

INHIBITING HUMAN INTEGRIN $\alpha 5 \beta 1$

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to, and the benefit of, U.S. provisional application No. 63/687,186, filed August 26, 2024, and U.S. provisional application No. 63/584,383, filed September 21, 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 $\alpha 5 \beta 1$ integrin. Diseases and conditions responsive to $\alpha 5 \beta 1$ integrin inhibition include, for example, hypertension such as pulmonary arterial hypertension (PAH).

BACKGROUND

[0003] Fibronectin (Fn) is an extracellular matrix protein that orchestrates complex cell adhesion and signaling through cell surface integrin receptors (Fibronectin-binding integrins (e.g., $\alpha 5 \beta 1$)) during tissue development, remodeling, and disease, such as hypertension and heart failure. Heart failure (HF) is a debilitating disease in which abnormal function of the heart leads to inadequately low perfusion of tissues and organs of the body. Hypertension is a responsible for various deleterious effects and with high morbidity and mortality including heart failure. One form of hypertension is pulmonary arterial hypertension (PAH). PAH is a rare but devastating disease, in which the normally low pulmonary arterial pressure becomes elevated due to vasoconstriction and remodeling of pulmonary vessels. Vasoconstriction and vascular remodeling increases workload on the right side of the heart, causing right heart hypertrophy, fibrosis and ultimately heart failure.

[0004] Integrins are a family of glycoprotein transmembrane receptors that mediate cell-cell and cell-matrix interactions. Integrins are heterodimers having two different chains, the alpha and beta subunits. In mammals, eighteen alpha and eight beta subunits have been described. The integrin superfamily of cell surface receptors is formed from a number of structurally and functionally related surface glycoproteins, with each receptor existing as a heterodimer of non-covalently linked α and β subunits. At least 18 different α and 8 β subunits have been identified in mammals, which are known to form more than 24 different receptors. Each integrin interacts specifically with defined extracellular ligands, including extracellular

matrix proteins such as, fibronectin, vitronectin, collagen and cell surface molecules such as VCAM, ICAM and PECAM, via linear adhesion motifs.

[0005] Integrin $\alpha 5 \beta 1$ is composed of subunits ITGA5 (integrin $\alpha 5$) and integrin $\beta 1$. Several integrins bind to fibronectin. Integrin $\alpha 5 \beta 1$ is selective for fibronectin since it requires both the 9th and 10th type II repeats of fibronectin (FNIII-9 and FNIII-10) for interaction. Expression of $\alpha 5 \beta 1$ integrin is mainly in the vasculature and connective tissue. Expression is significantly enhanced in tumor blood vessels, but also in tumor cells itself of many types of cancer, including colon, breast, ovarian, lung and brain tumors. It is further expressed to varying degrees in many cell types including fibroblasts, hematopoietic cell, immune cells, smooth muscle cells, and epithelial cells. High expression of $\alpha 5 \beta 1$ integrin has also been observed fibrotic tissue such as pulmonary fibrosis.

[0006] The integrin $\alpha 5 \beta 1$ ($\alpha 5 \beta 1$ or $\alpha 5 \beta 1$) is composed of an $\alpha 5$ ($\alpha 5$ or $\alpha 5$) and $\beta 1$ ($\beta 1$ or $\beta 1$) subunit. The $\alpha 5$ subunit forms a specific dimer with the $\beta 1$ subunit, and is widely expressed in most tissues. Integrin $\alpha 5 \beta 1$ almost exclusively mediates cell adhesion through an interaction with fibronectin, binding via the short arginine-glycine-aspartate (RGD) adhesion motif. Endothelial cells and platelets can however bind to fibrin via $\alpha 5 \beta 1$. The $\alpha 5 \beta 1$ interaction with fibronectin plays an important role in physiopathological angiogenesis and vascular integrity. Although endothelial cells express a variety of integrins, $\alpha 5 \beta 1$ is important for survival of endothelial cells on provisional matrix *in vitro*, suppressing apoptosis and promoting proliferation. $\alpha 5 \beta 1$ expression is upregulated in tumor vasculature and pulmonary hypertension patients. Consistent with a key functional role for the receptor- ligand pairing, the $\alpha 5 \beta 1$ ligand fibronectin is also upregulated in tumor tissue and during wound-healing.

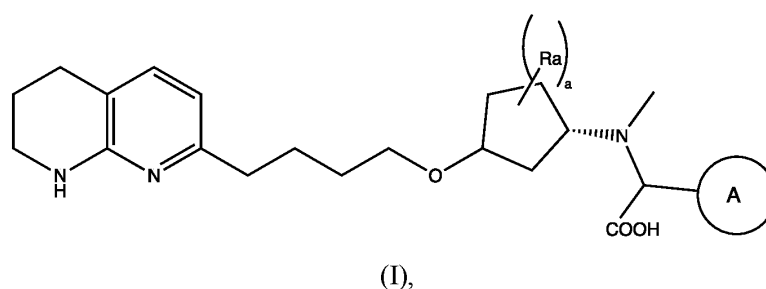
[0007] Current treatments include vasodilators targeting Ca channels or endothelin receptors. There is a need for new approaches in the treatment of pulmonary hypertension, PAH, heart failure and related diseases. Due to the limitations of current treatments for pulmonary hypertension, there remains a significant interest in and need for additional or alternative therapies for treating, stabilizing, preventing, and/or delaying pulmonary hypertension. Various processes have been developed in order to obtain more efficient and/or less toxic drugs for the treatment of pulmonary hypertension. However, these processes still present serious side effects, and the resulting drugs often exhibit short half-life and low bioavailability.

[0008] There remains a medical need for an effective and safe oral $\alpha_5\beta_1$ integrin inhibitor as an important addition to the therapeutic armamentarium for $\alpha_5\beta_1$ integrin-mediated conditions. In particular, there remains an unmet need for a small molecule designed to inhibit integrin $\alpha_5\beta_1$ 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

[0009] The present invention provides, among other things, methods, and compositions for treating a disease associated with increased expression or activity of integrin $\alpha_5\beta_1$. Many normal physiological and disease processes require cells to contact other cells and/or extracellular matrix. Cell-matrix and cell-cell adhesion is mediated through several families of proteins including integrins, selectins, cadherins, and immunoglobulins, and facilitates a variety of normal cellular functions such as proliferation, migration, differentiation, or survival. Cell adhesion is also key to a range of pathologies, and so pharmacological disruption of cell adhesion interactions can provide a mechanism for therapeutic intervention. Members of the integrin superfamily adhesion molecules play an important role in acute and chronic disease states such as cancer, inflammatory diseases, stroke, and neurodegenerative disorders. Thus, integrins represent a complex biological area.

[00010] In one aspect, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:



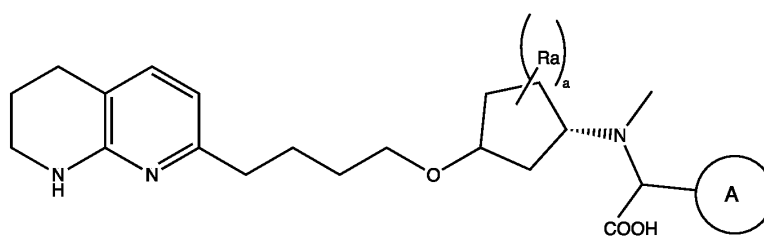
is a 6- to 12-member aryl ring structure (e.g., a phenyl) or a 3- to 19-member heterocyclyl ring structure (e.g., a 3- to 15-member heterocyclyl ring structure such as a

6-member heteroaryl), wherein  is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆ alkyloxy, a 3-8 member heterocyclyl ring structure, an aryl, or a 5- to 6-member heteroaryl, wherein the C₁₋₆ alkyl, the C₁₋₆ alkyloxy, the 3-8 member heterocyclyl ring structure, the aryl, or the 5- to 6-member heteroaryl are optionally substituted with one or more halogen, C₁₋₆ alkyloxy, or C₁₋₆ alkyl optionally substituted with one or more halogen;

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

R_a is C₁₋₆ alkyl.

[00011] In some embodiments, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



(I),

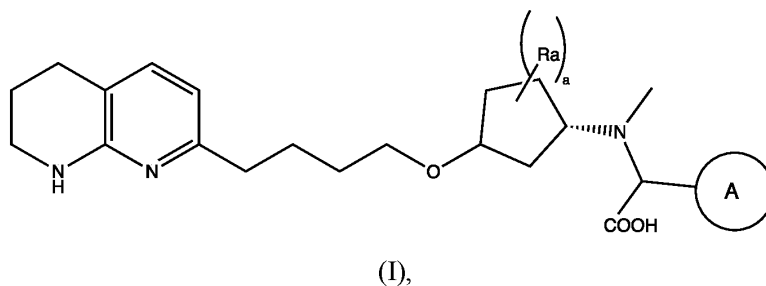
wherein:

 is a 6- to 12-member aryl ring structure (e.g., a phenyl), wherein  is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆alkyloxy, a 3-8 member heterocyclcyl ring structure, an aryl, or a 5- to 6-member heteroaryl, wherein the C₁₋₆ alkyl, the C₁₋₆alkyloxy, the 3-8 member heterocyclcyl ring structure, the aryl, or the 5- to 6-member heteroaryl are optionally substituted with one or more halogen, C₁₋₄alkyloxy, or C₁₋₆ alkyl optionally substituted with one or more halogen;

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

R_a is C₁₋₆ alkyl.

[00012] In some embodiments, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

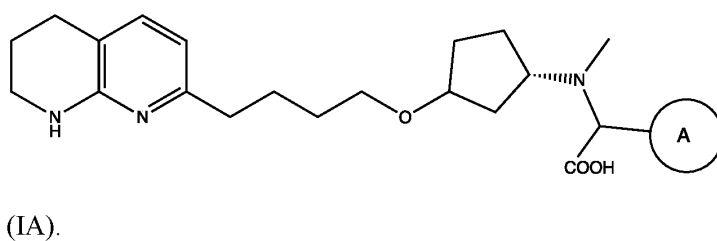
 is a 3- to 19-member heterocyclyl ring structure (e.g., a 3- to 15-member

heterocyclyl ring structure such as a 6-member heteroaryl), wherein  is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆alkyloxy, a 3-8 member heterocyclyl ring structure, an aryl, or a 5- to 6-member heteroaryl, wherein the C₁₋₆ alkyl, the C₁₋₆alkyloxy, the 3-8 member heterocyclyl ring structure, the aryl, or the 5- to 6-member heteroaryl are optionally substituted with one or more halogen, C₁₋₄alkyloxy, or C₁₋₆ alkyl optionally substituted with one or more halogen;

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

R_a is C₁₋₆ alkyl.

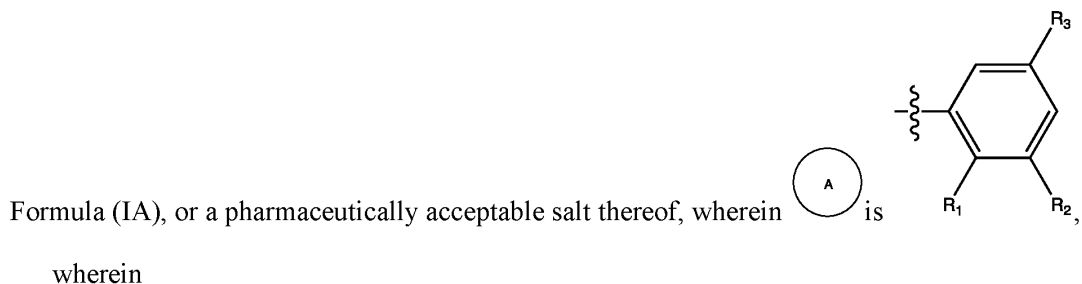
[00013] In some embodiments, the compound of Formula (I) is a compound of Formula (IA), or a pharmaceutically acceptable salt thereof:



[00014] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is phenyl or a 6-member heteroaryl.

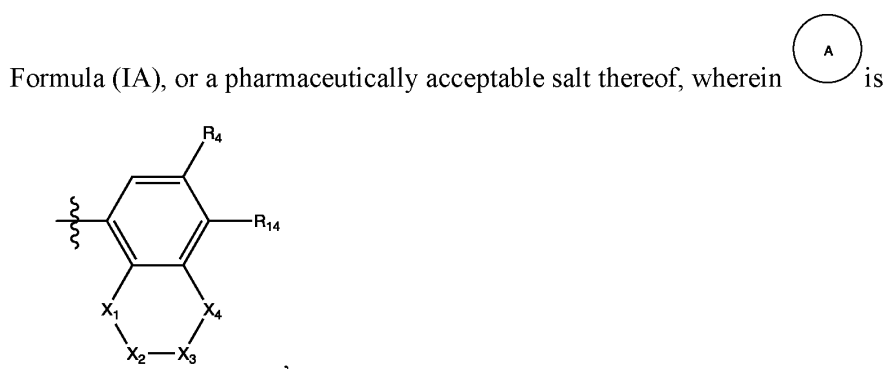
[00015] In some embodiments, the compound of Formula (I), such as a compound of



R_1 is C_{1-4} alkoxy; and R_2 is C_{1-4} alkyl optionally substituted with one or more halogen; or

 is a 9- to 19-member heterocyclyl when R_1 and R_2 are taken together to form a fused 5- to 8-member heterocycloalkyl ring, a fused 5- to 6-member heteroaryl ring, a fused 7- to 15-member spirocyclic heterocycloalkyl ring system, wherein the fused ring is optionally substituted with halogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, or a 4- to 8-member heterocycloalkyl ring, wherein the C_{1-4} alkyl, the C_{3-6} cycloalkyl, or the 4- to 8-member heterocycloalkyl ring is optionally substituted with one or more halogen or C_{1-4} alkyl optionally substituted with one or more halogen; and R_3 is C_{1-4} alkyl optionally substituted with one or more halogen. In some embodiments, R_1 is methoxy; R_2 is fluoro; and R_3 is C_{1-4} alkyl optionally substituted with one or more fluoro.

[00016] In some embodiments, the compound of Formula (I), such as a compound of



wherein

R_4 and R_{14} are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X_1 is $CR_{5a}R_{5b}$ or NR_{5c}

R_{5a} is H or a C₁₋₄ alkyl optionally substituted with one or more halogen, and R_{5b} is a C₁₋₄ alkyl or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen; or

R_{5a} and R_{5b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a spirocyclic C₃₋₆ cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 6-member spirocyclic heterocycloalkyl or a C₃₋₆ spirocyclic cycloalkyl optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{5c} is a C₁₋₄ alkyl or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen;

X₂ is CR_{6a}R_{6b}, -CH₂CR_{6a}R_{6b}, C=O, O or NR_{6c};

R_{6a} and R_{6b} are each independently H, a C₁₋₄ alkyl, a 5- to 6-member heteroaryl, a 6-member aryl, a C₃₋₇ cycloalkyl, or a 4- to 7-member heterocycloalkyl, wherein the C₁₋₄ alkyl, the 5- to 6-member heteroaryl, the 6-member aryl, the C₃₋₈ cycloalkyl, or the 4- to 7-member heterocycloalkyl is each optionally substituted with one or more halogen or C₁₋₄ alkyl;

R_{6c} is C₁₋₄ alkyl optionally substituted with one or more halogen

X₃ is a direct bond, CR_{7a}R_{7b}, O or NR_{7c};

R_{7a} and R_{7b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{7c} is a C₁₋₄ alkyl optionally substituted with one or more halogen;

X₄ is CR_{8a}R_{8b} or NR_{8c}

R_{8a} is H and R_{8b} is halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen;

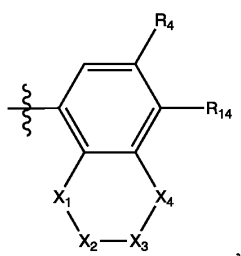
R_{8a} and R_{8b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a C₃₋₆ cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 8-member spirocyclic heterocycloalkyl or a C₃₋₇ spirocyclic cycloalkyl optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen; and

R_{8c} is H, C_{1-4} alkyl, a 4- to 8-member heterocycloalkyl, or a C_{3-6} cycloalkyl, wherein the C_{1-4} alkyl, the 4- to 8-member heterocycloalkyl, or the C_{3-6} cycloalkyl is optionally substituted with one or more halogen;

provided that no two of both X_2 and X_3 comprise O or N heteroatoms and no two of X_3 and X_4 comprise O or N heteroatoms.

[00017] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



R_4 and R_{14} are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X_1 is $CR_{5a}R_{5b}$ or NR_{5c}

R_{5a} is H or a C_{1-4} alkyl optionally substituted with one or more halogen, and R_{5b} is a C_{1-4} alkyl or a C_{3-6} cycloalkyl, wherein the C_{1-4} alkyl or the C_{3-6} cycloalkyl is optionally substituted with one or more halogen; or

R_{5a} and R_{5b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a spirocyclic C_{3-6} cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C_{3-6} cycloalkyl is optionally substituted with C_{1-4} alkyl optionally substituted with one or more halogen, a 4- to 6-member spirocyclic heterocycloalkyl or a C_{3-6} spirocyclic cycloalkyl optionally substituted with C_{1-4} alkyl optionally substituted with one or more halogen;

R_{5c} is a C_{1-4} alkyl or a C_{3-6} cycloalkyl, wherein the C_{1-4} alkyl or the C_{3-6} cycloalkyl is optionally substituted with one or more halogen;

X_2 is $CR_{6a}R_{6b}$, $-CH_2CR_{6a}R_{6b}$, $C=O$, O or NR_{6c} ;

R_{6a} and R_{6b} are each independently H, a C_{1-4} alkyl, a 5- to 6-member heteroaryl, a 6-member aryl, a C_{3-7} cycloalkyl, or a 4- to 7-member heterocycloalkyl, wherein the C_{1-4} alkyl, the 5- to 6-member heteroaryl, the 6-member aryl, the C_{3-8} cycloalkyl, or the 4- to 7-

member heterocycloalkyl is each optionally substituted with one or more halogen or C₁₋₄ alkyl;

R_{6c} is C₁₋₄ alkyl optionally substituted with one or more halogen

X₃ is a direct bond, CR_{7a}R_{7b}, O or NR_{7c};

R_{7a} and R_{7b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{7c} is a C₁₋₄ alkyl optionally substituted with one or more halogen;

X₄ is CR_{8a}R_{8b} or NR_{8c}

R_{8a} is H and R_{8b} is halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{8a} and R_{8b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a C₃₋₆ cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 8-member spirocyclic heterocycloalkyl or a C₃₋₇ spirocyclic cycloalkyl optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen; and

R_{8c} is H, C₁₋₄ alkyl, a 4- to 8-member heterocycloalkyl, or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl, the 4- to 8-member heterocycloalkyl, or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen;

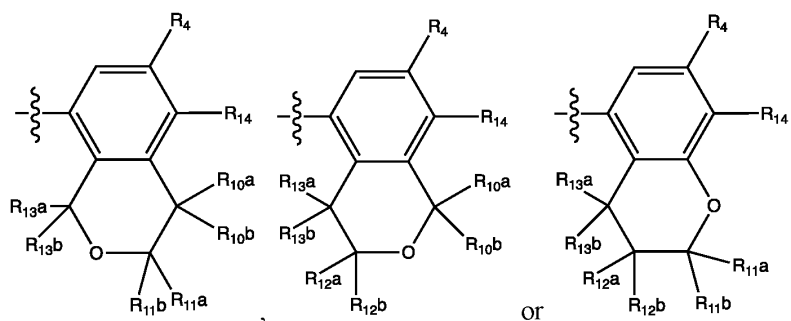
provided that no two of both X₂ and X₃ comprise O or N heteroatoms and no two of X₃ and X₄ comprise O or N heteroatoms.

[00018] In some embodiments, R₁ is methoxy; R₂ is fluoro; and R₃ is C₁₋₄ alkyl optionally substituted with one or more fluoro. In some embodiments, R₁₄ is H; and X₁ is CR_{5a}R_{5b} and R_{5a} is H, and R_{5b} is methyl or cyclopropyl. In some embodiments, R₄ is H, fluoro, or methyl; X₁ is CR_{5a}R_{5b} and R_{5a} is H, and R_{5b} is methyl; X₂ is O and X₃ is CR_{7a}R_{7b} and R_{7a} and R_{7b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen; or X₃ is O and X₂ is CR_{6a}R_{7b} and R_{6a} and R_{6b} are each independently H; and X₄ is CR_{8a}R_{8b} and R_{8a} and R_{8b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen, or R_{8a} and R_{8b} together form a 4- to 7-member heterocycloalkyl ring or a C₃₋₇ cycloalkyl ring, wherein the 4- to 7-member heterocycloalkyl or the C₃₋₇ cycloalkyl is optionally substituted with halogen, C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 7-member

spirocyclic heterocycloalkyl, or a C₃₋₇ spirocyclic cycloalkyl, optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen.

[00019] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



wherein

R_{10a} and R_{10b} are each independently H, halogen, or a C₁₋₄ alkyl optionally substituted with one or more halogen; or R_{10a} and R_{10b} together form a spirocyclic C₃₋₆ cycloalkyl or a spirocyclic 6-member heterocycloalkyl;

R_{11a} and R_{11b} are each independently H, halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{12a} and R_{12b} are each independently H, halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{13a} is methyl, ethyl, or cyclopropyl;

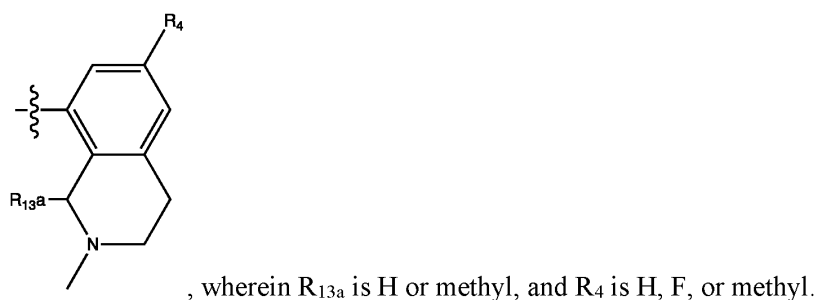
R_{13b} is H; and

R₁₄ is H, halogen, or a C₁₋₄ alkyl optionally substituted with one or more halogen.

[00020] In some embodiments, R_{10a} and R_{10b} are each independently H or methyl; R_{11a} and R_{11b} are each independently H, methyl, or ethyl; R_{12a} and R_{12b} are each independently H or methyl; R_{13a} is methyl, ethyl, or cyclopropyl; R_{13b} is H; and R₁₄ is H, fluoro, or methyl. In some embodiments, R₄ is H or fluoro; R_{13a} is methyl, ethyl, or cyclopropyl; and R₁₄ is H. In some embodiments, X₂ is NR_{6c} and R_{6c} is C₁₋₄ alkyl.

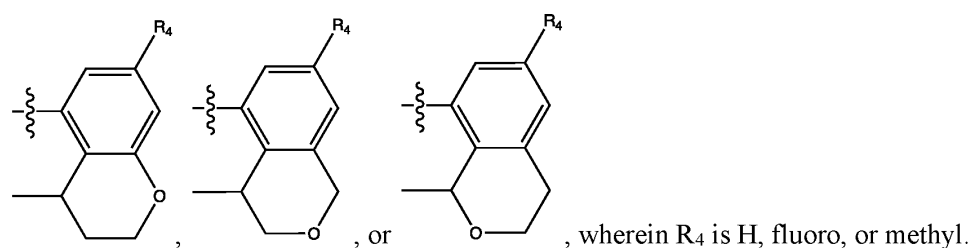
[00021] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



[00022] In some embodiments, the compound of Formula (I), such as a compound of

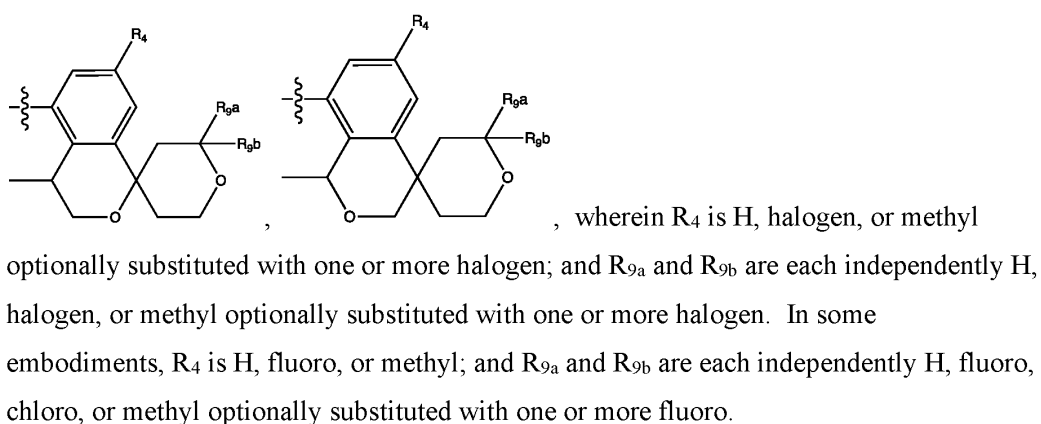
Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



In some embodiments, wherein R_{10a}, R_{10b}, and R_{11a} are each H or methyl. In some embodiments, wherein R_{11b} is H, methyl, or ethyl.

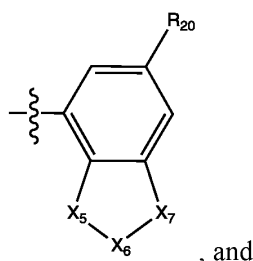
[00023] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



[00024] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



wherein

R_{20} is H, halogen, a C_{1-4} alkyl or a C_{1-4} alkoxy, wherein the C_{1-4} alkyl and the C_{1-4} alkoxy are each optionally substituted with one or more halogen;

X_5 is $CR_{25a}R_{25b}$ or NR_{25c} ;

R_{25a} and R_{25b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or alkoxy; or R_{25a} and R_{25b} together form a C_{3-6} cycloalkyl ring or a 4- to 6-member heterocyclyl ring, each optionally substituted with halogen, C_{1-4} alkyl, a spirocyclic C_{3-6} cycloalkyl, or a spirocyclic 4- to 6-member heterocyclyl ring, wherein the C_{1-4} alkyl, the spirocyclic C_{3-6} cycloalkyl or the spirocyclic 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen or C_{1-4} alkyl;

R_{25c} is C_{1-4} alkyl, a 5-6 member heteroaryl, or a C_6 aryl, wherein the C_{1-4} alkyl, the 5-6 member heteroaryl, or the C_6 aryl is optionally substituted with one or more halogen or C_{1-4} alkoxy;

X_6 is $CR_{26a}R_{26b}$ or $C=O$;

R_{26a} and R_{26b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkyl;

X_7 is $CR_{27a}R_{27b}$ or NR_{27c} ;

R_{27a} and R_{27b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or alkoxy; or R_{27a} and R_{27b} together form a C_{3-6} cycloalkyl ring or a 4- to 6-member heterocyclyl ring, wherein the C_{3-6} cycloalkyl ring or the 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen, one or more C_{1-4} alkyl, a spirocyclic C_{3-6} cycloalkyl or a spirocyclic 4 to 6 member heterocyclyl ring, wherein the C_{1-4}

alkyl, the spirocyclic C₃₋₆ cycloalkyl, or the spirocyclic 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen or C₁₋₄ alkyl; and

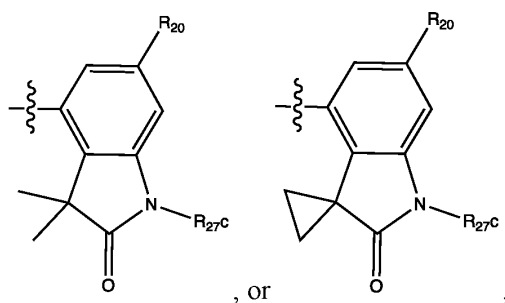
R_{27c} is H, a C₁₋₄ alkyl, a C₃₋₆ cycloalkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, a 5-6 member heteroaryl, or a C₆ aryl, wherein the C₁₋₄ alkyl, the C₃₋₆ cycloalkyl, the 4- to 6-member heterocycloalkyl, the 5- to 11-member spirocyclic heterocycloalkyl, the 5-6 member heteroaryl, or the C₆ aryl is optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

provided that only one of X₅ and X₇ comprise a N heteroatom.

[00025] In some embodiments, R₂₀ is H, halogen, a C₁₋₄ alkyl, or a C₁₋₄ alkoxy, wherein the C₁₋₄ alkyl and the C₁₋₄ alkoxy is optionally substituted with one or more halogen; X₅ is CR_{25a}R_{25b}; R_{25a} and R_{25b} are each independently methyl; or R_{25a} and R_{25b} together form a cyclopropyl; X₆ is C=O; R_{26a} and R_{26b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen or C₁₋₄ alkyl; X₇ is NR_{27c}; and R_{27c} is a C₁₋₄ alkyl, a C₃₋₆ cycloalkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, a 5-6 member heteroaryl, or a C₆ aryl, wherein the C₁₋₄ alkyl, the C₃₋₆ cycloalkyl, the 4- to 6-member heterocycloalkyl, the 5- to 11-member spirocyclic heterocycloalkyl, the 5-6 member heteroaryl, or the C₆ aryl is optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen. In some embodiments, R_{27c} is a C₁₋₄ alkyl. In some embodiments, R_{27c} is a 5-member heteroaryl. In some embodiments, R_{27c} is a C₃₋₆ cycloalkyl optionally substituted with one or more halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen. In some embodiments, R_{27c} is a C₁₋₄ alkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, wherein the C₁₋₄ alkyl, the 4- to 7-member heterocycloalkyl, and the 5- to 11-member spirocyclic heterocycloalkyl is optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen.

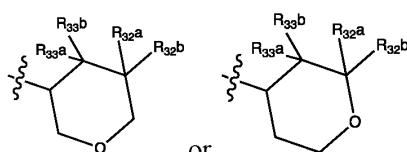
[00026] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is

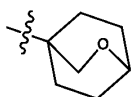


wherein R_{20} is H, fluoro, methyl, ethyl, methoxy, $-\text{CH}_2\text{-O-CH}_3$, or $-\text{CF}_3$.

In some embodiments, R_{27c} is a tetrahydropyran optionally substituted by one or more methyl or



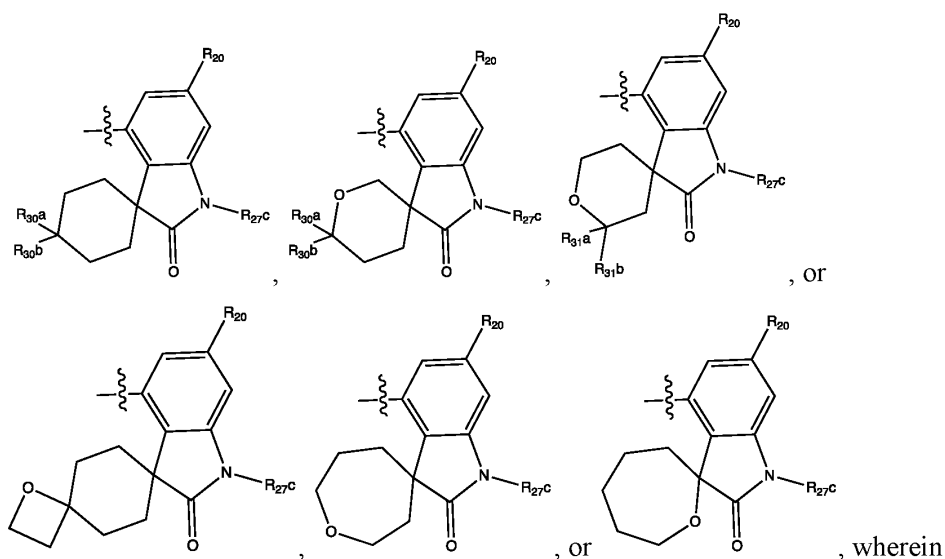
fluoro. In some embodiments, R_{27c} is , wherein R_{32a} , R_{32b} , R_{33a} and R_{33b} are each independently H, methyl, or fluoro; or one of R_{32a} and R_{32b} or R_{33a} and R_{33b} together form a spirocyclic C_{3-6} cycloalkyl or a spirocyclic 3- to 6-member heterocyclic



ring. In some embodiments, R_{27c} is

[00027] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



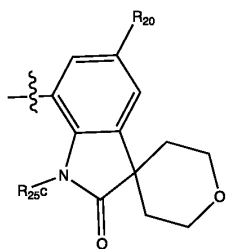
R_{30a} , R_{30b} , R_{31a} , and R_{31b} are each independently H, fluoro, or methyl;

R_{20} is H, fluoro, methyl, ethyl, methoxy, $-\text{CH}_2\text{-O-CH}_3$, or $-\text{CF}_3$; and

R_{27c} is methyl. In some embodiments, the compound is a compound of Formula (I), wherein R_{27c} is a C_{1-4} alkyl.

