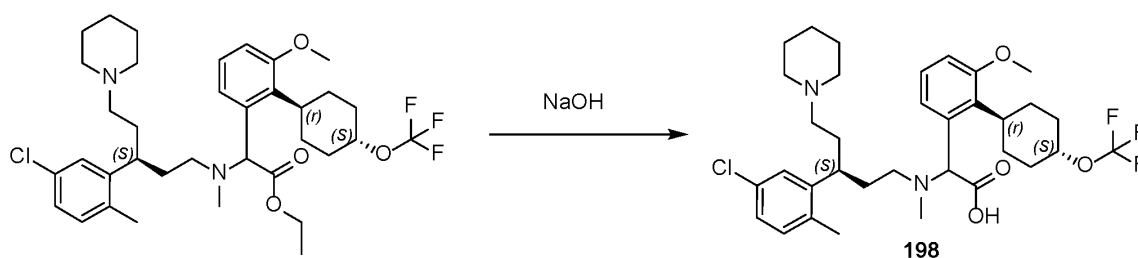
Step 1: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methoxy-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000485] To a solution of (R)-3-(5-chloro-2-methylphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (200 mg 0.46 mmol, crude) in ACN (10 mL) was added K₂CO₃ (317 mg,

2.3 mmol, 5.0 *eq.*). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(3-methoxy-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (140 mg, 0.46 mmol, 1.0 *eq.*) was then added. The reaction mixture was allowed to continue to stir at 80 °C for 2 hr. The reaction was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methoxy-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as a yellow oil (190 mg, 63%) (ESI 667.3 [M+H]⁺).

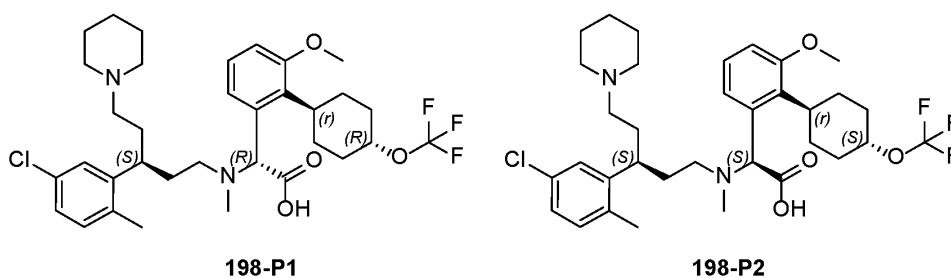
Step 2: 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methoxy-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



[000486] To a solution of ethyl 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methoxy-2-((1*r*,4*S*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate (190mg, 0.28 mmol, 1.0 *eq.*) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (56 mg, 1.4 mmol, 5.0 *eq.*). The reaction mixture was allowed to stir at 80 °C for 1 hr and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give the mixture of stereoisomers **198** as a white solid (130 mg, 71%). The stereoisomers were further separated by prep chiral SFC I to give **198-P1** (24 mg) and **198-P2** (20 mg).

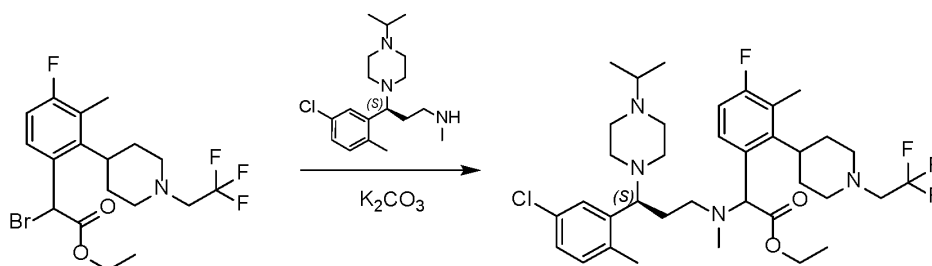
[000487] **198-P1**, assigned (R)-2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methoxy-2-((1*r*,4*R*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetic acid. LC/MS ESI 639.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.21 – 7.02 (m, 5H), 6.98 – 6.85 (m, 1H), 4.62 (s, 1H), 4.25 (s, 1H), 3.80 (s, 3H), 3.00 (s, 1H), 2.84 (d, *J* = 34.6 Hz, 2H), 2.65 – 2.15 (m, 15H), 2.06 (s, 3H), 1.91 (d, *J* = 9.9 Hz, 2H), 1.78–1.63 (m, 8H), 1.38 (d, *J* = 78.0 Hz, 3H).

[000488] **198-P2**, assigned as (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methoxy-2-((1*r*,4*S*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetic acid. LC/MS ESI 639.3 $[M+H]^+$. 1H NMR (400 MHz, CD_3OD) δ 7.28 – 7.01 (m, 5H), 6.92 (d, J = 8.0 Hz, 1H), 4.56 (s, 1H), 4.25 (t, J = 11.1 Hz, 1H), 3.81 (s, 3H), 3.19 – 2.92 (m, 2H), 2.58 (d, J = 48.3 Hz, 10H), 2.39 – 2.15 (m, 6H), 2.10 – 1.79 (m, 6H), 1.77 – 1.59 (m, 6H), 1.55 – 1.25 (m, 4H).



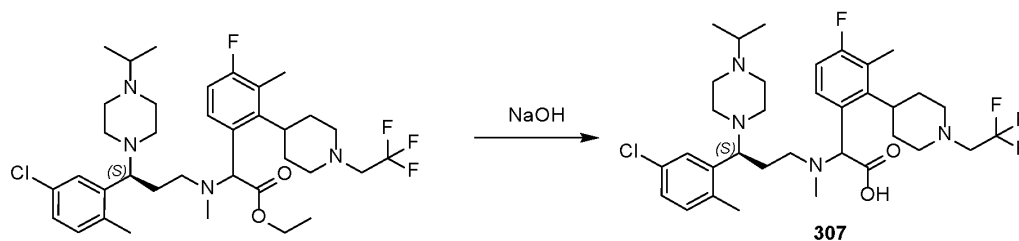
Example 24: Preparation of Compound 307-2P2

Step 1: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate



[000489] To a solution of ethyl 2-bromo-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate (240 mg 0.54 mmol, 1.0 *eq*) and (S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)-N-methylpropan-1-amine (190 mg 0.6 mmol, 1.1 *eq*) in ACN (5 mL) was added K_2CO_3 (224 mg, 1.62 mmol, 3.0 *eq*.). The mixture was allowed to stir at RT for 15 min and then at 80 °C for another 2 hr. The reaction was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (8:2 DCM: MeOH) to give ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate as a yellow solid (300 mg, 83%) (ESI 683.3 $[M+H]^+$).

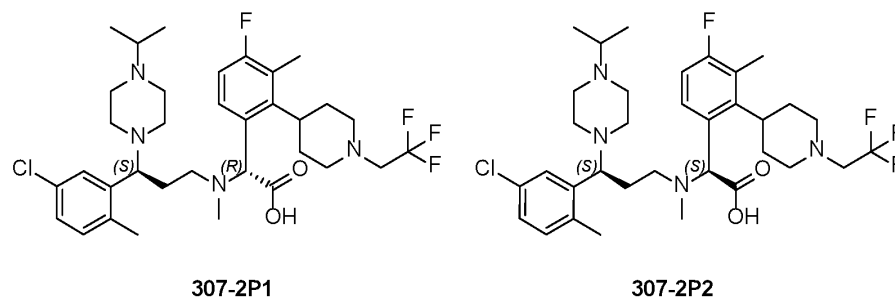
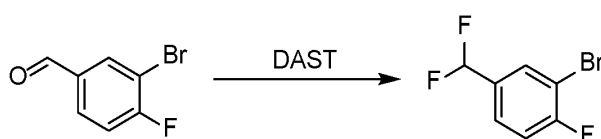
Step 2: 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid



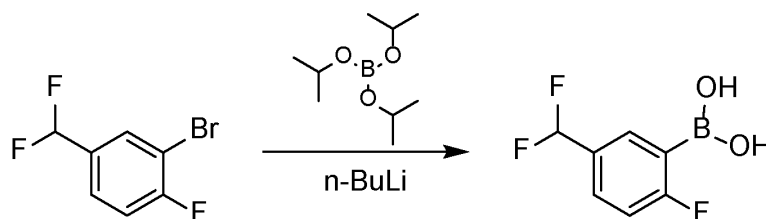
[000490] To a solution of ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetate (300 mg, 0.44 mmol, 1.0 eq) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (71 mg, 1.76mmol, 4.0 eq). The reaction mixture was allowed to stir at 70 °C for 1 hr and then allowed to cool to RT. The pH of the mixture was then adjusted to ~6-7 with 2N HCl. Solvents were removed *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give **307-2P1** (80.6 mg) and **307-2P2** (70.9 mg).

[000491] **307-2P1**, assigned as (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid. LC/MS ESI 655.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.50 (s, 1H), 7.22 – 7.15 (m, 3H), 6.97 – 6.90 (m, 1H), 5.15 – 4.62 (m, 1H), 3.88 (s, 1H), 3.14 – 2.29 (m, 30H), 1.91 (s, 1H), 1.72 – 1.49 (m, 2H), 1.14 (d, *J* = 5.5 Hz, 6H).

[000492] **307-2P2**, assigned as (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-3-(4-isopropylpiperazin-1-yl)propyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-(1-(2,2,2-trifluoroethyl)piperidin-4-yl)phenyl)acetic acid. LC/MS ESI 655.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.48 (s, 1H), 7.32 – 7.18 (m, 3H), 7.10 – 6.98 (m, 1H), 5.28 – 4.90 (m, 1H), 3.91 – 3.80 (d, *J* = 4.4 Hz, 1H), 3.47 – 3.32 (m, 3H), 3.22 – 2.94 (m, 10H), 2.76 – 2.07 (m, 18H), 1.76 – 1.41 (m, 2H), 1.34 (d, *J* = 5.8 Hz, 6H).

**Example 25: Preparation of Compound 308-1P2****Step 1: 2-bromo-4-(difluoromethyl)-1-fluorobenzene**

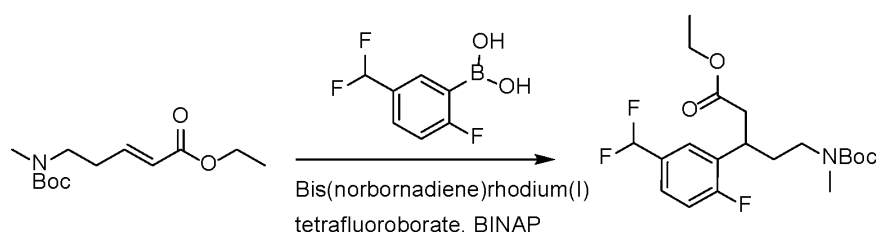
[000493] To a solution of 3-bromo-4-fluorobenzaldehyde (24.0 g, 118.8 mmol, 1.0 eq.) in DCM (250 mL) was added DAST (57.4 g, 356.4 mmol, 3.0 eq.) at 0 °C. The reaction mixture was then allowed to warm to RT and stir for 6 hr. The mixture was then poured into 300 mL of water and extracted with DCM (3 x 400 mL). The organic solutions were combined, washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (9:1 petroleum ether: EtOAc) to give 2-bromo-4-(difluoromethyl)-1-fluorobenzene (20.2 g, 76%) (ESI 225.0 [M+H]⁺).

Step 2: (5-(difluoromethyl)-2-fluorophenyl)boronic acid

[000494] To a solution of 2-bromo-4-(difluoromethyl)-1-fluorobenzene (20.2 g, 90.2 mmol, 1.0 eq.) in THF (200 mL) was added n-BuLi (2.5M in THF, 43.3 mL, 108.2 mmol, 1.2 eq) at -78°C. The reaction mixture was allowed to stir at -78°C for 1.5 hr. Triisopropyl borate (50.9 g, 270.6 mmol, 3.0 eq.) was then added and the mixture was allowed to stir at -78°C for another 2 hr. The reaction mixture was then poured into 300 mL of water and extracted with EtOAc (3 x 400 mL). The organic solutions were combined, washed with brine (2 x 500 mL), dried over anhydrous Na₂SO₄, filtered and the filtrate was concentrated *in vacuo*. The residue was purified

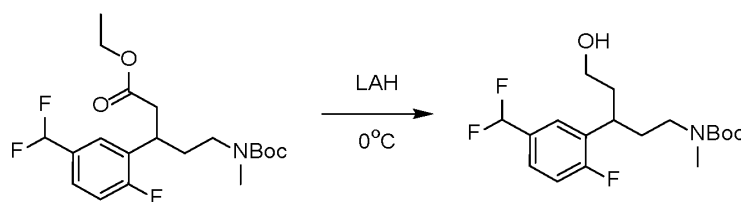
by silica gel column (9:1 petroleum ether: EtOAc) to give (5-(difluoromethyl)-2-fluorophenyl)boronic acid (6.7 g, 39%) (ESI 191.0 $[M+H]^+$).

Step 3: ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-(5-(difluoromethyl)-2-fluorophenyl)pentanoate



[000495] To a solution of (5-(difluoromethyl)-2-fluorophenyl)boronic acid (5.6 g, 30.0 mmol, 2.5 eq.), bis(norbornadiene)rhodium(I) tetrafluoroborate (360 mg, 1.0 mmol, 0.08 eq.), ethyl (E)-5-((tert-butoxycarbonyl)(methyl)amino)pent-2-enoate (3.0 g, 12.0 mmol, 1 eq.) and BINAP (750 mg, 1.2 mmol, 0.1 eq.) in dioxane (50 mL) was added a solution of KOH (1.0 g, 18.0 mmol, 1.5 eq.) in H₂O (7 mL) under an atmosphere of nitrogen. The reaction mixture was allowed to stir at RT for 6 hr. The mixture was then poured into 200 mL of water and extracted with EtOAc (3 x 400 mL). The organic solutions were combined, washed with brine (2 x 100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column (7:1 petroleum ether: EtOAc) to give ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-(5-(difluoromethyl)-2-fluorophenyl)pentanoate (2.0 g, 43%) (ESI 304.2 $[M-Boc+H]^+$).

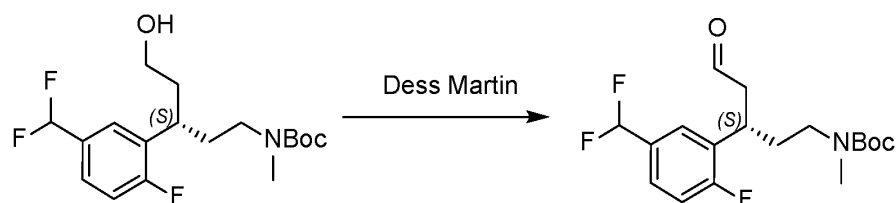
Step 4: : tert-butyl (3-(5-(difluoromethyl)-2-fluorophenyl)-5-hydroxypentyl)(methyl)-carbamate



[000496] To a solution of ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-(5-(difluoromethyl)-2-fluorophenyl)pentanoate (2.0 g, 4.9 mmol, 1.0 eq) in THF (20 mL) at 0 °C was added LAH (2.5M in THF, 2.6 mL, 6.5 mmol, 1.3 eq). The reaction mixture was allowed to stir at 0 °C for 1 hr and quenched by the addition of water (0.3 mL). The mixture was allowed to continue to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.3 mL) and water

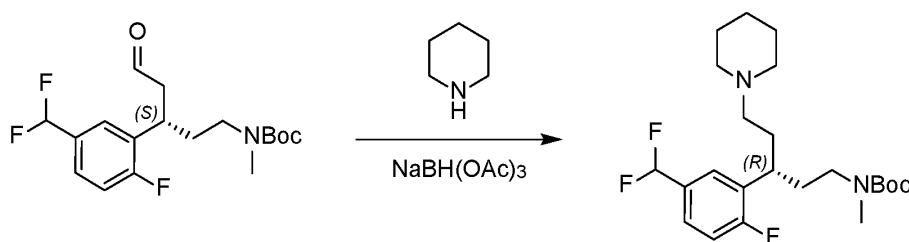
(1.0 mL) were then added at 0 °C, and the mixture was allowed to warm to RT and stir at RT for another 15 min. The mixture was then dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (7:2 petroleum ether: EtOAc) to give tert-butyl (3-(5-(difluoromethyl)-2-fluorophenyl)-5-hydroxypentyl)(methyl)carbamate (1.5 g, 84%) (ESI 362.2 [M+H]⁺). Enantiomers were separated by prep chiral SFC L to give peak 1, assigned as tert-butyl (S)-(3-(5-(difluoromethyl)-2-fluorophenyl)-5-hydroxypentyl)(methyl)carbamate (600mg), and peak 2, assigned as tert-butyl (R)-(3-(5-(difluoromethyl)-2-fluorophenyl)-5-hydroxypentyl)(methyl)carbamate (600mg), as white solids (ESI 362.2 [M+H]⁺).

Step 5: tert-butyl (S)-(3-(5-(difluoromethyl)-2-fluorophenyl)-5-oxopentyl)(methyl)carbamate



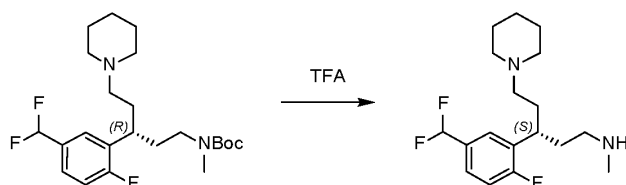
[000497] To a solution of tert-butyl (S)-(3-(5-(difluoromethyl)-2-fluorophenyl)-5-hydroxypentyl)(methyl)carbamate (240 mg, 0.67 mmol, 1.0 eq.) in DCM (6 mL) was added Dess-Martin periodinane (370 mg, 0.87 mmol, 1.3 eq.) at 0 °C. The reaction was then allowed to warm to RT and stir for 1 hr. The reaction mixture was diluted with saturated aqueous Na₂SO₃ (50 mL) and extracted with DCM (3 x 50 mL). The organic solutions were combined, washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to obtain tert-butyl (S)-(3-(5-(difluoromethyl)-2-fluorophenyl)-5-oxopentyl)(methyl)carbamate as a colorless oil (240 mg, 100%)(ESI 382.0 ([M+Na]⁺). The crude product was used without purification in the next step.

Step 6: tert-butyl (R)-(3-(5-(difluoromethyl)-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methyl)carbamate



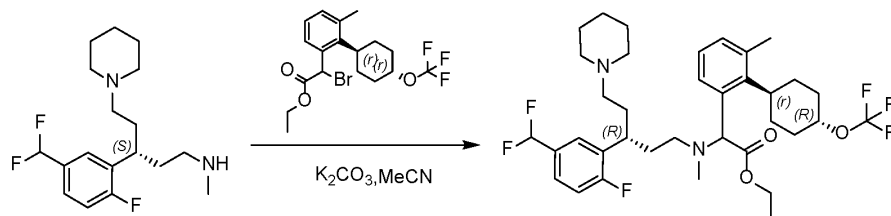
[000498] To a solution of tert-butyl (S)-3-(5-(difluoromethyl)-2-fluorophenyl)-5-oxopentyl(methyl)carbamate (240 mg, 0.67 mmol, 1.0 eq.) in dichloroethane (6 mL) was added piperidine (85 mg, 1.0 mmol, 1.5 eq.). The reaction mixture was allowed to stir at RT for 1 hr. NaBH(OAc)₃ (285 mg, 1.34 mmol, 2.0 eq.) was then added into the reaction, and the mixture was allowed to stir at RT for 2 hr. The mixture was poured into water (50 mL) and extracted with DCM (3 x 50 mL). The organic solutions were combined, washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 DCM: methanol) to give tert-butyl (R)-3-(5-(difluoromethyl)-2-fluorophenyl)-5-(piperidin-1-yl)pentyl(methyl)carbamate as a yellow oil (200 mg, 70%) (ESI 429.3 [M+H]⁺).