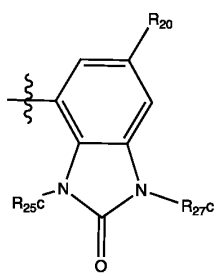
[00028] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



[00029] In some embodiments, the compound of Formula (I), such as a compound of

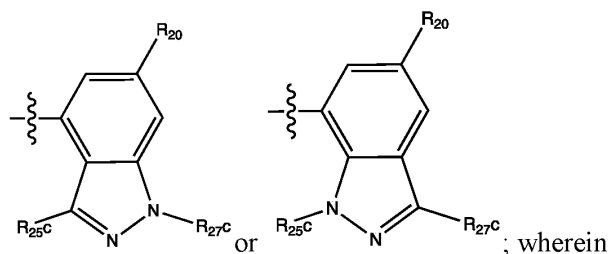
Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



wherein R_{20} is H, halogen, a C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy, a C_{1-4} alkyl optionally substituted with a 4- to 6-member heterocyclyl or one or more halogen. In some embodiments, R_{25c} is a C_{1-4} alkyl; and R_{27c} is a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkoxy, a C_{3-6} cycloalkyl or a 4- to 6-member heterocycloalkyl, wherein the C_{3-6} cycloalkyl or the 4- to 6-member heterocycloalkyl is optionally substituted with a C_{1-4} alkyl optionally substituted with one or more halogen. In some embodiments, R_{27c} is a C_{1-4} alkyl; and R_{25c} is a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkoxy, a C_{3-6} cycloalkyl or a 4- to 6-member heterocycloalkyl, wherein the C_{3-6} cycloalkyl or the 4- to 6-member heterocycloalkyl is optionally substituted with a C_{1-4} alkyl optionally substituted with one or more halogen. In some embodiments, R_{20} is H or methyl.

[00030] In some embodiments, the compound of Formula (I), such as a compound of

Formula (IA), or a pharmaceutically acceptable salt thereof, wherein  is



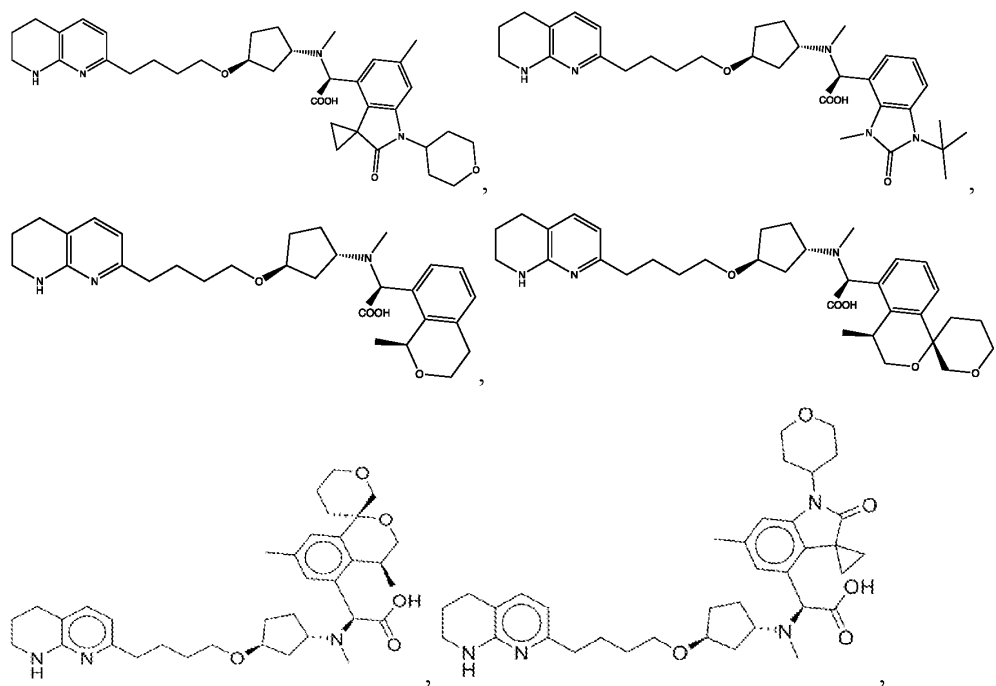
; wherein

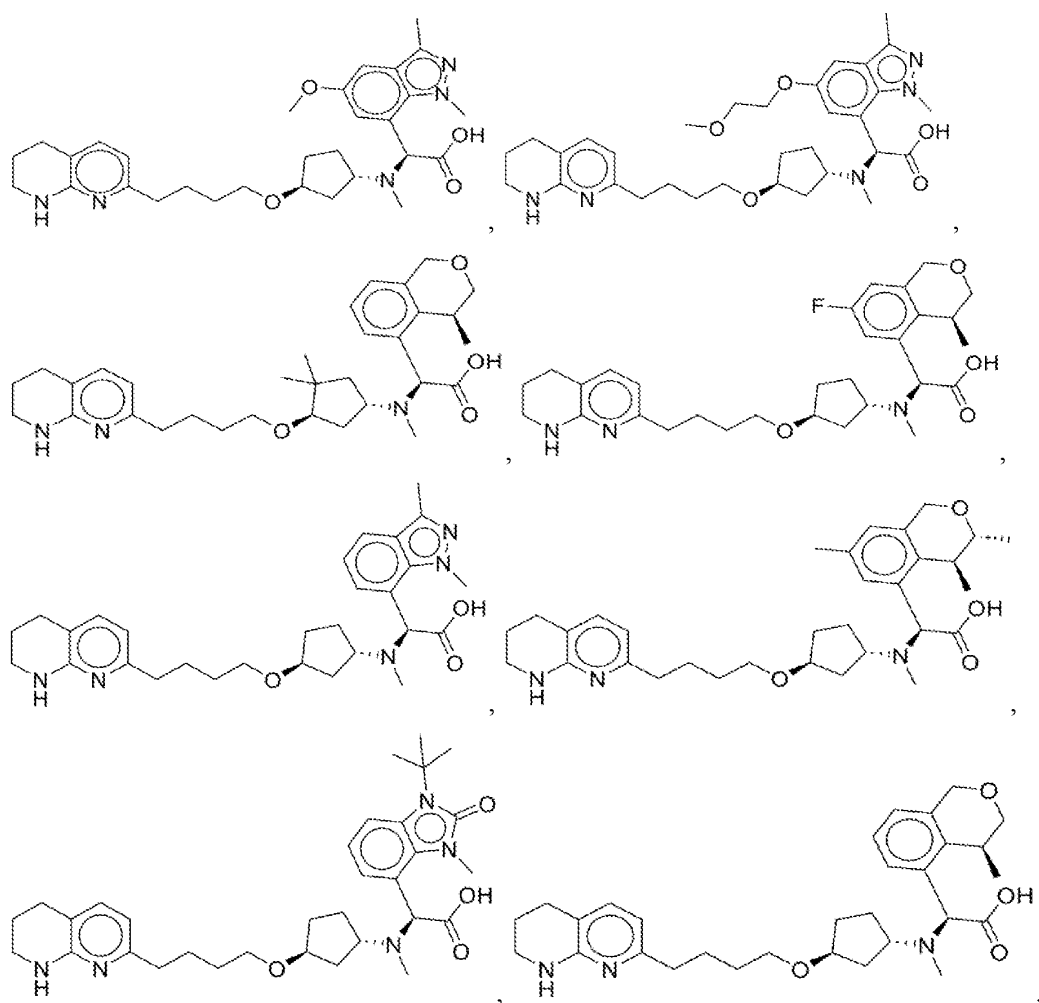
R_{20} is H, halogen, a C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy, C_{1-4} alkyl optionally substituted with a 4- to 6-member heterocyclyl or one or more halogen;

R_{25c} is a C_{1-4} alkyl; and

R_{27c} is a 4- to 6-member heterocyclyl or a C_{3-6} cycloalkyl, wherein the 4- to 6-member heterocyclyl or the C_{3-6} cycloalkyl is optionally substituted with C_{1-4} alkyl.

[00031] In some embodiments, the compound of Formula (I), is a compound selected from the group consisting of:





or a pharmaceutically acceptable salt thereof.

BRIEF DESCRIPTION OF THE FIGURES

[00032] Figure 1 is a table of compounds disclosed herein.

DETAILED DESCRIPTION

[00033] Compounds of Formula (I) are small-molecule integrin therapeutics targeting $\alpha 5\beta 1$ that can be administered to treat patients with diseases and conditions that are responsive to $\alpha 5\beta 1$ integrin inhibition.

[00034] The present invention provides methods and compositions for treating a disease associated with increased expression or activity of integrin $\alpha 5\beta 1$, comprising administering an integrin $\alpha 5\beta 1$ inhibitor. In some embodiments, the disease is characterized by the World Health

Organization (WHO) group. In some embodiments, the disease is pulmonary hypertension, WHO Group 1 pulmonary hypertension or pulmonary arterial hypertension (PAH), WHO Group 2 pulmonary hypertension, WHO Group 3 pulmonary hypertension, WHO Group 4 pulmonary hypertension, and WHO Group 5 pulmonary hypertension. In some embodiments, the disease is characterized by the World Health Organization (WHO) class system. In some embodiments, the disease is characterized by WHO functional class based on cardiac function. In some embodiments, the disease is pulmonary hypertension, WHO Class I pulmonary hypertension or pulmonary arterial hypertension (PAH), WHO Class II pulmonary hypertension, WHO Class III pulmonary hypertension, WHO Class IV pulmonary hypertension. In some embodiments, the disease associated with increased expression or activity of integrin $\alpha 5 \beta 1$ is heart failure or right ventricle failure.

[00035] The inhibition of integrin $\alpha 5 \beta 1$ by blocking the activity of $\alpha 5 \beta 1$ or inhibition of $\alpha 5 \beta 1$ fibronectin binding is effective in preventing and treating pulmonary hypertension, PAH, heart failure and right ventricle failure. The present invention provides a variety of compounds (e.g., small molecule compounds and antibodies) that inhibit that interaction. The compounds are referred to generically herein as “integrin $\alpha 5 \beta 1$ inhibitors”.

Exemplary Compounds of the Invention

[00036] This disclosure relates to novel chemical compounds and methods useful for inhibiting $\alpha 5 \beta 1$ integrin.

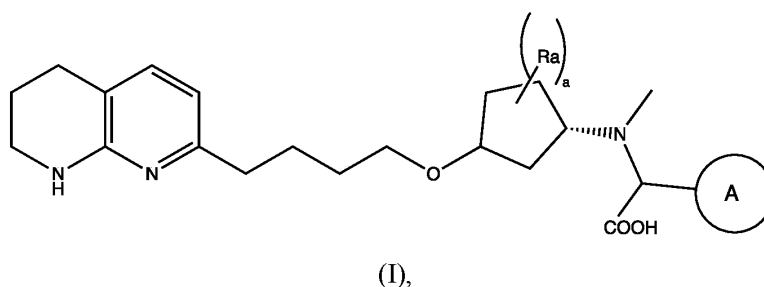
[00037] Exemplary formulas and compounds are described herein. Also provided herein are exemplary embodiments of structural features which may be present in any formula described herein. Any exemplary embodiment of a structural feature may occur in combination with any other exemplary structural feature 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.

Compounds of Formula (I)

[00038] In some embodiments, the integrin $\alpha 5 \beta 1$ inhibitor is a small molecule compound that binds integrin $\alpha 5 \beta 1$. In some embodiments, the integrin $\alpha 5 \beta 1$ inhibitor is a small molecule compound that specifically binds integrin $\alpha 5$. In some embodiments, the integrin $\alpha 5 \beta 1$ inhibitor is a small molecule compound that specifically binds integrin $\beta 1$. In some

embodiments, the integrin $\alpha 5 \beta 1$ inhibitor is a small molecule compound that specifically binds integrin $\alpha 5 \beta 1$. In some embodiments, the integrin $\alpha 5 \beta 1$ inhibitor is a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

[00039] In one aspect, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

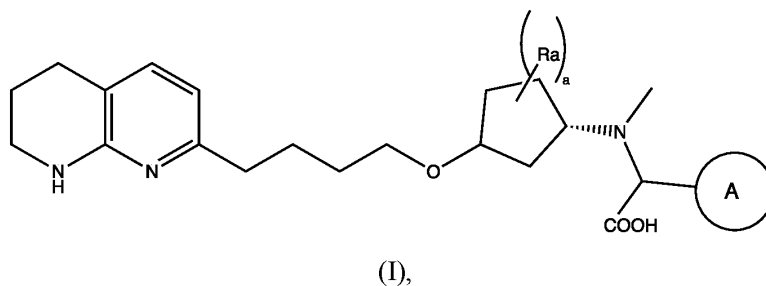
 is a 6- to 12-member aryl ring structure (e.g., phenyl) or a 3- to 19-member heterocyclyl ring structure (e.g., a 3- to 15-member heterocyclyl ring structure such as a

6-member heteroaryl), wherein  is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆alkyloxy, a 3-8 member heterocyclyl ring structure, an aryl, or a 5- to 6-member heteroaryl, wherein the C₁₋₆ alkyl, the C₁₋₆alkyloxy, the 3-8 member heterocyclyl ring structure, the aryl, or the 5- to 6-member heteroaryl are optionally substituted with one or more halogen, C₁₋₆alkyloxy, or C₁₋₆ alkyl optionally substituted with one or more halogen;

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

R_a is C₁₋₆ alkyl.

[00040] In some embodiments, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



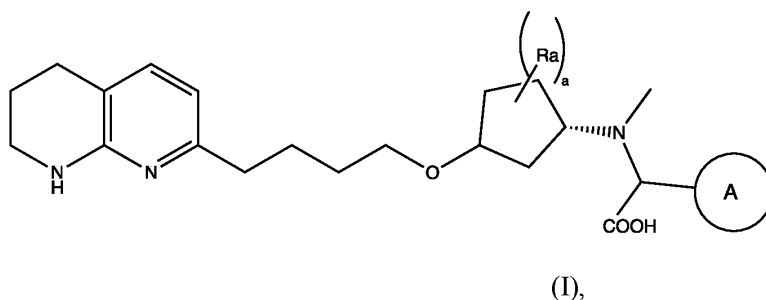
wherein:

 is a 6- to 12-member aryl ring structure (e.g., a phenyl), wherein  is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆alkyloxy, a 3-8 member heterocyclyl ring structure, an aryl, or a 5- to 6-member heteroaryl, wherein the C₁₋₆ alkyl, the C₁₋₆alkyloxy, the 3-8 member heterocyclyl ring structure, the aryl, or the 5- to 6-member heteroaryl are optionally substituted with one or more halogen, C₁₋₄alkyloxy, or C₁₋₆ alkyl optionally substituted with one or more halogen;

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

R_a is C₁₋₆ alkyl.

[00041] In some embodiments, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

 is a 3- to 19-member heterocyclyl ring structure (e.g., a 3- to 15-member heterocyclyl ring structure such as a 6-member heteroaryl), wherein  is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆alkyloxy, a 3-8 member heterocyclyl ring structure, an

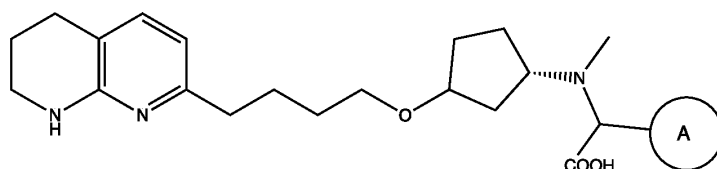
aryl, or a 5- to 6-member heteroaryl, wherein the C₁₋₆ alkyl, the C₁₋₆alkyloxy, the 3-8 member heterocyclyl ring structure, the aryl, or the 5- to 6-member heteroaryl are optionally substituted with one or more halogen, C₁₋₄alkyloxy, or C₁₋₆ alkyl optionally substituted with one or more halogen;

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

R_a is C₁₋₆ alkyl.

[00042] In some embodiments,  is a 3- to 15-member heterocycle ring structure.

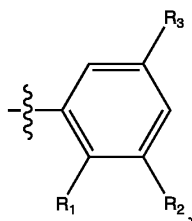
[00043] In some embodiments, the compound is a compound of Formula (I-A), or a pharmaceutically acceptable salt thereof.



(IA)

[00044] In some embodiments, the compound is a compound of Formula (I), wherein  is phenyl or a 6-member heteroaryl.

[00045] In some embodiments, the compound is a compound of Formula (I),  is



wherein

R₁ is a C₁₋₄ alkoxy; and R₂ is a C₁₋₄ alkyl optionally substituted with one or more halogen; or

 is a 9- to 19-member heterocyclyl when R₁ and R₂ are taken together to form a fused 5- to 8-member heterocycloalkyl ring, a fused 5- to 6-member heteroaryl ring,

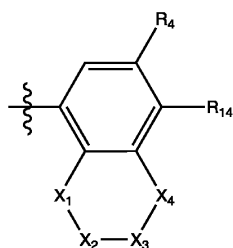
or a fused 7- to 15-member spirocyclic heterocycloalkyl ring system, wherein the fused ring is optionally substituted with halogen, C₁₋₄ alkyl, C₃₋₆ cycloalkyl, or a 4- to 8-member heterocycloalkyl ring, wherein the C₁₋₄ alkyl, the C₃₋₆ cycloalkyl, or the 4- to 8-member heterocycloalkyl ring is optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen; R₃ is C₁₋₄ alkyl optionally substituted with one or more halogen.

[00046] In some embodiments, the compound is a compound of Formula (I), wherein R₁ is methoxy; R₂ is fluoro; and R₃ is C₁₋₄ alkyl optionally substituted with one or more fluoro.

[00047] In some embodiments, the compound is a compound of Formula (I), wherein



is



, wherein R₄ and R₁₄ are each independently H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen; X₁ is CR_{5a}R_{5b} or NR_{5c}; R_{5a} is H or C₁₋₄ alkyl optionally substituted with one or more halogen, and R_{5b} is C₁₋₄ alkyl or C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl or C₃₋₆ cycloalkyl is optionally substituted with one or more halogen; or R_{5a} and R_{5b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a spirocyclic C₃₋₆ cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 6-member spirocyclic heterocycloalkyl, or a C₃₋₆ spirocyclic cycloalkyl optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen; R_{5c} is C₁₋₄ alkyl or C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl or C₃₋₆ cycloalkyl is optionally substituted with one or more halogen; X₂ is CR_{6a}R_{6b}, -CH₂CR_{6a}R_{6b}, C=O, O or NR_{6c}; R_{6a} and R_{6b} are each independently H, C₁₋₄ alkyl, a 5- to 6-member heteroaryl, a 6-member aryl, a C₃₋₇ cycloalkyl, or a 4- to 7-member heterocycloalkyl, wherein the C₁₋₄ alkyl, the 5- to 6-member heteroaryl, the 6-member aryl, the C₃₋₈ cycloalkyl, or the 4- to 7-member heterocycloalkyl is each optionally substituted with one or more halogen or C₁₋₄ alkyl; R_{6c} is C₁₋₄ alkyl optionally substituted with one or more halogen; X₃ is a direct bond, CR_{7a}R_{7b}, O, or NR_{7c}; R_{7a} and R_{7b} are each independently H or C₁₋₄ alkyl optionally substituted with one or more halogen; R_{7c} is C₁₋₄ alkyl optionally substituted with

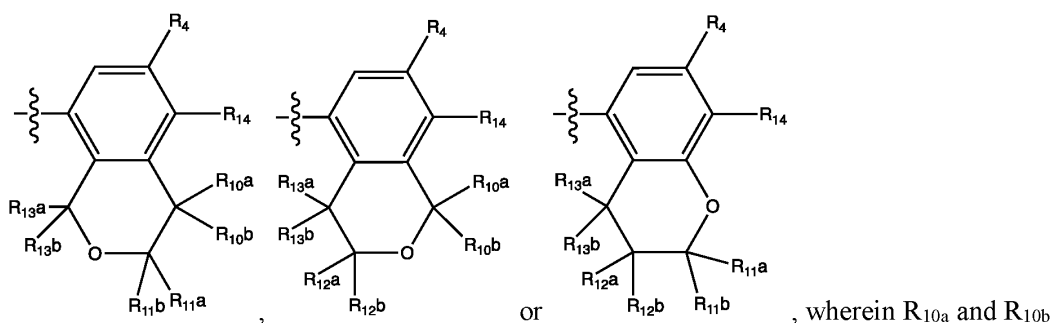
one or more halogen; X_4 is $CR_{8a}R_{8b}$ or NR_{8c} ; R_{8a} is H and R_{8b} is halogen or C_{1-4} alkyl optionally substituted with one or more halogen; R_{8a} and R_{8b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a C_{3-6} cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C_{3-6} cycloalkyl is optionally substituted with C_{1-4} alkyl optionally substituted with one or more halogen, a 4- to 8-member spirocyclic heterocycloalkyl or a C_{3-7} spirocyclic cycloalkyl optionally substituted with C_{1-4} alkyl optionally substituted with one or more halogen; and R_{8c} is H, C_{1-4} alkyl, a 4- to 8-member heterocycloalkyl, or C_{3-6} cycloalkyl, wherein the C_{1-4} alkyl, the 4- to 8-member heterocycloalkyl, or the C_{3-6} cycloalkyl is optionally substituted with one or more halogen; provided that no two of both X_2 and X_3 comprise O or N heteroatoms and no two of X_3 and X_4 comprise O or N heteroatoms.

[00048] In some embodiments, the compound is a compound of Formula (I), wherein R_{14} is H; X_1 is $CR_{5a}R_{5b}$; R_{5a} is H, and R_{5b} is methyl or cyclopropyl.

[00049] In some embodiments, the compound is a compound of Formula (I), wherein R_4 is H, fluoro, or methyl; X_1 is $CR_{5a}R_{5b}$; R_{5a} is H, R_{5b} is methyl; X_2 is O and X_3 is $CR_{7a}R_{7b}$ and R_{7a} and R_{7b} are each independently H or C_{1-4} alkyl optionally substituted with one or more halogen; or X_3 is O and X_2 is $CR_{6a}R_{6b}$ and R_{6a} and R_{6b} are each independently H; and X_4 is $CR_{8a}R_{8b}$ and R_{8a} and R_{8b} are each independently H or C_{1-4} alkyl optionally substituted with one or more halogen, or R_{8a} and R_{8b} together form a 4- to 7-member heterocycloalkyl ring or a C_{3-7} cycloalkyl ring, wherein the 4- to 7-member heterocycloalkyl or the C_{3-7} cycloalkyl is optionally substituted with halogen, C_{1-4} alkyl optionally substituted with one or more halogen, a 4- to 7-member spirocyclic heterocycloalkyl or a C_{3-7} spirocyclic cycloalkyl optionally substituted with C_{1-4} alkyl optionally substituted with one or more halogen.

[00050] In some embodiments, the compound is a compound of Formula (I), wherein





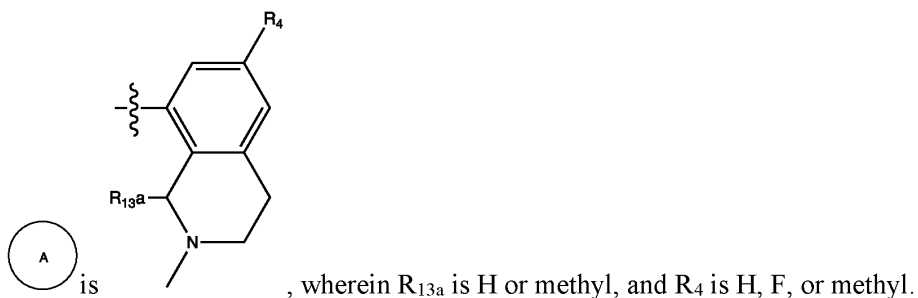
are each independently H, halogen, or C₁₋₄ alkyl optionally substituted with one or more halogen; or R_{10a} and R_{10b} together form a spirocyclic C₃₋₆ cycloalkyl or a spirocyclic 6-member heterocycloalkyl; R_{11a} and R_{11b} are each independently H, halogen, or C₁₋₄ alkyl optionally substituted with one or more halogen; R_{12a} and R_{12b} are each independently H, halogen, or C₁₋₄ alkyl optionally substituted with one or more halogen; R_{13a} is methyl, ethyl, or cyclopropyl; R_{13b} is H; and R₁₄ is H, halogen, or a C₁₋₄ alkyl optionally substituted with one or more halogen.

[00051] In some embodiments, the compound is a compound of Formula (I), wherein R_{10a} and R_{10b} are each independently H or methyl; R_{11a} and R_{11b} are each independently H, methyl, or ethyl; R_{12a} and R_{12b} are each independently H or methyl; R_{13a} is methyl, ethyl, or cyclopropyl; R_{13b} is H; and R₁₄ is H, fluoro, or methyl.

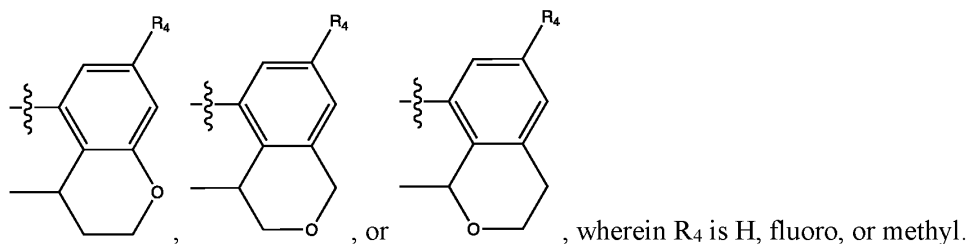
[00052] In some embodiments, the compound is a compound of Formula (I), wherein R₄ is H or fluoro; R_{13a} is methyl, ethyl, or cyclopropyl; and R₁₄ is H.

[00053] In some embodiments, the compound is a compound of Formula (I), wherein X₂ is NR_{6c} and R_{6c} is C₁₋₄ alkyl.

[00054] In some embodiments, the compound is a compound of Formula (I), wherein



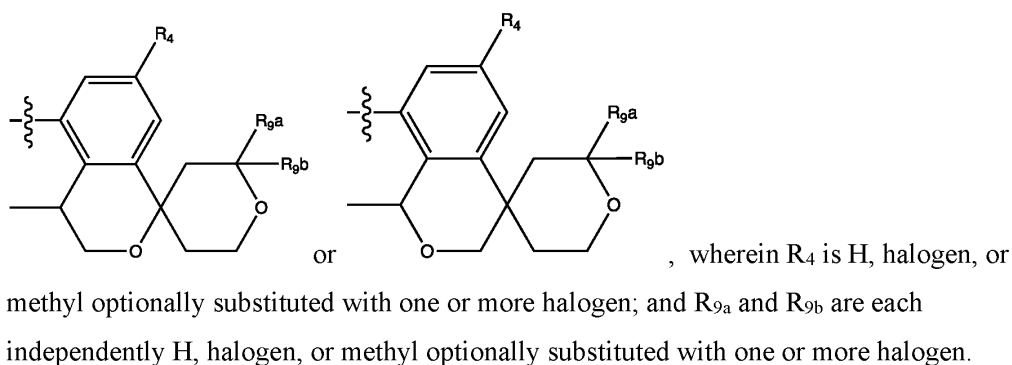
[00055] In some embodiments, the compound is a compound of Formula (I),  is



[00056] In some embodiments, the compound is a compound of Formula (I), wherein R_{10a}, R_{10b}, and R_{11a} are each H or methyl.

[00057] In some embodiments, the compound is a compound of Formula (I), wherein R_{11b} is H, methyl, or ethyl.

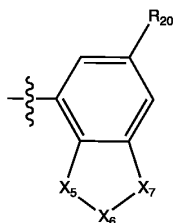
[00058] In some embodiments, the compound is a compound of Formula (I), wherein



[00059] In some embodiments, the compound is a compound of Formula (I), wherein R₄ is H, fluoro, or methyl; and R_{9a} and R_{9b} are each independently H, fluoro, chloro, or methyl optionally substituted with one or more fluoro.

[00060] In some embodiments, the compound is a compound of Formula (I), wherein





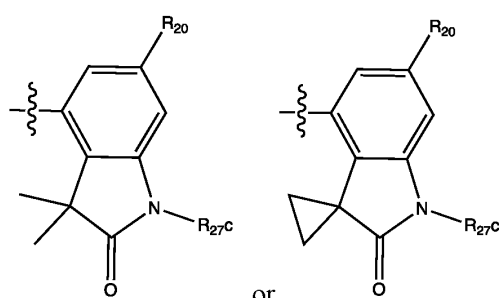
, R_{20} is H, halogen, a C_{1-4} alkyl, or a C_{1-4} alkoxy, wherein the C_{1-4} alkyl and the C_{1-4} alkoxy are each optionally substituted with one or more halogen; X_5 is $CR_{25a}R_{25b}$ or NR_{25c} ; R_{25a} and R_{25b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or alkoxy; or R_{25a} and R_{25b} together form a C_{3-6} cycloalkyl ring or 4- to 6-member heterocyclyl ring, each optionally substituted with halogen, C_{1-4} alkyl, a spirocyclic C_{3-6} cycloalkyl or a spirocyclic 4- to 6-member heterocyclyl ring, wherein the C_{1-4} alkyl, the spirocyclic C_{3-6} cycloalkyl, or the spirocyclic 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen or C_{1-4} alkyl; R_{25c} is C_{1-4} alkyl, a 5-6 member heteroaryl, or a C_6 aryl, wherein the C_{1-4} alkyl, the 5-6 member heteroaryl, or the C_6 aryl is optionally substituted with one or more halogen or C_{1-4} alkoxy; X_6 is $CR_{26a}R_{26b}$ or $C=O$; R_{26a} and R_{26b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkyl; X_7 is $CR_{27a}R_{27b}$ or NR_{27c} ; R_{27a} and R_{27b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or alkoxy; R_{27a} and R_{27b} together form a C_{3-6} cycloalkyl ring or 4- to 6-member heterocyclyl ring, wherein the C_{3-6} cycloalkyl ring or the 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen, one or more C_{1-4} alkyl, a spirocyclic C_{3-6} cycloalkyl, or a spirocyclic 4- to 6-member heterocyclyl ring, wherein the C_{1-4} alkyl, the spirocyclic C_{3-6} cycloalkyl, or the spirocyclic 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen or C_{1-4} alkyl; and R_{27c} is H, C_{1-4} alkyl, a C_{3-6} cycloalkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, a 5-6 member heteroaryl, or a C_6 aryl, wherein the C_{1-4} alkyl, the C_{3-6} cycloalkyl, the 4 to 6 member heterocycloalkyl, the 5 to 11 member spirocyclic heterocycloalkyl, the 5-6 member heteroaryl, or the C_6 aryl is optionally substituted with one or more halogen or C_{1-4} alkyl optionally substituted with one or more halogen; provided that only one of X_5 and X_7 comprise a N heteroatom.

[00061] In some embodiments, the compound is a compound of Formula (I), wherein R_{20} is H, halogen, a C_{1-4} alkyl, or a C_{1-4} alkoxy, wherein the C_{1-4} alkyl and the C_{1-4} alkoxy is optionally substituted with one or more halogen; X_5 is $CR_{25a}R_{25b}$; R_{25a} and R_{25b} are each independently methyl; or R_{25a} and R_{25b} together form a cyclopropyl; X_6 is $C=O$; R_{26a} and R_{26b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4}

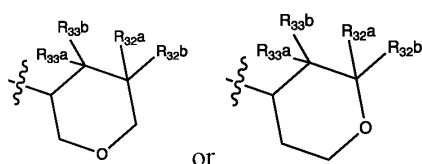
alkyl; X_7 is NR_{27c} ; and R_{27c} is a C_{1-4} alkyl, a C_{3-6} cycloalkyl, a 4- to 7-member heterocycloalkyl, a 5- to 11-member spirocyclic heterocycloalkyl, a 5-6 member heteroaryl, or a C_6 aryl, wherein the C_{1-4} alkyl, the C_{3-6} cycloalkyl, the 4- to 6-member heterocycloalkyl, the 5 to 11 member spirocyclic heterocycloalkyl, the 5-6 member heteroaryl, or the C_6 aryl is optionally substituted with one or more halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

[00062] In some embodiments, the compound is a compound of Formula (I), R_{27c} is a C_{1-4} alkyl. In some embodiments, the compound is a compound of Formula (I), wherein R_{27c} is a 5-member heteroaryl. In some embodiments, the compound is a compound of Formula (I), wherein R_{27c} is a C_{3-6} cycloalkyl 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 R_{27c} is a C_{1-4} alkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, wherein the C_{1-4} alkyl, the 4- to 7-member heterocycloalkyl, and the 5- to 11-member spirocyclic heterocycloalkyl is optionally substituted with one or more halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

[00063] In some embodiments, the compound is a compound of Formula (I), wherein



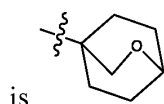
, wherein R_{20} is H, fluoro, methyl, ethyl, methoxy, $-CH_2-O-CH_3$, or $-CF_3$. In some embodiments, the compound is a compound of Formula (I), wherein R_{27c} is a tetrahydropyan optionally substituted by one or more methyl or fluoro. In some embodiments, the compound is a compound of Formula (I), wherein R_{27c} is



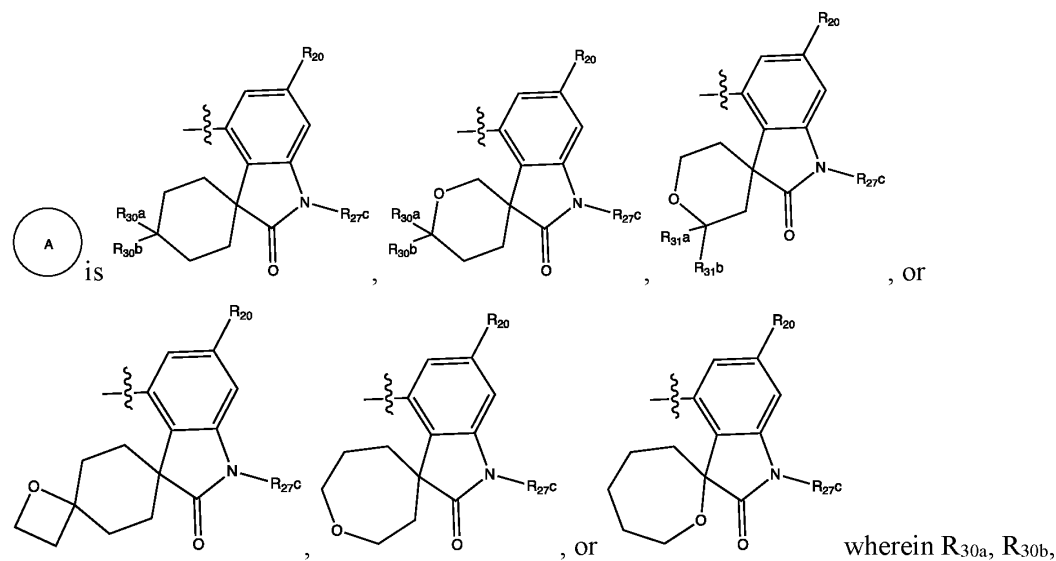
, wherein R_{32a} , R_{32b} , R_{33a} and R_{33b} are each independently

H, methyl, or fluoro; or one of R_{32a} and R_{32b} or R_{33a} and R_{33b} together form a spirocyclic C_{3-6} cycloalkyl or a spirocyclic 3- to 6-member heterocyclic ring.