Step 7: (S)-3-(5-(difluoromethyl)-2-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine



[000499] To a solution of tert-butyl (R)-3-(5-(difluoromethyl)-2-fluorophenyl)-5-(piperidin-1-yl)pentyl(methyl)carbamate (200 mg, 0.5 mmol, 1.0 eq.) in DCM (2 mL) was added TFA (0.2 mL, 2.8 mmol, 7.0 eq.). The reaction mixture was allowed to stir at RT for 2 hr. and concentrated *in vacuo* to give (S)-3-(5-(difluoromethyl)-2-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine as a colorless oil (155 mg 0.5 mmol, crude). (ESI 329.2 [M+H]⁺). The crude product was used without purification in the following step.

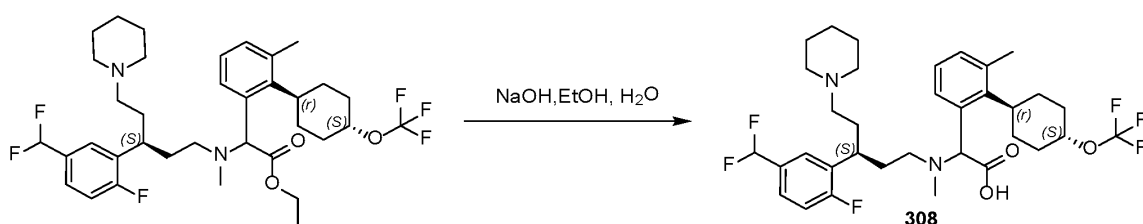
Step 8: ethyl 2-(((R)-3-(5-(difluoromethyl)-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)-(methyl)amino)-2-(3-methyl-2-((1R,4R)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000500] To a solution of (S)-3-(5-(difluoromethyl)-2-fluorophenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (155 mg 0.5 mmol, crude) in ACN (10 mL) was added K₂CO₃ (345 mg, 2.5 mmol, 5.0 eq.). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(3-

methyl-2-(((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (211 mg, 0.5 mmol, 1.0*eq*) was then added. The reaction was allowed to continue to stir at 80 °C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((*R*)-3-(5-(difluoromethyl)-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-(((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (190 mg, 60 %) (ESI 671.4 [M+H]⁺).

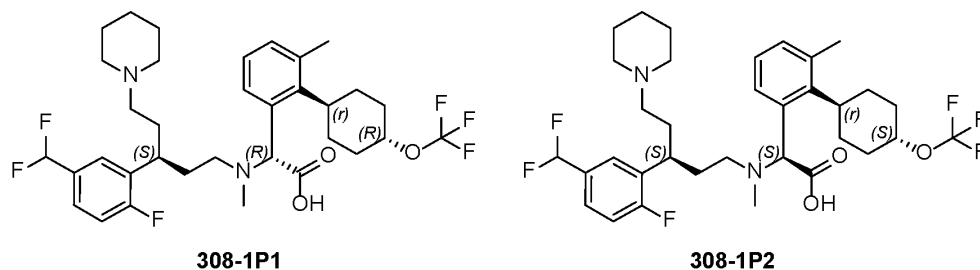
Step 9: 2-(((*S*)-3-(3-(difluoromethyl)phenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-(((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



[000501] To a mixture of ethyl 2-(((*S*)-3-(5-(difluoromethyl)-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-(((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetate (190 mg, 0.3 mmol, 1.0 *eq*) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (58 mg, 1.5 mmol, 5.0 *eq*). The reaction mixture was allowed to stir at 80 °C for 1 hr, cooled to RT and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give **308-1P1** (63.1mg) and **308-1P2** (51.1 mg).

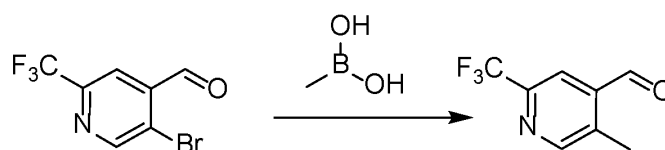
[000502] **308-1P1**, assigned as (*R*)-2-(((*S*)-3-(5-(difluoromethyl)-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-(((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetic acid. LC/MS ESI 643.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.62 – 7.30 (m, 3H), 7.26 – 6.92 (m, 3H), 6.85 – 6.57 (m, 1H), 4.75 – 4.27 (m, 2H), 3.22 – 2.76 (m, 3H), 2.73 – 2.37 (m, 11H), 2.36 – 1.85 (m, 10H), 1.85 – 1.26 (m, 10H).

[000503] **308-1P2**, assigned as (*S*)-2-(((*S*)-3-(5-(difluoromethyl)-2-fluorophenyl)-5-(piperidin-1-yl)pentyl)(methylamino)-2-(3-methyl-2-(((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetic acid. LC/MS ESI 643.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.72 – 7.32 (m, 3H), 7.26 – 6.97 (m, 3H), 6.89 – 6.59 (m, 1H), 4.75 – 4.23 (m, 2H), 3.46 – 3.33 (m, 1H), 3.22 – 2.99 (m, 1H), 2.94 – 2.53 (m, 7H), 2.50 – 2.40 (m, 5H), 2.39 – 2.22 (m, 2H), 2.22 – 1.72 (m, 10H), 1.71 – 1.56 (m, 6H), 1.56 – 1.40 (m, 2H).



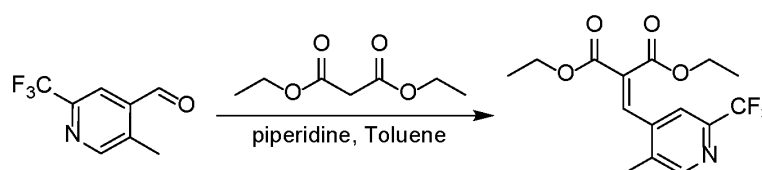
Example 26: Preparation of Compounds 309-2P2 and 309-2P1

Step 1: 5-methyl-2-(trifluoromethyl)isonicotinaldehyde



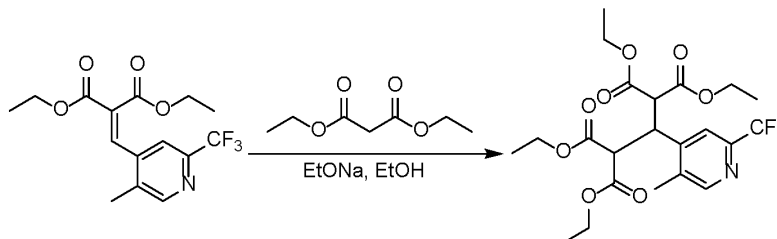
[000504] To a solution of 5-bromo-2-(trifluoromethyl)isonicotinaldehyde (14 g, 55 mmol, 1.0 eq.) and methylboronic acid (13.2 g, 220 mmol, 4.0 eq.) in dioxane (100 ml) and H₂O (50 mL) were added K₂CO₃ (15.2 g, 110 mmol, 2.0 eq.) and Pd(dppf)Cl₂ (495 mg, 0.55 mmol, 0.01 eq.). The reaction mixture was allowed to stir at 100 °C for 2 hr and then allowed to cool to RT. The mixture was poured into 100 mL water and extracted with EtOAc (2 x 200 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo* to give 5-methyl-2-(trifluoromethyl)isonicotinaldehyde (12 g). The crude product was used directly in the next step. ¹H NMR (400 MHz, CDCl₃) δ 12.39 (s, 1H), 8.96 (s, 1H), 8.02 (s, 1H), 2.76 (s, 3H).

Step 2: diethyl 2-((5-methyl-2-(trifluoromethyl)pyridin-4-yl)methylene)malonate



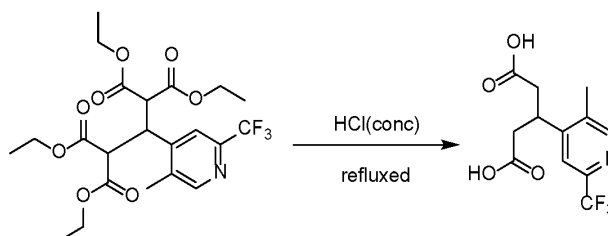
[000505] To a solution of 5-methyl-2-(trifluoromethyl)isonicotinaldehyde (12 g, 63 mmol, 1.0 eq.) in toluene (110 mL) was added diethyl malonate (15.1 g, 94.5 mmol, 1.5 eq.) and piperidine (807 mg, 9.5 mmol, 0.15 eq.). The mixture was allowed to stir at 110 °C for 16 hr and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give diethyl 2-((5-methyl-2-(trifluoromethyl)pyridin-4-yl)methylene)malonate as a yellow solid (12 g, 58.0 %) (ESI 332.1 [M+H]⁺).

Step 3: tetraethyl 2-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)propane-1,1,3,3-tetracarboxylate



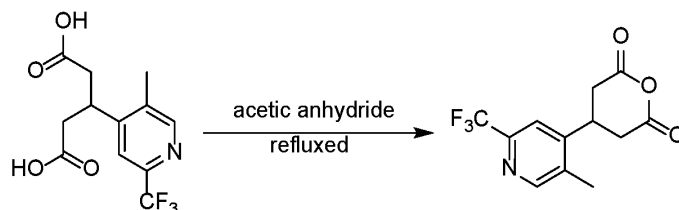
[000506] To a solution of diethyl malonate (7.9 g, 49.5 mmol, 1.5 eq) in EtOH (150 mL) was added EtONa (4.5 g, 66 mmol, 2.0 eq), and the mixture was allowed to stir at RT for 2 hr. Diethyl 2-((5-methyl-2-(trifluoromethyl)pyridin-4-yl)methylene)malonate (11 g, 33 mmol, 1 eq.) was then added. The reaction was allowed to continue to stir at RT for another 2 hr. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (80 mL) and extracted with EtOAc (3 x 50 mL). The organic solutions were combined, washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (5:1 petroleum ether: EtOAc) to give tetraethyl 2-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)propane-1,1,3,3-tetracarboxylate as yellow oil (13 g, 80%) (ESI 492 $[\text{M} + \text{H}]^+$).

Step 4: 3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)pentanedioic acid



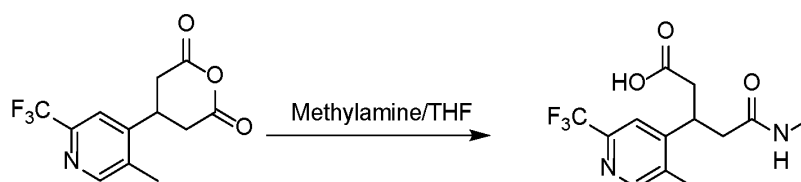
[000507] A solution of tetraethyl 2-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)propane-1,1,3,3-tetracarboxylate (12 g, 24.4 mmol, 1.0 eq.) in 36% aqueous HCl (100 mL) was allowed to stir at 110 °C for 16 hr. The mixture was cooled to 0 °C and allowed to stir for 1 hr. The precipitate that formed was filtered and collected to give 3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)pentanedioic acid. (5.5 g, 77%) (ESI 292 $[\text{M} + \text{H}]^+$).

Step 5: 4-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)dihydro-2H-pyran-2,6(3H)-dione



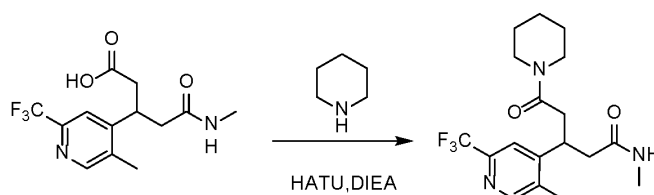
[000508] A mixture of 3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)pentanedioic acid (5.5 g, 18.9 mmol, 1.0 eq.) in acetic anhydride (50 mL) was allowed to stir at 130 °C for 16 hr. The reaction was concentrated to dryness under reduced pressure and triturated with EtOAc (150 mL). The precipitate was filtered to obtain 4-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)dihydro-2H-pyran-2,6(3H)-dione (5.0 g, 96%) (ESI 274 [M+H]⁺).

Step 6: 3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(methylamino)-5-oxopentanoic acid



[000509] To a solution of 4-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)dihydro-2H-pyran-2,6(3H)-dione (4.9 g, 18 mmol, 1.0 eq.) in THF (10mL) was added methylamine (1M in THF, 36mL, 36mmol, 2.0 eq). The reaction mixture was allowed to stir at RT for 3hr. The mixture was concentrated under reduced pressure and triturated with EtOAc (5 mL). The solid that formed was collected to give 3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(methylamino)-5-oxopentanoic acid (4.9 g, 89%) (ESI 305 [M+H]⁺).

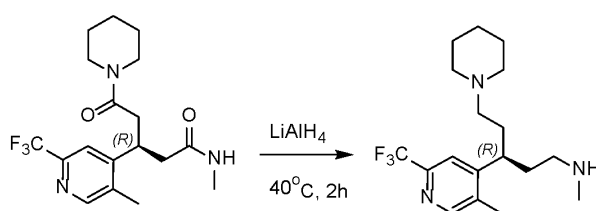
Step 7: N-methyl-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-oxo-5-(piperidin-1-yl)pentanamide



[000510] To a solution of 3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(methylamino)-5-oxopentanoic acid (3.0 g, 10 mmol, 1.0 eq) and piperidine (1.3 g, 15 mmol, 1.5 eq) in DCM (30 mL) was added HATU (4.2 g, 11 mmol, 1.1 eq) followed by TEA (3.0 g, 30 mmol, 3.0 eq). The reaction mixture was allowed to stir at RT for 2 hr. The mixture was concentrated *in vacuo* and purified by silica gel column chromatography (1:1 petroleum ether: EtOAc) to give

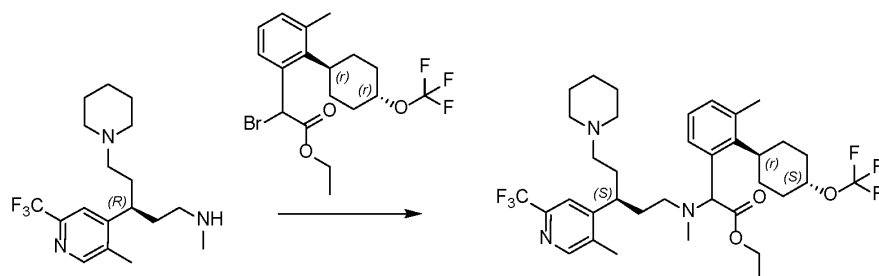
N-methyl-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-oxo-5-(piperidin-1-yl)pentanamide as a yellow solid (3.0 g, 81%). Stereoisomers (600 mg) were further separated by prep chiral SFC A to give peak 1, assigned as (S)-N-methyl-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-oxo-5-(piperidin-1-yl)pentanamide (230 mg), and peak 2, assigned as (R)-N-methyl-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-oxo-5-(piperidin-1-yl)pentanamide (230 mg), as a white solids (ESI 372.1 $[M+H]^+$).

Step 8: (R)-N-methyl-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(piperidin-1-yl)pentan-1-amine



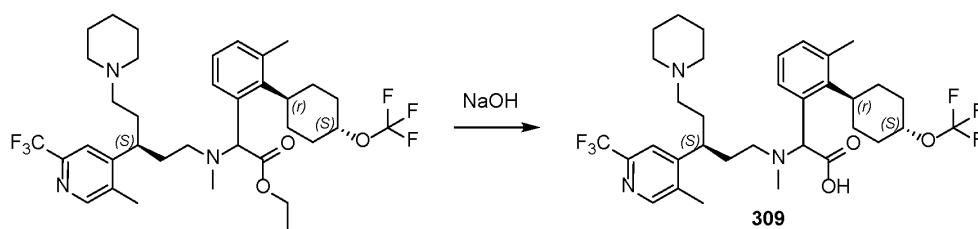
[000511] To a solution of (R)-N-methyl-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-oxo-5-(piperidin-1-yl)pentanamide (223 mg, 0.6 mmol, 1.0 eq.) in anhydrous THF (20 ml) was added $LiAlH_4$ (2.5 M in THF, 1.2 ml, 3.0 mmol, 5.0 eq.) dropwise at $0^\circ C$. The reaction mixture was allowed to warm and stirred at $40^\circ C$ for 2 hr. The reaction was quenched by the addition of water (0.2 mL) and allowed to stir at $0^\circ C$ for 10 min. 15% aqueous NaOH (0.2 mL) and water (0.6 mL) were then added sequentially at $0^\circ C$. The mixture was allowed to warm to RT and stir for 15 min, dried over Na_2SO_4 , filtered and concentrated in *vacuo* to give (R)-N-methyl-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(piperidin-1-yl)pentan-1-amine as a colorless oil (crude, 90 mg, 43%) (ESI 344.1 $[M+H]^+$). The crude product was used directly in the subsequent step without further purification.

Step 9: ethyl 2-(methyl((S)-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(piperidin-1-yl)pentyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000512] To a solution of (R)-N-methyl-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(piperidin-1-yl)pentan-1-amine (89 mg 0.3 mmol, 1.0 eq) in ACN (6 mL) was added K₂CO₃ (124 mg, 0.9 mmol, 3.0 eq.). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetate (127 mg, 0.3 mmol, 1.0 eq) was then added. The reaction mixture was allowed to continue to stir at 80 °C for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(methyl((S)-3-(5-methyl-2-(trifluoromethyl)-pyridin-4-yl)-5-(piperidin-1-yl)pentyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)-cyclohexyl)phenyl)acetate as a yellow oil (100 mg, 49%) (ESI 686.1 [M+H]⁺).

Step 10: 2-(methyl((S)-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(piperidin-1-yl)pentyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid

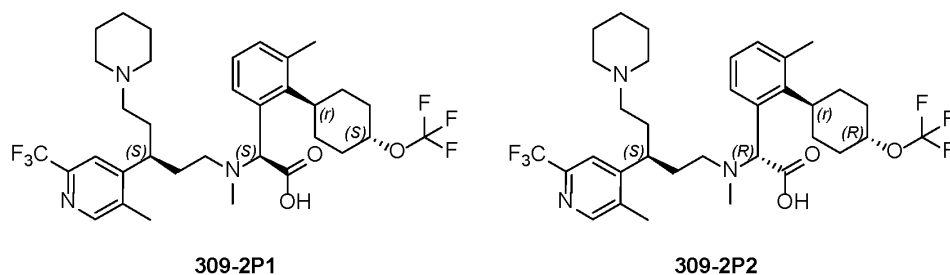


[000513] To a solution of ethyl 2-(methyl((S)-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(piperidin-1-yl)pentyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (100 mg, 0.15 mmol, 1.0 eq) in EtOH (5 mL) and H₂O (2 mL) was added NaOH (60 mg, 1.5 mmol, 10.0 eq). The reaction mixture was allowed to stir at 80 °C for 16 hr, cooled to RT and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give **309-2P1** (13.2 mg) and **309-2P2** (13.0 mg) as a white solids.

[000514] **309-2P1**, assigned as (S)-2-(methyl((S)-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(piperidin-1-yl)pentyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetic acid. LC/MS ESI 658.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 8.54 – 8.49 (m, 1H), 7.72 – 7.48 (m, 2H), 7.19 – 7.03 (m, 2H), 4.71 – 4.34 (m, 2H), 2.87 – 2.79 (m, 7H), 2.48 – 2.38 (m, 10H), 2.28 – 1.55 (m, 20H).

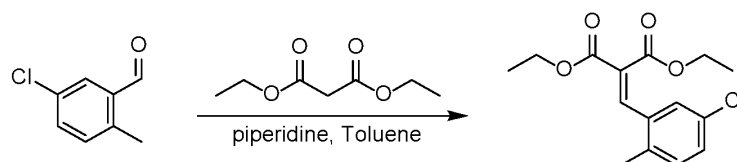
[000515] **309-2P2**, assigned as (R)-2-(methyl((S)-3-(5-methyl-2-(trifluoromethyl)pyridin-4-yl)-5-(piperidin-1-yl)pentyl)amino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetic acid. LC/MS ESI 658.3 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 8.50 – 8.44 (m,

1H), 7.64 – 7.37 (m, 2H), 7.14 – 7.00 (m, 2H), 4.77 – 4.30 (m, 2H), 3.24 – 1.94 (m, 27H), 1.79 – 1.51 (m, 10H).



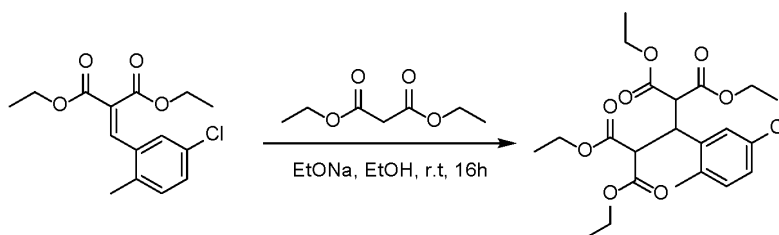
Example 27: Preparation of Compoundd 310-1P2

Step 1: diethyl 2-(5-chloro-2-methylbenzylidene)malonate



[000516] A solution of 5-chloro-2-methylbenzaldehyde (100.0 g, 0.65 mol), diethyl malonate (155.8 g, 0.97 mol) and piperidine (8.3 g, 97.5 mmol) in toluene (300 mL) was allowed to stir at 110 °C for 16 hr. The mixture was cooled to RT and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give diethyl 2-(5-chloro-2-methylbenzylidene)malonate as a colorless oil (180 g, 93%) (ESI 297.3 [M+H]⁺).

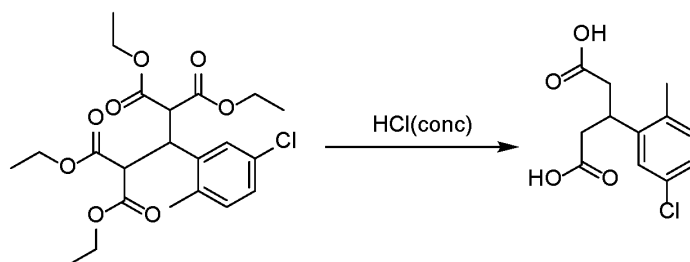
Step 2: tetraethyl 2-(5-chloro-2-methylphenyl)propane-1,1,3,3-tetracarboxylate



[000517] To a solution of diethyl malonate (194.6 g, 1.22 mol) in EtOH (400 mL) at RT was added EtONa (88.1 g, 1.3 mmol). The mixture was allowed to stir for 2 hr. Diethyl 2-(5-chloro-2-methylbenzylidene)malonate (180 g, 0.61 mol) was then added at RT and the reaction was allowed to continue to stir for 16 hr. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc (3 x 400 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated in *vacuo*. The

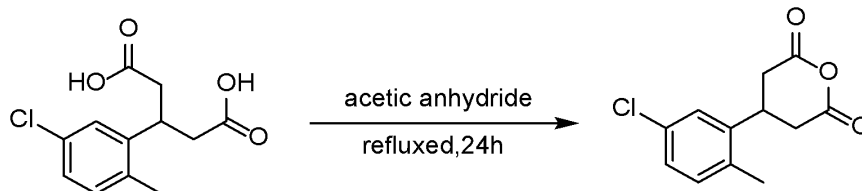
residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to give tetraethyl 2-(5-chloro-2-methylphenyl)propane-1,1,3,3-tetracarboxylate as a colorless oil (180.0 g, 60%) (ESI 457.2[M+H]⁺).

Step 3: 3-(5-chloro-2-methylphenyl)pentanedioic acid



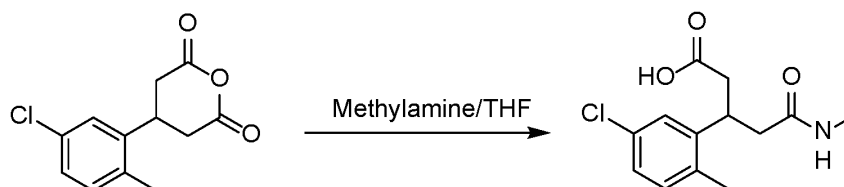
[000518] A solution of tetraethyl 2-(5-chloro-2-methylphenyl)propane-1,1,3,3-tetracarboxylate (180.0 g, 0.39 mol) in 36% aqueous HCl (700 mL) was allowed to stir at 130 °C for 36 hr. The mixture was then cooled to 0 °C and stirred at 0 °C for 1 hr. Solid formed was filtered to give 3-(5-chloro-2-methylphenyl)pentanedioic acid (100.2 g, 99%) (ESI 279.0 [M+Na]⁺). The crude product was used directly in the next step.

Step 4: 4-(5-chloro-2-methylphenyl)dihydro-2H-pyran-2,6(3H)-dione



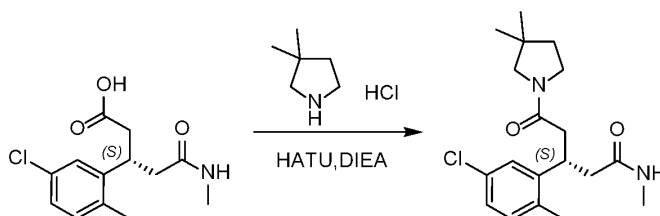
[000519] A mixture of 3-(5-chloro-2-methylphenyl)pentanedioic acid (100.0 g, 0.39 mol) and acetic anhydride (400 mL) was allowed to stir at 130 °C for 40 hr. The mixture was concentrated to dryness and triturated with EtOAc (150 mL). The solid that formed was filtered to give 4-(5-chloro-2-methylphenyl)dihydro-2H-pyran-2,6(3H)-dione (91.2 g, 97%) (ESI 239.1 [M+H]⁺). The product was used without purification the next step.

Step 5: 3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid



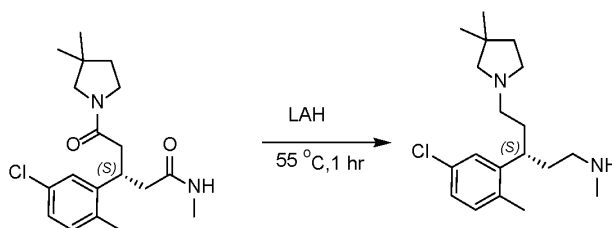
[000520] To a solution of 3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (91.2 g, 0.38 mol, 1.0 eq) in THF (300 mL) was added methylamine (1M in THF, 1.15 L, 1.15 mol, 3.0 eq), and the reaction mixture was allowed to stir at RT for 3 hr. The mixture was concentrated under reduced pressure and triturated with EtOAc (120 mL). The solid that formed was filtered to give 3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic as a white solid (75.0 g, 73%). The isomeric products were separated by prep chiral SFC K to give peak 1, assigned as (S)-3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (31.0 g), and peak 2, assigned as (R)-3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (31.0 g), as a white solids (ESI 270.1 $[M+H]^+$).

Step 6: (S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methyl-5-oxopentanamide



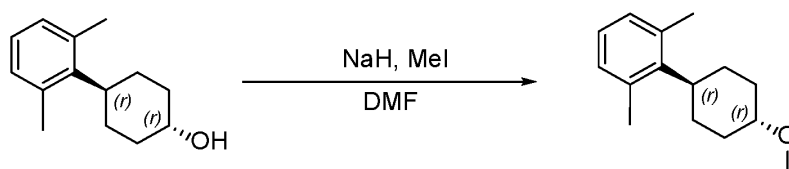
[000521] To a solution of (S)-3-(5-chloro-2-methylphenyl)-5-(methylamino)-5-oxopentanoic acid (15.0 g, 55.7 mmol, 1.0 eq) and 3,3-dimethylpyrrolidine (5.5 g, 55.7 mmol, 1.0 eq) in DMF (60 mL) was added HATU (25.4 g, 66.8 mmol, 1.2 eq) and DIPEA (14.4 g, 111.4 mmol, 2.0 eq). The reaction mixture was allowed to stir at RT for 2 hr. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (3 x 150 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The resulting product was purified by silica gel column chromatography (20:1 DCM: MeOH) to give (S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methyl-5-oxopentanamide as a colorless oil (16.6 g, 85%) (ESI 351.1 $[M+H]^+$).

Step 7: (S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine



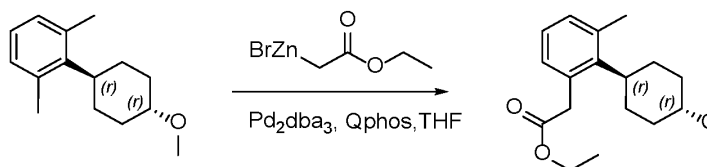
[000522] To a solution of (S)-3-(5-chloro-2-methylphenyl)-N-methyl-5-oxo-5-(piperidin-1-yl) pentanamide (16.6 g, 47.4 mmol, 1.0 eq) in THF (200 mL), LiAlH₄ (56.9 mL, 142.3 mmol, 3.0 eq) was added dropwise at RT. The reaction was then allowed to stir at 55 °C for 1 hr. The reaction was quenched by the addition of water (5.5 mL) at 0 °C and the mixture was allowed to stir for 10 min. 15% aqueous NaOH (5.5 mL) and water (16.5 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT and stir for another 15 min, dried over Na₂SO₄, filtered and concentrated in *vacuo* to give (S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine as a white solid (13.1 g, 85%) (ESI 323.3 [M+H]⁺). The crude product was used directly in the subsequent step.

Step 8: 1-iodo-2-((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylbenzene



[000523] To a solution of (1*r*,4*r*)-4-(2-iodo-6-methylphenyl)cyclohexan-1-ol (3 g, 9.5 mmol, 1.0 eq) in *N,N*-dimethylformamide (30 mL) at 0 °C was added sodium hydride (684 mg, 28.5 mmol, 1.5 eq, 60% in oil). The reaction mixture was allowed to stir at 0 °C for 1 hr. Iodomethane (2.7 g, 19 mmol, 2.0 eq) was then added. The mixture was allowed to warm to RT and stir for 16 hr. The reaction was quenched by the addition of ice-water (100 mL) and extracted with EtOAc (3 x 60 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (4:1 petroleum ether: EtOAc) to give 1-iodo-2-((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylbenzene as a white solid (2.4 g, 76.7 %) (ESI 299.1 [M-OMe]⁺).

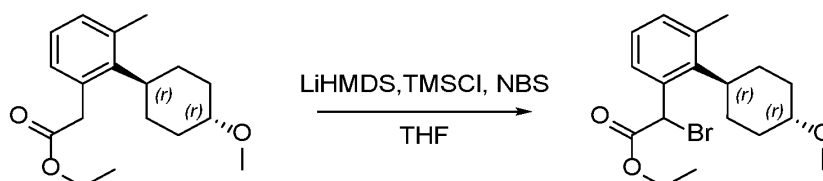
Step 9: ethyl 2-(2-((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylphenyl)acetate



[000524] To a suspension of 1-iodo-2-((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylbenzene (2.4 g, 7.3 mmol, 1.0 eq) in THF (30 mL) were added Pd₂dba₃ (200 mg, 0.22 mmol, 0.03 eq), Q-phos (156 mg, 0.22 mmol, 0.03 eq) and (2-ethoxy-2-oxoethyl)zinc(II) bromide (1M in THF, 21.9 mL, 21.9 mmol, 3.0 eq). The mixture was allowed to stir at 65 °C under an atmosphere of N₂ for 1 hr. The reaction mixture was poured into 80 mL saturated aqueous NH₄Cl solution and

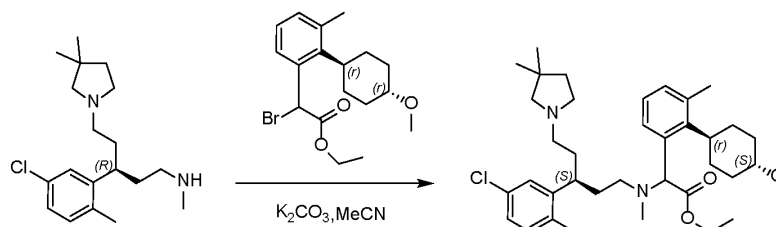
extracted with EtOAc (3 x 40 mL). The organic solutions were combined, washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (20:1 petroleum ether: EtOAc) to give ethyl 2-(2-((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylphenyl)acetate as a colorless oil (1.9 g, 90.4 %) (ESI 291.3 [M+H]⁺).

Step 10: ethyl 2-bromo-2-(2-((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylphenyl)acetate



[000525] To a solution of LiHMDS (1M in THF, 19.6 ml, 19.6 mmol, 3.0 eq.) at -78°C was added ethyl 2-(2-((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylphenyl)acetate (1.9 g, 6.5 mmol, 1.0 eq.) in THF (20 ml) dropwise. The reaction mixture was allowed to stir at -78°C for 0.5 hr. TMSCl (1.4 g, 13 mmol, 2.0 eq.) was then added, and the reaction mixture was allowed to continue to stir at -78°C for 15 min. A solution of NBS (2.3 g, 13 mmol, 2.0 eq.) in THF (15 mL) was then added dropwise. The reaction mixture was allowed to stir at -78°C for another 1 hr. The mixture was allowed to warm to 0 °C, quenched by the addition of saturated aqueous NH₄Cl solution (60 ml), and extracted with EtOAc (3 x 100 ml). The organic solutions were combined, washed with brine (3 x 100 ml), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl 2-bromo-2-(2-((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylphenyl)acetate as a colorless oil (1.6 g, 66.3%) (ESI 369.3 [M+H]⁺).

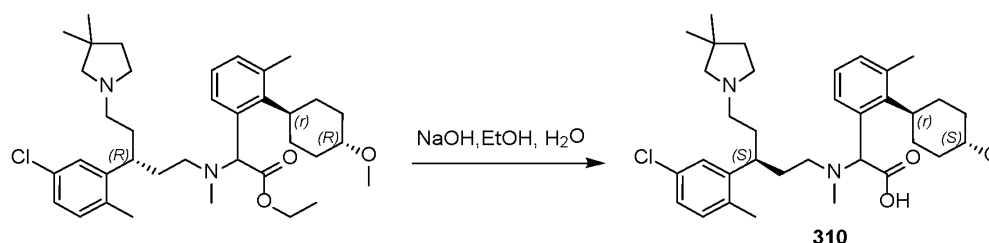
Step 11: ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(2-((1*r*,4*S*)-4-methoxycyclohexyl)-3-methylphenyl)acetate



[000526] To a solution of (R)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)-N-methylpentan-1-amine (200 mg 0.62 mmol, crude) in ACN (10 mL) was added K₂CO₃ (427 mg, 3.1 mmol, 5.0 eq.). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(2-((1*r*,4*S*)-4-methoxycyclohexyl)-3-methylphenyl)acetate (1.6 g, 6.5 mmol, 1.0 eq.) was then added dropwise. The reaction mixture was allowed to stir at RT for 1 hr. The mixture was allowed to warm to 0 °C, quenched by the addition of saturated aqueous NH₄Cl solution (60 ml), and extracted with EtOAc (3 x 100 ml). The organic solutions were combined, washed with brine (3 x 100 ml), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl 2-(((S)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methyl)amino)-2-(2-((1*r*,4*S*)-4-methoxycyclohexyl)-3-methylphenyl)acetate as a colorless oil (1.6 g, 66.3%) (ESI 369.3 [M+H]⁺).

((1*r*,4*r*)-4-methoxycyclohexyl)-3-methylphenyl)acetate (228 mg, 0.62 mmol, 1.0 *eq*) was then added. The reaction was allowed to continue to stir at 60 °C for another 16 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(2-((1*r*,4*S*)-4-methoxycyclohexyl)-3-methylphenyl)acetate as a yellow oil (220 mg, 58%) (ESI 611.3 $[M+H]^+$).

Step 12: 2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(2-((1*r*,4*S*)-4-methoxycyclohexyl)-3-methylphenyl)acetic acid

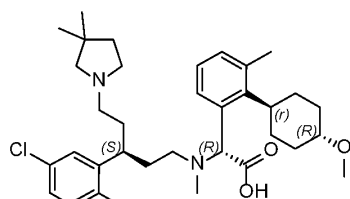


[000527] To a solution of ethyl 2-(((*R*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(2-((1*r*,4*R*)-4-methoxycyclohexyl)-3-methylphenyl)acetate (220 mg, 0.36 mmol, 1.0 *eq*) in EtOH (5 mL) and H₂O (1 mL) was added NaOH (72 mg, 1.8 mmol, 5.0 *eq*). The reaction mixture was allowed to stir at 60 °C for 16 hr and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give a mixture of stereoisomers **310** as a white solid (160 mg, 76%). The stereoisomers were separated by prep chiral SFC A to give **310-1P1** (78.96 mg) and **310-1P2** (79.9 mg).

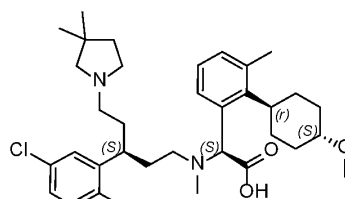
[000528] **310-1P1**, (*R*)-2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(2-((1*r*,4*R*)-4-methoxycyclohexyl)-3-methylphenyl)acetic acid. LC/MS ESI 583.2 $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ 7.54 – 7.38 (m, 1H), 7.14 – 7.01 (m, 5H), 4.66 (d, *J* = 38.5 Hz, 1H), 3.38 (s, 3H), 3.27 – 2.97 (m, 2H), 2.90 – 2.59 (m, 6H), 2.50 – 2.27 (m, 8H), 2.20 – 1.75 (m, 12H), 1.63 (t, *J* = 7.0 Hz, 2H), 1.55 – 1.21 (m, 4H), 1.07 (s, 6H).

[000529] **310-1P2**, (*S*)-2-(((*S*)-3-(5-chloro-2-methylphenyl)-5-(3,3-dimethylpyrrolidin-1-yl)pentyl)(methylamino)-2-(2-((1*r*,4*S*)-4-methoxycyclohexyl)-3-methylphenyl)acetic acid. LC/MS ESI 583.2 $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ 7.65 – 7.41 (m, 1H), 7.27 – 7.00 (m, 5H), 4.62 (d, *J* = 60.7 Hz, 1H), 3.38 (s, 3H), 3.28 – 3.20 (m, 1H), 2.97 (s, 1H), 2.89 – 2.53

(m, 6H), 2.52 – 2.30 (m, 8H), 2.18 – 1.77 (m, 12H), 1.70 – 1.61 (m, 2H), 1.51 – 1.25 (m, 4H), 1.09 (s, 6H).