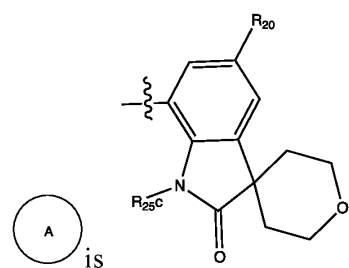
[00064] In some embodiments, the compound is a compound of Formula (I), wherein R_{27c}



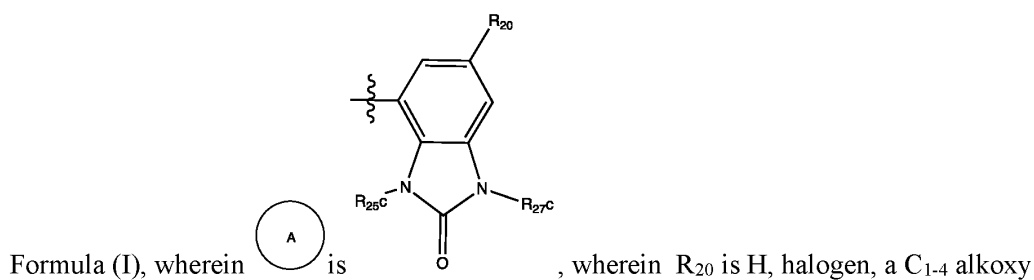
. In some embodiments, the compound is a compound of Formula (I), wherein



[00065] In some embodiments, the compound is a compound of Formula (I), wherein



. In some embodiments, the compound is a compound of

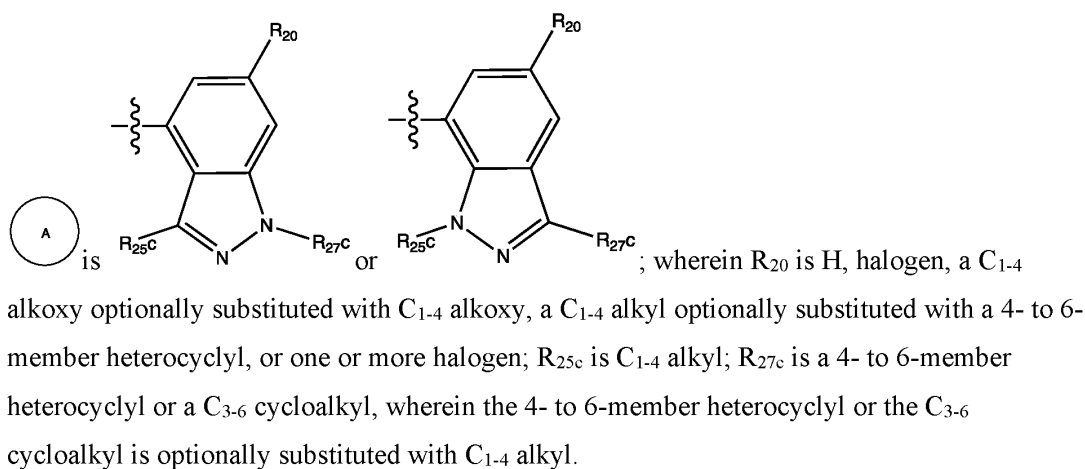


optionally substituted with C₁₋₄ alkoxy, a C₁₋₄ alkyl optionally substituted with 4- to 6-member heterocyclyl, or one or more halogen.

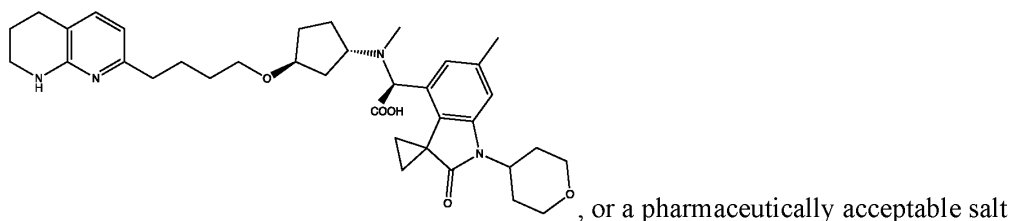
[00066] In some embodiments, the compound is a compound of Formula (I), wherein R_{25c} is a C₁₋₄ alkyl; and R_{27c} is a C₁₋₄ alkyl optionally substituted with one or more halogen or C₁₋₄ alkoxy, a C₃₋₆ cycloalkyl or a 4- to 6-member heterocycloalkyl, wherein the C₃₋₆ cycloalkyl or 4- to 6-member heterocycloalkyl is optionally substituted with a C₁₋₄ alkyl optionally substituted with one or more halogen.

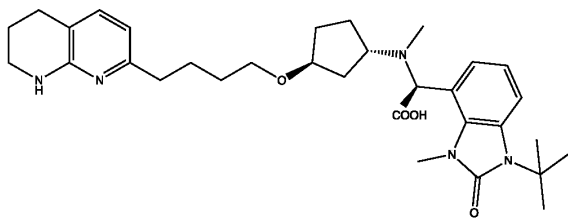
[00067] In some embodiments, the compound is a compound of Formula (I), wherein R_{27c} is C₁₋₄ alkyl; and R_{25c} is C₁₋₄ alkyl optionally substituted with one or more halogen or C₁₋₄ alkoxy, a C₃₋₆ cycloalkyl or a 4- to 6-member heterocycloalkyl, wherein the C₃₋₆ cycloalkyl or the 4- to 6-member heterocycloalkyl is optionally substituted with a C₁₋₄ alkyl optionally substituted with one or more halogen.

[00068] In some embodiments, the compound is a compound of Formula (I), wherein R₂₀ is H or methyl. In some embodiments, the compound is a compound of Formula (I), wherein



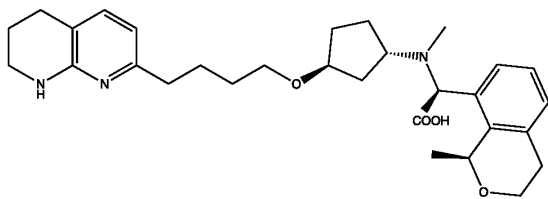
[00069] In some embodiments, the compound is a compound of the chemical formula





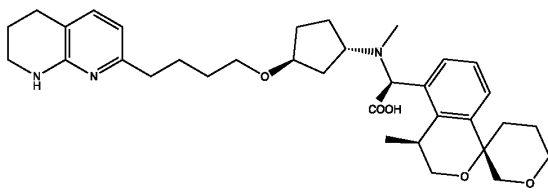
, or a pharmaceutically acceptable salt

thereof. In some embodiments, the compound is a compound of the chemical formula



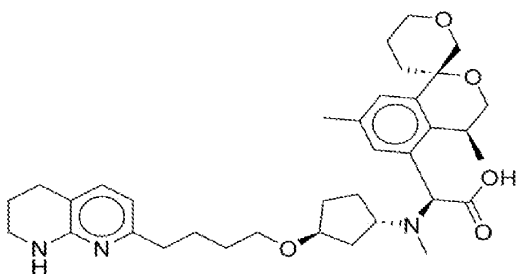
, or a pharmaceutically acceptable salt thereof.

In some embodiments, the compound is a compound of the chemical formula



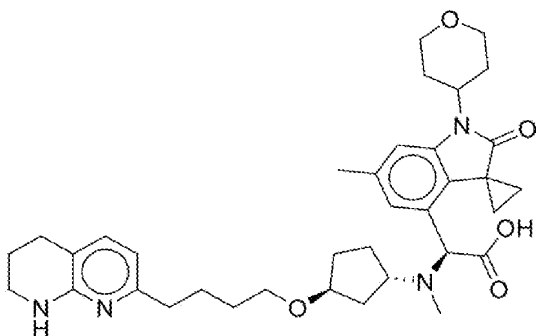
, or a pharmaceutically acceptable salt thereof.

[00070] In some embodiments, the compound is a compound of the chemical formula



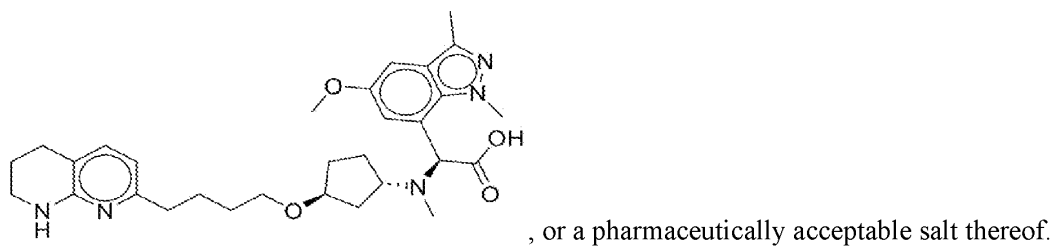
, or a pharmaceutically acceptable salt thereof.

[00071] In some embodiments, the compound is a compound of the chemical formula

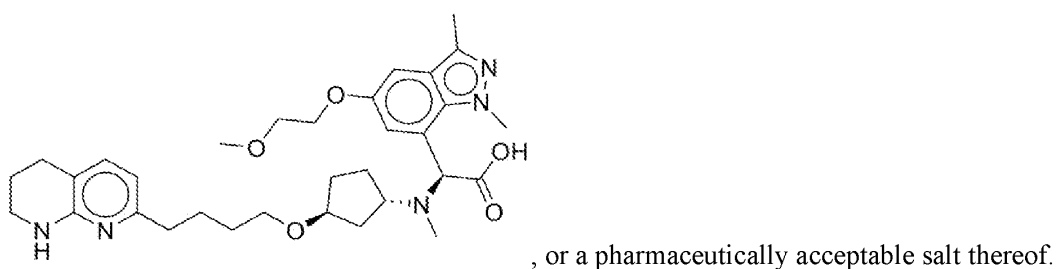


, or a pharmaceutically acceptable salt thereof.

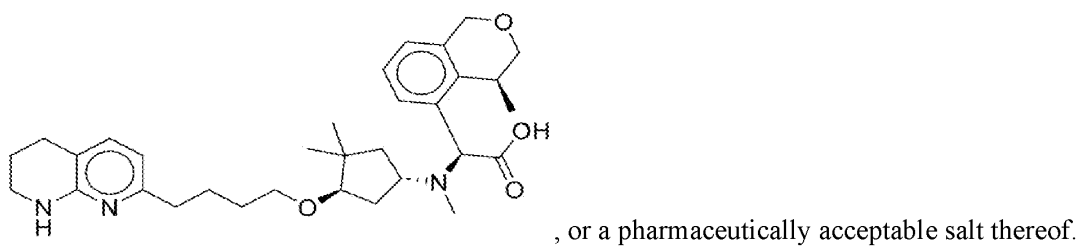
[00072] In some embodiments, the compound is a compound of the chemical formula



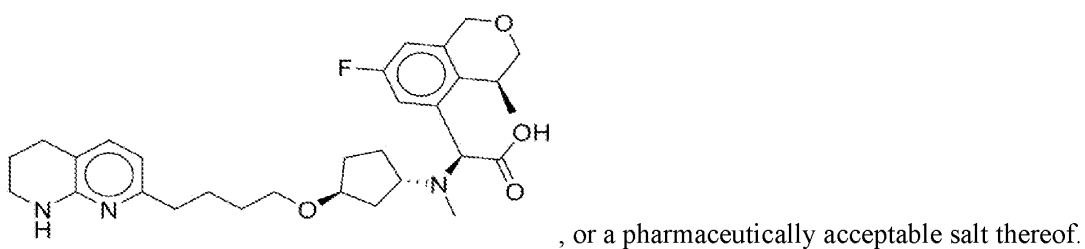
[00073] In some embodiments, the compound is a compound of the chemical formula



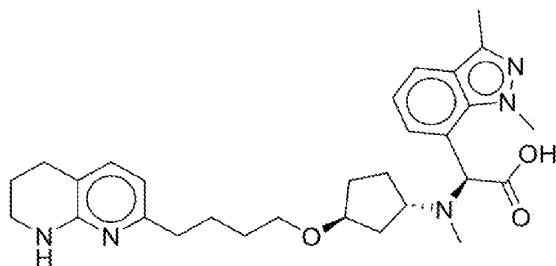
[00074] In some embodiments, the compound is a compound of the chemical formula



[00075] In some embodiments, the compound is a compound of the chemical formula

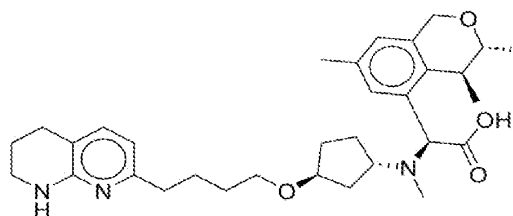


[00076] In some embodiments, the compound is a compound of the chemical formula



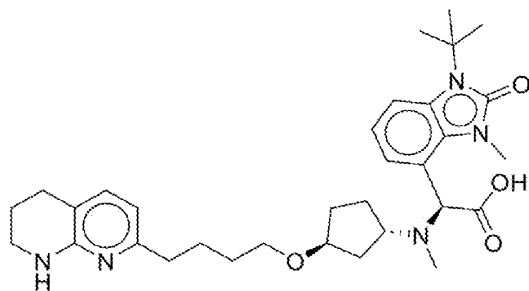
, or a pharmaceutically acceptable salt thereof.

[00077] In some embodiments, the compound is a compound of the chemical formula



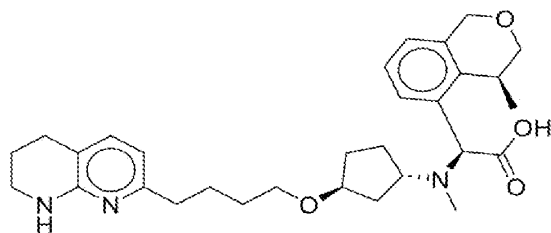
, or a pharmaceutically acceptable salt thereof.

[00078] In some embodiments, the compound is a compound of the chemical formula



, or a pharmaceutically acceptable salt thereof.

[00079] In some embodiments, the compound is a compound of the chemical formula



, or a pharmaceutically acceptable salt thereof.

[00080] In some embodiments, the compound is a compound selected from the group consisting of the compounds in Figure 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is a compound selected from the group consisting of compounds in Table 3, or a pharmaceutically acceptable salt thereof.

Definitions

[00081] 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.

[00082] In order for the present invention to be more readily understood, certain terms and phrases are defined below and throughout the specification.

[00083] 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.

[00084] 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.

[00085] 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.

[00086] 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.

[00087] 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.

[00088] 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.

[00089] 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.

[00090] 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.

[00091] 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.

[00092] 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.

[00093] 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.)

[00094] 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).

[00095] 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.

[00096] 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).

[00097] 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.

[00098] 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.

[00099] 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.

[000100] “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.

[000101] As used herein, the term “alkylene” refers to an alkyl group having the specified number of carbons, for example from 2 to 12 carbon atoms, that contains two points of attachment to the rest of the compound on its longest carbon chain. Non-limiting examples of alkylene groups include methylene $-(CH_2)-$, ethylene $-(CH_2CH_2)-$, n-propylene $-(CH_2CH_2CH_2)-$, isopropylene $-(CH_2CH(CH_3))-$, and the like. Alkylene groups can be cyclic or acyclic, branched or unbranched carbon chain moiety, and may be optionally substituted with one or more substituents.

[000102] “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).

[000103] 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.

[000104] 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.

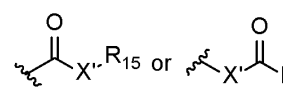
[000105] The term “halo”, “halide”, or “halogen” as used herein means halogen and includes, for example, and without being limited thereto, fluoro, chloro, bromo, iodo and the like, in both radioactive and non-radioactive forms. In a preferred embodiment, halo is selected from the group consisting of fluoro, chloro and bromo.

[000106] 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.

[000107] 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, imidazolinyl, 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.

[000108] The term “carbonyl” is art-recognized and includes such moieties as can be represented by the formula:

 ---C(=O)X'R_{15} or ---C(=O)X'R_{16} , wherein X' is a bond or represents an oxygen or a sulfur, and R₁₅ represents a hydrogen, an alkyl, an alkenyl, $-(\text{CH}_2)_m\text{---R}_{10}$ or a pharmaceutically acceptable salt, R₁₆ represents a hydrogen, an alkyl, an alkenyl or $-(\text{CH}_2)_m\text{---R}_{10}$, 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.

[000109] 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, heterocyclylalkyl, 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.

[000110] 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.

[000111] 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.

[000112] 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., Bundgard, 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.

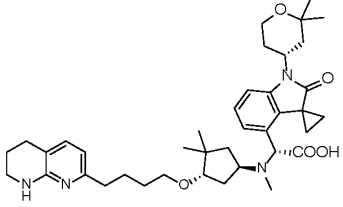
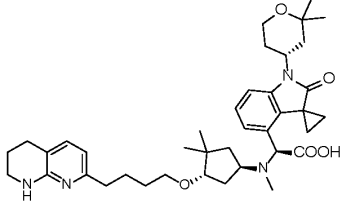
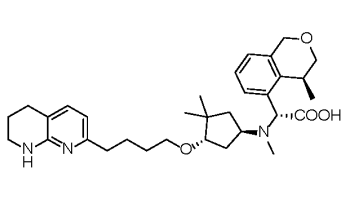
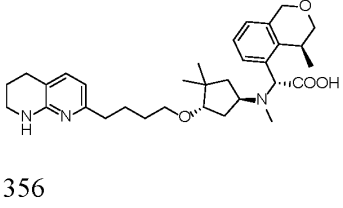
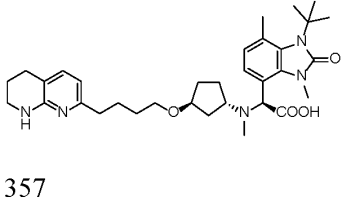
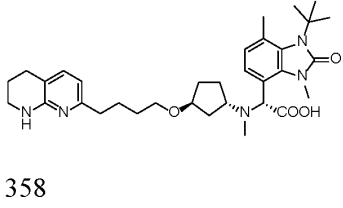
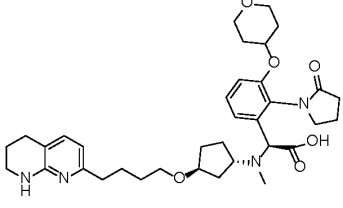
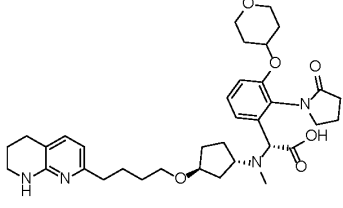
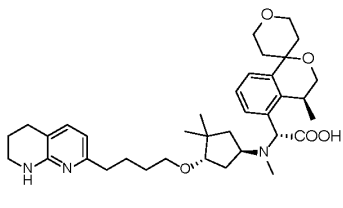
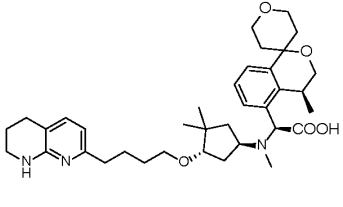
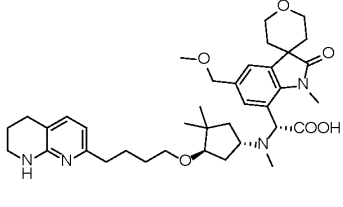
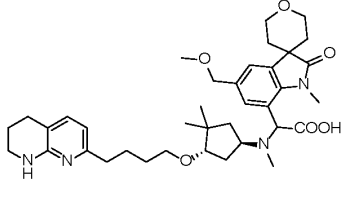
[000113] Prodrugs of compounds described herein may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to provide a compound described herein (i.e., the parent active compound). Prodrugs 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

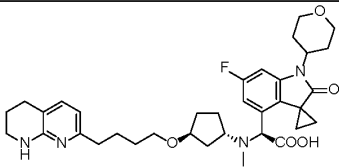
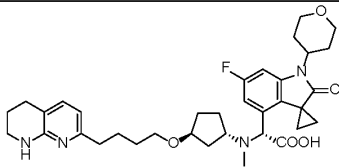
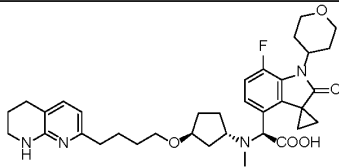
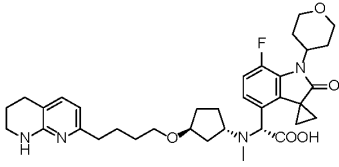
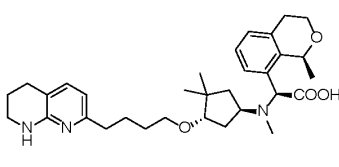
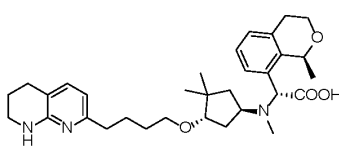
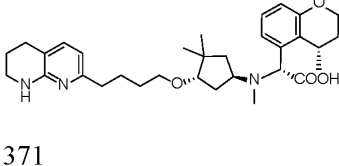
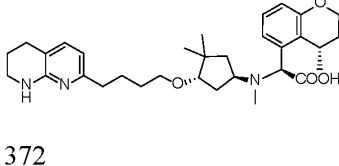
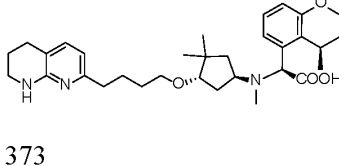
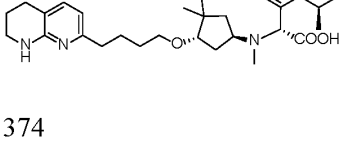
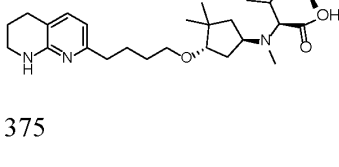
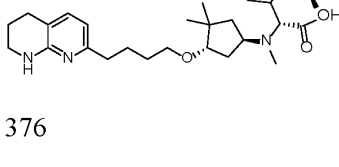
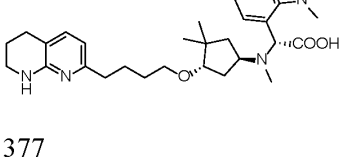
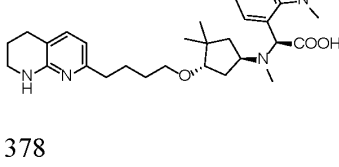
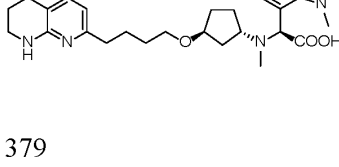
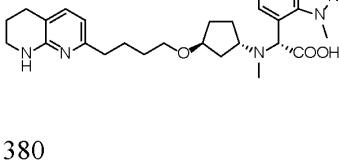
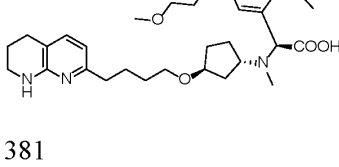
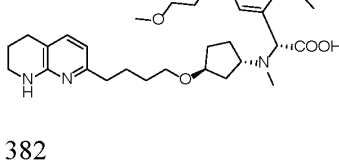
in the active compound and the like. Other examples of prodrugs include compounds that comprise —NO, —NO₂, —ONO, or —ONO₂ moieties.

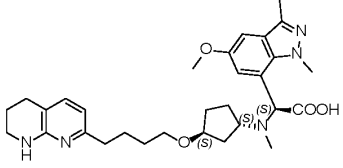
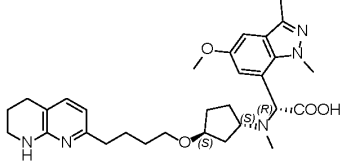
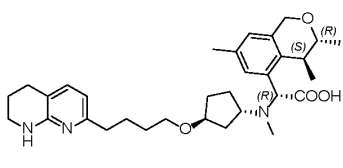
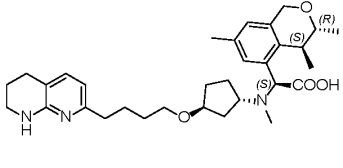
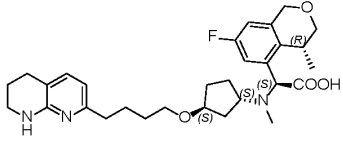
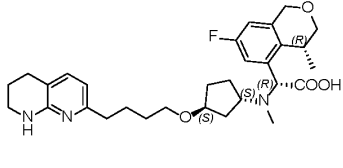
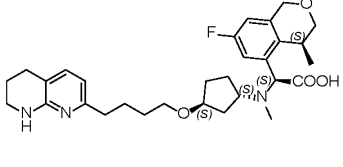
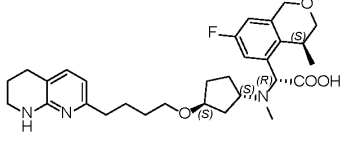
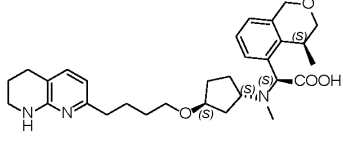
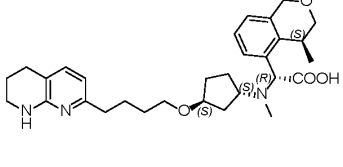
[000114] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th Ed., 1986-87, inside cover.

[000115] In some embodiments, the compound is a compound selected from Figure 1, or a pharmaceutically acceptable salt thereof. In some embodiments, the compound is a compound selected from Table 3, or a pharmaceutically acceptable salt thereof.

Table 3. Exemplary Compounds

 353	 354	 355
 356	 357	 358
 359	 360	 361
 362	 363	 364

 365	 366	 367
 368	 369	 370
 371	 372	 373
 374	 375	 376
 377	 378	 379
 380	 381	 382

 383	 384	 385
 386	 387	 388
 389	 390	 391
 392		

Therapeutic Uses of a Compound of Formula (I)

[000116] In tissues, normal fibroblasts are present in low population of only 4-5%. However, during fibrosis they proliferate and can occupy up to 80-90% of the organ mass.

Myofibroblasts in the fibrotic tissue produce large amounts of extracellular matrix proteins that make the tissue scarred and non-functional. Inhibition of myofibroblasts can counteract these processes. Integrins promote cell proliferation, survival, hypertrophic growth, and fibrosis. As described herein, integrin inhibition can modulate these key elements leading to the progression of pulmonary hypertension (e.g., PAH).

[000117] The present invention provides methods of treating a disease associated with increased expression or activity of integrin $\alpha 5 \beta 1$, comprising administering an integrin $\alpha 5 \beta 1$ inhibitor. In one aspect, the present invention provides an integrin $\alpha 5 \beta 1$ inhibitor for use in treating a disease associated with increased expression or activity of integrin $\alpha 5 \beta 1$ in a subject

in need of treatment thereof, comprising administering the integrin $\alpha 5\beta 1$ inhibitor and a pharmaceutical excipient to the subject.

[000118] In some embodiments, the disease is heart failure or right ventricle failure. In one aspect, the present invention provides a method of treating pulmonary arterial hypertension (PAH) in a subject, comprising administering an integrin $\alpha 5\beta 1$ inhibitor. In some embodiments, the integrin $\alpha 5\beta 1$ inhibitor is administered orally, intravenously, subcutaneously, intranasally, transdermally, intraperitoneally, intramuscularly, or intrapulmonarily. Also provided is a method for the treatment of a subject suffering from fibrosis or a fibrosis related disorder, comprising administering to said subject a therapeutically effective amount of integrin $\alpha 5\beta 1$ inhibitor according to the invention. The term “fibrosis” as used herein refers to a condition characterized by a deposition of extracellular matrix components in the skin or organs, including lungs, kidneys, heart, liver, skin and joints, resulting in scar tissue. The term also refers to the process of formation of scar tissue.

[000119] In some embodiments, the fibrosis-related disorder is a disorder or condition which may occur as a result of fibrosis, or which is associated with fibrosis. In some embodiments, fibrosis and/or a fibrosis-related disorders is a disease or condition selected from the group consisting of kidney fibrosis, liver fibrosis, liver cirrhosis, pulmonary fibrosis, skin fibrosis, biliary fibrosis, peritoneal fibrosis, myocardial fibrosis, pancreatic fibrosis, bone marrow and/or myelofibrosis, reperfusion injury after hepatic or kidney transplantation, Interstitial Lung Disease (ILD), cystic fibrosis (CF), atherosclerosis, systemic sclerosis, osteosclerosis, spinal disc herniation and other spinal cord injuries, fibromatosis, fibromyalgia, arthritis, restenosis. Pulmonary fibrosis includes idiopathic pulmonary fibrosis and scleroderma lung fibrosis.

[000120] 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.

[000121] 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.

[000122] 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 $\alpha 5\beta 1$ integrin activity. In some embodiments, the compounds described herein may be used to inhibit the activity of $\alpha 5\beta 1$ integrin. In some embodiments, the present disclosure provides a compound described herein useful as an inhibitor of $\alpha 5\beta 1$ 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. In some embodiments, the present disclosure provides a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier. 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 $\alpha 5\beta 1$ integrin.

[000123] 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.

[000124] 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.

[000125] In embodiments, a subject is an adult subject.

Dosage Amounts and Frequency

[000126] 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.

[000127] In some embodiments, the method of treating a disease associated with increased expression or activity of integrin $\alpha 5\beta 1$, comprises administering the integrin $\alpha 5\beta 1$ inhibitor at a dose of 1 mg/kg to 1000 mg/kg. In some embodiments, the dose is at least 2 mg/kg, at least 4 mg/kg, at least 6 mg/kg, or at least 8 mg/kg. In some embodiments, the dose is at least 10 mg/kg, at least 20 mg/kg, at least 30 mg/kg, at least 40 mg/kg, at least 50 mg/kg, at least 60 mg/kg, at least 70 mg/kg, at least 80 mg/kg, at least 90 mg/kg or at least 100 mg/kg. In some embodiments, the dose is at least 200 mg/kg, at least 300 mg/kg, at least 400 mg/kg, at least 500 mg/kg, at least 600 mg/kg, at least 700 mg/kg, at least 800 mg/kg, at least 900 mg/kg, or at least 1000 mg/kg.

[000128] In embodiments, a subject receives a dose of a compound of Formula (I) or a pharmaceutically acceptable salt thereof once daily. In embodiments, a subject receives a dose of a compound of Formula (I) or a pharmaceutically acceptable salt thereof twice daily.

Cardiac function parameters

[000129] Various endpoint parameters can be assessed to determine efficacy of a treatment of the present invention, e.g., $\alpha 5\beta 1$ level, pulmonary vascular resistance (PVR), mean pulmonary arterial pressure (PAP), cardiac index (CI), mean pulmonary capillary wedge pressure (PCWP), right atrial pressure (RAP), six-minute walk distance (6 MWD), brain natriuretic peptide (BNP) level, diffusion of lung capacity (DLCO), and death or survival. See, Chung et al. Chest (2010), 138(6):1383-1394.

[000130] PVR is commonly used as an endpoint parameter for determination of efficacy of treatment for PAH. A PVR of a subject of >240 dyn·sec/cm⁵ is an indication of mild PAH. A PVR of a subject of 600-800 dyn·sec/cm⁵ indicates moderate to severe PAH. After treatment using the methods and compositions of the invention, a decrease in PVR in a subject of 130 dyn·sec/cm⁵ or more indicates efficacious treatment. For example, administration of a A5B1 inhibitor to a subject with PAH that leads to a decrease in PVR of 180-350 dyn·sec/cm⁵ indicates efficacious treatment.