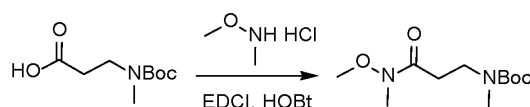
310-1P1



310-1P2

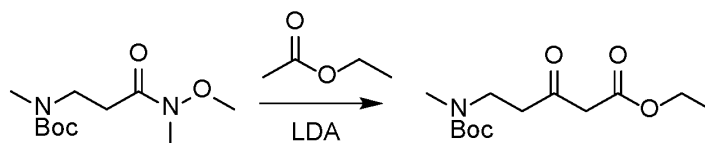
Example 28: Preparation of Compound 311-2P2

Step 1: tert-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)(methyl)carbamate



[000530] To a solution of 3-((tert-butoxycarbonyl)(methyl)amino)propanoic acid (15 g, 73.9 mmol, 1.0 eq.), *N,O*-dimethylhydroxylamine hydrochloride (7.6 g, 77.6 mmol, 1.05 eq.), HOBT (10.0 g, 73.9 mmol, 1.0 eq.) and TEA (16.4 g, 162.5 mmol, 2.2 eq.) in chloroform (100 ml) was added EDCI (15.6 g, 81.3 mmol, 1.1 eq.). The reaction mixture was allowed to stir at 50 °C for 1 hr, then diluted water (200 mL) and extracted with DCM (2 x 200 mL). The organic solutions were combined, washed with water (2 x 200 mL) and brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in *vacuo*. The crude residue was purified by silica gel column chromatography (95:5 DCM: MeOH) to give tert-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)(methyl)carbamate as a yellow solid (13.6 g, 74.7%) (ESI 147.2 [M-Boc+H]⁺).

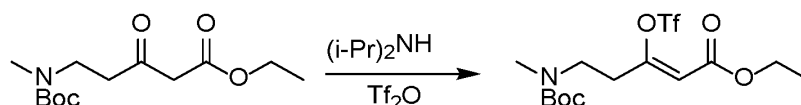
Step 2: ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-oxopentanoate



[000531] To a solution of ethyl acetate (7.57 g, 86 mmol, 2.0 eq.) in anhydrous THF (100 mL) at -78 °C was added LDA (2 M in THF and hexane, 54 mL, 108 mmol, 2.5 eq.). The reaction mixture was allowed to stir at -78 °C for 30 min. A solution of tert-butyl (3-(methoxy(methyl)amino)-3-oxopropyl)(methyl)carbamate (10.6 g, 43 mmol, 1.0 eq.) in THF (50 mL) was then added. The reaction mixture was allowed to continue to stir at -78 °C for 1 hr. The reaction was quenched by the addition of saturated aqueous NH₄Cl (200 mL) and

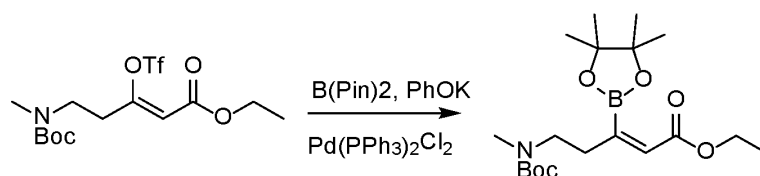
extracted with EtOAc (2 x 150 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl 5-((tert-butoxycarbonyl)(methyl)-amino)-3-oxopentanoate as a yellow solid (8.6 g, 73.2%) (ESI 296.2 [M+Na]⁺).

Step 3: ethyl (Z)-5-((tert-butoxycarbonyl)(methyl)amino)-3-(((trifluoromethyl)sulfonyl)-oxy)pent-2-enoate



[000532] To a solution of ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-oxopentanoate (6.4 g, 23.4 mmol, 1.0 eq.) in anhydrous THF (80 mL) at -78 °C was added diisopropylamine (7.1 g, 70.2 mmol, 3.0 eq.). The reaction mixture was allowed to stir at -78 °C for 30 min. Trifluoromethanesulfonyl anhydride (19.8 g, 70.2 mmol, 3.0 eq.) was then added dropwise. The reaction mixture was allowed to continue to stir at -78 °C for 30 min. The reaction was then quenched by the addition of saturated aqueous NaHCO₃ (300 mL) and extracted with EtOAc (2 x 200 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl (Z)-5-((tert-butoxycarbonyl)(methyl)-amino)-3-(((trifluoromethyl)sulfonyl)oxy)pent-2-enoate as a yellow solid (5.3 g, 56.0%) (ESI 406.1 [M+H]⁺).

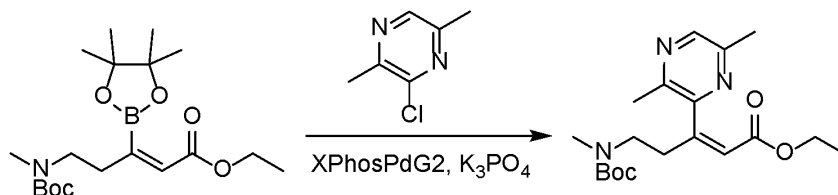
Step 4: ethyl (E)-5-((tert-butoxycarbonyl)(methyl)amino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate



[000533] Ethyl (Z)-5-((tert-butoxycarbonyl)(methyl)amino)-3-(((trifluoromethyl)sulfonyl)-oxy)pent-2-enoate (5.3 g, 13.1 mmol, 1.0 eq.), bis(pinacolato)diboron (5.05 g, 19.9 mmol, 1.2 eq.), potassium phenolate (2.6 g, 19.7 mmol, 1.5 eq) and Pd(PPh₃)₂Cl₂ (276 mg, 0.39 mmol, 0.03 eq.) were suspended in toluene (60 mL). The reaction mixture was allowed to stir for 2 hrs at 60 °C under an atmosphere of N₂. Solvents were then removed *in vacuo* and the residue was

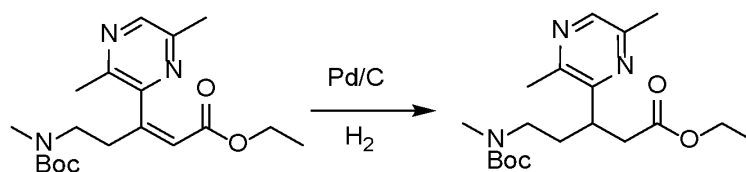
purified by silica gel column chromatography (10:1 petroleum ether: EtOAc) to give ethyl (E)-5-((tert-butoxycarbonyl)(methyl)amino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate as a yellow solid (2.5 g, 49.8%) (ESI 384.2 [M+H]⁺).

Step 5: ethyl (Z)-5-((tert-butoxycarbonyl)(methyl)amino)-3-(3,6-dimethylpyrazin-2-yl)pent-2-enoate



[000534] Ethyl (E)-5-((tert-butoxycarbonyl)(methyl)amino)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-2-enoate (1.6 g, 4.2 mmol, 1.0 eq.), 3-chloro-2,5-dimethylpyrazine (653 mg, 4.6 mmol, 1.1 eq.), K₃PO₄ (1.77 g, 8.3 mmol, 2.0 eq.) and XPhosPdG2 (99 mg, 0.13 mmol, 0.03 eq.) were suspended in a mixture of dioxane (15 mL) and water (3 mL). The reaction mixture was allowed to stir for 2 hr at 100 °C under an atmosphere of N₂. The mixture was poured into 100 mL water and extracted with EtOAc (2 x 100 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (2:1 petroleum ether: EtOAc) to give ethyl (Z)-5-((tert-butoxycarbonyl)(methyl)amino)-3-(3,6-dimethylpyrazin-2-yl)pent-2-enoate as a yellow solid (880 mg, 57.6%) (ESI 364.2 [M+H]⁺).

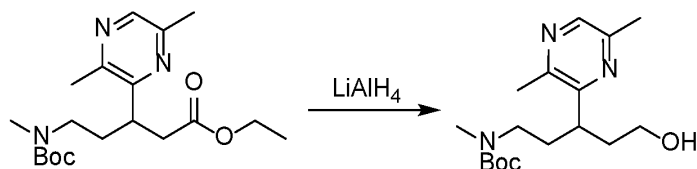
Step 6: ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-(3,6-dimethylpyrazin-2-yl)pentanoate



[000535] To a solution of ethyl (Z)-5-((tert-butoxycarbonyl)(methyl)amino)-3-(3,6-dimethylpyrazin-2-yl)pent-2-enoate (880 mg, 2.4 mmol, 1.0 eq.) in EtOH (20 mL) was added 10% Pd/C (148 mg, 0.07 mmol, 0.03 eq). The reaction mixture was allowed to stir at 70 °C under an atmosphere of H₂ (1 atm, 3L) for 16 hr. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo* to give ethyl 5-((tert-butoxycarbonyl)(methyl)amino)-3-(3,6-dimethylpyrazin-2-yl)pentanoate as a yellow oil (680 mg, 1.67 mmol).

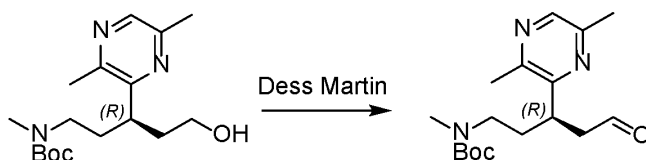
(ESI 366.2 $[M+H]^+$). The crude product was used directly in the next step without further purification.

Step 7: tert-butyl (3-(3,6-dimethylpyrazin-2-yl)-5-hydroxypentyl)(methyl)carbamate



[000536] To a solution ethyl 5-((tert-butoxycarbonyl)-(methyl)amino)-3-(3,6-dimethylpyrazin-2-yl)pentanoate (680 mg, 1.67 mmol, crude, 1.0 *eq*) in THF (10 mL) at 0 °C was added LAH (1M in THF, 3.3 mL, 3.3 mmol, 2.0 *eq*). The reaction mixture was allowed to stir at 0 °C for 30 min., and then quenched carefully with water (0.12 mL). The mixture was allowed to continue to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.12 mL) and water (0.36 mL) were then added sequentially. The mixture was allowed to warm to RT and stir for another 15 min, dried over Na₂SO₄, filtered and concentrated in *vacuo* to give tert-butyl (3-(3,6-dimethylpyrazin-2-yl)-5-hydroxypentyl)(methyl)carbamate as a yellow oil (450 mg, 83.1%) (ESI 324.2 $[M+H]^+$). The racemate was separated by prep chiral SFC G to give peak 1, assigned as tert-butyl (S)-(3-(3,6-dimethylpyrazin-2-yl)-5-hydroxypentyl)(methyl)carbamate (190 mg), and peak 2, assigned as tert-butyl (R)-(3-(3,6-dimethylpyrazin-2-yl)-5-hydroxypentyl)(methyl)carbamate (160 mg).

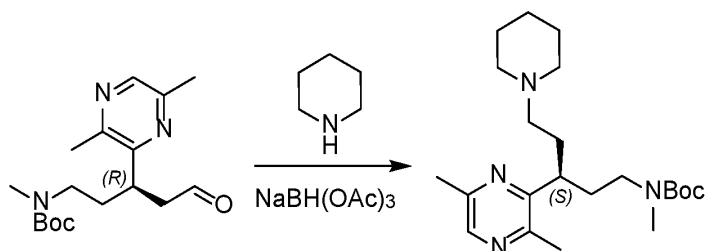
Step 8: tert-butyl (R)-(3-(3,6-dimethylpyrazin-2-yl)-5-oxopentyl)(methyl)carbamate



[000537] To a solution of tert-butyl (R)-(3-(3,6-dimethylpyrazin-2-yl)-5-hydroxypentyl)(methyl)carbamate (160 mg, 0.5 mmol, 1.0 *eq*) in DCM (5 mL) was added Dess-Martin periodinane (254 mg, 0.6 mmol, 1.2 *eq*) at 0 °C. The reaction was then allowed to warm to RT and stirred for 30 min. The reaction mixture was diluted with DCM (50 mL) and washed with saturated aqueous Na₂CO₃ (3 x 50 mL). The organic solution was separated, dried over anhydrous Na₂SO₄, filtered and concentrated in *vacuo* to give tert-butyl (R)-(3-(3,6-dimethylpyrazin-2-yl)-5-oxopentyl)(methyl)carbamate as a yellow oil (160 mg, 0.5 mmol, crude) (ESI 322.2 $[M+H]^+$). The crude product was used directly in the subsequent step.

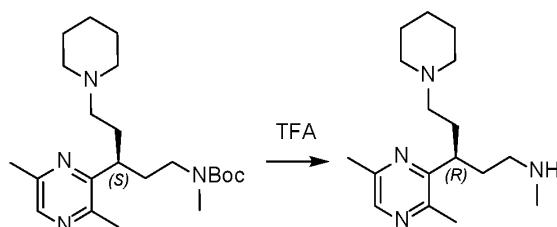
Step 9: tert-butyl (S)-(3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl)(methyl)-

carbamate



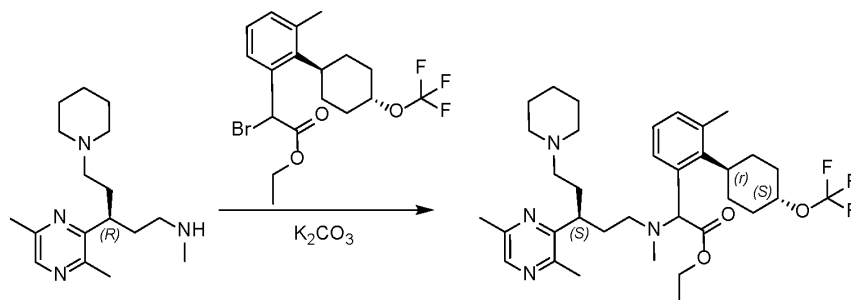
[000538] To a solution of tert-butyl (R)-3-(3,6-dimethylpyrazin-2-yl)-5-oxopentyl(methyl)carbamate (160 mg, 0.5 mmol, crude, 1.0 eq) in dichloroethane (5 mL) was added piperidine (85 mg, 1.0 mmol, 2 eq.). The reaction mixture was allowed to stir at RT for 1 hr. $\text{NaBH}(\text{OAc})_3$ (318 mg, 1.5 mmol, 3.0 eq.) was then added into the reaction. The reaction mixture was allowed to continue to stir at RT for another 1 hr. The reaction mixture was poured into water (50 mL) and extracted with DCM (2 x 50 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give tert-butyl (S)-3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl(methyl)carbamate as a yellow oil (140 mg, 71.7%) (ESI 391.3 $[\text{M}+\text{H}]^+$).

Step 10: (R)-3-(3,6-dimethylpyrazin-2-yl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine



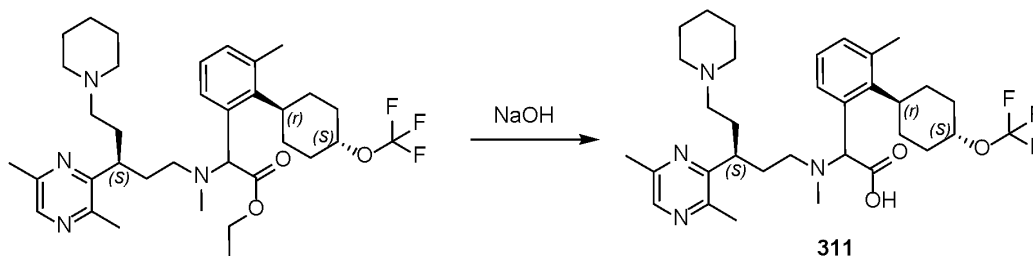
[000539] To a solution of tert-butyl (S)-3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl(methyl)carbamate (140 mg, 0.36 mmol, 1.0 eq) in DCM (1 mL) was added TFA (0.5 mL, 6.5 mmol, 18.1 eq.). The reaction mixture was allowed to stir at RT for 2 hr. and concentrated *in vacuo* to obtain (R)-3-(3,6-dimethylpyrazin-2-yl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (140 mg, 0.36 mmol, crude) (ESI 291.3 $[\text{M}+\text{H}]^+$). The crude product was used directly in the subsequent step.

Step 11: ethyl 2-(((S)-3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1R,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000540] To a solution of (R)-3-(3,6-dimethylpyrazin-2-yl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (140 mg, 0.36 mmol, crude, 1.0 eq.) in ACN (5 mL) was added K_2CO_3 (248 mg, 1.8 mmol, 5.0 eq.). The reaction mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (152 mg, 0.36 mmol, 1.0 eq) was then added. The reaction was allowed to continue to stir at 80 °C for another 1 hr. The reaction mixture was filtered and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography (95:5 DCM: MeOH) to give ethyl 2-(((S)-3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate as a yellow oil (150 mg, 65.8%) (ESI 633.4 $[M+H]^+$).

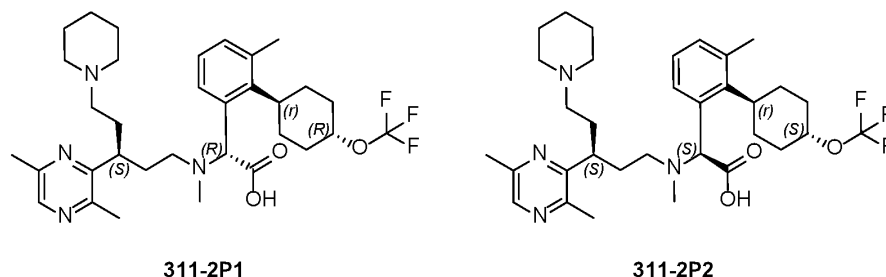
Step 12: 2-(((S)-3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



[000541] To a solution of ethyl 2-(((S)-3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1r,4S)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (150 mg, 0.24 mmol, 1.0 eq) in EtOH (4 mL) and H_2O (1 mL) was added NaOH (48 mg, 1.2 mmol, 5.0 eq). The reaction mixture was allowed to stir at 80 °C for 16 hr and then concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH_3CN) to give **311** as a white solid (130 mg, 89.5%). Stereoisomers were further separated by prep chiral SFC A to give **311-2P1** (52 mg) and **311-2P2** (46 mg).

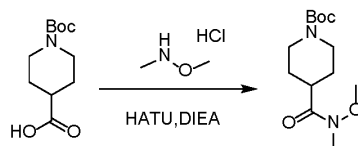
[000542] **311-2P1**, assigned as (R)-2-(((S)-3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 605.4 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 8.25 – 7.98 (m, 1H), 7.57 – 7.26 (m, 1H), 7.20 – 6.89 (m, 2H), 4.73 – 4.17 (m, 2H), 3.27 – 3.01 (m, 2H), 2.87 (s, 1H), 2.74 – 2.38 (m, 17H), 2.36 (s, 1H), 2.15 (d, *J* = 10.5 Hz, 5H), 2.09 – 1.94 (m, 3H), 1.91 – 1.64 (m, 4H), 1.57 (s, 5H), 1.46 (s, 2H).

[000543] **311-2P2**, assigned as (S)-2-(((S)-3-(3,6-dimethylpyrazin-2-yl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid. LC/MS ESI 605.4 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 8.21 – 8.04 (m, 1H), 7.71 – 7.24 (m, 1H), 7.27 – 6.81 (m, 2H), 4.74 – 4.23 (m, 2H), 3.40 (s, 1H), 3.22 (s, 1H), 2.94 – 2.53 (m, 7H), 2.52 – 2.40 (m, 12H), 2.38 (s, 1H), 2.30 – 2.06 (m, 5H), 2.05 – 1.86 (m, 4H), 1.80 – 1.56 (m, 7H), 1.51 (s, 2H).