[000131] Mean pulmonary arterial pressure (PAP) is also used as an endpoint parameter to determine efficacy of treatment for PAH. A subject without PAH has a mean PAP ranging from about 15-24 mmHg. A subject having mild PAH has a mean PAP of about 25-30 mmHg (e.g., >25 mmHg at rest or 30 mmHg with exercise). A subject having severe PAH has a PAP of greater than 30 mmHg, for e.g., 40-70 mmHg or 60-70 mmHg. After treatment, a decrease in PAP of greater than 1.5 mmHg indicates efficacious treatment. In some embodiments,

treatment leads to a decrease in PAP of greater than 5, 10, 20, 40, or 50 mmHg, which is indicative of efficacious treatment.

[000132] Cardiac index (CI) is also used as an endpoint parameter for determining efficacy of treatment for PAH. A low or decreased CI is indicative of heart failure. For e.g., a CI of 2.5 L/min/m² or less is indicative of PAH or heart failure. After treatment, a CI increase of more than 0.3 L/min/m² is indicative of efficacious treatment.

[000133] Mean pulmonary capillary wedge pressure (PCWP) can be used as an endpoint parameter for determining efficacy of treatment for PAH. A mean PCWP of less than or equal to 18 mmHg (e.g., less than or equal to 10 mmHg) indicates a subject having PAH. After treatment, an increase in mean PCWP of greater than 0.5 mmHg is indicative of efficacious treatment.

[000134] Right atrial pressure (RAP) is also used as an endpoint parameter to determine efficacy of treatment for PAH. A subject not suffering from PAH has a normal RAP of 0-8 mmHg. A RAP of 8 mmHg or greater is indicative of PAH. A subject suffering from severe PAH has a RAP of about 20 mmHg. After treatment, a decrease of greater than 0.5 mmHg is indicative of efficacious treatment.

[000135] Six-minute walk distance (6 MWD) is used as an endpoint parameter to determine efficacy of treatment of PAH. The mean 6 MWD of patients with CTD-PAH is about 300 m. After treatment, an increase in 6 MWD of 25 m or more, or greater than 10% increase indicates efficacious treatment. For example, after treatment, a 6 MWD of 1000 m or more indicates efficacious treatment.

[000136] Brain Natriuretic Peptide (BNP) is used as an endpoint parameter to determine efficacy of treatment of PAH. BNP is a sensitive marker for the worsening of heart failure and is a predictor of mortality in PAH patients. Normal levels of BNP are <100 pg/mL, e.g., 30-90 pg/mL. Higher levels of BNP indicate worsening of heart failure. A BNP level of about 100-200 pg/mL, e.g., 160 pg/mL or higher, indicates early heart failure. A BNP level of about 200-1000 pg/mL indicates real heart failure. The mean BNP level of CTD- PAH patients is about 430 pg/mL. After treatment, any reduction in BNP level indicates efficacious treatment.

[000137] N-Terminal pro Brain Natriuretic Peptide (NT-proBNP): Reproducible, noninvasive parameters are useful in following patients with PAH. BNP is produced in the cardiac ventricles and is elevated in PPH/IPAH. BNP levels have recently been shown to be

closely related to functional impairment in PPH/IPAH patients and parallel the extent of pulmonary hemodynamic changes and right heart failure. BNP levels longitudinally correlate with the functional assessments being made over the course of the study. Plasma NT-pro-BNP are measured by a sandwich immunoassay using polyclonal antibodies that recognize epitopes located in the N-terminal segment (1 to 76) of pro-BNP (1 to 108) (Elecsys analyzer, Roche Diagnostics, Mannheim, Germany).

[000138] Diffusion of lung capacity (DLCO), or diffusion capacity of CO, is also used as an endpoint parameter to determine efficacy of treatment of PAH. DLCO measures the ability of carbon monoxide (CO) to diffuse across membranes. A subject not suffering from PAH has a normal DLCO of greater than 80%. A subject suffering from PAH has an abnormal DLCO of less than 80%, less than 65%, or less than 45%. After treatment, any increase in % DLCO indicates efficacious treatment.

[000139] In some embodiments, administration of the integrin $\alpha 5 \beta 1$ inhibitor modulates the level of a biomarker in the subject, wherein the biomarker is selected from the group consisting of survivin, PCNA, Ki67, and annexin V.

Pulmonary Hypertension

[000140] Pulmonary hypertension (PH) is a syndrome characterized by increased pulmonary artery pressure. PH is defined hemodynamically as a systolic pulmonary artery pressure greater than 30 mm Hg or evaluation of mean pulmonary artery pressure greater than 25 mm Hg. See Zaiman et al., Am. J. Respir. Cell Mol. Biol. 33:425-31 (2005). Further, PH, as a result of the increased pressure, damages both the large and small pulmonary arteries. The walls of the smallest blood vessels thicken and are no longer able to transfer oxygen and carbon dioxide normally between the blood and the lungs. In time, pulmonary hypertension leads to thickening of the pulmonary arteries and narrowing of the passageways through which blood flows. Once pulmonary hypertension develops, the right side of the heart works harder to compensate; however, the increased effort causes it to become enlarged and thickened. Proliferation of smooth muscle and endothelial cells which normally exist in a quiescent state leads to remodeling of the vessels with obliteration of the lumen of the pulmonary vasculature. This causes a progressive rise in pulmonary pressures as blood is pumped through decreased lumen area. The enlarged right ventricle places a person at risk for pulmonary embolism because blood tends to pool in the ventricle and in the legs. If clots form in the pooled blood, they may eventually travel and lodge in the lungs. The progressive rise in pressure also places an

additional workload on the right ventricle which eventually fails and leads to premature death in these patients.

[000141] Various pathologic changes occur in pulmonary arteries as a result of PH. Persistent vasoconstriction and structural remodeling of the pulmonary vessels are cardinal features of PH. Pulmonary vascular smooth muscle cells undergo a phenotypic switch from contractile normal phenotype to a synthetic phenotype leading to cell growth and matrix deposition. Histological examination of tissue samples from patients with pulmonary hypertension shows intimal thickening, as well as smooth muscle cell hypertrophy, especially for those vessels <100 μ m diameter. Further, abnormal smooth muscle cells often overexpress endothelin and serotonin transporters, which likely play a role in the development of PH.

[000142] The most common symptom of pulmonary hypertension initially is shortness of breath upon exertion. Some people feel light-headed or fatigued upon exertion, and an angina-like chest pain is common. Because body tissues are not receiving enough oxygen, general weakness is another problem. Other symptoms, such as coughing and wheezing, may be caused by an underlying lung disease. Edema, particularly of the legs, may occur because fluid may leak out of the veins and into the tissues, signaling that cor pulmonale has developed. Some people with pulmonary hypertension have connective tissue disorders, especially scleroderma. When people have both conditions, pulmonary hypertension and connective tissue disorders, Raynaud's phenomenon often develops before symptoms of pulmonary hypertension appear, sometimes as long as years earlier.

[000143] Treatment of some types of pulmonary hypertension is often directed at the underlying lung disease. Currently, the treatment options available for those suffering from PH target cellular dysfunction that leads to constriction of the vasculature. Therapies such as prostanoids, phosphodiesterase-5 inhibitors and endothelin receptor antagonists primarily work by causing dilation of the pulmonary vessels. Vasodilators, such as calcium channel blockers, nitric oxide, and prostacyclin, are often helpful for pulmonary hypertension associated with scleroderma, chronic liver disease, and HIV infection. In contrast, these drugs have not been proven effective for people with pulmonary hypertension due to an underlying lung disease. For most people with pulmonary hypertension due to an unknown cause, vasodilators, such as prostacyclin, drastically reduce blood pressure in the pulmonary arteries. Prostacyclin given intravenously through a catheter surgically implanted in the skin improves the quality of life, increases survival, and reduces the urgency of lung transplantation. Unfortunately, many

patients respond poorly to these therapies or stop responding to them over time. The only remaining option at that point in time is a single or double lung transplantation to treat PH. Although there is some evidence that available therapies have secondary effects on vascular remodeling, there are currently no therapies that target abnormal cell proliferation in PAH.

[000144] In some embodiments, the pulmonary hypertension is pulmonary venous hypertension (PVH). In some embodiments, the PVH is due to left heart failure. In some embodiments, the pulmonary hypertension is pulmonary hypertension associated with disorders of the respiratory system and/or hypoxia. In some embodiments, the pulmonary hypertension is pulmonary hypertension due to chronic thrombotic and/or embolic disease. In some embodiments, the pulmonary hypertension is miscellaneous pulmonary hypertension. In some embodiments, the miscellaneous pulmonary hypertension is associated with sarcoidosis, eosinophilic granuloma, histiocytosis X, lymphangiolomyomatosis, or compression of pulmonary vessels (e.g., adenopath, tumor, or fibrosing medianstinitis). In some embodiments, the pulmonary hypertension is associated with chronic obstructive pulmonary disease (COPD). In some embodiments, the pulmonary hypertension is associated with pulmonary fibrosis. In some embodiments, the pulmonary hypertension is associated with cardiac fibrosis. In some embodiments, the pulmonary hypertension is early-stage pulmonary hypertension or advanced pulmonary hypertension.

[000145] In some embodiments, one or more symptoms of the pulmonary hypertension are ameliorated. In some embodiments, the pulmonary hypertension is delayed. In some embodiments, the pulmonary hypertension is prevented. In some embodiments, the methods of treatment provided herein reduce pulmonary pressure. In some embodiments, the methods of treatment provided herein inhibit and/or reduce abnormal cell proliferation in the pulmonary artery.

[000146] In some embodiments, the pulmonary hypertension is characterized by the World Health Organization (WHO) group. In some embodiments, the pulmonary hypertension is WHO Group 1 pulmonary hypertension or pulmonary arterial hypertension (PAH), WHO Group 2 pulmonary hypertension, WHO Group 3 pulmonary hypertension, WHO Group 4 pulmonary hypertension, and WHO Group 5 pulmonary hypertension. In some embodiments, the pulmonary hypertension is characterized by the World Health Organization (WHO) class system. In some embodiments, the pulmonary hypertension is characterized by WHO functional class based on cardiac function. In some embodiments, the pulmonary hypertension,

WHO Class I pulmonary hypertension or pulmonary arterial hypertension (PAH), WHO Class II pulmonary hypertension, WHO Class III pulmonary hypertension, WHO Class IV pulmonary hypertension.

[000147] In some embodiments, the pulmonary hypertension is associated with pulmonary capillary hemangiomatosis. In some embodiments, the disease is heart failure or right ventricle failure. In one aspect, the present invention provides a method of treating pulmonary arterial hypertension (PAH) in a subject, comprising administering an integrin $\alpha 5\beta 1$ inhibitor.

Pulmonary arterial hypertension (PAH)

[000148] In one aspect, the present invention provides a method of treating Pulmonary arterial hypertension (PAH), comprising administering an integrin $\alpha 5\beta 1$ inhibitor (e.g., small molecule compounds and antibodies disclosed herein). PAH is characterized by a progressive increase in pulmonary vascular resistance leading to right ventricular overload and eventually cardiac failure. PAH results in progressive obstruction and decreased compliance of pulmonary arteries (PA), leading to right ventricular (RV) failure and premature death. Like cancer cells, PA smooth muscle cells (PASMCs) and endothelial cells (PAECs) exhibit exaggerated proliferation and resistance to apoptosis in response to increased PA stiffness caused by extracellular matrix (ECM) remodeling. Integrins signaling could promote PAH- PASMCs and PAH-PAECs proliferation and resistance to apoptosis contributing to PAs vascular remodeling, while in the RV, maladaptive hypertrophy, and fibrosis, leading to RV failure in PAH. The present invention is based, in part, on the discovery that $\alpha 5\beta 1$ integrin inhibition could reverse PAs vascular remodeling and prevent RV dysfunction in PAH.

[000149] PAH is a chronic disorder that involves all layers of the pulmonary vessels. Vasoconstriction, structural changes in the pulmonary vessel wall (vascular remodeling) and thrombosis contribute to the increased pulmonary vascular resistance in PAH. Structural and functional changes of the endothelium lead to endothelial dysfunction. Increased vasoconstrictive factors (e.g., endothelin) and decreased vasodilation capacity (e.g., less prostacyclin) result in vasoconstriction and increased pulmonary vascular resistance. Current treatments that seek to address vasoconstriction may slow the progression of PAH or ameliorate the clinical symptoms for a limited time, but they have not proven to substantially reduce overall PAH morbidity and mortality rates. Underlying structural changes to the pulmonary vessels - vascular remodeling - are not affected by these treatments.

[000150] Vascular remodeling that occurs in PAH is characterized by proliferative and obstructive changes involving many cell types, including endothelial cells, smooth muscle cells and fibroblasts. Vascular remodeling can manifest itself, for example, as medial thickening of pulmonary vessels due to smooth muscle cell hyperplasia and hypertrophy, formation of a neointima made of smooth muscle cells and/or myofibroblasts, and/or formation of plexiform lesions, which consist of localized proliferations of endothelial cells, smooth muscle cells, lymphocytes, and mast cells. Vascular remodeling results in obstruction of the vessel lumen leading to pulmonary hypertension. There is a need for therapies that address the proliferative aspect of PAH.

[000151] In some embodiments, the pulmonary hypertension is pulmonary arterial hypertension (PAH). In some variations, the PAH is idiopathic PAH. In some variations, the PAH is familial PAH. In some variations, the PAH is associated with persistent pulmonary hypertension of a newborn. In some variations, the PAH is associated with pulmonary veno-occlusive disease.

[000152] In some embodiments, the pulmonary hypertension is associated with lung diseases. In some embodiments, the lung disease is Idiopathic pulmonary fibrosis (IPF) or interstitial pneumonia (IIP). IPF is a type of idiopathic interstitial pneumonia (IIP), which in turn is a type of interstitial lung disease (also known as diffuse parenchymal lung disease (DPLD)). Interstitial lung disease concerns alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and perilymphatic tissues. Other forms of idiopathic interstitial pneumonias include non-specific interstitial pneumonia (NSIP), desquamative interstitial pneumonia (DIP) and acute interstitial pneumonia (AIP). Examples of known causes of interstitial lung disease include sarcoidosis, hypersensitivity pneumonitis, pulmonary Langerhans cell histiocytosis, asbestosis and collagen vascular diseases such as scleroderma and rheumatoid arthritis.

[000153] Pulmonary fibrosis is the formation or development of excess fibrous connective tissue in the lungs.

Heart Failure (HF)

[000154] In one aspect, the present invention provides a method of treating heart failure (HF), comprising administering an integrin $\alpha 5 \beta 1$ inhibitor (e.g., small molecule compounds and antibodies disclosed herein). Heart failure refers to any condition characterized by the heart's inability to pump an adequate supply of blood to the body. The physiological state in

which cardiac output is insufficient to meet the needs of the body or to do so only at a higher filling pressure. There are many underlying causes of HF, including myocardial infarction, coronary artery disease, valvular disease, hypertension, and myocarditis. Chronic heart failure is associated with neurohormonal activation and alterations in autonomic control. Although these compensatory neurohormonal mechanisms provide valuable support for the heart under normal physiological circumstances, they also play a fundamental role in the development and subsequent progression of HF.

[000155] For example, one of the body's main compensatory mechanisms for reduced blood flow in HF is to increase the amount of salt and water retained by the kidneys. Retaining salt and water, instead of excreting it via urine, increases the volume of blood in the bloodstream and helps to maintain blood pressure. However, the larger volumes of blood also cause the heart muscle, particularly the ventricles, to become enlarged. As the heart chambers become enlarged, the wall thickness decreases and the heart's contractions weaken, causing a downward spiral in cardiac function. Another compensatory mechanism is vasoconstriction of the arterial system, which raises the blood pressure to help maintain adequate perfusion, thus increasing the load that the heart must pump against.

[000156] In low ejection fraction (EF) heart failure, high pressures in the heart result from the body's attempt to maintain the high pressures needed for adequate peripheral perfusion. However, as the heart weakens because of such high pressures, the disorder becomes exacerbated. Pressure in the left atrium may exceed 25 mm Hg, at which stage, fluids from the blood flowing through the pulmonary circulatory system transudate or flow out of the pulmonary capillaries into the pulmonary interstitial spaces and into the alveoli, causing lung congestion and if untreated the syndrome of acute pulmonary edema and death.

Standard of Care (SoC) and Combination Therapy

[000157] As described herein, a method of treating a disease associated with increased expression or activity of integrin $\alpha 5\beta 1$, comprising administering an integrin $\alpha 5\beta 1$ inhibitor can include a combination therapy in which a patient in need of treatment is administered an integrin $\alpha 5\beta 1$ inhibitor in combination with one or more drugs approved for the treatment of PH, PAH, heart failure, or right ventricle failure.

[000158] Approved drugs currently used in the treatment of PH, PAH, heart failure and right ventricle failure in the US or the European Union (EU) include the orally administered PDE-5 inhibitors: sildenafil (Revatio) and tadalafil (Adeirca); the dual endothelin-1A receptor

antagonist (ERA): bosentan (Tracleer), ambrisentan (Letairis in US; Volibris internationally). Patients with more advanced disease are often treated with prostacyclins or prostacyclin analogs such as iloprost (Ventavis) or treprostinil (Tyvaso) given as multiple daily inhalations, epoprostenol (Flolan/Veletri) or treprostinil (Remodulin) given as continuous intravenous infusions, or treprostinil also used as a continuous subcutaneous infusion. Intravenous injection of sildenafil is approved for patients who are currently prescribed but are temporarily unable to take oral sildenafil. Inhaled nitric oxide (INOmax) is approved for the neonatal form of PAH—persistent pulmonary hypertension of the newborn (PPHN). Thus, in accordance with the invention, combination therapies of any of these drugs and an integrin $\alpha 5\beta 1$ inhibitor are useful in the treatment of PAH or a disorder disclosed herein.

[000159] In some embodiments, the second therapy is selected from the group consisting of anticoagulants, diuretics, a digitalis glycosideglycosides, calcium channel blockers, endothelin receptor antagonists, phosphodiesterase 5 (PDE5) inhibitors, prostanoids, prostanoids receptor agonists, soluble guanylate cyclase stimulators, and/or surgery.

[000160] In some embodiments, the second therapy is oxygen, Warfarin, furosemide, bumetanide, bendroflumethiazide, metolazone, spironolactone, amiloride, Digoxin, nifedipine, diltiazem, nicardipine, amlodipine, ambrisentan, bosentan, macitentan, sildenafil, tadalafil, epoprostenol, iloprost, treprostinil, riociguat, selexipag, surgery, pulmonary endarterectomy, and/or atrial septostomy. In some embodiments, the second therapy is macitentan and/or tadalafil. Flolan (prostacyclin analog) is an approved therapy for PAH, but is extremely cumbersome and inconvenient to use (intravenous), and has unique safety concerns. As a result, Flolan is usually reserved for patients with severe functional status or rapidly progressive PAH. Patients must constitute the drug in sterile conditions several times daily. The drug is available as a freeze-dried preparation that needs to be dissolved in alkaline buffer. Because of its short half-life (3-5 min) and stability (8 h at room temperature), Flolan must be maintained in a refrigerated state while given by continuous infusion through a central venous catheter via a portable pump that is worn in a bag around the waist (CADD pump, Smith's Medical MD, St. Paul, Minn.). In 2008, the FDA also approved a new continuous intravenous formulation of epoprostenol that is stable at room temperature for up to 24 h after dilution and may be stored up to 5 days at refrigerator temperature before use (GeneraMedix Inc., Liberty Corner, N.J.). In 2009, GeneraMedix Inc. sold this formulation to Actelion, which began to market the drug (under the brand name Veletri) in April 2010. In late 2010, the Veletri label was expanded to allow preparation of medication up to 7 days at refrigerator temperature or up

to 48 h at room temperature in advance of use. Thus, in one embodiment of the invention, an integrin $\alpha 5\beta 1$ inhibitor is administered in combination with epoprostenol, in any of its approved forms, to treat PAH.

[000161] Remodulin (continuous subcutaneous infusion form of prostacyclin analog) was not generally used as initial therapy because of its expense, route of delivery, and limited efficacy. In 2004, the FDA and Health Canada approved an intravenous formulation of Remodulin for patients with PAH class II-IV disease who cannot tolerate the subcutaneous form. In early 2006, the FDA expanded the Remodulin label to include patients requiring transition from Flolan. In 2009, United Therapeutics received FDA approval for an inhaled formulation of treprostinil (Tyvaso). Thus, in one embodiment of the invention, an integrin $\alpha 5\beta 1$ inhibitor is administered in combination with treprostinil to treat PAH.

[000162] Ventavis (iloprost), a prostacyclin analogue administered via inhalation is also marketed in several member countries of the EU as Ilomedine as an intravenous formulation. The label for inhaled iloprost in the EU is restricted to patients with idiopathic PAH and functional class III symptoms. In contrast, the label in the US is broader: patients with PAH (regardless of etiology) and class III or IV symptoms. It is required 6 to 9 times a day administration. Thus, in one embodiment of the invention, an integrin $\alpha 5\beta 1$ inhibitor is administered in combination with iloprost, in any of its approved forms, to treat PAH.

[000163] In 2001, the nonselective ERA Tracleer (bosentan) became the first oral PAH therapy and was available only through a special centralized access program in the US because of its significant risk of (reversible) liver injury, teratogenicity, testicular atrophy, and male sterility. Treatment with Tracleer consists of an initial dosage of 62.5 mg twice daily for 4 weeks, followed by a maintenance dose of 125 mg twice daily. Tracleer was initially indicated for patients with PAH and moderate or severe functional status (WHO class III, IV). In 2008 (EU) and 2009 (US), the label was expanded to patients with mild symptoms (functional class II). Thus, in one embodiment of the invention, an integrin $\alpha 5\beta 1$ inhibitor is administered in combination with bosentan, in any of its approved forms, to treat PAH.

[000164] Ambrisentan is the oral selective ERA-receptor antagonist marketed by Gilead Sciences in the US (Letairis) and by GlaxoSmithKline in other regions (Volibris) for the once-daily treatment of patients with WHO class II or III symptoms to improve exercise capacity and delay clinical worsening. As with bosentan, ambrisentan has class effects of teratogenicity, testicular injury, reduced male fertility, and anemia. Thus, in one embodiment of the invention,

an integrin $\alpha 5\beta 1$ inhibitor is administered in combination with ambrisentan, in any of its approved forms, to treat PAH.

[000165] The oral PDE-5 inhibitor Revatio (sildenafil) was approved in the US for the treatment of PAH (WHO Group I) to improve exercise ability and delay of clinical worsening at a dose of 20 mg three times daily, regardless of functional class or etiology. The EU label is restricted to improvement of exercise capacity in patients with PAH, which is either idiopathic or associated with collagen vascular disease and with functional class III status. In 2009, the FDA approved an intravenous form of Revatio given as an injection (10 mg 3-times a day) for a patient unable to take the oral formulation. In May 2010, the EU approved Revatio as an oral suspension (compounded from 20 mg tablets) for the treatment of pediatric patient aged 1 to 17 years with PAH. Thus, in one embodiment of the invention, an integrin $\alpha 5\beta 1$ inhibitor is administered in combination with sildenafil, in any of its approved forms, to treat PAH.

[000166] The oral PDE-5 Inhibitor Adeirca (tadalafil) 40 mg once daily is indicated in the US to improve exercise ability in patients with PAH (WHO Group I) regardless of etiology or functional class (Packet Insert). The EU label is restricted to patients with functional class II and III status. Tadalafil has a long half-life (35 h) in patients with PAH (US Packet Insert) has also shown benefit in patients with PAH on concomitant bosentan.

[000167] Thus, the method of treating the patient may involve administering at least one additional active agent, i.e., in addition to an integrin $\alpha 5\beta 1$ inhibitor. The additional active agent may be, for example, a vasodilator such as prostacyclin, epoprostenol, and sildenafil; an endothelin receptor antagonist such as bosentan; a calcium channel blocker such as amlodipine, diltiazem, and nifedipine; an anticoagulant such as warfarin; a diuretic, a prostanoid (e.g., prostacyclin or PGI₂), drugs for treating diseases associated with overactive B cells or dysfunctional B cells such as Rituximab, and/or a Type V phosphodiesterase (PDE5) inhibitor.

[000168] When the method of the invention involves combination therapy, i.e., wherein a secondary agent such as a vasodilator is co-administered with an integrin $\alpha 5\beta 1$ inhibitor, the agents may be administered separately, at the same, or at different times of the day, or they may be administered in a single composition. Thus, the present invention provides novel pharmaceutical formulations in which an integrin $\alpha 5\beta 1$ inhibitor is combined with one of the active agents discussed above and unit dose forms of those formulations.

[000169] In the combination therapies of the invention, each agent can be administered in an “immediate release” manner or in a “controlled release manner.” When the additional active

agent is a vasodilator, for instance, any dosage form containing both active agents i.e., both the integrin $\alpha 5\beta 1$ inhibitor and the vasodilator, can provide for immediate release or controlled release of the vasodilator, and either immediate release or controlled release of the integrin $\alpha 5\beta 1$ inhibitor.

[000170] As a general example, a combination dosage form of the invention for once- daily administration might contain in the range of about 1 mg to about 1000 mg of an integrin $\alpha 5\beta 1$ inhibitor of an integrin $\alpha 5\beta 1$ inhibitor, in a controlled release (e.g., sustained release) or immediate release form, and either sildenafil in immediate release form, or in controlled release form, with the additional active agent present in an amount that provides a weight ratio of the an integrin $\alpha 5\beta 1$ inhibitor to sildenafil, or a weight ratio of the an integrin $\alpha 5\beta 1$ inhibitor to sildenafil, specified as above. In other formulations of the invention, two or more additional active agents, which may or may not be in the same class of drug (e.g., vasodilators), can be present in combination, along with an integrin $\alpha 5\beta 1$ inhibitor. In such a case, the effective amount of either or each individual additional active agent present will generally be reduced relative to the amount that would be required if only a single added agent were used.

[000171] The additional active agent may also be, as discussed above, a Type V phosphodiesterase inhibitor, administered with an integrin $\alpha 5\beta 1$ inhibitor, or with both the integrin $\alpha 5\beta 1$ inhibitor and a vasodilator. Examples of Type V phosphodiesterase inhibitors include, without limitation, avanafil, sildenafil, tadalafil, zaprinast, dipyridamole, vardenafil and acid addition or other pharmaceutically acceptable salts thereof. Sildenafil is an excellent example. In an exemplary embodiment, an integrin $\alpha 5\beta 1$ inhibitor is co-administered with a Type V phosphodiesterase inhibitor selected from the group consisting of avanafil, tadalafil, and sildenafil, and the daily dose of a compound of the integrin $\alpha 5\beta 1$ inhibitor is as given above for the monotherapeutic regimen.

[000172] In one embodiment, the vasodilator is selected from sildenafil, avanafil, tadalafil, zaprinast, dipyridamole, vardenafil, bosentan, and pharmaceutically acceptable salts thereof. The additional active agent may also be, as discussed above, an endothelin receptor antagonist, e.g., bosentan, sitaxsentan, or ambrisentan, with bosentan being an exemplary active agent.

[000173] A pharmaceutical composition of the invention is a pharmaceutical formulation containing an active agent formulated in a manner compatible with its intended route of administration. A variety of routes are contemplated, including but not limited to, oral, pulmonary, inhalational, sublingual, intranasal, parenteral, intradermal, transdermal, topical,

transmucosal, subcutaneous, intravenous, intramuscular, intraperitoneal, buccal, rectal, and the like. The term “parenteral” as used herein is intended to include subcutaneous, intravenous, and intramuscular injection.

[000174] Generally, pharmaceutical formulations of the invention are prepared for oral administration and in an immediate release form suitable for once per day (QD) administration. Certain formulations are suitable for intranasal administration to a patient.

[000175] Certain pharmaceutical formulations of the invention comprise an integrin $\alpha 5\beta 1$ inhibitor or a salt thereof and one or more pharmaceutically acceptable (approved by a state or federal regulatory agency for use in humans, or is listed in the U.S. Pharmacopoeia, the European Pharmacopoeia) excipients or carriers. The term excipient or carrier as used herein broadly refers to a biologically inactive substance used in combination with the active agents of the formulation. An excipient can be used, for example, as a solubilizing agent, a stabilizing agent, a diluent, an inert carrier, a preservative, a binder, a disintegrant, a coating agent, a flavoring agent, or a coloring agent. Preferably, at least one excipient is chosen to provide one or more beneficial physical properties to the formulation, such as increased stability and/or solubility of the active agent(s). An integrin $\alpha 5\beta 1$ inhibitor or a salt thereof as described herein is an exemplary active agent suitable for use in the formulations of the present invention.

[000176] Examples of suitable excipients include certain inert proteins such as albumins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as aspartic acid (which may alternatively be referred to as aspartate), glutamic acid (which may alternatively be referred to as glutamate), lysine, arginine, glycine, and histidine; fatty acids and phospholipids such as alkyl sulfonates and caprylate; surfactants such as sodium dodecyl sulphate and polysorbate; nonionic surfactants such as TWEEN®, PLURONICS®, or polyethylene glycol (PEG); carbohydrates such as glucose, sucrose, mannose, maltose, trehalose, and dextrans, including cyclodextrins; polyols such as mannitol and sorbitol; chelating agents such as EDTA; and salt-forming counter-ions such as sodium.

[000177] Solutions or suspensions used for the delivery can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol, polysorbate, tocopherol, polyethylene glycol succinate (TPGS), or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents

for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. These preparations can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[000178] In some embodiments, the pharmaceutical formulations of the present invention contain a plurality of liposomes or microparticles comprising the integrin $\alpha 5 \beta 1$ inhibitor active agent. In various embodiments, the pharmaceutical formulation of the integrin $\alpha 5 \beta 1$ inhibitor is a powder comprising solid particles (e.g., liposomes or microparticles) suitable for administration via inhalation. The solid particles comprise the active agent, a carrier, optionally a surfactant, and optionally additional recipients. The powder may be prepared by any convenient method. An example of a preparatory method is spray drying a solution containing the active agent (and other components) onto a powder comprising the carrier compound. Another example is freeze drying a solution comprising all of the components of the final powder.

[000179] Suitable liposomes for use in the present formulations of the invention are known in the art. For example, suitable liposomes include cholesterol, 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and PEG-DSPE, with the weight ratio being about 5:10:1. In some embodiments, the liposome formulation comprises about 0.1-25%, e.g., 0.1%, 1%, 5%, 10% or 20% (w/w) of a phospholipid, such as dipalmitoylphosphatidylcholine (DPPC) and 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC). In some embodiments, the liposome formulation comprises about 0.5-20%, e.g., 1%, 5%, or 10% (w/w) of a hydrophilic polymer, such as polyvinylpyrrolidone (PVP). In some embodiments, the liposome formulation comprises about 10-35% of an amino acid, such as L-leucine.

[000180] Suitable microparticles for use in the formulations of the invention are known in the art. For example, microparticles are formed of one or more hydrophilic polymers such as polyvinylpyrrolidone (e.g., PVP-10), polyvinyl alcohol (e.g., PVA-30), polyvinyl acetate, or Poloxamer (e.g., Poloxamer-188). In some embodiments, the microparticle formulation comprises about 70-85 wt % of polyvinyl alcohol (e.g., PVA-30), about 5-15% PVP (e.g., PVP-10), 1-5% Poloxamer (e.g., Poloxamer-188), 0-10% L-leucine, and about 0.5-10% of an integrin $\alpha 5 \beta 1$ inhibitor compound (e.g., 5%). In some embodiments, the formulation is suitable for administration via the respiratory tract.

[000181] The pharmaceutical formulations of an integrin $\alpha 5 \beta 1$ inhibitor useful in the methods of the invention can be prepared as a liquid or in a solid form such as a powder, tablet,

pill, or capsule for oral administration. Liquid formulations of the invention may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In one embodiment, the formulation is an aqueous solution. In another embodiment, the final formulation is lyophilized. In some embodiments, the integrin $\alpha 5\beta 1$ inhibitor is formulated for inhalation.

[000182] In various embodiments, the formulations of the invention comprise an integrin $\alpha 5\beta 1$ inhibitor at a concentration of from 0.25 wt % to 100 wt %, or from 0.25 wt % in 50 wt %, or from 0.8 wt % to 25 wt %, or from 1 wt % to 10%, or from 1.5 wt % to 5 wt %. In certain embodiments, an integrin $\alpha 5\beta 1$ inhibitor compound is formulated at a concentration of from about 0.5 wt % to about 5 wt %. In certain embodiments, an integrin $\alpha 5\beta 1$ inhibitor compound is formulated at a concentration of about 0.25 wt % to about 10 wt %.

[000183] The present invention also provides a pharmaceutical pack or kit comprising one or more containers filled with a solid or liquid formulation of an integrin $\alpha 5\beta 1$ inhibitor. In a particular embodiment, the formulation is a powder formulation of an integrin $\alpha 5\beta 1$ inhibitor. In various embodiments, an integrin $\alpha 5\beta 1$ inhibitor is formulated at a concentration of at least about 0.5 wt % and the formulation is suitable for delivery via inhalation to a human.