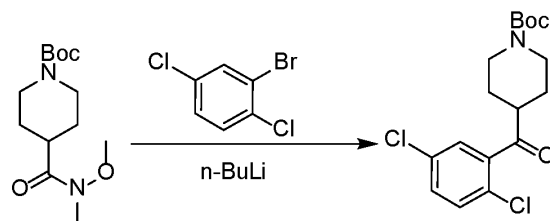


Example 29: Preparation of Compound 312-2P2

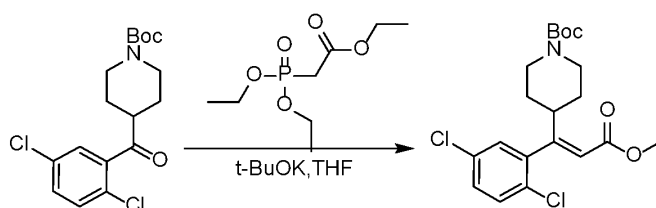
Step 1: tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate



[000544] To a solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (15 g, 65.5 mmol, 1.0 eq.), *N,O*-dimethylhydroxylamine hydrochloride (7.0 g, 72.0 mmol, 1.1 eq.) and DIEA (21 g, 163.8 mmol, 2.5 eq.) in DCM (100 ml) was added HATU (30 g, 78.6 mmol, 1.2 eq.). The reaction mixture was allowed to stir at RT for 3 hr and was then diluted with water (300 mL) and extracted with DCM (2 x 300 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (3:2 petroleum ether: EtOAc) to give tert-butyl 4-(methoxy(methyl)carbamoyl)piperidine-1-carboxylate as a colorless oil (15 g, 84%) (ESI 217.1 [M-tButyl+H]⁺).

Step 2: tert-butyl 4-(2,5-dichlorobenzoyl)piperidine-1-carboxylate

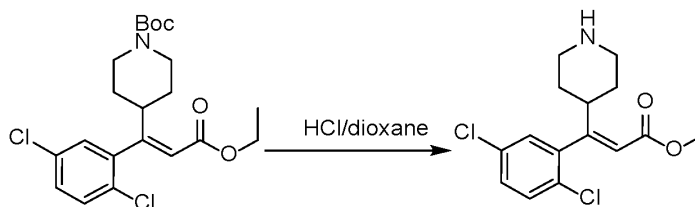
[000545] To a solution of 2-bromo-1,4-dichlorobenzene (7.5 g, 33.1 mmol, 1.2 eq.) in anhydrous THF (60 mL) at -78 °C was added n-BuLi (1.6 M in hexane, 24 mL, 38.6 mmol, 1.4 eq.). The reaction mixture was allowed to stir at -78°C for 1 hr. A solution of tert-butyl 4-(methoxy(methyl)-carbamoyl)piperidine-1-carboxylate (7.5 g, 27.6 mmol, 1.0 eq.) in THF (15 mL) was then added. The reaction was allowed to continue to stir at -78°C for 1 hr. The reaction was quenched by the addition of saturated aqueous NH₄Cl (100 mL) and extracted with EtOAc (2 x 150 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (85:15 petroleum ether: EtOAc) to give tert-butyl 4-(2,5-dichlorobenzoyl)piperidine-1-carboxylate as a yellow solid (7.4 g, 76%) (ESI 380.0 [M+Na]⁺).

Step 3: tert-butyl (E)-4-(1-(2,5-dichlorophenyl)-3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate

[000546] To a solution of ethyl 2-(diethoxyphosphoryl)acetate (13.2 g, 58.8 mmol, 3.0 eq) in anhydrous THF (100 mL) at 0 °C was added t-BuOK (6.6 g, 58.8 mmol, 3.0 eq). The reaction mixture was allowed to stir at RT for 3 hr. A solution of tert-butyl 4-(2,5-dichlorobenzoyl)-piperidine-1-carboxylate (7.0 g, 19.6 mmol, 1.0 eq) in THF (20 mL) was then added and the reaction mixture was allowed to continue to stir at 0 °C for another 12 hr. The reaction was then quenched by the addition of saturated aqueous NH₄Cl (200 mL) and extracted with EtOAc (3 x 200 mL). The organic solutions were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (85:15 petroleum ether: EtOAc) to give tert-butyl (E)-4-(1-(2,5-

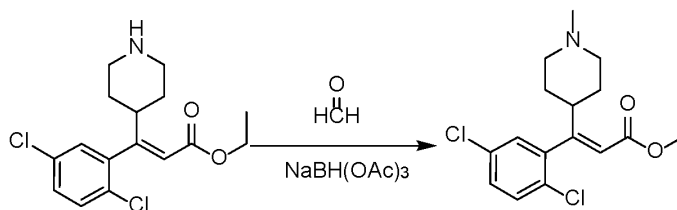
dichlorophenyl)-3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate as a colorless oil (7.0 g, 83%) (ESI 450.1 $[M+Na]^+$).

Step 4: ethyl (E)-3-(2,5-dichlorophenyl)-3-(piperidin-4-yl)acrylate hydrochloride



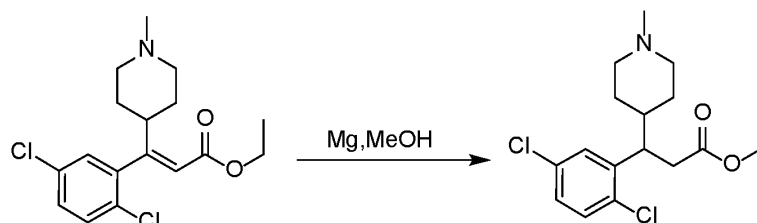
[000547] To a solution of tert-butyl (E)-4-(1-(2,5-dichlorophenyl)-3-ethoxy-3-oxoprop-1-en-1-yl)piperidine-1-carboxylate (4.0 g, 9.4 mmol, 1.0 *eq*) in DCM (30 mL) was added 4M HCl-dioxane (11.8 mL, 47.0 mmol, 5.0 *eq*). The reaction mixture was allowed to stir at RT for 2 hr and then concentrated *in vacuo* to obtain ethyl (E)-3-(2,5-dichlorophenyl)-3-(piperidin-4-yl)acrylate hydrochloride as a white solid (4.0 g, 9.4 mmol, crude) (ESI 328.1 $[M+H]^+$). The crude product was used directly in the subsequent step.

Step 5: ethyl (E)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)acrylate



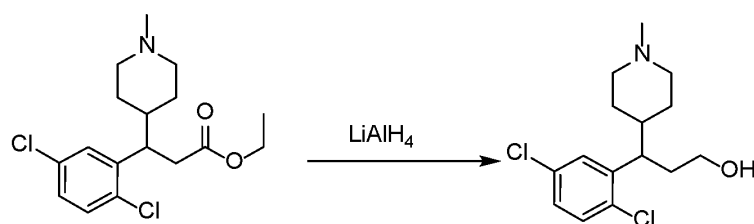
[000548] To a solution of ethyl (E)-3-(2,5-dichlorophenyl)-3-(piperidin-4-yl)acrylate hydrochloride (4.0 g, 9.4 mmol, 1.0 *eq*) in MeOH (30 mL) was added 33% aqueous HCHO (4.7 g, 47 mmol, 5.0 *eq*). The reaction mixture was allowed to stir at RT for 1 hr. NaBH(OAc)₃ (4.0 g, 18.8 mmol, 2.0 *eq*) was then added, and the reaction was allowed to continue to stir at RT for 3 hr. The reaction mixture was poured into water (200 mL) and extracted with DCM (3 x 200 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (90:10 DCM: MeOH) to give ethyl (E)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)acrylate as colorless oil (2.7 g, 84%) (ESI 342.1 $[M+H]^+$).

Step 6: ethyl 3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propanoate



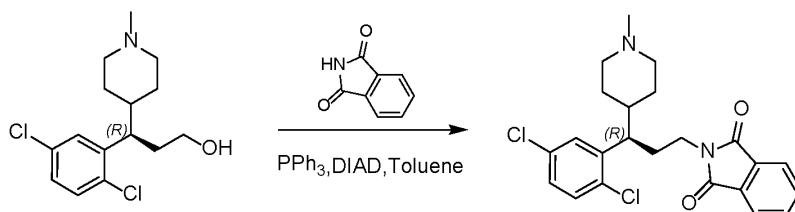
[000549] To a solution of ethyl (E)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)acrylate (2.4 g, 7.0 mmol, 1.0 eq.) in MeOH (40 mL) at 0 °C was added Mg (1.0 g, 42 mmol, 6.0 eq.). The reaction mixture was allowed to stir at RT for 3hr. The reaction was then quenched by the addition of saturated aqueous NH_4Cl (100 mL) and extracted with EtOAc (2 x 150 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (90:10 DCM: MeOH) to give ethyl 3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propanoate as a colorless oil (2.1 g, 88%) (ESI 344.0 $[\text{M}+\text{H}]^+$).

Step 7: (S)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propan-1-ol



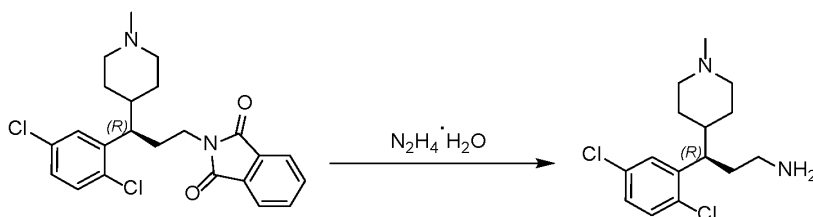
[000550] To a solution of ethyl 3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propanoate (2.1 g, 6.1 mmol, 1.0 eq) in THF (20 mL) at 0 °C was added LAH (2.5M in THF, 3.2 mL, 7.9 mmol, 1.3 eq). The reaction mixture was allowed to stir at 0 °C for 1 hr and then quenched by the addition of water (0.23 mL). The mixture was allowed to continue to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.23 mL) and water (0.69 mL) were then added sequentially. The mixture was allowed to warm to RT and stir for another 15 min. The mixture was dried over Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (90:10 DCM: MeOH) to give racemic 3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propan-1-ol (1.5 g, 83 %) as a colorless oil. The enantiomers were separated by prep chiral SFC O to give peak 1, assigned as (S)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propan-1-ol (700mg), and peak 2, assigned as (R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propan-1-ol as a colorless oil (650mg). (ESI 302.1 $[\text{M}+\text{H}]^+$).

Step 8: (R)-2-(3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)isoindoline-1,3-dione



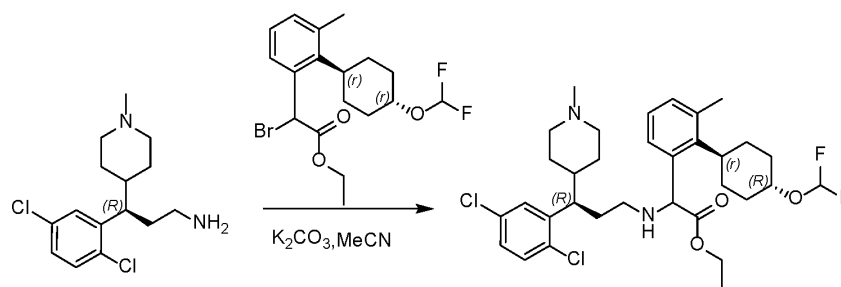
[000551] To a solution of (R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propan-1-ol (650 mg, 2.2 mmol, 1.0 eq) and isoindoline-1,3-dione (420 mg, 2.9 mmol, 1.3 eq) in toluene (20 mL) at 0 °C was added triphenylphosphine (750 mg, 2.9 mmol, 1.3 eq) and DIAD (580 mg, 2.9 mmol, 1.3 eq). The reaction mixture was allowed to stir at 70 °C for 3 hr. After cooling to RT, the reaction was filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (90:10 DCM: MeOH) to give (R)-2-(3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)isoindoline-1,3-dione as a colorless oil (800 g, 87 %) (ESI 431.1 [M+H]⁺).

Step 9: (R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propan-1-amine



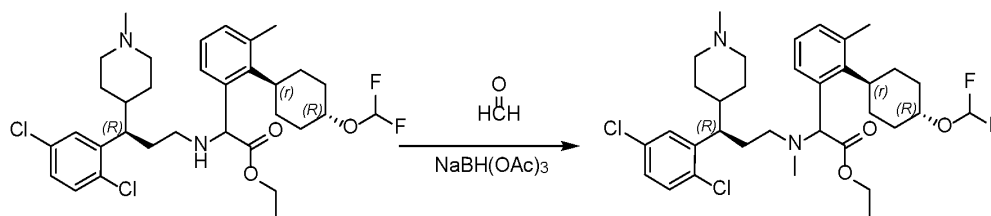
[000552] To a solution of (R)-2-(3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)isoindoline-1,3-dione (800 mg, 1.9 mmol, 1.0 eq) in EtOH (30 mL) at RT was added 98% hydrazine hydrate (480 g, 9.5 mmol, 5.0 eq). The reaction mixture was warmed to 80 °C and allowed to stir for 1 hr. The mixture was filtered and concentrated *in vacuo* to obtain (R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propan-1-amine as a colorless oil (560 mg, 1.9 mmol, crude) (ESI 301.1 [M+H]⁺). The crude product was used directly in the subsequent step.

Step 10: ethyl 2-(((R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)amino)-2-(2-((1*r*,4*R*)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetate



[000553] To a solution of (R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propan-1-amine (200 mg, 0.7 mmol, crude) in ACN (6 mL) was added K_2CO_3 (210 mg, 1.5 mmol, 3.0 *eq.*). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(2-((1R,4R)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetate (200 mg, 0.5 mmol, 1.0 *eq.*) was then added, and the mixture was heated at 80 °C and allowed to stir for 2 hr. The reaction mixture was filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (9:1 DCM: MeOH) to give ethyl 2-(((R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)amino)-2-(2-((1R,4R)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetate as a colorless oil (210 mg, 68%) (ESI 625.3 $[M+H]^+$).

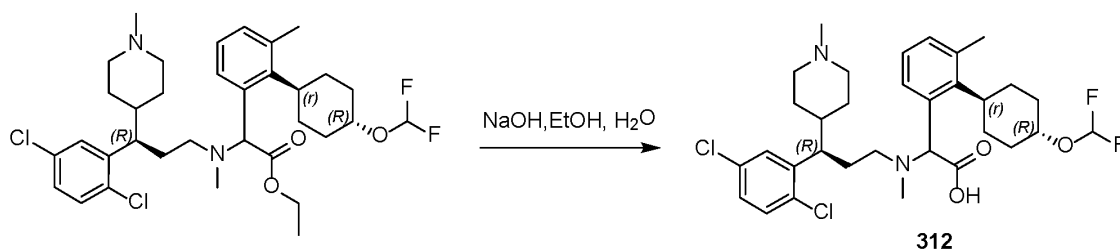
Step 11: ethyl 2-(((R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)(methyl)amino)-2-(2-((1R,4R)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetate



[000554] To a solution of ethyl 2-(((R)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)amino)-2-(2-((1R,4R)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetate (210 mg, 0.34 mmol, 1.0 *eq.*) in MeOH (6 mL) was added 33% aqueous HCHO (170 mg, 1.7 mmol, 5.0 *eq.*). The reaction mixture was allowed to stir at RT for 1 hr. $NaBH(OAc)_3$ (220 g, 1.02 mmol, 3.0 *eq.*) was then added, and the reaction mixture was allowed to continue to stir at RT for 3 hr. The reaction mixture was poured into water (80 mL) and extracted with DCM (3 x 80 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated *in vacuo*. The crude residue was purified by silica gel column chromatography (90:10 DCM: MeOH) to give ethyl 2-(((R)-3-(2,5-dichlorophenyl)-3-(1-

methylpiperidin-4-yl)propyl)(methyl)amino)-2-(2-((1*r*,4*R*)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetate as colorless oil (190 mg, 90%) (ESI 639.2 $[M+H]^+$).

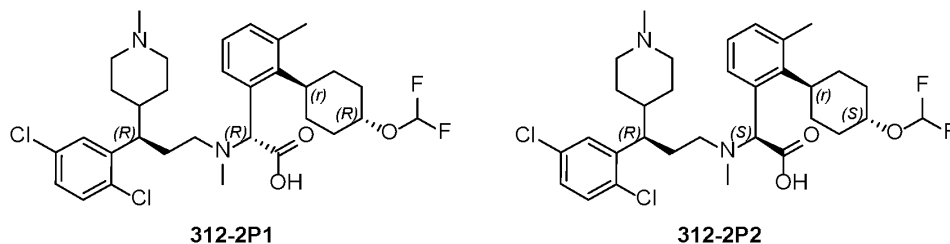
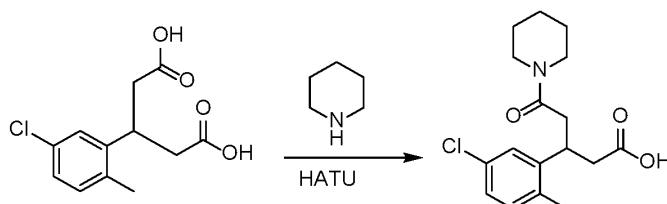
Step 12: 2-(((*R*)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)(methyl)amino)-2-(2-((1*r*,4*R*)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetic acid



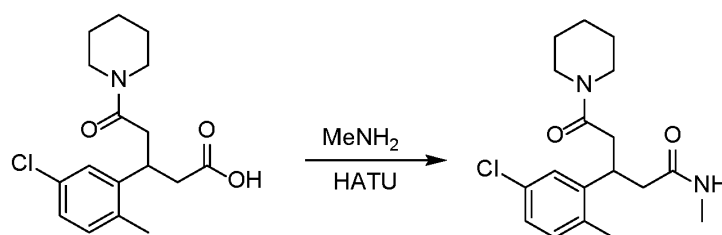
[000555] To a mixture of ethyl 2-(((*R*)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)(methyl)amino)-2-(2-((1*r*,4*R*)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetate (190 mg, 0.3 mmol, 1.0 eq) in EtOH (3 mL) and H₂O (1 mL) was added NaOH (120 mg, 3.0 mmol, 10.0 eq). The reaction mixture was allowed to stir at 60 °C for 16 hr. and concentrated *in vacuo*. The crude residue was purified by prep HPLC A (30 - 70% CH₃CN) to give a mixture of stereoisomeric products **312** as a white solid (130 mg, 70%). The stereoisomers were further separated by prep chiral SFC I to give **312-P1** (65 mg) and **312-P2** (60 mg).

[000556] **312-2P1**, assigned as (*R*)-2-(((*R*)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)(methyl)amino)-2-(2-((1*r*,4*R*)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetic acid. LC/MS ESI 583.2 $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ 7.72 – 6.64 (m, 5H), 6.61 – 6.16 (m, 1H), 4.80 – 4.58 (m, 1H), 4.28 – 3.96 (m, 1H), 3.57 – 3.36 (m, 1H), 3.25 – 2.97 (m, 2H), 2.95 – 2.28 (m, 14H), 2.30 – 1.89 (m, 7H), 1.85 – 1.26 (m, 7H), 1.18 – 0.95 (m, 1H).

[000557] **312-2P2**, assigned as (*S*)-2-(((*R*)-3-(2,5-dichlorophenyl)-3-(1-methylpiperidin-4-yl)propyl)(methyl)amino)-2-(2-((1*r*,4*S*)-4-(difluoromethoxy)cyclohexyl)-3-methylphenyl)acetic acid. LC/MS ESI 583.2 $[M+H]^+$. ¹H NMR (400 MHz, CD₃OD) δ 7.55 – 6.94 (m, 5H), 6.66 – 6.01 (m, 1H), 4.84 – 4.74 (m, 1H), 4.35 – 4.05 (m, 1H), 3.43 (d, *J* = 12.1 Hz, 1H), 3.29 – 3.19 (m, 1H), 3.16 – 2.98 (m, 1H), 2.96 – 2.57 (m, 10H), 2.55 – 2.41 (m, 3H), 2.39 – 2.26 (m, 2H), 2.22 – 1.73 (m, 8H), 1.72 – 1.42 (m, 5H), 1.37 – 1.23 (m, 1H).

**Example 30: Preparation of Compound 313-1P2****Step 1: 3-(5-chloro-2-methylphenyl)-5-oxo-5-(piperidin-1-yl)pentanoic acid**

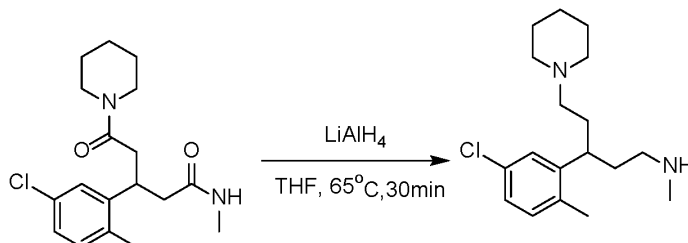
[000558] To a solution of 3-(5-chloro-2-methylphenyl)pentanedioic acid (4.2 g, 16.4 mmol, 1.0 eq.), DIEA (4.23 g, 32.8 mmol, 2.0 eq) and HATU (7.49 g, 19.7 mmol, 1.2 eq.) in DCM (50 mL) was added piperidine (1.67 g, 19.7 mmol, 1.2 eq.) dropwise. The reaction mixture was allowed to stir at RT for 3 hr. The mixture was then diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (9:1 DCM: methanol) to give 3-(5-chloro-2-methylphenyl)-5-oxo-5-(piperidin-1-yl)pentanoic acid as a yellow solid (1.3 g, 24.5%) (ESI 324.1 [M+H]⁺).

Step 2: 3-(5-chloro-2-methylphenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide

[000559] HATU (1.82 g, 4.8 mmol, 1.2 eq.) was added to a solution of 3-(5-chloro-2-methylphenyl)-5-oxo-5-(piperidin-1-yl)pentanoic acid (1.3 g, 4.0 mmol, 1.0 eq.), DIEA (1.55 g, 12.0 mmol, 3.0 eq) and methylamine hydrochloride (405 mg, 6.0 mmol, 1.5 eq) in DCM (20 mL). After stirring at RT for 3 hr, the mixture was diluted with water (100 mL) and extracted with DCM (2 x 100 mL). The organic solutions were combined, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by silica gel

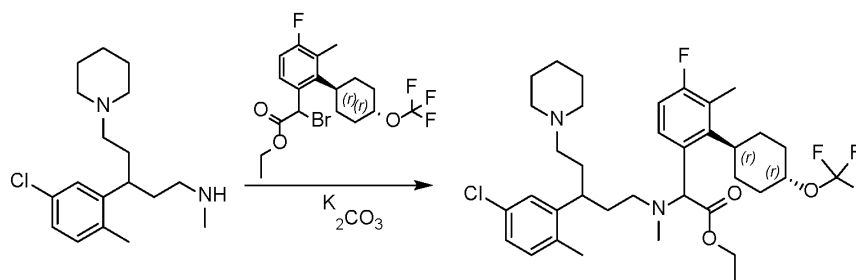
column chromatography (9:1 DCM: methanol) to give 3-(5-chloro-2-methylphenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide as a yellow solid (930 mg, 69.0%) (ESI 337.2 [M+H]⁺).

Step 3: 3-(5-chloro-2-methylphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine



[000560] To a solution of 3-(5-chloro-2-methylphenyl)-N-methyl-5-oxo-5-(piperidin-1-yl)pentanamide (930mg, 2.8 mmol, 1.0 eq) in THF (25 mL) at 0 °C was added LAH (2.5M in THF, 2.2 mL, 5.5 mmol, 2.0 eq). The reaction mixture was allowed to stir at 65 °C for 0.5 hr and then quenched by the addition of water (0.3 mL). The mixture was allowed to continue to stir at 0 °C for another 10 min. 15% aqueous NaOH (0.3 mL) and water (1.0 mL) were then added sequentially at 0 °C. The mixture was allowed to warm to RT and stir for another 15 min, then dried over Na₂SO₄, filtered and concentrated *in vacuo* to give 3-(5-chloro-2-methylphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine as yellow oil (450 mg) (ESI 309.2 [M+H]⁺). The crude product was used directly in next step.

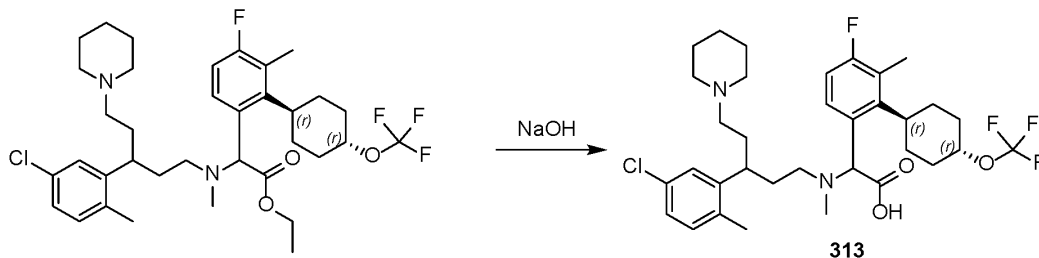
Step 4: ethyl 2-((3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl-amino)-2-(4-fluoro-3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate



[000561] To a solution of 3-(5-chloro-2-methylphenyl)-N-methyl-5-(piperidin-1-yl)pentan-1-amine (450 mg, 1.5 mmol) in ACN (10 mL) was added K₂CO₃ (607 mg, 4.4 mmol, 3.0 eq.). The mixture was allowed to stir at RT for 15 min. Ethyl 2-bromo-2-(4-fluoro-3-methyl-2-((1r,4r)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetate (528 mg, 1.2 mmol, 0.8 eq.) was then added. The reaction mixture was allowed to stir at 70 °C for another 16 hr and then filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (6:1 DCM: methanol) to give ethyl 2-((3-(5-chloro-2-methylphenyl)-5-

(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetate as a brown oil (410 mg, 51%) (ESI 669.3 [M+H]⁺).

Step 5: 2-((3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid



[000562] To a solution of ethyl 2-((3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)-(methyl)amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*r*)-4-(trifluoromethoxy)cyclohexyl)-phenyl)acetate (410 mg, 0.61 mmol, 1.0 eq.) in ethanol (4 mL) and water (1 mL) was added NaOH (122 mg, 3.0 mmol, 5.0 eq.). The reaction mixture was allowed to stir at 60 °C for 16 hr. The pH of the mixture was adjusted to ~ 6 with 1N HCl. Solvents were then removed *in vacuo*, and the residue was purified by prep HPLC A (30 - 70% CH₃CN) to give a mixture of stereoisomers **313** as a white solid (350 mg, 90%). The stereoisomers were further separated by prep chiral SFC G to give **313-1** (120 mg) and **313-2** (120 mg). **313-1** was further separated by prep chiral SFC A to give **313-1P1** (40 mg) and **313-1P2** (38 mg). **313-2** was separated by prep chiral SFC A to give **313-2P1** (407mg) and **313-2P2** (40 mg).

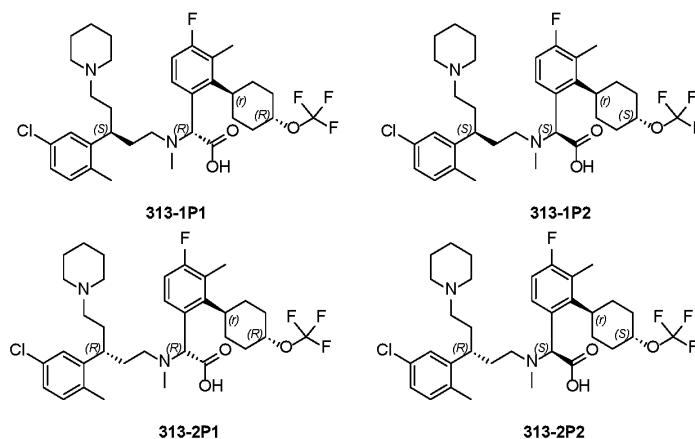
[000563] **313-1P1**, (R)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)-amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid, LC/MS ESI 641.3 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.57 – 7.42 (m, 1H), 7.17 (s, 1H), 7.14 – 7.05 (m, 2H), 6.86 (s, 1H), 4.41 (d, *J* = 34.8 Hz, 2H), 3.43 (d, *J* = 36.3 Hz, 1H), 3.04 (t, *J* = 40.9 Hz, 2H), 2.84 (s, 3H), 2.71 (s, 3H), 2.43 (s, 4H), 2.34 (d, *J* = 2.5 Hz, 3H), 2.24 (d, *J* = 20.4 Hz, 4H), 2.17 – 2.07 (m, 4H), 2.00 – 1.80 (m, 4H), 1.76 – 1.50 (m, 8H).

[000564] **313-1P2**, (S)-2-(((S)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)-amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid, LC/MS ESI 641.3 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.60 (d, *J* = 89.3 Hz, 1H), 7.26 – 7.05 (m, 3H), 6.86 (s, 1H), 4.40 (d, *J* = 29.4 Hz, 2H), 3.42 (d, *J* = 46.2 Hz, 1H), 3.25 – 2.94 (m, 1H), 2.94 – 2.57 (m, 7H), 2.42 (s, 4H), 2.30

(d, $J = 29.4$ Hz, 3H), 2.21 (s, 3H), 2.18 – 2.02 (m, 4H), 1.99 – 1.76 (m, 5H), 1.76 – 1.49 (m, 8H).

[000565] 313-2P1, (R)-2-(((R)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)-amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*R*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid, LC/MS ESI 641.3 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 7.59 – 7.39 (m, 1H), 7.10 (d, $J = 23.7$ Hz, 3H), 6.86 (d, $J = 8.4$ Hz, 1H), 4.50 (t, $J = 60.9$ Hz, 2H), 3.26 – 2.96 (m, 1H), 2.89 (s, 1H), 2.81 – 2.52 (m, 9H), 2.42 – 2.26 (m, 5H), 2.24 – 1.95 (m, 10H), 1.92 – 1.73 (m, 4H), 1.71 – 1.49 (m, 8H).

[000566] 313-2P2, (S)-2-(((R)-3-(5-chloro-2-methylphenyl)-5-(piperidin-1-yl)pentyl)(methyl)-amino)-2-(4-fluoro-3-methyl-2-((1*r*,4*S*)-4-(trifluoromethoxy)cyclohexyl)phenyl)acetic acid, LC/MS ESI 641.3 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 11.35 (d, $J = 33.7$ Hz, 1H), 11.06 (d, $J = 24.3$ Hz, 3H), 10.83 (t, $J = 8.9$ Hz, 1H), 8.62 – 8.26 (m, 2H), 7.09 (s, 1H), 6.92 – 6.49 (m, 10H), 6.26 (d, $J = 2.5$ Hz, 5H), 6.21 – 6.01 (m, 8H), 5.78 (d, $J = 41.7$ Hz, 5H), 5.71 – 5.44 (m, 9H).



[000567] Additional compounds of the invention were prepared using synthetic routes similar to those described in Examples 1-30, substituting the appropriate reagents, purification and separation conditions.

LCMS Characterization of Additional Compounds:

Patent ID	Exact MW	ESI (M+H) ⁺	Patent ID	Exact MW	ESI (M+H) ⁺	Patent ID	Exact MW	ESI (M+H) ⁺
1-P2	595.28	596.3	69-P1	600.35	601.5	137-P2	634.31	635.1
2-P2	613.27	614.3	70-P2	642.33	643.3	138-P2	620.3	621.2
3-P2	585.31	586.3	71-P2	629.38	630.5	139-P2	612.35	613.2
4-P2	599.25	600.3	72-P2	656.3	657.0	140-P1	624.35	625.5

5-P1	621.29	622.3		73-P2	644.38	645.0		141-P2	606.34	607.3
6-P1	567.32	568.3		74-P2	626.29	627.3		142-P1	632.36	633.3
7-P2	541.31	542.3		75-P2	641.3	642.3		143-P2	618.42	619.2
8-P2	595.28	596.3		76-P2	641.3	642.3		144-P2	673.31	674.3
9-P2	613.27	614.3		77-P2	630.34	631.1		145-P2	675.33	676.3
10-P2	609.29	610.3		78-P2	614.37	615.2		146-P1	637.33	638.3
11-P2	640.31	641.2		79-P2	626.29	627.3		147-P1	652.31	653.2
12-P2	583.35	584.3		80-P2	669.33	670.2		148-P2	610.33	611.2
13-P2	601.34	602.3		81-P2	659.25	660.0		149-P2	632.36	633.4
14-P2	629.31	630.2		82-P2	626.29	627.0		150-P2	612.27	613.3
15-P2	623.31	624.2		83-P1	622.31	623.3		151-P2	620.3	621.3
16-P2	594.29	595.3		84-P2	614.37	615.3		152-P2	624.34	625.3
17-P2	612.29	613.0		85-P2	626.29	627.0		153-P2	642.4	643.3
18-P2	619.34	620.3		86-P2	633.35	634.1		154-P2	628.27	629.3
19-P2	665.32	666.3		87-P2	633.35	634.0		155-P2	628.38	629.4
20-P2	629.31	630.3		88-P2	628.38	629.4		156-P1	630.26	631.2
21-P1	647.3	648.2		89-P2	639.32	640.2		157-P2	654.32	655.2
22-P2	622.33	623.3		90-P1	645.28	646.3		158-P2	626.37	627.4
23-P2	647.3	648.3		91-P1	641.3	642.1		159-P2	598.33	599.3
24-P2	626.3	627.3		92-P2	655.32	656.2		160-P2	616.32	617.3
25-P2	637.33	638.3		93-P2	629.38	630.3		161-P2	640.31	641.2
26-P2	623.31	624.3		94-P2	645.28	646.2		162-P2	636.33	637.2
27-P2	608.31	609.2		95-P1	610.39	611.4		163-P2	654.32	655.2
28-P2	621.29	622.3		96-P2	618.34	619.3		164-P2	650.35	651.2
29-P1	640.32	641.3		97-P2	644.28	645.0		165-P1	646.38	647.2
30-P2	631.26	632.2		98-P2	661.31	662.3		166-P1	612.35	613.3
31-P2	641.3	642.3		99-P2	609.29	610.3		167-P2	624.41	625.3
32-P2	659.29	660.3		100-P2	627.29	628.3		168-P2	653.34	654.2
33-P2	621.29	622.3		101-P2	633.35	634.2		169-P2	657.31	658.2
34-P1	621.29	622.3		102-P2	659.37	660.3		170-P2	610.39	611.4
35-P2	614.37	615.4		103-P2	667.32	668.3		171-P2	638.31	639.3
36-P2	596.37	597.3		104-P2	660.32	661.1		172-P2	608.3	609.2
37-P2	626.29	627.3		105-P2	626.29	627.3		173-P2	602.37	603.3
38-P2	608.3	609.3		106-P2	622.31	623.3		174-P2	588.43	589.3
39-P2	625.31	626.3		107-P2	637.33	638.2		175-P2	644.28	645.3
40-P2	632.36	633.3		108-P2	637.33	638.1		176-P2	629.38	630.3
41-P2	659.33	660.3		109-P2	644.28	645.0		177-P2	642.4	643.3
42-P2	643.3	644.3		110-P2	636.33	637.3		178-P2	643.39	644.3
43-P2	616.32	617.3		111-P2	609.29	610.3		179-P2	598.33	599.2
44-P2	632.36	633.3		112-P2	627.29	628.3		180-P2	626.29	627.1
45-P2	598.33	599.2		113-P2	615.36	616.3		181-P2	612.35	613.3
46-P2	622.31	623.3		114-P2	641.3	642.3		182-P2	659.29	660.3
47-P2	628.39	629.4		115-P1	637.33	638.2		183-P2	655.32	656.2
48-P2	657.31	658.3		116-P2	626.29	627.2		184-P2	622.31	623.2
49-P2	671.33	672.3		117-P2	637.33	638.4		185-P2	668.34	669.2
50-P2	620.3	621.3		118-P2	638.29	639.1		186-P2	608.3	609.2
51-P2	636.33	637.3		119-P2	626.37	627.5		187-P2	612.27	613.2
52-P2	626.37	627.2		120-P2	624.35	625.3		188-P2	628.38	629.4

53-P2	614.37	615.3		121-P2	628.32	629.2		189-P2	669.33	670.2
54-P1	612.35	613.4		122-P2	655.32	656.3		190-P2	640.31	641.3
55-P2	639.32	640.3		123-P1	666.32	667.3		191-P2	687.36	688.3
56-P2	612.35	613.3		124-P2	602.33	603.3		192-P2	671.33	672.3
57-P2	612.35	613.3		125-P2	608.37	609.3		193-P2	630.26	630.7
58-P2	632.36	633.3		126-P2	651.32	652.2		194-P2	641.3	641.7
59-P2	618.34	619.3		127-P2	606.34	607.3		195-P2	628.32	628.7
60-P4	629.38	630.2		128-P2	627.29	628.3		196-P2	647.35	648.2
61-P2	661.29	662.3		129-P2	629.38	630.4		197-P2	665.34	666.2
62-P2	630.34	631.3		130-P2	666.32	667.3		198-P2	638.31	639.3
63-P2	614.37	615.3		131-P2	624.34	625.2		199-P2	626.29	627.2
64-P2	616.32	617.1		132-P2	622.39	623.3		200-P2	626.29	627.2
65-P2	634.31	635.3		133-P2	610.33	611.3		201-P2	640.31	641.3
66-P2	632.36	633.2		134-P2	594.42	595.3		202-P2	627.29	628.3
67-P1	630.34	631.3		135-P2	652.31	653.3		203-P2	628.31	629.2
				136-P2	608.37	609.3		204-P2	651.34	652.3

LCMS Characterization of Additional Compounds:

Patent ID	Exact MW	ESI (M+H)+	Patent ID	Exact MW	ESI (M+H)+	Patent ID	Exact MW	ESI (M+H)+
080-P2	670.2	670.2	358-1P2	638.8	639.3	384-2P2	601.1	601.3
99-P2*	609.3	610.3	359-1P2	656.7	657.3	385-1P2	587.2	587.3
132-P2	623.3	623.3	360-1P2	662.3	662.3	386-1P2	631.7	631.4
152-P2	624.7	625.3	361-2P2	660.2	660.3	387-2P2	611.3	611.3
171-P2	639.2	639.3	362-1P2	605.2	605.2	388-2P2	579.1	579.2
198-P2	639.2	639.3	363-1P2	609.2	609.3	389-2P2	569.2	569.3
300-P3	613.1	613.2	364-2P2	624.7	625.2	390-2P2	614.1	614.1
301-P2	624.2	624.2	365-2P2	637.2	637.3	391-1P2	629.6	629.1
302-P2	624.2	623.8	366-2P2	659.2	659.3	392-1P2	677.7	678.3
303-1P2	623.2	623.3	367-2P2	641.2	641.3	393-1P2	677.7	678.2
304-P2	660.7	661.3	368-1P2	622.2	622.3	394-1P2	624.7	625.3
305-2P1	601.2	601.5	369-1P2	644.2	644.3	395-1P2	624.7	625
307-2P2	655.2	655.3	370-1P2	640.2	640.2	396-1P2	673.7	674.3
308-1P2	642.7	643.2	371-1P2	659.2	659.2	399-1P2	662.3	662.4
309-2P1	657.7	658.3	372-1P2	655.2	655.2	400-1P1	606.7	607.4
310-1P2	583.2	583.3	373-2P2	674.2	674.3	401-P3	642.7	643.2
311-2P2	604.7	605.4	374-2P2	670.2	670.4	402-1P1	589.6	589.3
312-2P2	611.6	611.2	375-2P2	659.2	659.3	403-1P2	597.3	597.2
313-1P2	640.3	641.3	376-2P2	655.2	655.3	404-2P2	643.7	644.2
350-1P1	641.2	641.3	377-2P1	656.2	656.3	405-2P2	625.7	626.3
351-2P2	616.2	616.4	378-1P2	730.3	730.3	406-2P2	603.8	604.3
352-1P2	631.1	631.2	379-1P2	609.2	609.3	407-2P2	602.8	603.4
353-1P2	630.1	630.3	380-1P2	623.2	623.3	408-1P2	616.8	617.4
354-1P2	613.1	613.1	381-2P2	642.2	642.3	409-1P1	619.2	619.3
355-P2	621.3	621.3	382-P2	643.7	644.4	410-1P2	603.7	603.3
356-1P2	643.2	643.2	383-2P2	604.7	605.4	411-1P2	620.8	621.5

357-2P2	638.2	638.2							
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Assay Conditions

[000568] Fluorescence Polarization (FP) assays were used to measure compound activity through binding competition with the fluorescein-labeled peptide CRSDTLCGE{Lys(FITC)}. In the assay, 6.5 nM of integrin $\alpha 4\beta 7$ was incubated with the test compound in 2 mM manganese chloride, 0.1 mM calcium chloride, 20 mM HEPES buffer at pH 7.3, 150 mM sodium chloride, 0.01% Triton X-100, 2% DMSO, and 3 nM of the fluorescein-labeled peptide. Running the assays in 384-well plates, the integrin protein was pre-incubated with the test compounds for 15 minutes at 22°C before the fluorescein-labeled peptide was added. After the fluorescein-labeled peptide was added, the assay was incubated at 22°C for 1 hour and fluorescence polarization was measured. IC₅₀ values were determined by nonlinear regression, 4-parameter curve fitting. IC₅₀ values of Table 1 as determined by the fluorescence polarization assay are categorized as:

- A: < 5 nM;
- B: 5-500 nM; and
- C: >500 nM.