[000184] The present invention also provides for a use of a formulation of an integrin $\alpha 5\beta 1$ inhibitor in the manufacture of a medicament for treating PAH, or a disorder disclosed herein, in a subject in need thereof. Generally, the pharmaceutical formulation is sterile.

[000185] Generally, the dosage forms, e.g., an inhalable dosage form, provide for sustained release, i.e., gradual, release of a compound of the current invention, for e.g., an integrin $\alpha 5\beta 1$ inhibitor, from the dosage form to the patient's body over an extended time period, typically providing for a substantially constant blood level of the agent over a time period in the range of about 4 to about 12 hours, typically in the range of about 6 to about 10 hours. In a particularly preferred embodiment, there is a very gradual increase in blood level of the drug following nasal administration of the dosage form containing a compound of the current invention, for e.g., an integrin $\alpha 5\beta 1$ inhibitor, such that peak blood level is not reached until at least 4-6 hours have elapsed, with the rate of increase of blood level drug approximately linear. In addition, in the preferred embodiment, there is an equally gradual decrease in blood level at the end of the sustained release period.

[000186] Although the pharmaceutical compositions of the invention are preferably formulated for inhalation, e.g., as a solution in saline, as a dry powder, or as an aerosol, other modes of administration are suitable as well. For example, administration may be sublingual, oral, parenteral, transdermal, via an implanted depot, transmucosal, e.g., rectal or vaginal, preferably using a suppository that contains, in addition to the active agent, excipients such as a suppository wax. Transmucosal administration also encompasses transurethral.

[000187] Depending on the intended mode of administration, the pharmaceutical formulation may be a solid, semi-solid or liquid, such as, for example, a tablet, a capsule, a caplet, a liquid, a suspension, an emulsion, a suppository, granules, pellets, beads, a powder, or the like, preferably in unit dosage form suitable for single administration of a precise dosage. Suitable pharmaceutical compositions and dosage forms may be prepared using conventional methods known to those in the field of pharmaceutical formulation and described in the pertinent texts and literature, e.g., in Remington: The Science and Practice of Pharmacy (Easton, Pa.: Mack Publishing Co., 1995). For those compounds that are orally active, oral dosage forms are generally preferred, and include tablets, capsules, caplets, solutions, suspensions and syrups, and may also comprise a plurality of granules, beads, powders, or pellets that may or may not be encapsulated. Preferred oral dosage forms are tablets and capsules.

[000188] In embodiments, it may be especially advantageous to formulate compositions of the invention in unit dosage form for ease of administration and uniformity of dosage. The term “unit dosage forms” as used herein refers to physically discrete units suited as unitary dosages for the individuals to be treated. That is, the compositions are formulated into discrete dosage units each containing a predetermined, “unit dosage” quantity of an active agent calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specifications of unit dosage forms of the invention are dependent on the unique characteristics of the active agent to be delivered. Dosages can further be determined by reference to the usual dose and manner of administration of the ingredients. It should be noted that, in some cases, two or more individual dosage units in combination provide a therapeutically effective amount of the active agent, e.g., two tablets or capsules taken together may provide a therapeutically effective dosage of an integrin $\alpha 5 \beta 1$ inhibitor, such that the unit dosage in each tablet or capsule is approximately 50% of therapeutically effective amount.

[000189] Tablets may be manufactured using standard tablet processing procedures and equipment. Direct compression and granulation techniques are preferred. In addition to the active agent, tablets will generally contain inactive, pharmaceutically acceptable carrier materials such as binders, lubricants, disintegrants, fillers, stabilizers, surfactants, coloring agents, and the like.

[000190] Capsules are another oral dosage forms for those compounds of the current invention, e.g., an integrin $\alpha 5\beta 1$ inhibitors, that are orally active, in which case the active agent-containing composition may be encapsulated in the form of a liquid or solid (including particulates such as granules, beads, powders or pellets). Suitable capsules may be either hard or soft, and are generally made of gelatin, starch, or a cellulosic material, with gelatin capsules preferred. Two-piece hard gelatin capsules are preferably sealed, such as with gelatin bands or the like. See, for example, Remington: The Science and Practice of Pharmacy, cited earlier herein, which describes materials and methods for preparing encapsulated pharmaceuticals.

[000191] Oral dosage forms, whether tablets, capsules, caplets, or particulates, if desired, may be formulated so as to provide for controlled release of the compounds of the current invention, for e.g., an integrin $\alpha 5\beta 1$ inhibitors, and in a preferred embodiment, the present formulations are controlled release oral dosage forms.

[000192] Generally, as will be appreciated by those of ordinary skill in the art, sustained release dosage forms are formulated by dispersing the active agent within a matrix of a gradually hydrolyzable material such as a hydrophilic polymer, or by coating a solid, drug-containing dosage form with such a material. Hydrophilic polymers useful for providing a sustained release coating or matrix include, by way of example: cellulosic polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, cellulose acetate, and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, acrylic acid alkyl esters, methacrylic acid alkyl esters, and the like, e.g. copolymers of acrylic acid, methacrylic acid, methyl acrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate; and vinyl polymers and copolymers such as polyvinyl pyrrolidone, polyvinyl acetate, and ethylene-vinyl acetate copolymer.

[000193] Preparations according to this invention for parenteral administration include sterile aqueous and nonaqueous solutions, suspensions, and emulsions. Injectable aqueous solutions contain the active agent in water-soluble form. Examples of nonaqueous solvents or

vehicles include fatty oils, such as olive oil and corn oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, low molecular weight alcohols such as propylene glycol, synthetic hydrophilic polymers such as polyethylene glycol, liposomes, and the like. Parenteral formulations may also contain adjuvants such as solubilizers, preservatives, wetting agents, emulsifiers, dispersants, and stabilizers, and aqueous suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, and dextran. Injectable formulations are rendered sterile by incorporation of a sterilizing agent, filtration through a bacteria-retaining filter, irradiation, or heat. They can also be manufactured using a sterile injectable medium. The active agent may also be in dried, e.g., lyophilized, form that may be rehydrated with a suitable vehicle immediately prior to administration via injection.

[000194] The active agent may also be administered through the skin using conventional transdermal drug delivery systems, wherein the active agent is contained within a laminated structure that serves as a drug delivery device to be affixed to the skin. In such a structure, the drug composition is contained in a layer, or “reservoir,” underlying an upper backing layer. The laminated structure may contain a single reservoir, or it may contain multiple reservoirs. In one embodiment, the reservoir comprises a polymeric matrix of a pharmaceutically acceptable contact adhesive material that serves to affix the system to the skin during drug delivery. Alternatively, the drug-containing reservoir and skin contact adhesive are present as separate and distinct layers, with the adhesive underlying the reservoir which, in this case, may be either a polymeric matrix as described above, or it may be a liquid or hydrogel reservoir, or may take some other form. Transdermal drug delivery systems may in addition contain a skin permeation enhancer.

[000195] In addition to the formulations described previously, the active agent may be formulated as a depot preparation for controlled release of the active agent, preferably sustained release over an extended time period. These sustained release dosage forms are generally administered by implantation (e.g., subcutaneously or intramuscularly or by intramuscular injection).

[000196] Certain compounds or active agents of the present invention are capable of further forming salts. All of these forms are also contemplated within the scope of the claimed invention. The compounds of the present invention can also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in

a compound can be converted to its corresponding ester, e.g., a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, e.g., an acetate, propionate or other ester.

[000197] Certain compounds of the present invention can also be prepared as prodrugs, for example, pharmaceutically acceptable prodrugs. The terms “pro-drug” and “prodrug” are used interchangeably herein and refer to any compound which releases an active parent drug in vivo. Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc.), the compounds of the present invention can be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. “Prodrugs” are intended to include any covalently bonded carriers that release an active parent drug of the present invention in vivo when such prodrug is administered to a subject. Prodrugs in the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or in vivo, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, sulfhydryl, carboxy or carbonyl group is bonded to any group that may be cleaved in vivo to form a free hydroxyl, free amino, free sulfhydryl, free carboxy or free carbonyl group, respectively.

[000198] Examples of prodrugs include, but are not limited to, esters (e.g., acetate, dialkylaminoacetates, formates, phosphates, sulfates and benzoate derivatives) and carbamates (e.g., N,N-dimethylaminocarbonyl) of hydroxy functional groups, esters (e.g., ethyl esters, morpholinoethanol esters) of carboxyl functional groups, N-acyl derivatives (e.g., N-acetyl) N-Mannich bases, Schiff bases and enamines of amino functional groups, oximes, acetals, ketals and enol esters of ketone and aldehyde functional groups in compounds of the invention, and the like, See Bundegaard, H., Design of Prodrugs, p 1-92, Elsevier, New York-Oxford (1985).

[000199] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

[000200] In some embodiments, the composition is suitable for inhalation. In one embodiment, the composition is an inhalable formulation used for treating PAH, or a disorder disclosed herein.

[000201] In still another aspect, the present disclosure provides a pharmaceutical composition comprising an integrin $\alpha 5 \beta 1$ inhibitor and a plurality of particles, wherein the plurality of particles is a plurality of liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino(polyethylene glycol)] (PEG-DSPE) or a plurality of microparticles comprising a hydrophilic polymer. In one embodiment, the composition is suitable for inhalation, in one embodiment, the composition is an inhalable formulation used for treating PAH, or a disorder disclosed herein.

Pharmaceutical Compositions

[000202] The pharmaceutical compositions described herein can be administered in a variety of different ways. Examples include administering a pharmaceutical composition comprising a peptide according to the invention or multimeric, preferably peptide according to the invention and containing a pharmaceutically acceptable carrier via oral, intranasal, rectal, topical, intraperitoneal, intravenous, intramuscular, subcutaneous, subdermal, transdermal, intrathecal, and intracranial methods. For oral administration, the active ingredient can be administered in solid dosage forms, such as capsules, tablets, and powders, or in liquid dosage forms, such as elixirs, syrups, and suspensions.

[000203] Pharmaceutical compositions according to the invention comprise at least one pharmaceutically acceptable carrier, diluent or excipient. Examples of suitable carriers for instance comprise keyhole limpet haemocyanin (KLH), serum albumin (e.g. BSA or RSA) and ovalbumin. In some embodiments said suitable carrier is a solution, for example saline. Examples of excipients which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatine; an excipient such as microcrystalline cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose

as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor. A pharmaceutical composition according to the invention is preferably suitable for human use.

[000204] Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the integrin $\alpha 5 \beta 1$ inhibitor of the invention in a vehicle for injection, such as water or a naturally occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like may also be incorporated.

[000205] Compositions for topical administration can also be formulated according to conventional pharmaceutical practice. "Topical administration" as used herein refers to application to a body surface such as the skin or mucous membranes to locally treat conditions resulting from microbial or parasitic infections. Examples of formulations suitable for topical administration include, but are not limited to a cream, gel, ointment, lotion, foam, suspension, spray, aerosol, powder aerosol. Topical medicaments can be epicutaneous, meaning that they are applied directly to the skin. Topical medicaments can also be inhalational, for instance for application to the mucosal epithelium of the respiratory tract, or applied to the surface of tissues other than the skin, such as eye drops applied to the conjunctiva, or ear drops placed in the ear. Said pharmaceutical composition formulated for topical administration preferably comprises at least one pharmaceutical excipients suitable for topical application, such as an emulsifier, a diluent, a humectant, a preservatives, a pH adjuster and/or water.

Exemplary Embodiments

[000206] 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.

[000207] Certain examples below relate to methods for treating or preventing a disease responsive to an $\alpha 5 \beta 1$ integrin inhibitor by administering a compound of formula (I) to a human in need of such treatment.

EXAMPLES

[000208] 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.

[000209] 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
9-BBN	9-Borabicyclo[3.3.1]nonane dimer
Ac	acetyl
ACN	acetonitrile
APhos Pd G3	(4- (N,N-Dimethylamino)phenyl)di-tert-butylphosphine, [4-(Di-tert-butylphosphino)-N,N-dimethylaniline-2- (2'-aminobiphenyl)]palladium (II) methanesulfonate
Boc	tert-butyloxycarbonyl
Bu	butyl
CMBP	4-Chlorine-4'-Maleimide Benzophenone
cod	cyclooctadiene
Cp	cyclopentadienyl
dba	dibenzylideneacetone
DCM	dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium
DIEA	N,N-diisopropylethylamine
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide

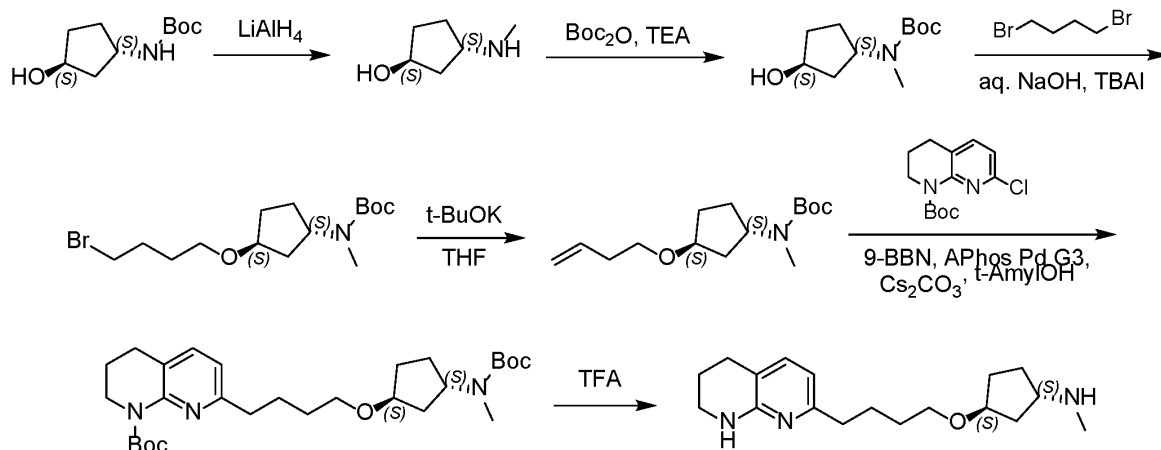
dppf	1,1-bis(diphenylphosphino)ferrocene
dtbpy	4,4'-Di-tert-butyl-2,2'-dipyridyl
Et	ethyl
HATU	Hexafluorophosphate Azabenzotriazole Tetramethyl Uronium
HMDS	Hexamethyldisilazane
Hz	Hertz
iPr	isopropyl
LDA	lithium diisopropyl amide
m-CPBA	Meta-chloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
MTBE	Methyl tert-butyl ether
NBS	N-bromosuccinimide
NMR	Nuclear Magnetic Resonance
Ph	phenyl
Pin	pinacolato
Piv	2,2-dimethylacetyl
prep-HPLC	preparative high performance liquid chromatography
SFC	supercritical fluid chromatography
TBAI	Tetrabutylammonium Iodide
t-Bu	tertiary-butyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	trimethylsilyl
Ts	<i>p</i> -toluenesulfonyl

Analytical Methods, Materials, and Instrumentation

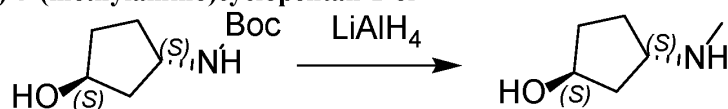
[000210] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers.

Left-Side Intermediates

Preparation of (1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine

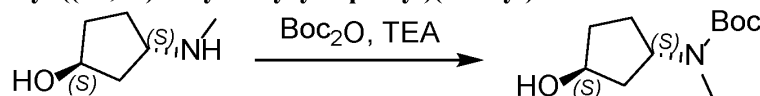


Step 1: (1S,3S)-3-(methylamino)cyclopentan-1-ol



[000211] To a solution of LiAlH_4 (18.86 g, 496.86 mmol, 2 eq) in THF (500 mL) was added dropwise 1/3 solution of tert-butyl ((1S,3S)-3-hydroxycyclopentyl)carbamate (50 g, 248.43 mmol, 1 eq) in THF (500 mL) slowly at 20 °C under N_2 and the solution was stirred at 80 °C, then the 2/3 solution of tert-butyl ((1S,3S)-3-hydroxycyclopentyl)carbamate was added to the solution slowly at 80 °C under N_2 and the solution was stirred at 80 °C for 2 hrs. TLC (Petroleum ether/Ethyl acetate = 1/1) indicated the starting material was consumed completely and one new spot formed. The reaction mixture was quenched by H_2O (20 mL), aq NaOH (15%, 20 mL) and H_2O (60 mL) dropwise slowly at 10 °C under N_2 . The mixture was dried over Na_2SO_4 , filtered and the filtrate was concentrated under reduced pressure to give a residue. (1S,3S)-3-(methylamino)cyclopentan-1-ol (28.61 g, crude) was obtained as yellow oil. The residue was used directly without further purification.

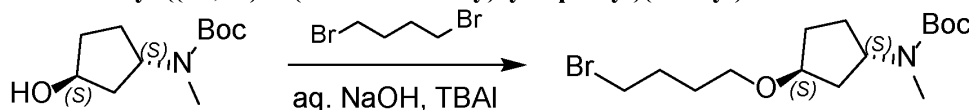
Step 2: tert-butyl ((1S,3S)-3-(methylamino)cyclopentyl)carbamate



[000212] To a solution of (1S,3S)-3-(methylamino)cyclopentan-1-ol (56 g, 486.23 mmol, 1 eq) in THF (600 mL) was added NaHCO_3 (81.69 g, 972.45 mmol, 37.82 mL, 2 eq) in H_2O (90 mL) and $(\text{Boc})_2\text{O}$ (137.95 g, 632.09 mmol, 145.21 mL, 1.3 eq) at 25 °C under N_2 and the

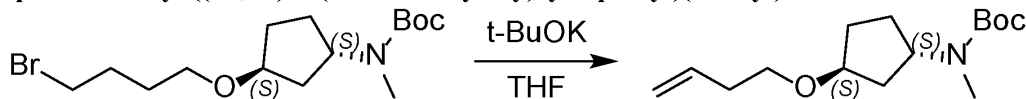
solution was stirred at 25 °C for 16 hrs. TLC (Petroleum ether/Ethyl acetate = 1/1, R_f = 0.4) indicated the starting material was consumed completely and one new spot formed. H₂O (200 mL) was added to the reaction and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 1/1). tert-butyl ((1S,3S)-3-hydroxycyclopentyl)(methyl)carbamate (82.16% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 4.74 (br s, 1H), 4.39 (br s, 1H), 2.73 (s, 3H), 2.03 - 1.97 (m, 2H), 1.88 - 1.72 (m, 2H), 1.66 - 1.54 (m, 2H), 1.47 (s, 9H).

Step 3: tert-butyl ((1S,3S)-3-(4-bromobutoxy)cyclopentyl)(methyl)carbamate



[000213] To a solution of tert-butyl ((1S,3S)-3-hydroxycyclopentyl)(methyl)carbamate (85 g, 394.82 mmol, 1 eq), NaOH (247.09 g, 6.18 mol, 500 mL, 15.65 eq) in toluene (1000 mL) was added 1,4-dibromobutane (170.49 g, 789.64 mmol, 95.25 mL, 2 eq) and TBAI (218.75 g, 592.23 mmol, 1.5 eq) at 25 °C and the solution was stirred at 50 °C for 16 hrs. TLC (Petroleum ether/Ethyl acetate = 5/1, R_f = 0.6) indicated the starting material remained and one new spot formed. The reaction mixture was quenched by addition H₂O (1000mL) at 0 °C, extracted with ethyl acetate (300 mL x 3). The combined organic layers were washed with brine (300 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 5/1). tert-butyl ((1S,3S)-3-(4-bromobutoxy)cyclopentyl)(methyl)carbamate (28.92% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 4.61 (br s, 1H), 3.91 (br d, J = 2.9 Hz, 1H), 3.47 - 3.37 (m, 4H), 2.72 (s, 3H), 2.00 - 1.82 (m, 6H), 1.72 - 1.62 (m, 4H), 1.46 (s, 9H).

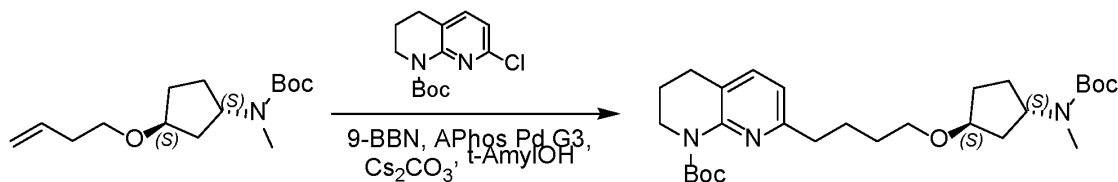
Step 4: tert-butyl ((1S,3S)-3-(but-3-en-1-yloxy)cyclopentyl)(methyl)carbamate



[000214] To a solution of tert-butyl ((1S,3S)-3-(4-bromobutoxy)cyclopentyl)(methyl)carbamate (33 g, 94.21 mmol, 1 eq) in THF (400 mL) was added t-BuOK (26.43 g, 235.52 mmol, 2.5 eq) at 0 °C and the mixture was stirred at 20 °C for 16 hrs. TLC (Petroleum ether/Ethyl acetate = 5/1, R_f = 0.61) indicated the starting material

was consumed completely and one new spot formed. The reaction mixture was quenched by addition H₂O (100 mL) at 0°C, extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 5/1). tert-butyl ((1S,3S)-3-(but-3-en-1-yloxy)cyclopentyl)(methyl)carbamate (90.63% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 5.82 (tdd, *J* = 6.7, 10.3, 17.1 Hz, 1H), 5.14 - 4.99 (m, 2H), 4.61 (br s, 1H), 3.94 - 3.89 (m, 1H), 3.43 - 3.37 (m, 2H), 2.72 (s, 3H), 2.32 - 2.27 (m, 2H), 1.99 - 1.84 (m, 4H), 1.69 - 1.61 (m, 2H), 1.46 (s, 9H).

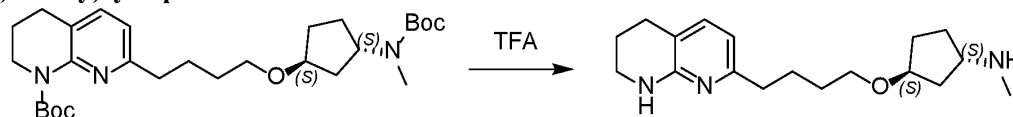
Step 5: tert-butyl 7-(4-(((1S,3S)-3-((tert-butoxycarbonyl)(methyl)amino)-cyclopentyl)oxy)butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate



[000215] To a solution of tert-butyl ((1S,3S)-3-(but-3-en-1-yloxy)cyclopentyl)(methyl)carbamate (23 g, 85.38 mmol, 1 *eq*) in THF (50 mL) was added 9-BBN (0.5 M, 341.53 mL, 2 *eq*) and the mixture was stirred at 25 °C for 2 hrs. TLC (Petroleum ether/Ethyl acetate = 5/1, *R_f* = 0.53) indicated the starting material was consumed completely and one new spot formed. The above solution (34.87 g, 89.09 mmol, 1 *eq*) in tAmylOH (400 mL) was added tert-butyl 7-chloro-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (21.55 g, 80.18 mmol, 0.9 *eq*), APhos Pd G3 (5.66 g, 8.91 mmol, 0.1 *eq*) and Cs₂CO₃ (58.06 g, 178.18 mmol, 2 *eq*) at 25 °C. The mixture was stirred under N₂ at 80°C for another 14 hrs. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was quenched by addition H₂O (500mL) at 0 °C, extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (200 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 1/1). tert-butyl 7-(4-(((1S,3S)-3-((tert-butoxycarbonyl)(methyl)amino)-cyclopentyl)oxy)butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (62.40% yield) was obtained as red oil. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.23 (br d, *J* = 7.6 Hz, 1H),

6.75 (d, $J = 7.6$ Hz, 1H), 3.90 - 3.77 (m, 1H), 3.70 - 3.66 (m, 2H), 3.31 (t, $J = 6.6$ Hz, 2H), 2.65 (br s, 3H), 2.64 (s, 3H), 1.92 - 1.74 (m, 6H), 1.73 - 1.50 (m, 8H), 1.45 (s, 9H), 1.38 (s, 9H).

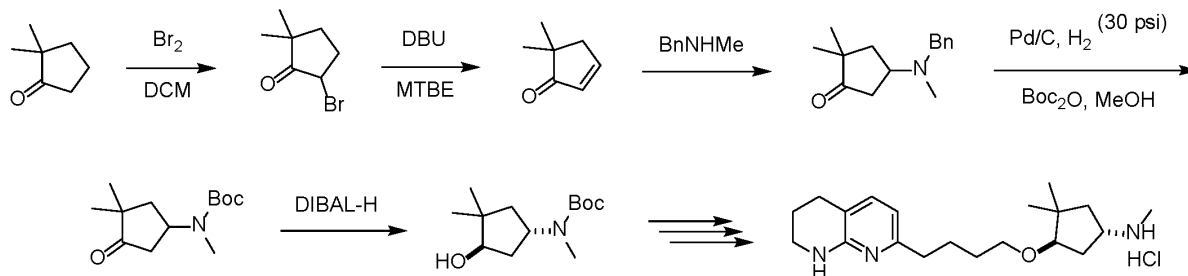
Step 6: (1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine



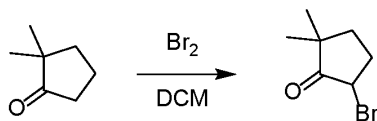
[000216] To a solution of tert-butyl 7-(4-(((1S,3S)-3-((tert-butoxycarbonyl)(methyl)amino)cyclopentyl)oxy)butyl)-3,4-dihydro-1,8-naphthyridine-1(2H)-carboxylate (28 g, 55.59 mmol, 1 *eq*) in DCM (300 mL) was added TFA (153.50 g, 1.35 mol, 100.00 mL, 24.22 *eq*) at 25 °C under N₂ and the solution was stirred at 25 °C for 16 hrs. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. The residue was adjusted to pH ~7 by aq. NaHCO₃ solution, extracted with DCM (100 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Welch Xtimate C18 250 x 100 mm x 10 um; mobile phase: [water (NH₃H₂O+NH₄HCO₃)-ACN];B%: 0%-50%,35min) to give (1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine (54.54% yield) as a yellow oil.

[000217] LCMS: [M+1] = 304.2; SFC: $R_t = 2.070$ min; ¹H NMR (400 MHz, METHANOL-d₄) $\delta = 7.11$ (d, $J = 7.4$ Hz, 1H), 6.35 (d, $J = 7.4$ Hz, 1H), 4.07 - 3.82 (m, 1H), 3.41 - 3.34 (m, 4H), 3.10 (quin, $J = 7.1$ Hz, 1H), 2.68 (t, $J = 6.3$ Hz, 2H), 2.51 (t, $J = 7.6$ Hz, 2H), 2.32 (s, 3H), 2.03 - 1.91 (m, 3H), 1.90 - 1.83 (m, 2H), 1.71 - 1.59 (m, 3H), 1.57 - 1.46 (m, 3H), 1.38 - 1.28 (m, 1H).

Preparation of rac-(1S,4R)-N,3,3-trimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine hydrochloride

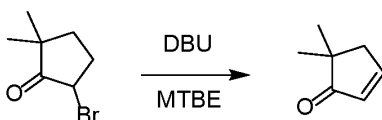


Step 1: 5-bromo-2,2-dimethylcyclopentan-1-one



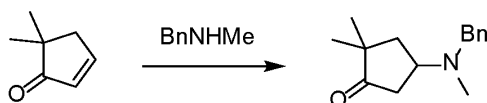
[000218] To a solution of 2,2-dimethylcyclopentan-1-one (250 g, 2.23 mol, 279.64 mL, 1 *eq*) in DCM (2000 mL) was added a solution of Br_2 (391.8 g, 2.45 mol, 126.31 mL, 1.1 *eq*) in DCM (500 mL) at 0 °C. The mixture was allowed to stir at 20 °C for 16 hrs. The reaction was quenched by the addition of H_2O (2000 mL) and sat. $\text{Na}_2\text{S}_2\text{O}_3$ was added at 25 °C until the solution turned colorless. The pH of the solution was adjusted to pH = 7 by the addition of sat. NaHCO_3 . The mixture was diluted with DCM (2000 mL) and extracted with DCM (1000 mL x 3). The organic solutions were combined, washed with brine (1000 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 5-bromo-2,2-dimethylcyclopentan-1-one (350 g, crude) as a brown solid.

Step 2: 5,5-dimethylcyclopent-2-en-1-one

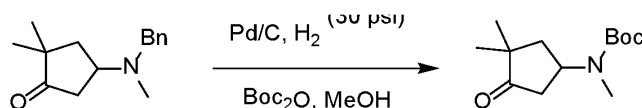


[000219] A mixture of 5-bromo-2,2-dimethylcyclopentan-1-one (350 g, 1.83 mol, 1 *eq*) and DBU (334.65 g, 2.20 mol, 331.34 mL, 1.2 *eq*) in MTBE (2000 mL) was degassed and purged with nitrogen 3 times. The mixture was allowed to stir at 25 °C for 16 hrs under an atmosphere of N_2 . The mixture was distilled under vacuum (62 °C, -0.08 MPa/water pump). 5,5-dimethylcyclopent-2-en-1-one (110 g, 798.89 mmol, 44.81% yield over 2 steps) was obtained as a light yellow oil.

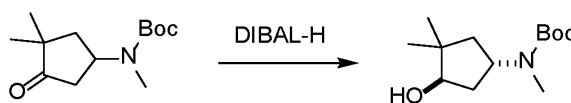
Step 3: 4-(benzyl(methyl)amino)-2,2-dimethylcyclopentan-1-one



[000220] BnMeNH (114.96 g, 948.68 mmol, 122.43 mL, 0.95 *eq*) was added to 5,5-dimethylcyclopent-2-en-1-one (110 g, 998.61 mmol, 1 *eq*) dropwise at 25 °C and the mixture was allowed to stir at 50 °C for 2 hrs. The reaction mixture was cooled to 0 °C and solids were formed. The mixture was filtered and the filter cake was dried under vacuum. 4-(benzyl(methyl)amino)-2,2-dimethylcyclopentan-1-one (51.95% yield) was obtained as a yellow solid.

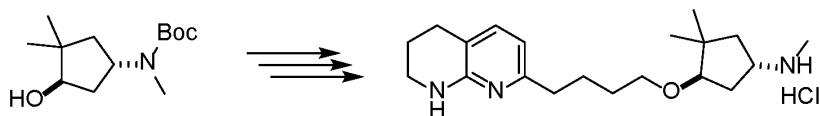
Step 4: tert-butyl (3,3-dimethyl-4-oxocyclopentyl)(methyl)carbamate

[000221] To a solution of Pd/C (5 g, 10% purity) in MeOH (1000 mL) was added Boc₂O (84.91 g, 389.05 mmol, 89.38 mL, 1.5 *eq*) and 4-(benzyl(methyl)amino)-2,2-dimethylcyclopentan-1-one (60 g, 259.37, 1 *eq*) under Ar at 25 °C. The suspension was degassed under vacuum and purged with H₂ three times. The mixture was allowed to stir under H₂ (30 psi) at 25 °C for 12 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=1/0 to 3/1). tert-butyl (3,3-dimethyl-4-oxocyclopentyl)(methyl)carbamate (51.92% yield) was obtained as light yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 4.81 (br d, *J* = 1.0 Hz, 1H), 2.77 (s, 3H), 2.61 - 2.48 (m, 1H), 2.39 - 2.25 (m, 1H), 2.02 - 1.93 (m, 1H), 1.89 - 1.77 (m, 1H), 1.47 (s, 9H), 1.13 (s, 3H), 1.06 (s, 3H).

Step 6: rac-tert-butyl ((1S,4R)-4-hydroxy-3,3-dimethylcyclopentyl)(methyl)carbamate

[000222] To a solution of tert-butyl (3,3-dimethyl-4-oxocyclopentyl)(methyl)carbamate (130 g, 538.69 mmol, 1 *eq*) in THF (1000 mL) was added DIBAL-H (1 M, 538.69 mL, 1 *eq*) at 0 °C under an atmosphere of N₂. Then the reaction mixture was warmed up to 20 °C and stirred at 20 °C under an atmosphere of N₂ for 16 hrs. The mixture was quenched by the addition of Na₂SO₄·10 H₂O (100 g). Then the mixture was dried over Na₂SO₄, filtered and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate=1/0 to 3/1). Rac-tert-butyl ((1S,4R)-4-hydroxy-3,3-dimethylcyclopentyl)(methyl)carbamate (41.96% yield) was obtained as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 4.72 (m, 1H), 3.83 (t, *J* = 7.8 Hz, 1H), 2.73 (s, 3H), 2.06 - 1.96 (m, 2H), 1.88 (br dd, *J* = 7.7, 10.4 Hz, 1H), 1.75 (dd, *J* = 8.6, 12.9 Hz, 1H), 1.46 (s, 9H), 1.06 (s, 3H), 0.94 (s, 3H).