Table 1. Potency Data Table

Compound	$\alpha 4\beta 7$ IC ₅₀		Compound	$\alpha 4\beta 7$ IC ₅₀		Compound	$\alpha 4\beta 7$ IC ₅₀
1-P2	B		69-P1	B		137-P2	A
2-P2	A		70-P2	A		138-P2	A
3-P2	B		71-P2	B		139-P2	A
4-P2	B		72-P2	A		140-P1	B
5-P1	A		73-P2	B		141-P2	A
6-P1	B		74-P2	A		142-P1	B
7-P2	C		75-P2	A		143-P2	A
8-P2	B		76-P2	A		144-P2	A
9-P2	A		77-P2	B		145-P2	B
10-P2	A		78-P2	A		146-P1	A
11-P2	A		79-P2	B		147-P1	B
12-P2	B		80-P2	B		148-P2	B
13-P2	B		81-P2	A		149-P2	A
14-P2	B		82-P2	A		150-P2	A
15-P2	A		83-P1	A		151-P2	B
16-P2	B		84-P2	A		152-P2	A
17-P2	B		85-P2	A		153-P2	A
18-P2	B		86-P2	B		154-P2	A
19-P2	A		87-P2	B		155-P2	B
20-P2	A		88-P2	A		156-P1	B

21-P1	B		89-P2	A		157-P2	A
22-P2	B		90-P1	B		158-P2	A
23-P2	B		91-P1	A		159-P2	B
24-P2	B		92-P2	A		160-P2	B
25-P2	A		93-P2	B		161-P2	B
26-P2	B		94-P2	B		162-P2	A
27-P2	B		95-P1	B		163-P2	A
28-P2	B		96-P2	B		164-P2	A
29-P1	B		97-P2	A		165-P1	B
30-P2	A		98-P2	B		166-P1	B
31-P2	A		99-P2			167-P2	B
32-P2	B		100-P2	B		168-P2	A
33-P2	B		101-P2	B		169-P2	B
34-P1	A		102-P2	B		170-P2	B
35-P2	B		103-P2	A		171-P2	A
36-P2	B		104-P2	A		172-P2	A
37-P2	A		105-P2	A		173-P2	A
38-P2	A		106-P2	A		174-P2	B
39-P2	B		107-P2	B		175-P2	A
40-P2	B		108-P2	A		176-P2	B
41-P2	B		109-P2	A		177-P2	B
42-P2	B		110-P2	A		178-P2	B
43-P2	A		111-P2	A		179-P2	A
44-P2	B		112-P2	A		180-P2	A
45-P2	A		113-P2	B		181-P2	A
46-P2	B		114-P2	A		182-P2	B
47-P2	B		115-P1	A		183-P2	B
48-P2	B		116-P2	A		184-P2	A
49-P2	B		117-P2	A		185-P2	B
50-P2	A		118-P2	A		186-P2	A
51-P2	A		119-P2	B		187-P2	A
52-P2	B		120-P2	A		188-P2	B
53-P2	B		121-P2	B		189-P2	A
54-P1	B		122-P2	A		190-P2	A
55-P2	A		123-P1	B		191-P2	B
56-P2	B		124-P2	B		192-P2	B
57-P2	A		125-P2	B		193-P2	A
58-P2	B		126-P2	A		194-P2	A
59-P2	A		127-P2	B		195-P2	A
60-P4	A		128-P2	A		196-P2	B
61-P2	B		129-P2	B		197-P2	B
62-P2	B		130-P2	A		198-P2	A
63-P2	B		131-P2	A		199-P2	A
64-P2	A		132-P2	B		200-P2	A
65-P2	B		133-P2	A		201-P2	A
66-P2	B		134-P2	B		202-P2	A
67-P1	B		135-P2	A		203-P2	B
68-P1	B		136-P2	A		204-P2	A

Table 1a. Additional Potency Data Table

<i>Compound</i>	<i>a4b7 IC₅₀</i>		<i>Compound</i>	<i>a4b7 IC₅₀</i>		<i>Compound</i>	<i>a4b7 IC₅₀</i>
080-P2	B		358-1P2	A		384-2P2	A
99-P2	A		359-1P2	A		385-1P2	B
132-P2	B		360-1P2	B		386-1P2	B
152-P2	A		361-2P2	B		387-2P2	A
171-P2	A		362-1P2	A		388-2P2	A
198-P2	A		363-1P2	B		389-2P2	B
300-P3	A		364-2P2	A		390-2P2	B
301-P2	A		365-2P2	B		391-1P2	A
302-P2	A		366-2P2	B		392-1P2	B
303-1P2	A		367-2P2	B		393-1P2	B
304-P2	B		368-1P2	B		394-1P2	B
305-2P1	B		369-1P2	A		395-1P2	B
307-2P2	B		370-1P2	A		396-1P2	B
308-1P2	A		371-1P2	A		399-1P2	B
309-2P1	B		372-1P2	A		400-1P1	B
310-1P2	A		373-2P2	A		401-P3	A
311-2P2	B		374-2P2	A		402-1P1	A
312-2P2	A		375-2P2	B		403-1P2	A
313-1P2	A		376--2P2	A		404-2P2	B
350-1P1	A		377-2P1	B		405-2P2	A
351-2P2	C		378-1P2	B		406-2P2	B
352-1P2	A		379-1P2	A		407-2P2	A
353-1P2	B		380-1P2	A		408--1P2	B
354-1P2	A		381-2P2	B		409-1P1	B
355-P2	B		382-P2	B		410-1P2	A
356-1P2	A		383-2P2	B		411-1P2	B
357-2P2	A						

[000569] From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

[000570] All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein in their entireties. Where any inconsistencies arise, material literally disclosed herein controls.

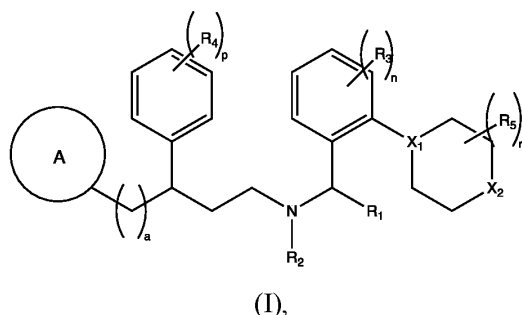
Equivalents and Scope

[000571] The invention is not to be limited in scope by the specific embodiments disclosed in the examples that are intended as illustrations of a few aspects of the invention and any embodiments that are functionally equivalent are within the scope of this invention. Indeed,

various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the scope of the appended claims. A number of references have been cited, the entire disclosures of which are incorporated herein by reference for all purposes.

CLAIMS

1. A compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

 is a 3 to 12 member heterocyclcyl ring structure optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl and C₁₋₄alkyloxy are optionally substituted with one or more halogen;

a is 0, 1, 2 or 3;

X₁ is N or CR_a;

R_a is H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

X₂ is NR_b or CR_b'R_b'';

R_b is H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R_b' and R_b'' are each independently H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R₁ is H or -COOR_{1b};

R_{1b} is H or C₁₋₄ alkyl;

R₂ is H or C₁₋₄ alkyl;

R₃ is H, C₁₋₄ alkyl, or halogen;

n is 0, 1, 2, 3, or 4;

R₄ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

p is 0, 1, 2, 3, 4 or 5;

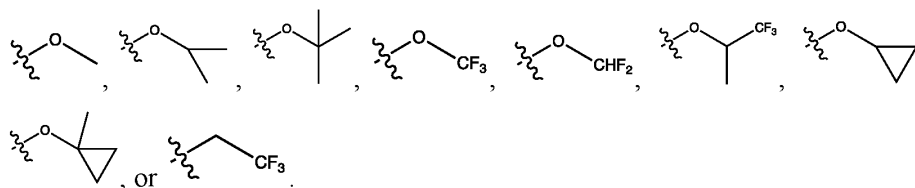
R₅ is H, C₁₋₄alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₇;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

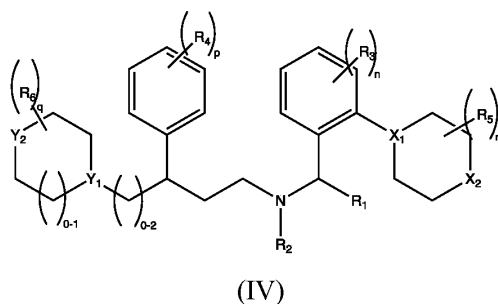
each R₇ is independently halogen.

2. The compound of claim 1, wherein R₁ is COOH.
3. The compound of any one of claims 1-2, wherein R₂ is methyl.
4. The compound of any one of claims 1-3, wherein R_b^{''} is H.
5. The compound of any one of claims 1-4, wherein X₁ is CR_a.
6. The compound of claim 5, wherein R_a is H.
7. The compound of any one of claims 1-6, wherein X₂ is NR_b.
8. The compound of claim 7, wherein R_b is C₁₋₄alkyl optionally substituted with one or more halogen.
9. The compound of claim 8, wherein R_b is C₁₋₄alkyl optionally substituted with one or more fluoro.
10. The compound of claim 9, wherein R_b is -CH₂CF₃.
11. The compound of any one of claims 1-6, wherein X₂ is CR_b[']R_b^{''}.
12. The compound of claim 11, wherein R_b^{''} is H.
13. The compound of any one of claims 11-12, wherein R_b['] is -O-C₁₋₄ alkyl, wherein the C₁₋₄ alkyl is optionally substituted with one or more halogen.
14. The compound of claim 13, wherein R_b['] is -O-C₁₋₄ alkyl or -O-C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl is optionally substituted with one or more fluoro.
15. The compound of claim 14, wherein R_b['] is -O-CF₃.
16. The compound of claim 14, wherein R_b['] is -O-CH₃.
17. The compound of claim 14, wherein R_b['] is -O-C₃ cycloalkyl optionally substituted with C₁₋₄ alkyl.

18. The compound of claim 14, wherein $R_{b'}$ is $-O-C_3$ cycloalkyl optionally substituted with methyl.
19. The compound of claim 13, wherein $R_{b'}$ is $-O-C_{1-4}$ alkyl optionally substituted with one or more fluoro.
20. The compound of any one of claims 1-4, wherein X_1 is CH and X_2 is $CHR_{b'}$ and $R_{b'}$ is



21. The compound of any one of claims 1-20, wherein m is 0.
22. The compound of any one of claims 1-21, wherein R_3 and R_4 are each independently halogen or C_{1-4} alkyl optionally substituted with one or more halogen.
23. The compound of any one of claims 1-21, wherein R_3 and R_4 are each independently fluoro, chloro or methyl optionally substituted with one or more fluoro.
24. The compound of any one of claims 1-23, wherein n and p are each independently 1 or 2.
25. The compound of claim 24, wherein n is 1.
26. The compound of any one of claims 1-25, wherein m is 1.
27. The compound of any one of claims 1-25, wherein m is 2.
28. The compound of any one of claims 1-27, wherein the compound is a compound of Formula (IV), or a pharmaceutically acceptable salt thereof,



wherein

Y_1 is N or CR_c ;

R_c is H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

Y₂ is NR_d or CR_d'R_d'';

R_d is H, halogen, C₁₋₄ alkyl or 3-6 member heterocycloalkyl, wherein the C₁₋₄ alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

R_d' and R_d'' are each independently H, halogen, or C₁₋₄ alkyl, and each C₁₋₄ alkyl is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R₆ is H, C₁₋₅alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₈;

q is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R₈ is independently halogen.

29. The compound of claim 28, wherein Y₁ is N and Y₂ is NR_d.

30. The compound of claim 29, wherein R_d is C₁₋₄ alkyl, C₃₋₆ cycloalkyl or 3-6 member heterocycloalkyl.

31. The compound of claim 30, wherein R_d is methyl.

32. The compound of claim 30, wherein R_d is isopropyl.

33. The compound of claim 30, wherein R_d is cyclopropyl.

34. The compound of claim 30, wherein R_d is tetrahydrofuran.

35. The compound of claim 28, wherein Y₂ is CR_d'R_d''.

36. The compound of claim 35, wherein R_d'' is H.

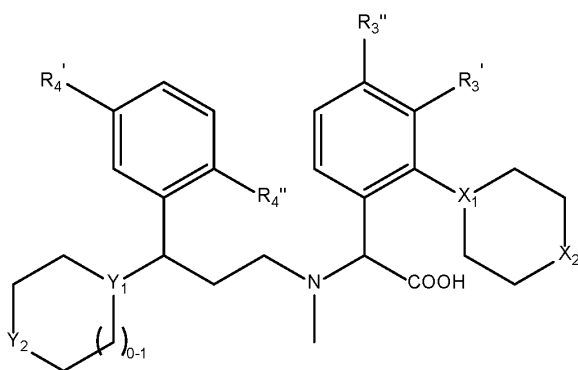
37. The compound of claim 36, wherein R_d' is fluoro.

38. The compound of claim 36, wherein R_d' is methoxy.

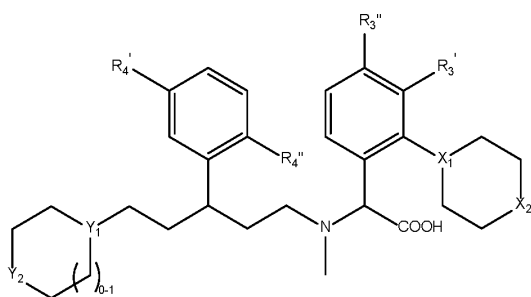
39. The compound of claim 36, wherein R_d' is methyl.

40. The compound of claim 35, wherein R_d'' is methyl.

41. The compound of claim 28, wherein the compound is a compound of Formula (II), Formula (III), or a pharmaceutically acceptable salt thereof,



(II)



(III)

wherein

R_3' , R_3'' , R_4' , and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

42. The compound of claim 41, wherein X_1 is N.

43. The compound of any one of claims 41-42, wherein X_2 is NR_b .

44. The compound of claim 43, wherein R_b is C_{1-4} alkyl optionally substituted with one or more halogen.

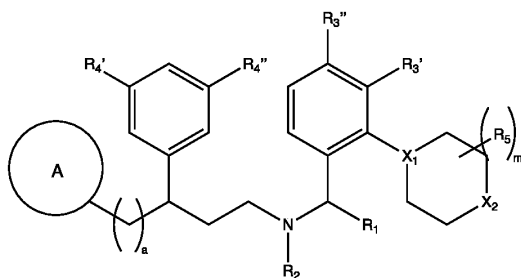
45. The compound of claim 43, wherein R_b is C_{1-4} alkyl optionally substituted with one or more fluoro.

46. The compound of claim 43, wherein R_b is $-\text{CH}_2\text{CF}_3$.

47. The compound of any one of claims 41-42, wherein X_2 is $\text{CR}_b'\text{R}_b''$.

48. The compound of claim 47, wherein R_b'' is H.

49. The compound of any one of claims 47-48, wherein R_b' is $-O-C_{1-4}$ alkyl, wherein the C_{1-4} alkyl is optionally substituted with one or more halogen.
50. The compound of claim 49, wherein R_b' is $-O-C_{1-4}$ alkyl or $-O-C_{3-6}$ cycloalkyl, wherein the C_{1-4} alkyl is optionally substituted with one or more fluoro.
51. The compound of claim 50, wherein R_b' is $-O-CF_3$.
52. The compound of claim 50, wherein R_b' is $-O-CH_3$.
53. The compound of claim 50, wherein R_b' is $-O-C_3$ cycloalkyl optionally substituted with C_{1-4} alkyl.
54. The compound of claim 50, wherein R_b' is $-O-C_3$ cycloalkyl optionally substituted with methyl.
55. The compound of claim 50, wherein R_b' is $-O-C_{1-4}$ alkyl optionally substituted with one or more fluoro.
56. The compound of any one of claims 41-55, wherein Y_1 is N.
57. The compound of claim 56, wherein Y_2 is NR_d .
58. The compound of claim 57, wherein R_d is C_{1-4} alkyl, C_{3-6} cycloalkyl or 3-6 member heterocycloalkyl.
59. The compound of claim 58, wherein R_d is methyl.
60. The compound of claim 58, wherein R_d is isopropyl.
61. The compound of claim 58, wherein R_d is cyclopropyl.
62. The compound of claim 58, wherein R_d is tetrahydrofuran.
63. The compound of claim 56, wherein Y_2 is $CR_d'R_d''$.
64. The compound of claim 63, wherein R_d'' is H.
65. The compound of claim 63, wherein R_d' is fluoro.
66. The compound of claim 63, wherein R_d' is methoxy.
67. The compound of claim 63, wherein R_d' is methyl.
68. The compound of claim 63, wherein R_d'' is methyl.
69. The compound of claim 1, wherein the compound is a compound of Formula (V)



(V),

wherein,

a is 1 or 2;

R_3' , R_3'' , R_4' , and R_4'' are each independently H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

R_5 is H, C₁₋₄alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R_7 ;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R_7 is independently halogen.