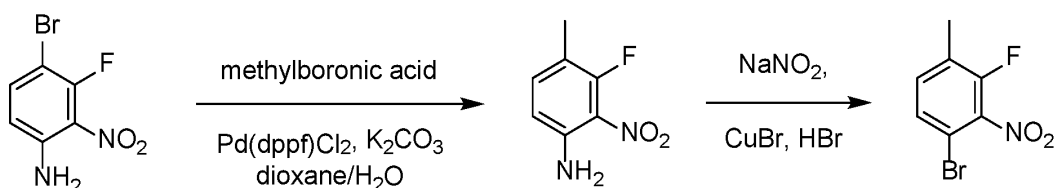
Final Steps: rac-(1S,4R)-N,3,3-trimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine hydrochloride



[000223] Rac-tert-butyl ((1S,4R)-4-hydroxy-3,3-dimethylcyclopentyl)(methyl)carbamate was converted to rac-(1S,4R)-N,3,3-trimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine hydrochloride by methods similar to those described above in Steps 3-6 for the synthesis of rac-(1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine. LCMS $[M + 1] = 332.2$, 96.78% ^1H NMR (400 MHz, CD_3OD) $\delta = 7.58$ (d, $J = 7.3$ Hz, 1H), 6.60 (d, $J = 7.4$ Hz, 1H), 3.64 (br dd, $J = 6.8, 8.5$ Hz, 1H), 3.57 (s, 5H), 2.82 (t, $J = 6.1$ Hz, 2H), 2.73 (t, $J = 7.7$ Hz, 2H), 2.65 (s, 3H), 2.13 - 1.93 (m, 5H), 1.82 - 1.73 (m, 2H), 1.62 (br dd, $J = 6.2, 8.7$ Hz, 2H), 1.45 (dd, $J = 8.8, 13.1$ Hz, 1H), 1.11 (s, 3H), 0.94 (s, 3H).

Right-Side Intermediates

Preparation of 1-bromo-3-fluoro-4-methyl-2-nitrobenzene



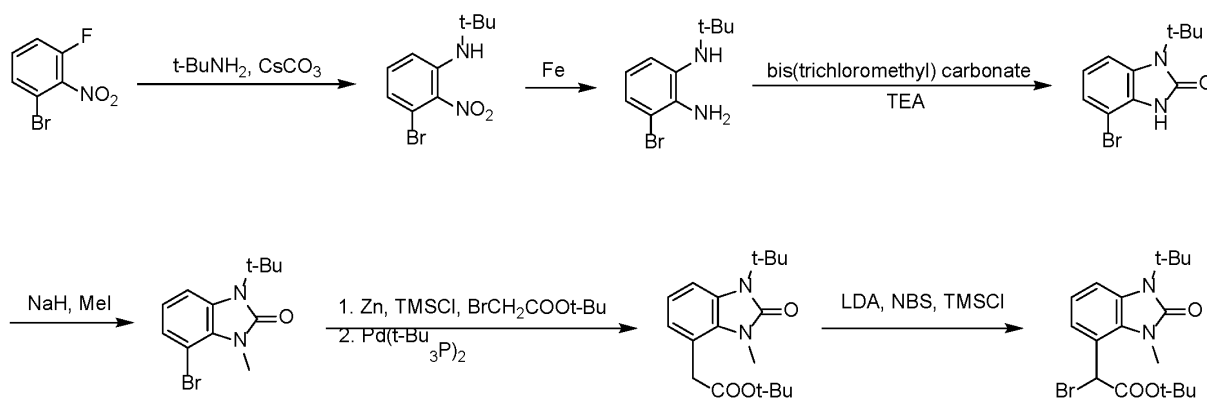
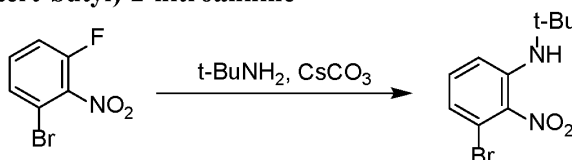
Step 1: 3-fluoro-4-methyl-2-nitroaniline

[000224] Two reactions were carried out in parallel. To a mixture of 4-bromo-3-fluoro-2-nitroaniline (25 g, 106.38 mmol, 1 *eq*) and methylboronic acid (31.84 g, 531.89 mmol, 5 *eq*) in dioxane (250 mL) and H_2O (62.5 mL) were added $\text{Pd}(\text{dppf})\text{Cl}_2$ (3.89 g, 5.32 mmol, 0.05 *eq*) and K_2CO_3 (44.11 g, 319.13 mmol, 3 *eq*) at 25°C . The mixture was allowed to stir at 90°C for 16 hrs under an atmosphere of N_2 . The mixture was quenched by the addition of H_2O (300 mL) and filtered. The filtrate was extracted with ethyl acetate (200 mL x 3). The organic solutions were combined, washed with brine (150 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/1 to 5/1). 3-fluoro-4-methyl-2-nitroaniline (55.25% yield) was obtained as a yellow oil. LCMS: $R_t = 0.557$ min, $[M+1] = 171.1$, 55.30%. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.11$ (t, $J = 8.1$ Hz, 1H), 6.50 (dd, $J = 1.6, 8.6$ Hz, 1H), 2.19 (d, $J = 2.5$ Hz, 3H).

Step 2: 1-bromo-3-fluoro-4-methyl-2-nitrobenzene

[000225] To a solution of HBr (111.75 g, 455.77 mmol, 75.00 mL, 33% purity, 15.51 *eq*) in H₂O (500 mL) was added 3-fluoro-4-methyl-2-nitroaniline and the mixture was allowed to stir at 70°C for 30 min. The mixture is cooled to -5 °C and NaNO₂ (12.57 g, 182.20 mmol, 6.2 *eq*) dissolved in H₂O (62.5 mL) was added slowly. The mixture was allowed to stir at -5°C for 30 min. A solution of CuBr (52.70 g, 367.34 mmol, 11.19 mL, 12.5 *eq*) in aqueous HBr (260.75 g, 1.06 mol, 175.00 mL, 33% purity, 36.19 *eq*) was added dropwise at 0 °C. The mixture was allowed to stir at 70 °C for 30 min. The reaction was quenched by the addition of water (200 mL) and extracted with DCM (200 mL x 3). The organic solutions were combined, washed with aq. NaOH (4 M, 150 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 5/1). 1-bromo-3-fluoro-4-methyl-2-nitrobenzene (79.97% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.36 (dd, *J* = 1.4, 8.3 Hz, 1H), 7.26 - 7.20 (m, 1H), 2.33 (d, *J* = 2.1 Hz, 3H).

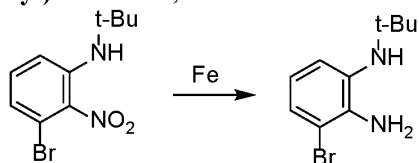
Preparation of tert-butyl 2-bromo-2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzof[d]imidazol-4-yl)acetate

**Step 1: 3-bromo-N-(tert-butyl)-2-nitroaniline**

[000226] To a solution of 1-bromo-3-fluoro-2-nitrobenzene (50 g, 227.28 mmol, 1 *eq*) in DMSO (100 mL) was added Cs₂CO₃ (148.10 g, 454.55 mmol, 2 *eq*) and t-BuNH₂ (16.62 g, 227.28 mmol, 23.88 mL, 1 *eq*) at 25°C. The mixture was stirred at 60°C for 12 hrs. TLC (Petroleum ether: Ethyl acetate = 5:1, R_f = 0.63) showed starting material was consumed

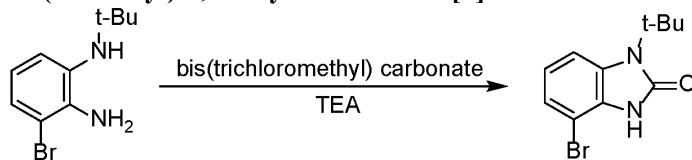
completely, and a new spot with lower polarity was detected. The mixture was quenched by H₂O (300 mL) and ethyl acetate (150 mL) was added to the mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate (100 mL x 3). The combined organic phases were washed with brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give 3-bromo-N-(tert-butyl)-2-nitroaniline (64.4% yield) as red oil. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.21 - 7.16 (m, 2H), 6.98 (dd, J = 2.4, 6.5 Hz, 1H), 1.39 (s, 9H)

Step 2: 3-bromo-N¹-(tert-butyl)benzene-1,2-diamine



[000227] To the solution of 3-bromo-N-(tert-butyl)-2-nitroaniline (30 g, 109.84 mmol, 1 eq) in CH₃COOH (75 mL) and EtOAc (225 mL) was added H₂O (25 mL) at 25°C. The mixture was heated at 50°C. Then Fe (30.67 g, 549.20 mmol, 5 eq) was added in portions at 50°C and then the mixture was heated to 80°C and then stirred for 16 hrs. TLC (Petroleum ether: Ethyl acetate = 5:1, R_f = 0.61) showed starting material was consumed completely, and some new spots with larger polarity were detected. The reaction mixture was filter at 80°C and then concentrated to give a residue. The residue was dissolved with EtOAc (200 mL) and adjusted pH to 7-8 by sat. NaHCO₃. The organic phase was separated and washed by brine (100 mL x 3). The organic phase was dried over Na₂SO₄, filtered and concentrated to give a crude product. The residue was purified by flash silica gel chromatography (ISCO®; 200 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum gradient @ 150 mL/min). 3-bromo-N¹-(tert-butyl)benzene-1,2-diamine (74.9% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.00 (dd, J = 1.3, 8.0 Hz, 1H), 6.88 (dd, J = 1.3, 7.9 Hz, 1H), 6.52 (t, J = 7.9 Hz, 1H), 1.27 (s, 9H).

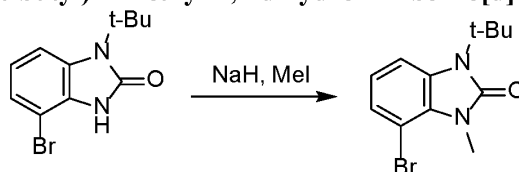
Step 3: 4-bromo-1-(tert-butyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one



[000228] To a solution of 3-bromo-N¹-(tert-butyl)benzene-1,2-diamine (20 g, 82.26 mmol, 1 eq) in THF (200 mL) was added TEA (24.97 g, 246.77 mmol, 3 eq) and bis(trichloromethyl) carbonate (24.41 g, 82.26 mmol, 1 eq). The mixture was stirred at 20°C

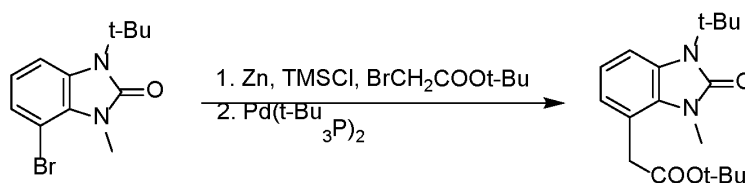
for 16 hrs. LCMS ($R_t = 0.675$ min) showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction was quenched by ice water (200 mL) slowly, adjusted to pH = 7, extracted with ethyl acetate (100 mL x 2). The combined organic phase was washed with brine (200 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 200 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum gradient @ 150 mL/min). 4-bromo-1-(tert-butyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (84.0% yield) was obtained as a yellow oil. LCMS: $[M+1] = 270.9$. ^1H NMR (400 MHz, METHANOL- d_4) $\delta = 7.45$ (d, $J = 8.3$ Hz, 1H), 7.15 (d, $J = 8.2$ Hz, 1H), 6.91 (t, $J = 8.3$ Hz, 1H), 1.77 (s, 9H).

Step 4: 4-bromo-1-(tert-butyl)-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one



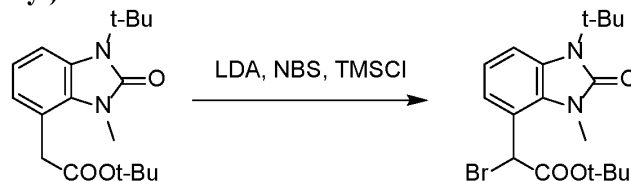
[000229] To a solution of 4-bromo-1-(tert-butyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (18.6 g, 69.11 mmol, 1 eq) in DMF (190 mL) was added and NaH (5.53 g, 138.22 mmol, 60% purity, 2 eq). The mixture was stirred at 0°C for 0.5 hr. Then MeI (19.62 g, 138.22 mmol, 62.42 mL, 2 eq) was added the above mixture, the mixture was stirred at 20°C for 1 hr. LCMS ($R_t = 1.661$ min) showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was quenched by addition NH_4Cl (200 mL) at 0°C, and extracted with EtOAc (150 mL x 3). The combined organic layers were washed with brine 450 mL, dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (ISCO®; 200 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum gradient @ 150 mL/min). 4-bromo-1-(tert-butyl)-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (97.09% yield) was obtained as a yellow oil. LCMS: $[M+1] = 283.1$. ^1H NMR (400 MHz, METHANOL- d_4) $\delta = 7.52$ (d, $J = 8.3$ Hz, 1H), 7.21 (d, $J = 8.1$ Hz, 1H), 6.92 (t, $J = 8.3$ Hz, 1H), 3.70 (s, 3H), 1.77 (s, 9H).

Step 5: tert-butyl 2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate



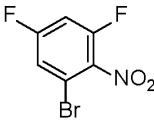
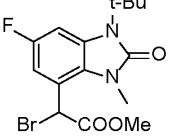
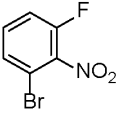
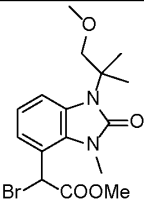
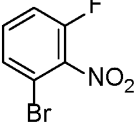
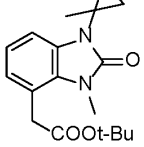
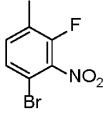
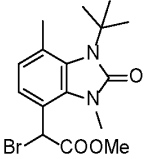
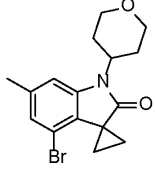
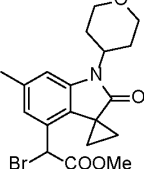
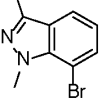
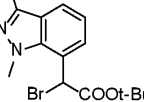
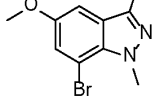
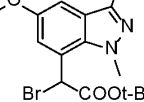
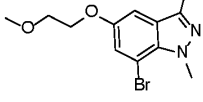
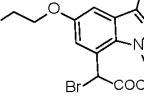
[000230] To a solution of 4-bromo-1-(tert-butyl)-3-methyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (19 g, 67.10 mmol, 1 eq) and bromo-(2-tert-butoxy-2-oxo-ethyl)zinc (1M, 167.75 mL, 2.5 eq) in THF (200 mL) was added Pd(t-Bu₃P)₂ (1.71 g, 6.71 mmol, 0.05 eq). The mixture was stirred at 80°C for 2 hrs. TLC (Petroleum ether: Ethyl acetate = 5:1, R_f = 0.43) showed starting material was consumed completely, and a new spot with larger polarity was detected. The reaction was quenched by ice water (200 mL) slowly, extracted with ethyl acetate (100 mL x 2). The combined organic phase was washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 200 g SepaFlash® Silica Flash Column, Eluent of 0-50% Ethyl acetate/Petroleum gradient @ 120 mL/min). tert-butyl 2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (93.61% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.47 (dd, *J* = 0.7, 8.2 Hz, 1H), 7.02 - 6.94 (m, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 3.91 (s, 2H), 3.57 (s, 3H), 1.79 (s, 9H), 1.44 (s, 9H).

Step 6: tert-butyl 2-bromo-2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate

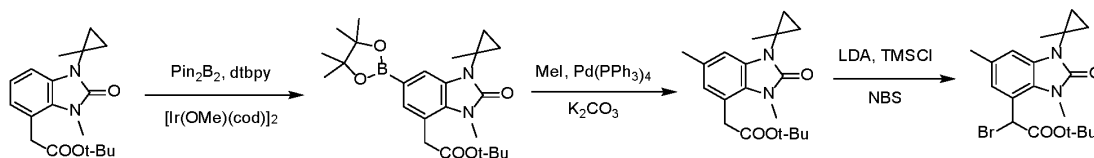


[000231] To a solution of tert-butyl 2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (3 g, 9.42 mmol, 1 eq) in THF (30 mL) was added LDA (2 M, 14.13 mL, 3 eq) at -70°C and the mixture was stirred at -70°C for 45 min. TMSCl (3.07 g, 28.27 mmol, 3.59 mL, 3 eq) was added. After 15 min, a solution of NBS (5.03 g, 28.27 mmol, 3 eq) in THF (15 mL) was added and the mixture was stirred at -70 °C for 1 hr. TLC (Petroleum ether: Ethyl acetate = 5:1, R_f = 0.69) showed starting material was consumed completely, and a new spot with lower polarity was detected. The reaction was quenched by ice water (30 mL) slowly, extracted with ethyl acetate (15 mL x 2). The combined organic phase was washed with brine (30 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The residue was purified by flash silica gel chromatography (ISCO®; 20 g SepaFlash® Silica Flash Column, Eluent of 0~50% Ethyl acetate/Petroleum gradient @ 80 mL/min). tert-butyl 2-bromo-2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (90.83% yield) was obtained as a yellow oil.

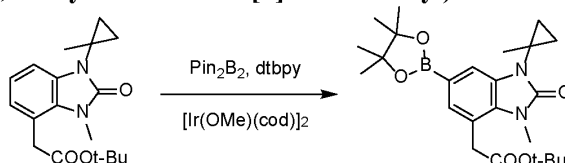
[000232] Intermediates in the table below were prepared according to similar procedures as those described for tert-butyl 2-bromo-2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate from the starting materials shown, substituting the appropriate reagents and purified using appropriate conditions:

Starting Materials	Product	Product Characterization
 <chem>Brc1cc(F)c(F)cc1[N+](=O)[O-]</chem> <chem>CC(C)(C)N</chem>	 <chem>CC(C)(C)N1C(=O)N(C1Cc2cc(F)c(F)cc2[N+](=O)[O-])C(C)C</chem>	^1H NMR (400 MHz, CDCl_3) δ = 7.16 (dd, J = 2.4, 9.9 Hz, 1H), 7.11 (dd, J = 2.4, 10.4 Hz, 1H), 6.10 (s, 1H), 3.84 (s, 3H), 3.71 (s, 3H), 1.78 (s, 9H).
 <chem>Brc1cc(F)cc([N+](=O)[O-])cc1</chem> <chem>CC(C)(C)N</chem>	 <chem>CC(C)(C)N1C(=O)N(C1Cc2cc(F)cc([N+](=O)[O-])cc2)C(C)C</chem>	^1H NMR (400 MHz, CDCl_3) δ = 7.40 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.01 (t, J = 8.2 Hz, 1H), 6.15 (s, 1H), 3.88 (d, J = 7.6 Hz, 2H), 3.83 (s, 3H), 3.74 (s, 3H), 3.36 (s, 3H), 1.79 (s, 6H).
 <chem>Brc1cc(F)cc([N+](=O)[O-])cc1</chem> <chem>C1CC1N</chem>	 <chem>CC(C)(C)N1C(=O)N(C1Cc2cc(F)cc([N+](=O)[O-])cc2)C(C)C</chem>	^1H NMR (400 MHz, CDCl_3) δ = 7.15 (dd, J = 1.0, 7.8 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 3.82 (s, 2H), 3.60 (s, 3H), 1.48 (s, 3H), 1.46 (s, 9H), 1.18-1.11 (m, 2H), 1.00-0.94 (m, 2H).
 <chem>Brc1cc(F)cc([N+](=O)[O-])cc1</chem> <chem>CC(C)(C)N</chem>	 <chem>CC(C)(C)N1C(=O)N(C1Cc2cc(F)cc([N+](=O)[O-])cc2)C(C)C</chem>	^1H NMR (400 MHz, CDCl_3) δ = 7.30 (s, 1H), 6.88 (d, J = 8.4 Hz, 1H), 6.15 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 2.63 (s, 3H), 1.77 (s, 9H).
 <chem>Brc1cc(F)cc([N+](=O)[O-])cc1</chem> <chem>CC(C)(C)N</chem>	 <chem>CC(C)(C)N1C(=O)N(C1Cc2cc(F)cc([N+](=O)[O-])cc2)C(C)C</chem>	LCMS $[M+1] = 410.1$; ^1H NMR (400 MHz, CDCl_3) δ = 6.94 (s, 1H), 6.74 (s, 1H), 4.74 (s, 1H), 4.42-4.25 (m, 1H), 3.97-3.88 (m, 3H), 3.57 (s, 3H), 3.31 (dt, J = 1.8, 12.0 Hz, 3H), 2.34-2.28 (m, 2H), 2.17 (s, 3H), 1.79-1.70 (m, 1H), 1.69-1.64 (m, 1H), 1.54-1.48 (m, 2H).
 <chem>Brc1cc(F)cc([N+](=O)[O-])cc1</chem> <chem>CC(C)(C)N</chem>	 <chem>CC(C)(C)N1C(=O)N(C1Cc2cc(F)cc([N+](=O)[O-])cc2)C(C)C</chem>	^1H NMR (400 MHz, CDCl_3) δ = 7.64 (d, J = 8.0 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 6.06 (s, 1H), 4.36 (s, 3H), 2.55 (s, 3H), 1.50 (s, 9H).
 <chem>Brc1cc(F)cc([N+](=O)[O-])cc1</chem> <chem>CC(C)(C)N</chem>	 <chem>CC(C)(C)N1C(=O)N(C1Cc2cc(F)cc([N+](=O)[O-])cc2)C(C)C</chem>	^1H NMR (400 MHz, CDCl_3) δ = 7.35 (br s, 1H), 6.97 (d, J = 2.2 Hz, 1H), 5.97 (s, 1H), 4.31 (s, 3H), 3.86 (s, 3H), 2.51 (s, 3H), 1.50 (s, 9H).
 <chem>Brc1cc(F)cc([N+](=O)[O-])cc1</chem> <chem>CC(C)(C)N</chem>	 <chem>CC(C)(C)N1C(=O)N(C1Cc2cc(F)cc([N+](=O)[O-])cc2)C(C)C</chem>	^1H NMR (400 MHz, CDCl_3) δ = 7.42 (br s, 1H), 7.01 (d, J = 2.2 Hz, 1H), 5.96 (br s, 1H), 4.30 (s, 3H), 4.19 - 4.14 (m, 2H), 3.78 (dd, J = 4.1, 5.2 Hz, 2H), 3.48 (s, 3H), 2.49 (s, 3H), 1.49 (s, 9H).

Preparation of tert-butyl 2-bromo-2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate

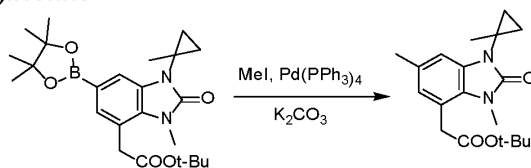


Step 1: tert-butyl 2-(3-methyl-1-(1-methylcyclopropyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate



[000233] To a solution of tert-butyl 2-(3-methyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (2 g, 6.32 mmol, 1 *eq*) in dioxane (40 mL) was added dtbpy (101.80 mg, 379.27 μ mol, 0.06 *eq*) and [Ir(OMe)(cod)]₂ (251.41 mg, 379.27 μ mol, 0.06 *eq*) and Pin₂B₂ (3.21 g, 12.64 mmol, 2 *eq*) at 20°C under N₂. The mixture was heated up to 80°C and stirred at 80°C under N₂ for 16 hrs. TLC (Petroleum ether/ethyl acetate = 5/1, R_f = 0.52) indicated the starting material was consumed completely, and one major new spot with lower polarity was detected. The reaction mixture was filtered and concentrated under reduced pressure to give a residue to give crude product. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 10/1). tert-Butyl 2-(3-methyl-1-(1-methylcyclopropyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (4.5 g, crude) was obtained as a yellow oil.

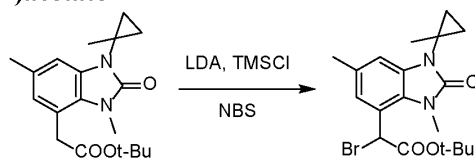
Step 2: tert-butyl 2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate



[000234] To a solution of tert-butyl 2-(3-methyl-1-(1-methylcyclopropyl)-2-oxo-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (3.5 g, 7.91 mmol, 1 *eq*.) in toluene (35 mL), EtOH (14 mL) and H₂O (14 mL) was added K₂CO₃ (3.28 g, 23.74 mmol, 3 *eq*.), Pd(PPh₃)₄ (457.15 mg, 395.61 μ mol, 0.05 *eq*.) and MeI (5.62 g, 39.56 mmol, 2.46 mL, 5 *eq*.) in turns at 20°C under N₂. Then the reaction mixture was heated up to 100°C and stirred at 100°C under N₂ for 16 hrs. LCMS (R_t = 0.797, [M+1] = 331.1,

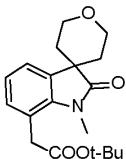
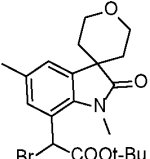
56.55%) showed compound **2** was consumed completely, 56.55% of desired MS was detected. The reaction mixture was quenched with water (150 mL) at 20°C and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/0 to 80/20). tert-Butyl 2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (42.08% yield) was obtained as a yellow oil.

Step 3: tert-butyl 2-bromo-2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate

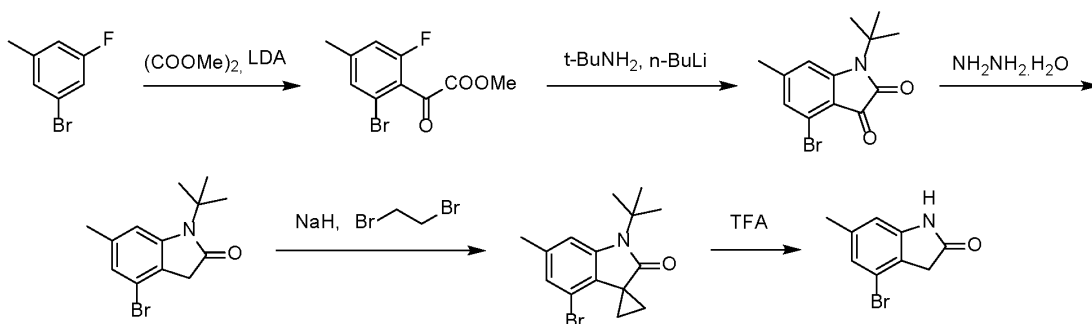


[000235] To a solution of tert-butyl 2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (550 mg, 1.66 mmol, 1 eq) in THF (10 mL) and then added LDA (2 M, 2.50 mL, 3 eq) at -70°C under N₂. Then the mixture was stirred at -70°C under N₂ for 0.5 hrs. Then to the above reaction mixture was added TMSCl (542.52 mg, 4.99 mmol, 633.78 µL, 3 eq) at -70°C under N₂. Then the mixture was stirred at -70°C under N₂ for 0.5 hrs. Then to the above reaction mixture was added the solution of NBS (888.79 mg, 4.99 mmol, 3 eq) in THF (10 mL) at -70°C under N₂. Then the mixture was stirred at -70°C under N₂ for 1 hr. LCMS showed the starting material was consumed completely, and 87.45% of the desired MS was detected. The reaction mixture was quenched with saturated aqueous NH₄Cl (100 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated to give residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 10/1). tert-Butyl 2-bromo-2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate (77.79% yield) was obtained as a yellow oil. LCMS: [M+1] = 411.1. ¹H NMR (400 MHz, CDCl₃) δ = 7.15 (s, 1H), 6.99 (d, *J* = 0.8 Hz, 1H), 5.94 (s, 1H), 3.71 (s, 3H), 2.41 (s, 3H), 2.05 (s, 2H), 1.49 (s, 9H), 1.15-1.12 (m, 2H), 1.00-0.96 (m, 2H), 0.21-0.13 (m, 1H).

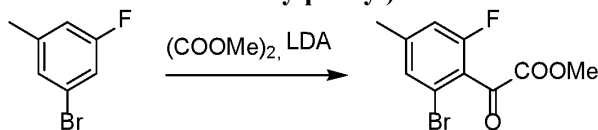
[000236] Intermediates in the table below were prepared according to similar procedures as those described for tert-butyl 2-bromo-2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)acetate from the starting materials shown, substituting the appropriate reagents and purified using appropriate conditions:

Starting Material	Product	Product Characterization
		$^1\text{H NMR}$ (400 MHz, CDCl_3) δ = 7.37 (s, 1H), 7.07 (d, J = 1.0 Hz, 1H), 5.98 (s, 1H), 4.32 - 4.25 (m, 2H), 3.94 - 3.87 (m, 2H), 3.57 (s, 3H), 2.34 (s, 3H), 1.97 - 1.88 (m, 2H), 1.78 - 1.71 (m, 2H), 1.49 (s, 9H).

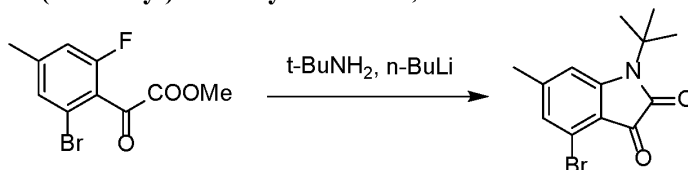
Preparation of 4-bromo-6-methylindolin-2-one



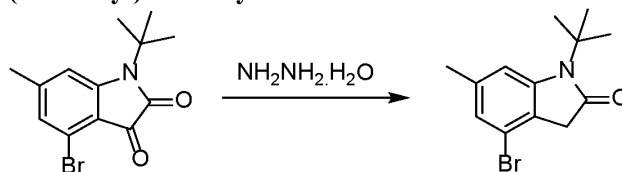
Step 1: methyl 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxoacetate



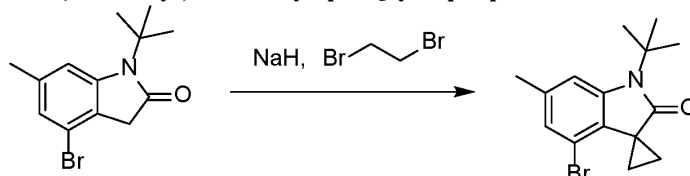
[000237] To the solution of 1-bromo-3-fluoro-5-methylbenzene (100 g, 529.03 mmol, 1 *eq*) in THF (500 mL) was added LDA (2 M, 317.42 mL, 1.2 *eq*) dropwise at -70°C under N_2 . Then the reaction mixture was stirred at -70°C for 0.5 hrs. Then to the above reaction mixture was added the solution of dimethyl oxalate (81.21 g, 687.74 mmol, 1.3 *eq*) in THF (500 mL) at -70°C under N_2 . Then the reaction mixture was stirred at -70°C under N_2 for 1 hr. TLC (Petroleum ether/Ethyl acetate = 5/1, R_f = 0.43) indicated the starting material was consumed completely and one new spot formed. The residue was quenched with aq. NH_4Cl (1000 mL), extracted with EtOAc (500mL x3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/1 to 5/1). Methyl 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxoacetate (65.28% yield) was obtained as red oil. $^1\text{H NMR}$ (400 MHz, CHLOROFORM-d) δ = 7.29 (s, 1H), 6.96 (d, J = 10.3 Hz, 1H), 3.95 (s, 3H), 2.40 (s, 3H).