70. The compound of claim 69, wherein  is a 5- to 10-membered heterocyclyl ring structure, whose ring structures include one to four heteroatoms, optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl and C₁₋₄alkyloxy are optionally substituted with one or more halogen.

71. The compound of claim 70, wherein  is a 5- to 10-membered heterocyclyl ring structure, whose ring structures include one or two heteroatoms, optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl and C₁₋₄alkyloxy are optionally substituted with one or more halogen.

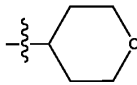
72. The compound of claim 71, wherein  is a 5- to 6-membered monocyclic heterocyclyl ring structure, whose ring structures include one or two heteroatoms, optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl and C₁₋₄alkyloxy are optionally substituted with one or more halogen.

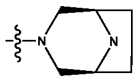
73. The compound of claim 71, wherein  is a 7- to 8-membered bicyclic bridged heterocyclyl ring structure, whose ring structures include one or two heteroatoms, optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl and C₁₋₄alkyloxy are optionally substituted with one or more halogen.

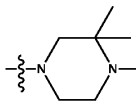
74. The compound of claim 71, wherein  is a 7- to 8-membered spirocyclic heterocyclyl ring structure, whose ring structures include one or two heteroatoms, optionally substituted with halogen, C₁₋₅ alkyl or C₁₋₄alkyloxy, wherein the C₁₋₄ alkyl and C₁₋₄alkyloxy are optionally substituted with one or more halogen.

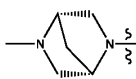
75. The compound of anyone of claim 70-74, wherein the heterocyclyl ring structure is saturated.

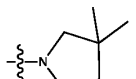
76. The compound of claim 69, wherein  is tetrahydrofuran.

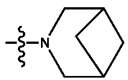
77. The compound of claim 69, wherein  is .

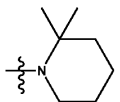
78. The compound of claim 69, wherein  is .

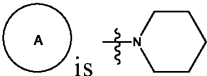
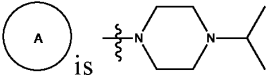
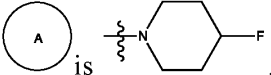
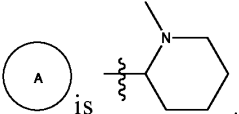
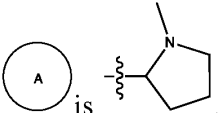
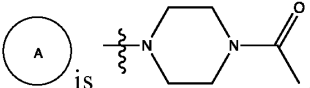
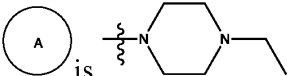
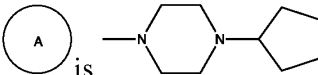
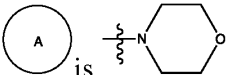
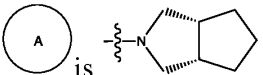
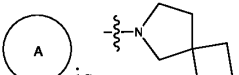
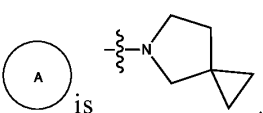
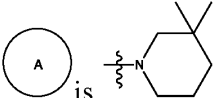
79. The compound of claim 69, wherein  is .

80. The compound of claim 69, wherein  is .

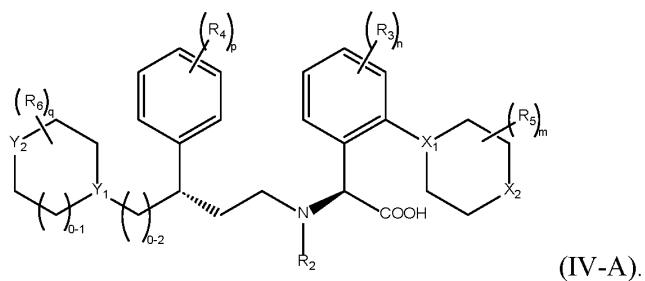
81. The compound of claim 69, wherein  is .

82. The compound of claim 69, wherein  is .

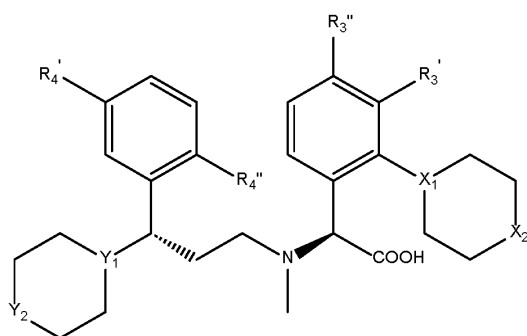
83. The compound of claim 69, wherein  is .

84. The compound of claim 69, wherein  is .
85. The compound of claim 69, wherein  is .
86. The compound of claim 69, wherein  is .
87. The compound of claim 69, wherein  is .
88. The compound of claim 69, wherein  is .
89. The compound of claim 69, wherein  is .
90. The compound of claim 69, wherein  is .
91. The compound of claim 69, wherein  is .
92. The compound of claim 69, wherein  is .
93. The compound of claim 69, wherein  is .
94. The compound of claim 69, wherein  is .
95. The compound of claim 69, wherein  is .
96. The compound of claim 69, wherein  is .

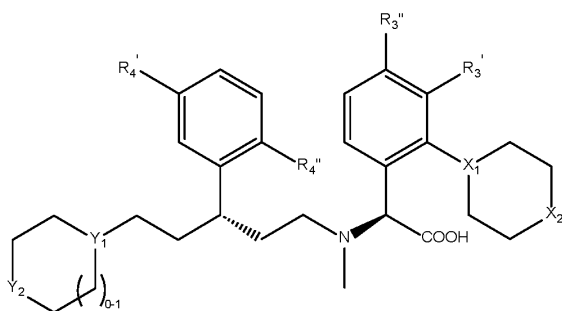
97. The compound of any one of claim 28-40, wherein the compound is a compound of Formula (IV-A), or a pharmaceutically acceptable salt thereof,



98. The compound of any one of claim 41-68, wherein the compound is a compound of Formula (II-A), Formula (III), or a pharmaceutically acceptable salt thereof,



(II-A)

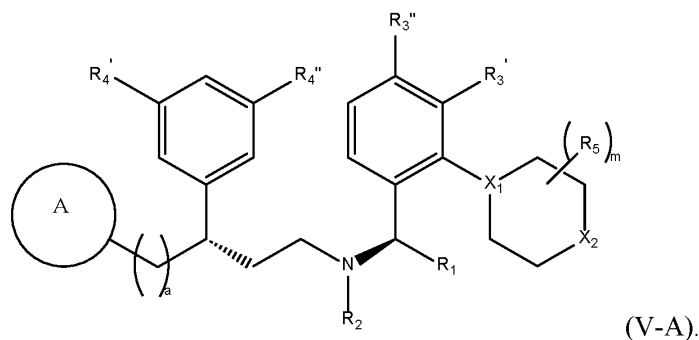


(III-A)

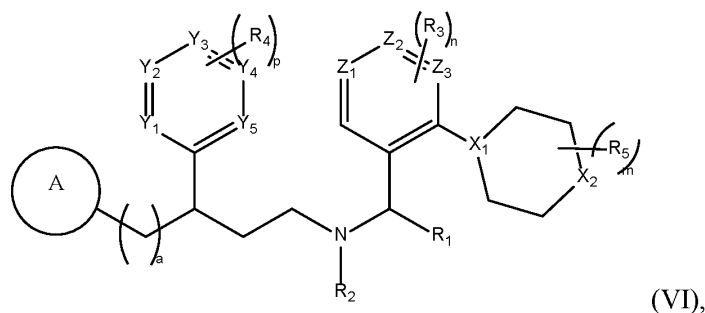
wherein

R_3' , R_3'' , R_4' , and R_4'' are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

99. The compound of any one of claim 69-96, wherein the compound is a compound of Formula (V-A), or a pharmaceutically acceptable salt thereof



100. A compound Formula (VI) or a pharmaceutically acceptable salt thereof,



wherein

Y_1 , Y_2 , Y_3 , Y_4 , Y_5 and Z_1 , Z_2 and Z_3 are each CH or N, provided that at least three of Y_1 , Y_2 , Y_3 , Y_4 , and Y_5 are CH and at least one of Z_1 , Z_2 and Z_3 is CH;



is a 3 to 12 member heterocyclyl ring structure (including monocyclic heterocyclic, bicyclic bridged, and bicyclic spirocyclic ring structures) optionally substituted with halogen, C_{1-5} alkyl or C_{1-4} alkyloxy, wherein the C_{1-4} alkyl (e.g., methyl) and C_{1-4} alkyloxy (e.g., methoxy) are optionally substituted with one or more halogen (e.g., one or more fluoro);

a is 0, 1, 2 or 3;

X_1 is N or CR_a ;

R_a is H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X_2 is NR_b or $CR_b'R_b''$;

R_b is H, halogen, C_{1-4} alkyl, C_{1-4} alkyloxy, OH, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, C_{3-6} cycloalkyloxy, or C_{1-4} alkyl- C_{3-6} cycloalkyloxy, and each C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, C_{3-6}

cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R_{b'} and R_{b''} are each independently H, halogen, C₁₋₄ alkyl, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy, and each C₁₋₄ alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, C₃₋₆cycloalkyloxy, or C₁₋₄alkyl-C₃₋₆cycloalkyloxy is optionally substituted with one or more halogen, C₁₋₄ alkyl or C₁₋₄alkyloxy;

R₁ is H or -COOR_{1b};

R_{1b} is H or C₁₋₄ alkyl;

R₂ is H or C₁₋₄ alkyl;

R₃ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

n is 0, 1, 2, 3, or 4;

R₄ is H, C₁₋₄ alkyl optionally substituted with one or more halogen, or halogen;

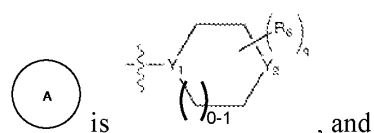
p is 0, 1, 2, 3, 4 or 5;

R₅ is H, C₁₋₄alkyl, halogen, C₁₋₄alkyloxy, OH, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, and each C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyl-OH, C₁₋₄alkyl-C₁₋₄alkyloxy, C₁₋₄alkyloxy-C₁₋₄alkyloxy, is optionally substituted with 1 to 4 R₇;

m is 0, 1, 2, 3, 4, 5, 6, 7 or 8; and

each R₇ is independently halogen.

101. The compound of claim 97, wherein



Y₁ is N or CR_c;

R_c is H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

Y₂ is NR_d or CR_{d'}R_{d''};

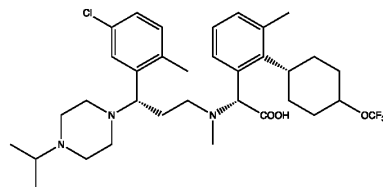
R_d is H, halogen, C₁₋₄ alkyl or 3-6 member heterocycloalkyl, wherein the C₁₋₄ alkyl or 3-6 member heterocycloalkyl is optionally substituted with one or more halogen;

R_d' and R_d'' are each independently H, halogen, or C_{1-4} alkyl, and each C_{1-4} alkyl is optionally substituted with one or more halogen, C_{1-4} alkyl or C_{1-4} alkyloxy;

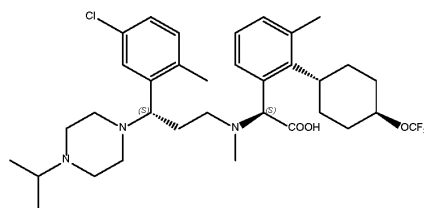
q is 0, 1, 2, 3, 4, 5, 6, 7 or 8;

R_6 is H, C_{1-5} alkyl, halogen, C_{1-4} alkyloxy, OH, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, and each C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyl-OH, C_{1-4} alkyl- C_{1-4} alkyloxy, C_{1-4} alkyloxy- C_{1-4} alkyloxy, is optionally substituted with 1 to 4 R_8 ; and each R_8 is independently halogen.

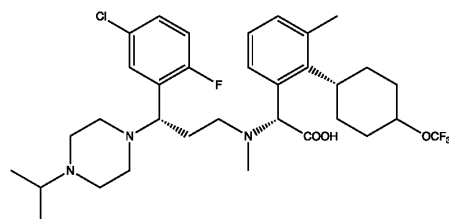
102. The compound of claim 98, wherein Y_1 is N and Y_2 is CH_2 or $C(CH_3)_2$.



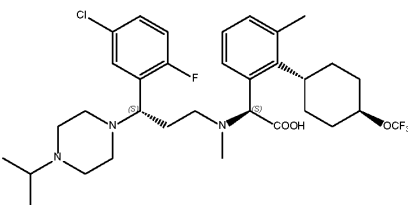
103. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.



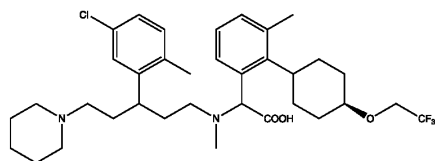
104. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

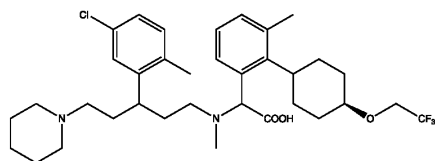


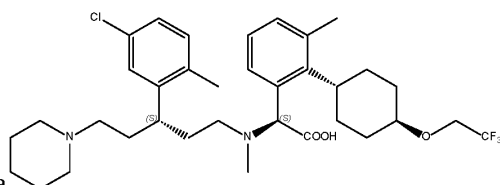
105. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

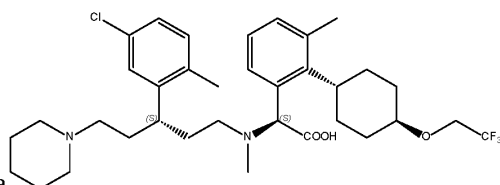


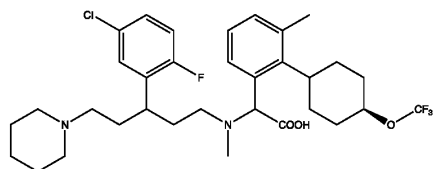
106. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

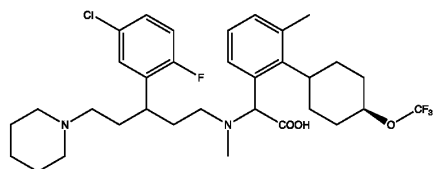


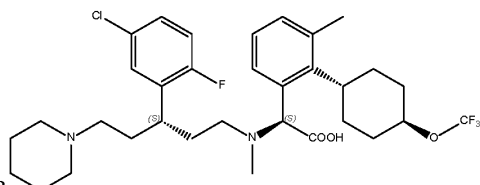
107. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

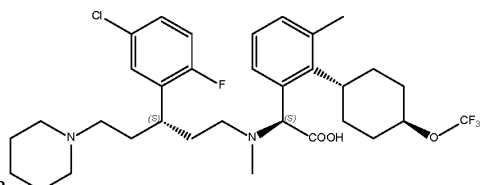


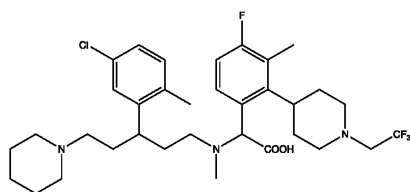
108. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

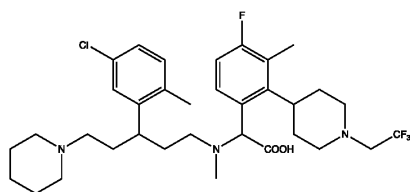


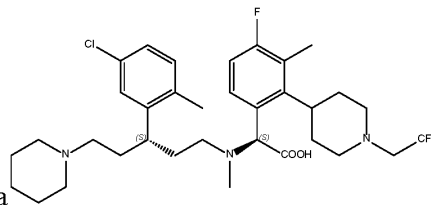
109. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

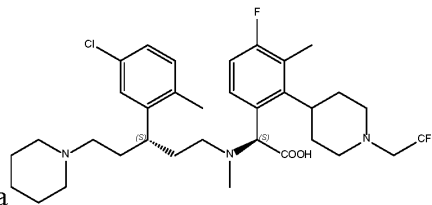


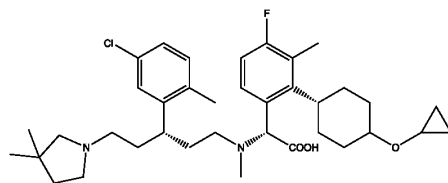
110. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

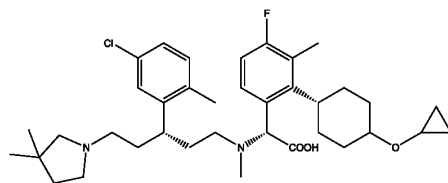


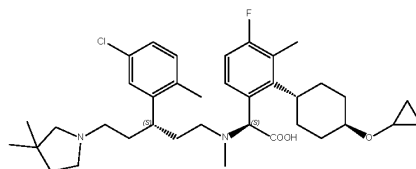
111. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

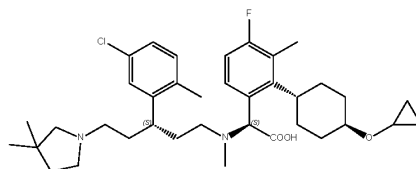


112. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

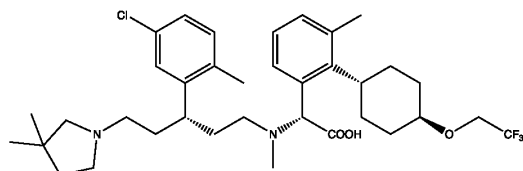


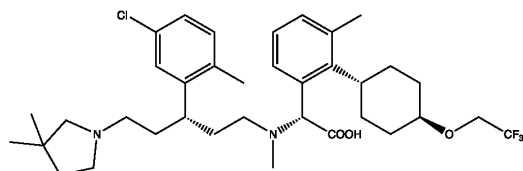
113. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

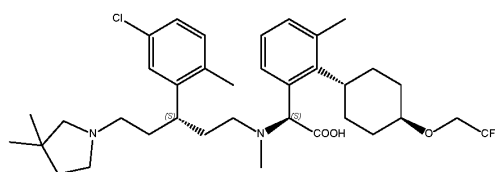


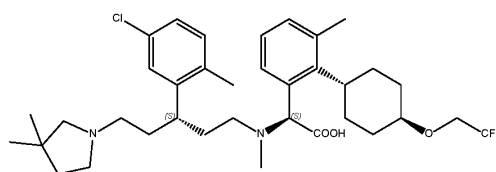
114. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.

115. A compound of the chemical formula



- , or a pharmaceutically acceptable salt thereof.



116. A compound of the chemical formula , or a pharmaceutically acceptable salt thereof.
117. A compound selected from the group consisting of the compounds in Figure 1, or a pharmaceutically acceptable salt thereof.
118. A compound selected from the group consisting of the compounds in Table 2, or a pharmaceutically acceptable salt thereof.

119. A compound selected from the group consisting of the compounds in Table 3, or a pharmaceutically acceptable salt thereof.
120. A compound selected from the group consisting of the compounds in Table 4, or a pharmaceutically acceptable salt thereof.
121. A pharmaceutical composition comprising the compound of any one of claims 1-120, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.
122. A method of treating inflammatory bowel disease, ulcerative colitis, or Crohn's disease, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-120, or a pharmaceutically acceptable salt thereof, or the pharmaceutical composition of claim 121.