Step 2: 4-bromo-1-(tert-butyl)-6-methylindoline-2,3-dione

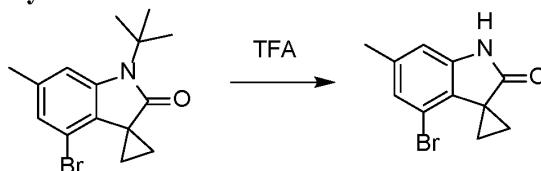
[000238] To a solution of t-BuNH₂ (5.85 g, 79.98 mmol, 8.40 mL, 2.2 *eq*) in THF (100 mL) was added n-BuLi (2.5 M, 30.54 mL, 2.1 *eq*) at -70°C under N₂. The mixture was stirred at -70°C for 0.5 hrs. Methyl 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxoacetate (10 g, 36.35 mmol, 1 *eq*) in THF (100 mL) was added at -70°C under N₂. The mixture was stirred at 20°C for 2 hrs. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was quenched with iced aqueous HCl (200 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with PE: EA = 3:1 at 20°C for 30 min. 4-Bromo-1-(tert-butyl)-6-methylindoline-2,3-dione (63.47% yield) was obtained as a red solid. LCMS: [M+1] = 296.0. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.07 (s, 2H), 2.42 (s, 3H), 1.74 (s, 9H)

Step 3: 4-bromo-1-(tert-butyl)-6-methylindolin-2-one

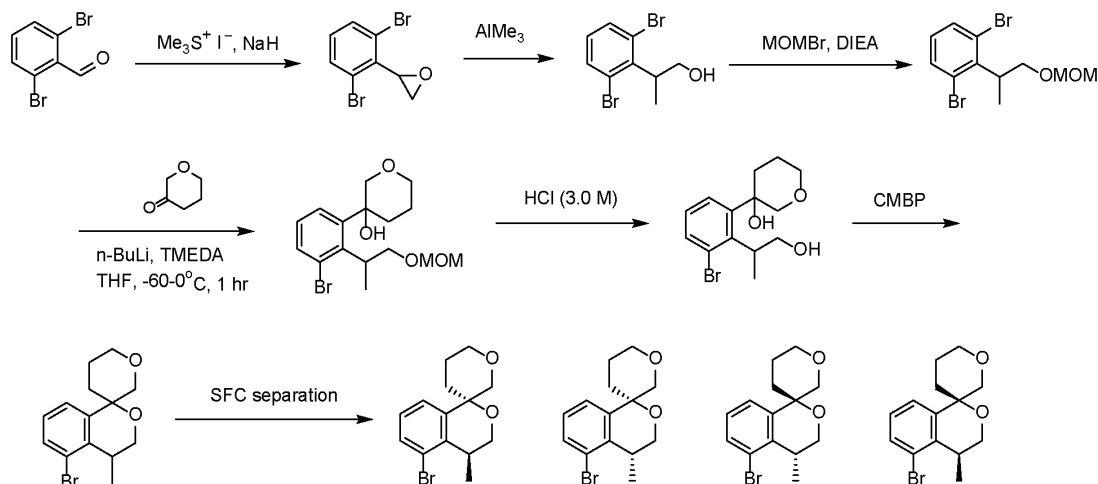
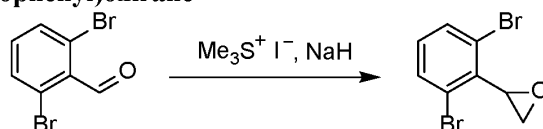
[000239] To a solution of 4-bromo-1-(tert-butyl)-6-methylindoline-2,3-dione (39 g, 131.69 mmol, 1 *eq*) in glycol (400 mL) was added NH₂NH₂.H₂O (82.56 g, 1.62 mol, 80 mL, 98% purity, 12.27 *eq*) at 25°C under N₂. The mixture was stirred at 130°C for 3 hrs. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure and quenched by addition H₂O (200 mL), extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was used directly without further purification. 4-Bromo-1-(tert-butyl)-6-methylindolin-2-one (94.19% yield) was obtained as a red solid. LCMS: [M+1] = 284.0. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 6.99 (d, J = 9.7 Hz, 2H), 3.38 (s, 2H), 2.36 (s, 3H), 1.71 (s, 9H)

Step 4: 4'-bromo-1'-(tert-butyl)-6'-methylspiro[cyclopropane-1,3'-indolin]-2'-one

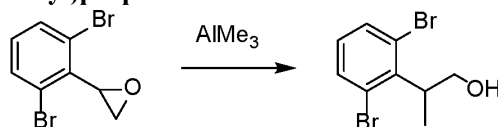
[000240] To a solution of 4-bromo-1-(tert-butyl)-6-methylindolin-2-one (42 g, 148.84 mmol, 1 *eq*) in DMF (400 mL) was added NaH (17.86 g, 446.53 mmol, 60% purity, 3 *eq*) at 0°C under N₂ and the solution was stirred at 0°C for 0.5 hrs, then 1, 2-dibromoethane (83.89 g, 446.53 mmol, 33.69 mL, 3 *eq*) was added to the solution at 0°C and the solution was stirred at 25°C for 1 hr. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction was quenched with sat. NH₄Cl (400 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 5/1). 4'-Bromo-1'-(tert-butyl)-6'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (47.96% yield) was obtained as a yellow oil. LCMS: [M+1] = 310.1. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.03 (s, 1H), 6.85 (s, 1H), 2.28 (s, 3H), 2.15 (q, J = 3.7 Hz, 2H), 1.67 (s, 9H), 1.35 (q, J = 3.7 Hz, 2H), 1.31 (s, 3H).

Step 5: 4-bromo-6-methylindolin-2-one

[000241] To a solution of 4'-bromo-1'-(tert-butyl)-6'-methylspiro[cyclopropane-1,3'-indolin]-2'-one (22 g, 71.38 mmol, 1 *eq*) in TFA (100 mL) under N₂ and the solution was stirred at 25°C for 0.5 hrs. LCMS showed the starting material was consumed completely and one main peak with desired mass was detected. The reaction was concentrated under reduced pressure to give a residue. The crude product was triturated with MeCN at 20°C for 30 min. 4-Bromo-6-methylindolin-2-one (77.80% yield) was obtained as a yellow solid. LCMS: [M+1] = 253.9. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 6.94 (s, 1H), 6.76 (s, 1H), 2.33 (s, 3H), 2.28 (d, J = 3.9 Hz, 2H), 1.56 (d, J = 3.9 Hz, 2H).

Preparation of 5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]**Step 1: 2-(2,6-dibromophenyl)oxirane**

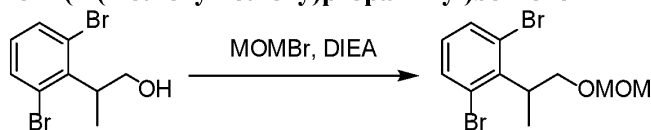
[000242] To a solution of 2,6-dibromobenzaldehyde (30 g, 113.67 mmol, 1 eq) and $\text{Me}_3\text{S}^+\text{I}^-$ (69.59 g, 341.02 mmol, 3 eq) in THF (500 mL) and DMSO (100 mL) was added NaH (13.64 g, 341.02 mmol, 60% purity, 3 eq) at -10°C under N_2 . The mixture was stirred at 20°C for 1 hr. TLC (petroleum ether/ethyl acetate = 10/1, R_f = 0.6) indicated 2,6-dibromobenzaldehyde was consumed, and one major new spot with larger polarity was detected. The mixture was quenched by aq. NH_4Cl (1.5 L) and extracted with ethyl acetate (500 mL x 3). The combined organic layers were washed with brine (1000 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The crude product was triturated with EtOH at 20°C for 10 min to get 2-(2,6-dibromophenyl)oxirane (66.47% yield) as a white solid. ^1H NMR (400 MHz, CHLOROFORM-d) δ = 7.55 (d, J = 8.1 Hz, 2H), 7.06 (t, J = 8.1 Hz, 1H), 3.94-3.85 (m, 1H), 3.33 (dd, J = 4.3, 5.0 Hz, 1H), 2.98 (dd, J = 2.8, 5.1 Hz, 1H).

Step 2: 2-(2,6-dibromophenyl)propan-1-ol

[000243] To a solution of AlMe_3 (2.0 M, 82.75 mL, 1 eq) in toluene (500 mL) was added drop-wise a solution of 2-(2,6-dibromophenyl)oxirane (46 g, 165.50 mmol, 1 eq) in toluene (300 mL) at -60°C under N_2 . The mixture was stirred at 0°C for 1 hr. TLC (petroleum

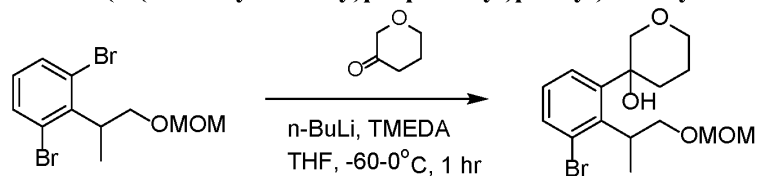
ether/ethyl acetate = 3/1, R_f = 0.3) indicated 2-(2,6-dibromophenyl)oxirane was consumed, and one major new spot with larger polarity was detected. The mixture was quenched by adding $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ (100 g) and THF (500 mL). The mixture was filtered and the filtrate was concentrated. The residue was purified by column chromatography (SiO_2 , petroleum ether / ethyl acetate = 5/1 to 3/1) to get 2-(2,6-dibromophenyl)propan-1-ol (61.66% yield) as colorless oil.

Step 3: 1,3-dibromo-2-(1-(methoxymethoxy)propan-2-yl)benzene



[000244] To a solution of 2-(2,6-dibromophenyl)propan-1-ol (28 g, 95.24 mmol, 1 eq) and DIEA (49.24 g, 380.97 mmol, 66.36 mL, 4 eq) in DCM (200 mL) was added MOMBr (23.80 g, 190.49 mmol, 15.55 mL, 2 eq) at 0°C and the mixture was stirred at 20°C for 16 hrs. TLC (petroleum ether/ethyl acetate = 1/1, R_f = 0.59) indicated 2-(2,6-dibromophenyl)propan-1-ol was consumed, and one major new spot with lower polarity was detected. The reaction mixture was quenched by addition aq. NaHCO_3 (300 mL), and extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether / ethyl acetate = 10/1 to 5/1) to get 1,3-dibromo-2-(1-(methoxymethoxy)propan-2-yl)benzene (86.97% yield) as colorless oil. ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ = 7.57 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 8.0 Hz, 1H), 4.67-4.56 (m, 2H), 4.17-4.05 (m, 2H), 3.93 (dd, J = 6.8, 8.9 Hz, 1H), 3.31 (s, 3H), 1.44 (d, J = 7.0 Hz, 3H).

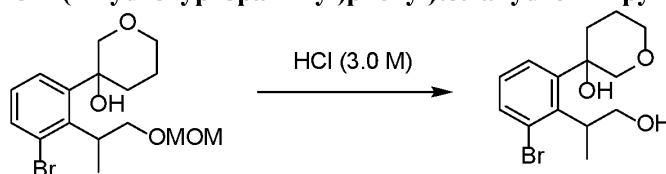
Step 4: 3-(3-bromo-2-(1-(methoxymethoxy)propan-2-yl)phenyl)tetrahydro-2H-pyran-3-ol



[000245] To a solution of 1,3-dibromo-2-(1-(methoxymethoxy)propan-2-yl)benzene (5.2 g, 15.38 mmol, 1 eq) and TMEDA (1.97 g, 16.92 mmol, 2.55 mL, 1.1 eq) in THF (60 mL) was added drop-wise $n\text{-BuLi}$ (2.5 M, 6.15 mL, 1 eq) at -60°C under N_2 . The mixture was stirred at -60°C for 0.5 hr. Then dihydro-2H-pyran-3(4H)-one (4.62 g, 46.15 mmol, 3 eq) was added

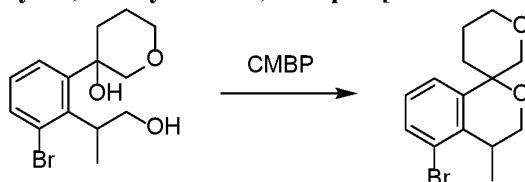
drop-wise to the system at -60°C and the mixture was stirred at 0°C for 0.5 hr. TLC (petroleum ether/ethyl acetate = 10/1, R_f = 0.4) indicated 1,3-dibromo-2-(1-(methoxymethoxy)propan-2-yl)benzene was consumed, and one major new spot with larger polarity was detected. The mixture was quenched by aqNH₄Cl (300 mL) and extracted with ethyl acetate (200 mL x 2). The combined organic layers were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether / ethyl acetate = 3/1 to 2/1) to get 3-(3-bromo-2-(1-(methoxymethoxy)propan-2-yl)phenyl)tetrahydro-2H-pyran-3-ol (37.09% yield) as colorless oil.

Step 5: 3-(3-bromo-2-(1-hydroxypropan-2-yl)phenyl)tetrahydro-2H-pyran-3-ol



[000246] To a solution of 3-(3-bromo-2-(1-(methoxymethoxy)propan-2-yl)phenyl)tetrahydro-2H-pyran-3-ol (14 g, 38.97 mmol, 1 eq) in MeCN (50 mL) was added HCl (100 mL) at 20°C and the mixture was stirred at 20°C for 12 hrs. TLC (petroleum ether/ethyl acetate = 3/1, R_f = 0.42) indicated 3-(3-bromo-2-(1-(methoxymethoxy)propan-2-yl)phenyl)tetrahydro-2H-pyran-3-ol was consumed, and one major new spot with larger polarity was detected. The mixture was quenched by H₂O (10 mL) and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether / ethyl acetate = 3/1 to 1/1) to get 3-(3-bromo-2-(1-hydroxypropan-2-yl)phenyl)tetrahydro-2H-pyran-3-ol (10.7 g, 23.76 mmol, 60.98% yield, 70% purity) as a yellow oil. LCMS: $[M+1] = 296.9$.

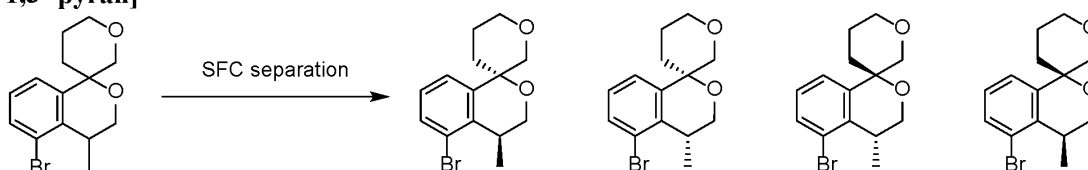
Step 6: 5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]



[000247] To a solution of 3-(3-bromo-2-(1-hydroxypropan-2-yl)phenyl)tetrahydro-2H-pyran-3-ol (10.7 g, 23.76 mmol, 1 eq) in toluene (100 mL) was added CMBP (8.60 g, 35.64 mmol, 1.5 eq) at 20°C . The mixture was stirred at 80°C for 16 hrs. LCMS showed 3-(3-

bromo-2-(1-hydroxypropan-2-yl)phenyl)tetrahydro-2H-pyran-3-ol was consumed and ~53% of desired compound was detected. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 10/1) and purified by prep-HPLC (column: Phenomenex luna c18 250mm*100mm*10um; mobile phase: [H₂O (0.1%TFA)-ACN]; gradient: 30%-65% B over 24.0 min) to get 5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] (67.97% yield) as a yellow oil.

Step 7: Stereoisomers of 5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]



[000248] 5-Bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] (4.8 g, 16.15 mmol, 1 *eq*) was separated by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm, 10um); mobile phase: [CO₂-MeOH]; B%:15%, isocratic elution mode) to give 4 isomers.

[000249] Peak 1, arbitrarily assigned as (1S,4S)-5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] (20.83% yield), was obtained as a white solid. LCMS: [M+1] = 297.2. SFC: Rt = 1.656. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.46 (d, J = 7.5 Hz, 1H), 7.13-7.06 (m, 2H), 4.08 (br dd, J = 4.2, 11.2 Hz, 1H), 4.01 (br d, J = 12.4 Hz, 1H), 3.96-3.91 (m, 1H), 3.87-3.82 (m, 1H), 3.56-3.49 (m, 1H), 3.39 (d, J = 12.5 Hz, 1H), 3.00 (q, J = 6.2 Hz, 1H), 2.30-2.19 (m, 1H), 2.06-1.97 (m, 2H), 1.57 (br d, J = 9.3 Hz, 1H), 1.39 (d, J = 6.9 Hz, 3H).

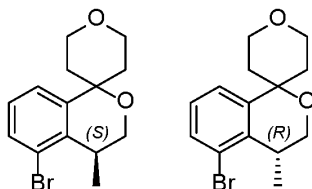
[000250] Peak 2, arbitrarily assigned as (1S,4R)-5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] (16.88% yield), was obtained as a white solid. LCMS: [M+1] = 297.2. SFC: Rt = 1.848. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.46 (dd, J = 2.3, 6.6 Hz, 1H), 7.11-7.06 (m, 2H), 4.08 (br dd, J = 3.0, 12.4 Hz, 1H), 3.91-3.85 (m, 2H), 3.76-3.74 (m, 1H), 3.71-3.67 (m, 1H), 3.54 (br t, J = 11.8 Hz, 1H), 3.05-2.98 (m, 1H), 2.24-2.14 (m, 2H), 1.79-1.71 (m, 1H), 1.51 (br d, J = 13.5 Hz, 1H), 1.39 (d, J = 6.9 Hz, 3H).

[000251] Peak 3, arbitrarily assigned as (1R,4R)-5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] (22.92% yield), was obtained as a white solid. LCMS: [M+1] =

297.2. SFC: $R_t = 2.441$. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 7.46$ (dd, $J = 1.6, 7.4$ Hz, 1H), 7.12-7.05 (m, 2H), 4.08 (br dd, $J = 4.4, 11.2$ Hz, 1H), 4.02 (br d, $J = 12.4$ Hz, 1H), 3.96-3.92 (m, 1H), 3.87-3.83 (m, 1H), 3.56-3.49 (m, 1H), 3.39 (d, $J = 12.4$ Hz, 1H), 3.03-2.97 (m, 1H), 2.29-2.19 (m, 1H), 2.06-1.98 (m, 2H), 1.56 (br s, 1H), 1.39 (d, $J = 6.9$ Hz, 3H).

[000252] Peak 4, arbitrarily assigned as (1R,4S)-5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] (22.92% yield), was obtained as a white solid. LCMS: $[M+1] = 297.2$. SFC: $R_t = 2.441$. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 7.46$ (dd, $J = 2.2, 6.7$ Hz, 1H), 7.11-7.06 (m, 2H), 4.11-4.06 (m, 1H), 3.90-3.85 (m, 2H), 3.74 (br d, $J = 2.0$ Hz, 1H), 3.71-3.67 (m, 1H), 3.57-3.51 (m, 1H), 3.01 (q, $J = 6.8$ Hz, 1H), 2.24-2.14 (m, 2H), 1.79-1.71 (m, 1H), 1.56-1.49 (m, 1H), 1.39 (d, $J = 6.9$ Hz, 3H).

Preparation of 5-bromo-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]

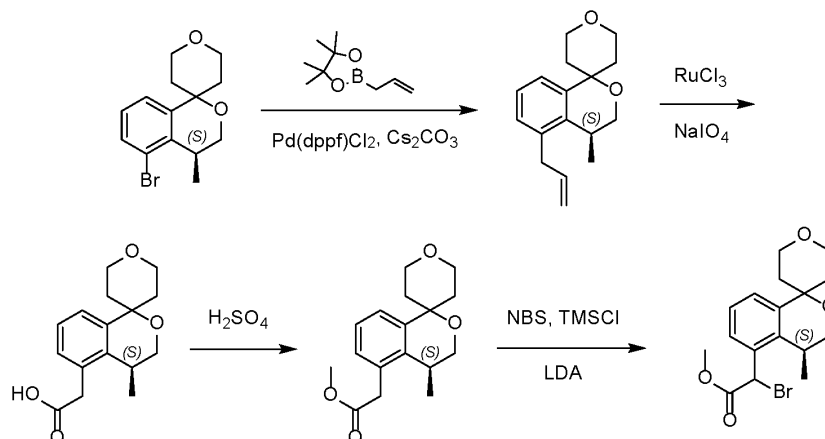


[000253] Isomers of 5-bromo-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran] were prepared using a method similar to that described above for the preparation of 5-bromo-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] and separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 μm); mobile phase: $[\text{CO}_2\text{-EtOH}]$; B%: 15%, isocratic elution mode).

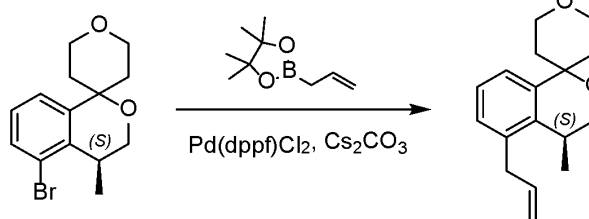
[000254] Peak 1, arbitrarily assigned as (S)-5-bromo-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran], was obtained as a white solid. SFC $R_t = 1.638$ min. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.44$ (dd, $J = 1.6, 7.4$ Hz, 1H), 7.14 - 7.07 (m, 2H), 3.99 - 3.92 (m, 1H), 3.90 - 3.86 (m, 2H), 3.85 - 3.82 (m, 2H), 3.80 (s, 1H), 3.04 - 2.96 (m, 1H), 2.23 - 2.16 (m, 1H), 1.93 - 1.87 (m, 2H), 1.65 (br d, $J = 13.5$ Hz, 1H), 1.38 (d, $J = 6.9$ Hz, 3H).

[000255] Peak 2, arbitrarily assigned as (R)-5-bromo-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran], was obtained as a white solid. SFC $R_t = 1.873$ min. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.44$ (dd, $J = 1.6, 7.4$ Hz, 1H), 7.15 - 7.08 (m, 2H), 3.99 - 3.92 (m, 1H), 3.87 (dd, $J = 4.7, 7.1$ Hz, 2H), 3.85 - 3.83 (m, 2H), 3.80 (s, 1H), 3.02 - 2.96 (m, 1H), 2.25 - 2.17 (m, 1H), 1.92 - 1.87 (m, 2H), 1.65 (br d, $J = 13.6$ Hz, 1H), 1.38 (d, $J = 6.9$ Hz, 3H).

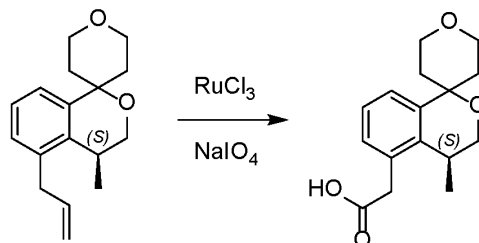
Preparation of methyl 2-bromo-2-((S)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetate



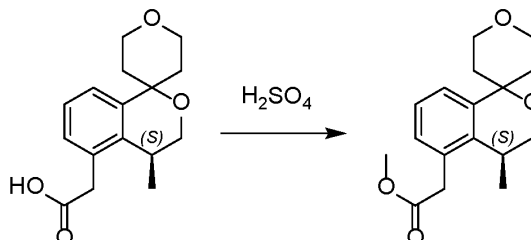
Step 1: (S)-5-allyl-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]



[000256] To a solution of (S)-5-bromo-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran] (0.7 g, 2.36 mmol, 1 eq) in dioxane (10 mL) was added 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (791.61 mg, 4.71 mmol, 2 eq), Pd(dppf)Cl₂ (172.35 mg, 235.54 μmol, 0.1 eq) and Cs₂CO₃ (1.53 g, 4.71 mmol, 2 eq) at 20 °C. The mixture was allowed to stir at 80 °C for 16 hrs under an atmosphere of N₂. The reaction was quenched by the addition of H₂O (50 mL) and extracted with ethyl acetate (10 mL x 3). The organic solutions were combined, washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 5/1) to give (S)-5-allyl-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran] (0.62 g, 1.20 mmol, 50.94% yield, 50% purity) as a white solid.

Step 2: (S)-2-(4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetic acid

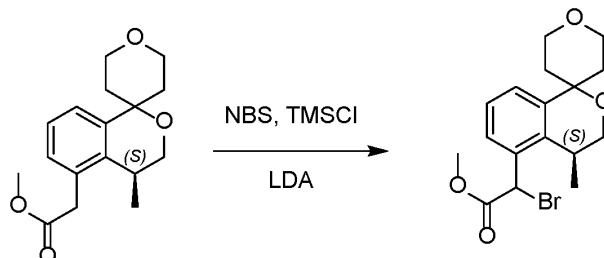
[000257] To a solution of (S)-5-allyl-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran] (0.6 g, 1.16 mmol, 1 eq) in MeCN (5 mL), hexane (5 mL) and H₂O (10 mL) was added RuCl₃ (24.09 mg, 116.12 μmol, 7.74 μL, 0.1 eq) and NaIO₄ (993.47 mg, 4.64 mmol, 257.38 μL, 4 eq) in portions at -10 °C. The mixture was allowed to stir at -10 °C for 1 hr. The reaction was quenched by the slow addition of aq. Na₂SO₃ (100 mL), adjusted to pH = 5 and extracted with ethyl acetate (50 mL x 2). The organic solutions were combined, washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give (S)-2-(4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetic acid (0.5 g, 904.73 μmol, 77.91% yield, 50% purity) as a white solid.

Step 3: methyl (S)-2-(4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetate

[000258] To a solution of (S)-2-(4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetic acid (0.5 g, 904.73 μmol, 1 eq) in MeOH (10 mL) was added H₂SO₄ (460.00 mg, 4.69 mmol, 250.00 μL, 5.18 eq) at 20 °C. The mixture was allowed to stir at 70 °C for 16 hrs. The reaction was quenched by the addition of NaHCO₃ (50 mL) and extracted with ethyl acetate (20 mL x 3). The organic solutions were combined, washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 5/1) to give methyl (S)-2-(4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetate (95.17% yield) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.23 - 7.18 (m, 1H), 7.16 - 7.09 (m, 2H), 3.99 - 3.91 (m, 1H), 3.90 - 3.81 (m, 4H), 3.78 (d, *J* = 8.2 Hz, 1H), 3.76 - 3.72 (m, 1H), 3.71 (s,

3H), 3.65 - 3.59 (m, 1H), 2.87 (q, $J = 6.6$ Hz, 1H), 2.22 (dt, $J = 5.3, 13.1$ Hz, 1H), 1.95 - 1.89 (m, 2H), 1.66 (br d, $J = 13.6$ Hz, 1H), 1.33 (d, $J = 6.9$ Hz, 3H)

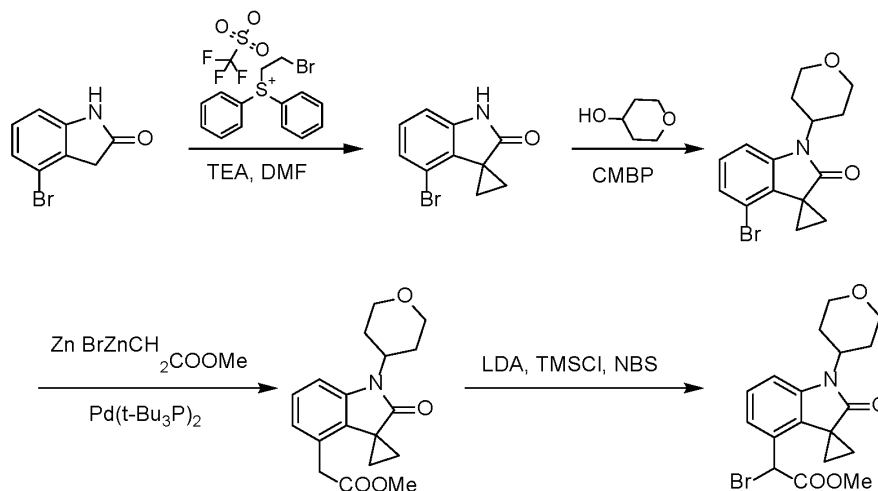
Step 4: methyl 2-bromo-2-((S)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetate



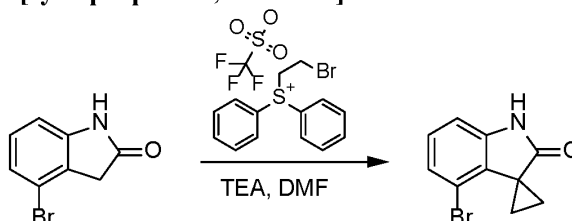
[000259] To a solution of methyl (S)-2-(4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetate (0.25 g, 861.02 μmol , 1 eq) in THF (3 mL) was added LDA (2 M, 861.02 μL , 2 eq) at -60 $^{\circ}\text{C}$ and the mixture was allowed to stir at -60 $^{\circ}\text{C}$ for 30 min. TMSCl (205.79 mg, 1.89 mmol, 240.41 μL , 2.2 eq) was added at -60 $^{\circ}\text{C}$ and the mixture was allowed to stir at -60 $^{\circ}\text{C}$ for 0.5 hrs. A solution of NBS (199.22 mg, 1.12 mmol, 1.3 eq) in THF (3 mL) was added at -60 $^{\circ}\text{C}$. The mixture was allowed to stir at -60 $^{\circ}\text{C}$ for 1 hr. The mixture was diluted with NH_4Cl (50 mL) and extracted with ethyl acetate (20 mL x 3). The organic solutions were combined, washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 10/1 to 5/1) to give methyl 2-bromo-2-((S)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetate (78.63% yield) as a yellow solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.59 (d, $J = 7.8$ Hz, 1H), 7.31 - 7.28 (m, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 5.69 (s, 1H), 3.94 (br d, $J = 12.3$ Hz, 1H), 3.86 (br dd, $J = 3.0, 10.6$ Hz, 4H), 3.83 (s, 3H), 3.80 - 3.78 (m, 1H), 2.93 - 2.87 (m, 1H), 2.19 (dt, $J = 5.4, 12.9$ Hz, 1H), 1.95 - 1.91 (m, 2H), 1.65 (br d, $J = 14.0$ Hz, 1H), 1.45 (d, $J = 7.0$ Hz, 3H).

[000260] By similar procedures, methyl 2-bromo-2-((R)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetate was prepared from (R)-5-bromo-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran].

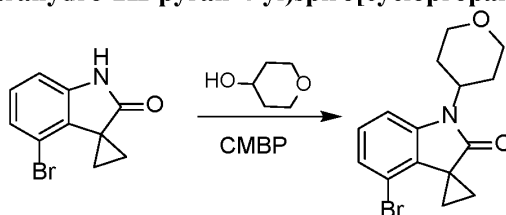
Preparation of methyl 2-bromo-2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate



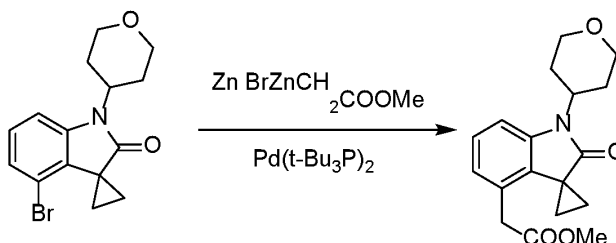
Step 1: 4'-bromospiro[cyclopropane-1,3'-indolin]-2'-one



[000261] To a solution of 4'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (6 g, 28.30 mmol, 1 *eq*) in DMF (250 mL) was added (2-bromoethyl)diphenylsulfonium trifluoromethanesulfonate (18.82 g, 42.44 mmol, 1.5 *eq*) at 25°C under N₂ and the solution was stirred at 25°C for 6 min, then TEA (8.59 g, 84.89 mmol, 11.82 mL, 3 *eq*) was added to the solution at 25°C and the solution was stirred at 25°C for 6 hrs. LCMS showed the starting material consumed completely and one peak with desired mass was detected. The reaction mixture was quenched by addition H₂O (750 mL) at 0°C, extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1). 4'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (62.34% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.12 - 7.06 (m, 2H), 6.96 (dd, J = 2.3, 6.4 Hz, 1H), 2.29 (q, J = 3.9 Hz, 2H), 1.47 (q, J = 3.9 Hz, 2H).

Step 2: 4'-bromo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one

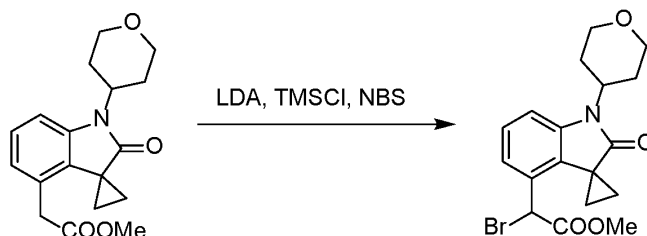
[000262] To a solution of 4'-bromospiro[cyclopropane-1,3'-indolin]-2'-one (3.4 g, 14.28 mmol, 1 *eq*) in toluene (10 mL) was added CMBP (6.89 g, 28.56 mmol, 2 *eq*) and tetrahydro-2H-pyran-4-ol (5.83 g, 57.12 mmol, 5.72 mL, 4 *eq*) at 25°C under N₂ and the solution was stirred at 120°C for 16 hrs. LCMS showed the starting material remained and two peaks with desired mass were detected. The reaction mixture was quenched by addition H₂O (50 mL) at 0°C, extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was further purified by prep-HPLC (column: Welch Xtimate C18 250 * 70 mm # 10 um; mobile phase: [water (TFA) - ACN]; B%: 25%-55%, 20 min. HPLC: R_t = 3.332 min) to give a product. 4'-bromo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (34.77% yield) was obtained as a yellow solid.

Step 3: methyl 2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate

[000263] To a solution of 4'-bromo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (1.6 g, 4.97 mmol, 1 *eq*) in THF (15 mL) was added Pd(t-Bu₃P)₂ (126.89 mg, 248.30 umol, 0.05 *eq*) and BrZnCH₂COOMe (1 M, 14.90 mL, 3 *eq*) at 25°C under N₂ and the solution was stirred at 80°C for 2 hrs. LCMS (R_t = 0.602 min) showed the starting material remained and two peaks with desired mass were detected. The reaction mixture was quenched by addition H₂O (50 mL) at 0°C, extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (10 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1). Methyl 2-(2'-oxo-1'-

(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (1.6 g, crude) was obtained as a yellow solid.

Step 4: methyl 2-bromo-2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate

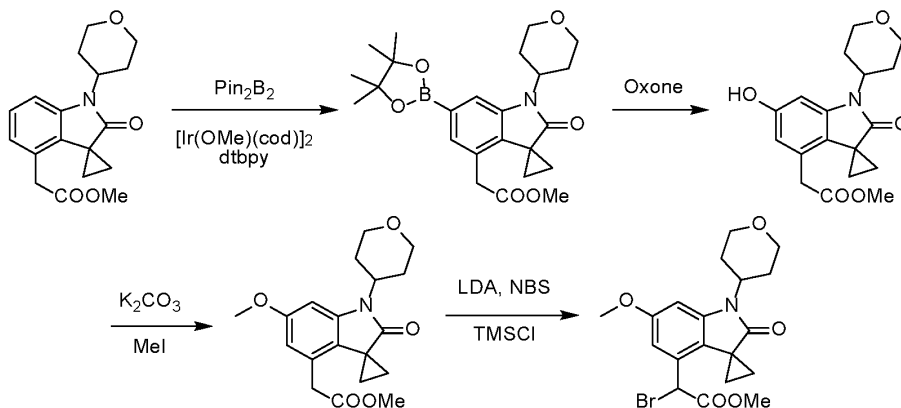


[000264] To a solution of methyl 2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (600 mg, 1.90 mmol, 1 *eq*) in THF (4 mL) was added LDA (2 M, 1.71 mL, 1.8 *eq*) dropwisely at -70°C under N₂ and the solution was stirred at -78°C for 0.5 hrs, then TMSCl (413.40 mg, 3.81 mmol, 482.94 uL, 2 *eq*) was added to the solution at -78°C and the solution was stirred at -78°C for 0.5 hrs. Then NBS (677.24 mg, 3.81 mmol, 2 *eq*) in THF (2 mL) was added to the solution at -78°C and the solution was stirred at -78°C for 1 hr. LCMS showed the starting material remained and one peak with desired mass was detected. The reaction mixture was quenched by addition aq. NH₄Cl (10 mL) at 0°C, extracted with ethyl acetate (5 mL x 3). The combined organic layers were washed with brine (5 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1). Methyl 2-bromo-2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (79.99% yield) was obtained as a yellow oil.

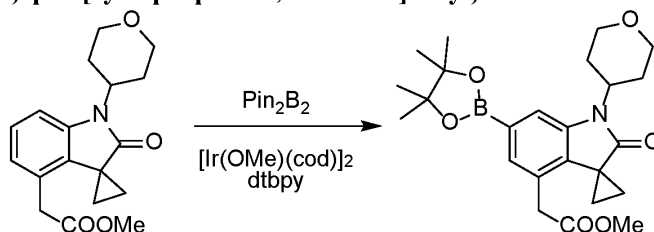
[000265] Intermediates in the table below were prepared according to similar procedures as those described for methyl 2-bromo-2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate from the starting materials shown, substituting the appropriate reagents and purified using appropriate conditions:

Starting Materials	Product	Product Characterization
		LCMS: [M+1] = 369.3. ¹ H NMR (400 MHz, CDCl ₃) δ = 7.75-7.58 (m, 1H), 7.29 (br d, J = 4.9 Hz, 1H), 7.25 (d, J = 4.9 Hz, 1H), 7.17-7.13 (m, 1H), 5.69 (d, J = 11.7 Hz, 1H), 4.11-4.00 (m, 2H), 3.97-3.91 (m, 1H), 3.89-3.84 (m, 1H), 3.80 (d, J = 19.1 Hz, 3H), 3.57-3.50 (m, 1H), 3.42 (dd, J = 9.0, 12.5 Hz, 1H), 2.98-2.88 (m, 1H), 2.30-2.17 (m, 1H), 2.04-1.96 (m, 2H), 1.52 (br s, 1H), 1.45 (dd, J = 4.1, 6.9 Hz, 3H).
		LCMS: R _t = 0.463 min, [M+1] = 344.2 and R _t = 0.471 min, [M+1] = 344.2.
		¹ H NMR (400 MHz, CDCl ₃) δ = 7.17 (s, 1H), 6.95 (s, 1H), 4.98 (s, 1H), 4.63 - 4.51 (m, 1H), 4.18 - 4.12 (m, 1H), 3.80 (s, 3H), 3.65 - 3.54 (m, 2H), 2.53 - 2.44 (m, 1H), 2.40 (s, 3H), 2.22 - 2.09 (m, 1H), 2.00 - 1.94 (m, 1H), 1.93 - 1.87 (m, 1H), 1.78 - 1.63 (m, 4H), 1.30 - 1.27 (m, 3H).
		¹ H NMR (400 MHz, CDCl ₃) δ = 7.23 - 7.18 (m, 1H), 7.10 (d, J = 7.9 Hz, 1H), 6.94 (d, J = 7.9 Hz, 1H), 4.82 - 4.69 (m, 1H), 3.96 - 3.89 (m, 1H), 3.86 - 3.78 (m, 1H), 3.71 (s, 3H), 3.39 (s, 2H), 2.50 (dq, J = 5.1, 12.5 Hz, 1H), 2.33 (t, J = 13.0 Hz, 1H), 1.96 - 1.89 (m, 2H), 1.72 - 1.65 (m, 3H), 1.63 - 1.56 (m, 1H), 1.36 (s, 3H), 1.32 (s, 3H).

Preparation of methyl 2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate



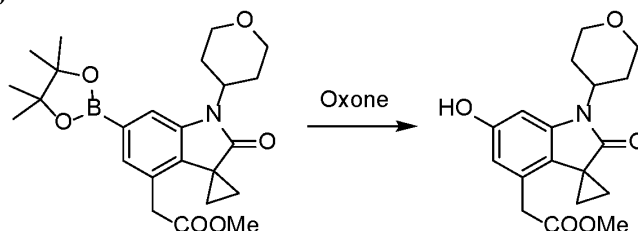
Step 1: methyl 2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)-6'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate



[000266] To a solution of methyl 2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (300 mg, 951.29 μmol , 1 *eq*) in dioxane (6 mL) was added Pin_2B_2 (483.14 mg, 1.90 mmol, 2 *eq*), $[\text{Ir}(\text{OMe})(\text{cod})]_2$ (51.06 mg, 190.26 μmol , 0.2 *eq*) and dtbpy (50.00 mg, 75.43 μmol , 7.93e-2 *eq*) at 25°C under N_2 . The mixture was warmed up to 60 °C and stirred at 60 °C for 2 hrs under N_2 . LCMS showed the starting material was consumed completely and 77.62% with desired Ms was detected. The reaction mixture was added H_2O (50 mL) and extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (50 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/1 to 3/1). Methyl 2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)-6'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (2.3 g, crude) was obtained as a yellow solid. LCMS: $[\text{M}+1] = 442.3$. ^1H NMR (400 MHz, METHANOL-d_4) δ = 7.47 (s, 1H), 7.34 (s, 1H), 4.47 (ddd, J = 4.2, 8.0, 12.3 Hz, 1H), 4.09 (br dd, J = 4.2, 11.5 Hz, 2H), 3.68 (s, 3H), 3.59 (br t,

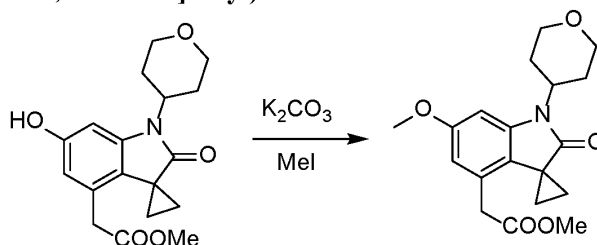
$J = 11.4$ Hz, 2H), 3.47 (s, 2H), 2.66 - 2.55 (m, 2H), 2.06 - 1.99 (m, 2H), 1.68 (br dd, $J = 2.0$, 12.3 Hz, 2H), 1.60 - 1.54 (m, 2H), 1.37 (s, 12H).

Step 2: methyl 2-(6'-hydroxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate



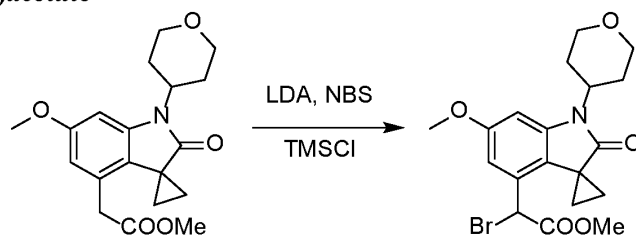
[000267] To a solution of methyl 2-(2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)-6'-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (2.3 g, 3.65 mmol, 1 *eq*) in acetone (100 mL) was added Oxone (3.36 g, 5.47 mmol, 1.5 *eq*) in H₂O (50 mL) at 0 °C. The mixture warmed up to 25 °C and was stirred at 25 °C for 1 hr. LCMS showed the starting material was consumed completely and 86.72% with desired Ms was detected. The mixture was quenched with Na₂SO₃ (100 mL) and ethyl acetate (100 mL) was added to the mixture. The layers were separated and the aqueous phase was extracted with ethyl acetate (100 mL x 3). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 1/1). Methyl 2-(6'-hydroxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (64.52% yield) was obtained as a yellow solid. LCMS: $[M+1] = 332.1$. ¹H NMR (400 MHz, CHLOROFORM-*d*) $\delta = 6.74$ (d, $J = 2.1$ Hz, 1H), 6.42 (d, $J = 2.0$ Hz, 1H), 4.56 (tt, $J = 4.1$, 12.4 Hz, 1H), 4.14 (br dd, $J = 4.4$, 11.5 Hz, 2H), 3.71 (s, 3H), 3.58 - 3.51 (m, 2H), 3.31 (s, 2H), 2.60 - 2.49 (m, 2H), 1.87 - 1.80 (m, 2H), 1.69 (br dd, $J = 2.3$, 12.8 Hz, 2H), 1.64 - 1.59 (m, 3H).

Step 3: methyl 2-bromo-2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate



[000268] To a mixture of methyl 2-(6'-hydroxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (680 mg, 2.05 mmol, 1 *eq*) and K₂CO₃ (425.42 mg, 3.08 mmol, 1.5 *eq*) in DMF (10 mL) was added MeI (1.75 g, 12.31 mmol, 766.52 μ L, 6 *eq*) at 25°C under N₂ in portions. The mixture was stirred 25°C for 2 hrs. LCMS showed ~8% of starting material was remained and 87.09% with desired mass was detected. The reaction mixture was added H₂O (20 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (20 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 1/1). Methyl 2-bromo-2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (73.37% yield) was obtained as a yellow solid. LCMS: [M+1] = 346.1. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 6.71 (d, *J* = 2.1 Hz, 1H), 6.46 (d, *J* = 2.1 Hz, 1H), 4.52 (tt, *J* = 4.3, 12.4 Hz, 1H), 4.12 (dd, *J* = 4.6, 11.5 Hz, 2H), 3.83 (s, 3H), 3.71 (s, 3H), 3.53 (dt, *J* = 1.9, 12.0 Hz, 2H), 3.35 (s, 2H), 2.60 - 2.49 (m, 2H), 1.86 - 1.81 (m, 2H), 1.68 (br dd, *J* = 2.6, 12.5 Hz, 2H), 1.63 - 1.59 (m, 2H).

Step 4: methyl 2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate



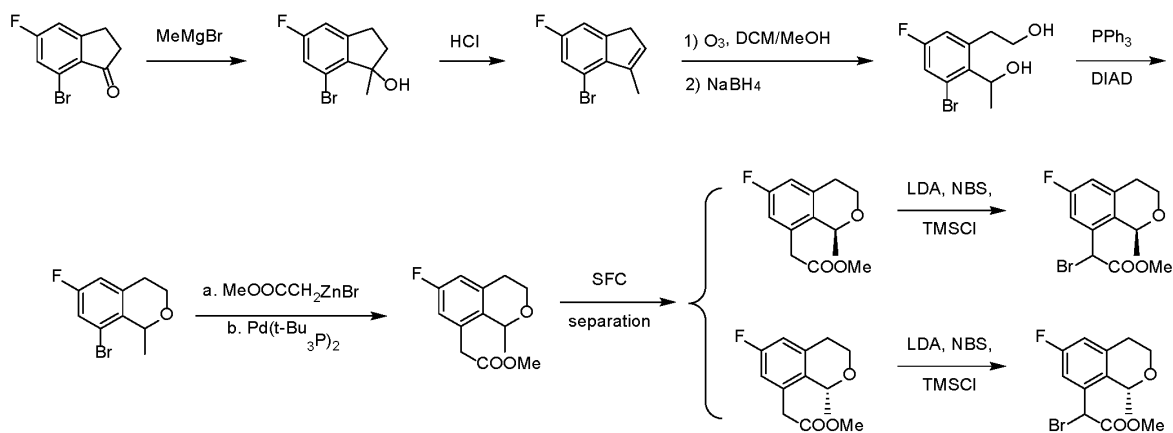
[000269] A mixture of methyl 2-bromo-2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (570 mg, 1.65 mmol, 1 *eq*) in THF (20 mL) was allowed to stir at 25°C under N₂. The mixture was cooled down to -70°C under N₂. Then was added LDA (2 M, 2.48 mL, 3 *eq*) at -70°C and then the mixture was stirred at -70°C under N₂ for 30 min. Then TMSCl (537.88 mg, 4.95 mmol, 628.36 μ L, 3 *eq*) was added and stirred at -70°C under N₂ for 30 min. Then a solution of NBS (881.19 mg, 4.95 mmol, 3 *eq*) in THF (10 mL) was added into the mixture at -70°C and the mixture was stirred at -70°C under N₂ for 1 hr. LCMS showed 33.57% of starting material was remained and 62.09% with desired mass was detected. The mixture was quenched with NH₄Cl (10 mL) and ethyl acetate (10 x 3 mL) was added to the mixture. The combined organic phases were washed by brine (10 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by

column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 3/1). Methyl 2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (58.55% yield) was obtained as a yellow oil. LCMS: [M+1] = 426.4. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 6.88 (d, *J* = 2.1 Hz, 1H), 6.75 (d, *J* = 2.1 Hz, 1H), 4.96 (s, 1H), 4.56 - 4.47 (m, 1H), 4.13 (br dd, *J* = 2.0, 9.4 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 3.56 - 3.49 (m, 2H), 2.56 - 2.47 (m, 2H), 1.96 - 1.90 (m, 1H), 1.89 - 1.84 (m, 1H), 1.75 - 1.65 (m, 4H).

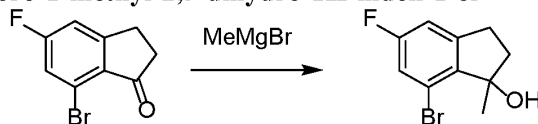
[000270] Using procedures similar to those described above in steps 1, 2 and 3 starting from 7-bromo-1,3-dimethyl-1H-indazole was prepared 7-bromo-5-methoxy-1,3-dimethyl-1H-indazole as a white solid. ¹H NMR (400 MHz, CD₃OD) δ = 7.24 (d, *J* = 2.1 Hz, 1H), 7.04 (d, *J* = 2.1 Hz, 1H), 4.23 (s, 3H), 3.83 (s, 3H), 2.46 (s, 3H).

[000271] Using procedures similar to those described above in steps 1, 2 and 3 starting from 7-bromo-1,3-dimethyl-1H-indazole was prepared 7-bromo-5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazole as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.31 (d, *J* = 2.1 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 4.29 (s, 3H), 4.18 - 4.12 (m, 2H), 3.82 - 3.74 (m, 2H), 3.48 (s, 3H), 2.49 (s, 3H).

Preparation of methyl 2-bromo-2-((S)-6-fluoro-1-methylisochroman-8-yl)acetate and methyl 2-bromo-2-((R)-6-fluoro-1-methylisochroman-8-yl)acetate



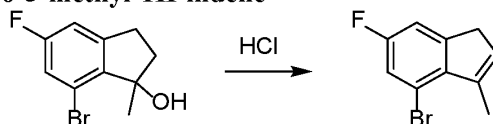
Step 1: 7-bromo-5-fluoro-1-methyl-2,3-dihydro-1H-inden-1-ol



[000272] To a solution of MeMgBr (3 M, 145.53 mL, 5 *eq*) was added 7-bromo-5-fluoro-2,3-dihydro-1H-inden-1-one (20 g, 87.32 mmol, 1 *eq*) in THF (200 mL) at 0°C under N₂

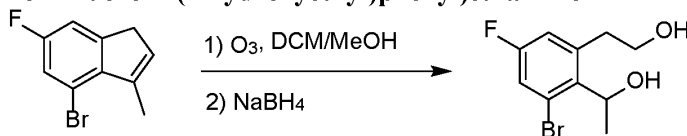
atmosphere. The mixture was stirred at 0°C for 2 hrs. TLC (petroleum ether/ethyl acetate = 5/1, R_f = 0.47) indicated the starting material was consumed completely and one new spot with lower polarity was formed. The reaction mixture was quenched with aq. NH_4Cl (500 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 7-bromo-5-fluoro-1-methyl-2,3-dihydro-1H-inden-1-ol (22.2 g, crude) as a white solid. The crude product was used for next step directly without purification. ^1H NMR (400 MHz, CHCl_3 - d) δ = 7.11 (dd, J = 1.9, 8.4 Hz, 1H), 6.87 (dd, J = 0.9, 8.1 Hz, 1H), 2.97 - 2.86 (m, 1H), 2.84 - 2.76 (m, 1H), 2.29 (dd, J = 5.6, 8.6 Hz, 2H), 1.63 (s, 3H).

Step 2: 4-bromo-6-fluoro-3-methyl-1H-indene



[000273] To a solution of 7-bromo-5-fluoro-1-methyl-2,3-dihydro-1H-inden-1-ol (22.2 g, 90.58 mmol, 1 *eq*) in THF (200 mL) was added HCl (12 M, 200 mL, 26.50 *eq*) at 0°C under N_2 atmosphere. The mixture was stirred at 20°C for 2 hrs. TLC (petroleum ether/ethyl acetate = 5/1, R_f = 0.69) indicated the starting material was remained and one new spot with lower polarity was formed. The reaction mixture was quenched with H_2O (400 mL) and extracted with MTBE (200 mL x 4). The combined organic layers were washed with brine (400 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~5% ethyl acetate/petroleum ether gradient @ 90 mL/min). 4-Bromo-6-fluoro-3-methyl-1H-indene (97.24% yield) was obtained as a white solid. ^1H NMR (400 MHz, CHCl_3 - d) δ = 7.19 (dd, J = 2.3, 8.8 Hz, 1H), 7.10 (dd, J = 2.3, 8.0 Hz, 1H), 6.26 - 6.22 (m, 1H), 3.29 (t, J = 2.0 Hz, 2H), 2.40 (q, J = 2.0 Hz, 3H).

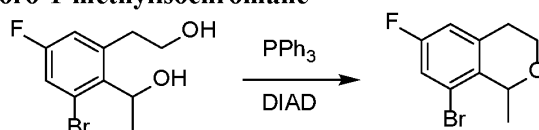
Step 3: 1-(2-bromo-4-fluoro-6-(2-hydroxyethyl)phenyl)ethan-1-ol



[000274] A solution of 4-bromo-6-fluoro-3-methyl-1H-indene (20 g, 88.08 mmol, 1 *eq*) in DCM (200 mL) and MeOH (40 mL) was bubbled with O_3 (21.14 g, 440.39 mmol, 5 *eq*) for 2 hrs at -70°C. Then NaBH_4 (11.30 g, 298.58 mmol, 3.39 *eq*) was added at 0°C and the mixture was stirred at 25°C for 16 hrs. TLC (petroleum ether/ethyl acetate = 3/1, R_f = 0.41) indicated the starting material was consumed completely and one new spot with higher polarity was

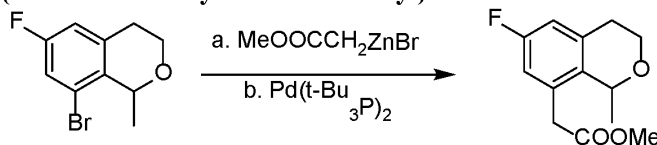
formed. The reaction mixture was quenched with H₂O (300 mL) and extracted with DCM (100 mL x 3). The combined organic layers were washed with brine (300 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 1-(2-bromo-4-fluoro-6-(2-hydroxyethyl)phenyl)ethan-1-ol (20 g, crude) as a white solid. The crude product was used for next step directly without purification. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.21 (dd, *J* = 2.6, 7.7 Hz, 1H), 6.95 (dd, *J* = 2.6, 9.2 Hz, 1H), 5.59 (q, *J* = 6.7 Hz, 1H), 3.99 (td, *J* = 5.1, 10.2 Hz, 1H), 3.84 (dt, *J* = 5.1, 9.7 Hz, 1H), 3.64 - 3.52 (m, 1H), 2.84 (td, *J* = 4.7, 13.7 Hz, 1H), 1.55 (d, *J* = 6.8 Hz, 3H).

Step 4: 8-bromo-6-fluoro-1-methylisochromane



[000275] To a solution of 1-(2-bromo-4-fluoro-6-(2-hydroxyethyl)phenyl)ethan-1-ol (20 g, 76.02 mmol, 1 *eq*) in THF (300 mL) was added PPh₃ (29.91 g, 114.02 mmol, 1.5 *eq*) and DIAD (26.13 g, 129.23 mmol, 25.05 mL, 1.7 *eq*) at 0°C and the mixture was stirred at 25°C for 16 hrs under N₂ atmosphere. TLC (petroleum ether/ethyl acetate = 10/1, R_f = 0.57) indicated the starting material was consumed completely and two new spots with lower polarity were formed. The top point was desired. The reaction mixture was quenched with H₂O (500 mL) and extracted with ethyl acetate (200 mL x 3). The combined organic layers were washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 220 g SepaFlash® Silica Flash Column, Eluent of 0~22% ethyl acetate/petroleum ether gradient @ 80 mL/min). 8-Bromo-6-fluoro-1-methylisochromane (40.79% yield) was obtained as purple oil. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.15 (dd, *J* = 2.5, 8.1 Hz, 1H), 6.83 (dd, *J* = 2.5, 8.7 Hz, 1H), 5.02 (q, *J* = 6.4 Hz, 1H), 4.08 (ddd, *J* = 4.3, 9.6, 11.7 Hz, 1H), 3.85 (ddd, *J* = 3.5, 6.0, 11.7 Hz, 1H), 2.97 - 2.85 (m, 1H), 2.78 - 2.67 (m, 1H), 1.57 (d, *J* = 6.4 Hz, 3H).

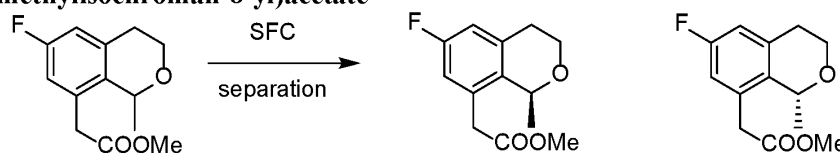
Step 5: methyl 2-(6-fluoro-1-methylisochroman-8-yl)acetate



[000276] To a solution of 8-bromo-6-fluoro-1-methylisochromane (7.5 g, 30.60 mmol, 1 *eq*) in THF (80 mL) was added Pd(t-Bu₃P)₂ (1.56 g, 3.06 mmol, 0.1 *eq*) and MeOOCCH₂ZnBr (1 M, 45.90 mL, 1.5 *eq*) at 25°C. The mixture was stirred at 80°C for 2 hrs under N₂ atmosphere.

TLC (petroleum ether/ethyl acetate = 5/1, R_f = 0.36) indicated the starting material was consumed completely and three new spots with larger polarity were formed. The reaction mixture was quenched with H₂O (150 mL). The mixture was filtered and the filtrate was extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 120 g SepaFlash® Silica Flash Column, Eluent of 0~28% ethyl acetate/petroleum ether gradient @ 80 mL/min). Methyl 2-(6-fluoro-1-methylisochroman-8-yl)acetate (96.01% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 6.85 (dd, J = 2.6, 9.4 Hz, 1H), 6.77 (dd, J = 2.3, 8.8 Hz, 1H), 5.06 (q, J = 6.5 Hz, 1H), 4.13 - 4.05 (m, 1H), 3.82 (td, J = 5.4, 10.8 Hz, 1H), 3.72 (s, 3H), 3.64 - 3.46 (m, 2H), 2.99 - 2.88 (m, 1H), 2.81 - 2.72 (m, 1H), 1.46 (d, J = 6.5 Hz, 3H).

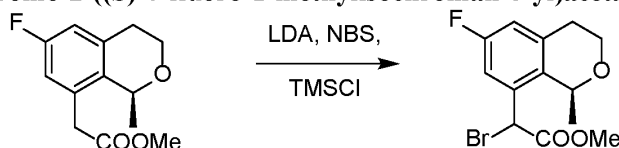
Step 6: methyl (S)-2-(6-fluoro-1-methylisochroman-8-yl)acetate and methyl (R)-2-(6-fluoro-1-methylisochroman-8-yl)acetate



[000277] Methyl 2-(6-fluoro-1-methylisochroman-8-yl)acetate (7 g) was separated by SFC separation (column: ChiralPak IH, 250 * 50 mm, 10 μ m; mobile phase: [CO₂-IPA (0.1% NH₃H₂O)]; B%: 11%, isocratic elution mode).

[000278] Peak 1 (44.29% yield) was obtained as a yellow oil and arbitrarily assigned as methyl (S)-2-(6-fluoro-1-methylisochroman-8-yl). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 6.85 (dd, J = 2.5, 9.5 Hz, 1H), 6.77 (dd, J = 2.3, 8.9 Hz, 1H), 5.06 (q, J = 6.5 Hz, 1H), 4.08 (ddd, J = 4.4, 8.7, 11.5 Hz, 1H), 3.88 - 3.78 (m, 1H), 3.72 (s, 3H), 3.65 - 3.47 (m, 2H), 2.97 - 2.85 (m, 1H), 2.81 - 2.72 (m, 1H), 1.46 (d, J = 6.5 Hz, 3H)

[000279] Peak 2 (45.71% yield) was obtained as a yellow oil and arbitrarily assigned as methyl (R)-2-(6-fluoro-1-methylisochroman-8-yl)acetate. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 6.85 (dd, J = 2.5, 9.4 Hz, 1H), 6.77 (dd, J = 2.3, 8.9 Hz, 1H), 5.06 (q, J = 6.5 Hz, 1H), 4.08 (ddd, J = 4.5, 8.8, 11.5 Hz, 1H), 3.87 - 3.78 (m, 1H), 3.72 (s, 3H), 3.65 - 3.45 (m, 2H), 2.99 - 2.87 (m, 1H), 2.82 - 2.70 (m, 1H), 1.46 (d, J = 6.5 Hz, 3H)

Step 7: methyl 2-bromo-2-((S)-6-fluoro-1-methylisochroman-8-yl)acetate

[000280] To a solution of arbitrarily assigned methyl (S)-2-(6-fluoro-1-methylisochroman-8-yl) (1 g, 4.20 mmol, 1 *eq*) in THF (20 mL) was added LDA (2 M, 6.30 mL, 3 *eq*) at -78°C under N₂ atmosphere. The mixture was stirred at -78°C for 30 min. TMSCl (1.37 g, 12.59 mmol, 1.60 mL, 3 *eq*) was added at -78°C. After the reaction mixture had stirred at -78°C for 30 min, NBS (2.24 g, 12.59 mmol, 3 *eq*) in THF (40 mL) was added. The mixture was stirred at -78°C for 1 hr. TLC (petroleum ether/ethyl acetate = 5/1, R_f = 0.45, 0.51) indicated the starting material was consumed completely and two new spots with lower polarity were formed. The reaction mixture was quenched by addition aqueous NH₄Cl (40 mL), and extracted with ethyl acetate (20 mL x 3). The combined organic layers were washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (ISCO®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~22% ethyl acetate/petroleum ether gradient @ 80 mL/min). Arbitrarily assigned methyl 2-bromo-2-((S)-6-fluoro-1-methylisochroman-8-yl)acetate (97.66% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.36 (ddd, *J* = 2.6, 9.7, 16.4 Hz, 1H), 6.83 (br d, *J* = 8.6 Hz, 1H), 5.45 - 5.35 (m, 1H), 5.23 - 5.10 (m, 1H), 4.09 - 4.04 (m, 1H), 3.87 - 3.77 (m, 4H), 3.01 - 2.88 (m, 1H), 2.81 - 2.71 (m, 1H), 1.56 (dd, *J* = 6.6, 12.1 Hz, 3H).

[000281] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (R)-2-(6-fluoro-1-methylisochroman-8-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-((R)-6-fluoro-1-methylisochroman-8-yl)acetate. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.36 (ddd, *J* = 2.6, 9.7, 16.3 Hz, 1H), 6.83 (br d, *J* = 8.6 Hz, 1H), 5.46 - 5.35 (m, 1H), 5.22 - 5.06 (m, 1H), 4.09 - 4.03 (m, 1H), 3.86 - 3.77 (m, 4H), 2.99 - 2.88 (m, 1H), 2.79 - 2.72 (m, 1H), 1.56 (dd, *J* = 6.6, 12.0 Hz, 3H).

[000282] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (R)-2-(1-methylisochroman-8-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-((R)-1-methylisochroman-8-yl)acetate. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.68 - 7.51 (m, 1H), 7.26 - 7.20 (m, 1H), 5.66 - 5.34 (m, 1H), 4.18 - 4.05 (m, 2H), 3.76 (s, 3H), 3.05 - 2.87 (m, 2H), 2.87 - 2.64 (m, 2H), 1.57 (s, 3H).

[000283] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (S)-2-(6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-((S)-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)acetate (79.6% yield) as a yellow solid.

[000284] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (R)-2-(6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-((R)-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)acetate.

[000285] By a similar procedure as described above in Step 6, methyl 2-(1'-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate was separated (SFC (column: DAICEL CHIRALPAK IG (250 mm * 30 mm, 10 μ m); mobile phase: [CO₂-MeOH]; B%:20%, isocratic elution mode) to give arbitrarily assigned methyl (S)-2-(1'-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate and arbitrarily assigned methyl (R)-2-(1'-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate.

[000286] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (R)-2-(1'-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-(1'-((R)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (78.26% yield) as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.38 (d, J = 8.0 Hz, 1H), 7.30 - 7.28 (m, 1H), 7.14 (d, J = 8.1 Hz, 1H), 5.00 (s, 1H), 4.83 - 4.69 (m, 1H), 3.96 - 3.90 (m, 1H), 3.86 - 3.81 (m, 1H), 3.80 (s, 3H), 2.52 - 2.43 (m, 1H), 2.35 - 2.28 (m, 1H), 1.98 - 1.91 (m, 1H), 1.78 (s, 2H), 1.71 - 1.60 (m, 3H), 1.36 (s, 3H), 1.32 (s, 3H).

[000287] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (S)-2-(1'-(2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-(1'-((S)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate.

[000288] By a similar procedure as described above in Step 6, methyl 2-(4-methylchroman-5-yl)acetate was separated by SFC (column: DAICEL CHIRALPAK IC(250 mm*30 mm, 10 μ m);mobile phase: [CO₂-IPA(0.1%NH₃H₂O)];B%:25%, isocratic elution mode) to give 2 compounds. **Peak 1**, arbitrarily assigned methyl (S)-2-(4-methylchroman-5-yl)acetate, was obtained as a yellow oil. SFC R_t = 0.900 min. ¹H NMR (400 MHz, CD₃OD) δ = 7.00 (t, J =

7.9 Hz, 1H), 6.73 (dd, $J = 0.8, 7.4$ Hz, 1H), 6.65 (d, $J = 8.3$ Hz, 1H), 4.23 - 4.15 (m, 2H), 3.75 - 3.57 (m, 5H), 3.14 - 3.01 (m, 1H), 2.16 - 1.94 (m, 1H), 1.75 (qd, $J = 2.2, 13.8$ Hz, 1H), 1.24 (d, $J = 7.0$ Hz, 3H). **Peak 2**, arbitrarily assigned methyl (R)-2-(4-methylchroman-5-yl)acetate, was obtained as a yellow oil. SFC $R_t = 1.170$ min. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.00$ (t, $J = 7.9$ Hz, 1H), 6.73 (dd, $J = 0.7, 7.4$ Hz, 1H), 6.66 (d, $J = 8.3$ Hz, 1H), 4.28 - 4.12 (m, 2H), 3.76 - 3.69 (m, 1H), 3.67 (s, 3H), 3.65 - 3.58 (m, 1H), 3.12 - 3.01 (m, 1H), 2.11 - 1.95 (m, 1H), 1.82 - 1.67 (m, 1H), 1.24 (d, $J = 7.1$ Hz, 3H).

[000289] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (S)-2-(4-methylchroman-5-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-((S)-4-methylchroman-5-yl)acetate as a yellow oil. LCMS $[M+1] = 299.0$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.33 - 7.21$ (m, 1H), 7.14 (dt, $J = 2.7, 8.0$ Hz, 1H), 6.80 (ddd, $J = 0.8, 3.5, 8.0$ Hz, 1H), 5.67 (d, $J = 1.8$ Hz, 1H), 4.33 - 4.19 (m, 2H), 3.80 (d, $J = 19.9$ Hz, 3H), 3.26 - 3.10 (m, 1H), 2.21 - 2.08 (m, 1H), 1.78 (qdd, $J = 2.2, 4.5, 13.8$ Hz, 1H), 1.39 (dd, $J = 2.3, 7.1$ Hz, 3H).

[000290] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (R)-2-(4-methylchroman-5-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-((R)-4-methylchroman-5-yl)acetate as a yellow oil. LCMS $[M+1] = 219.1$.

[000291] By a similar procedure as described above in Step 7 starting from arbitrarily assigned methyl (S)-2-(1-methylisochroman-8-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-((S)-1-methylisochroman-8-yl)acetate (92.03% yield) as a yellow oil. LCMS $[M+1] = 300.9$.

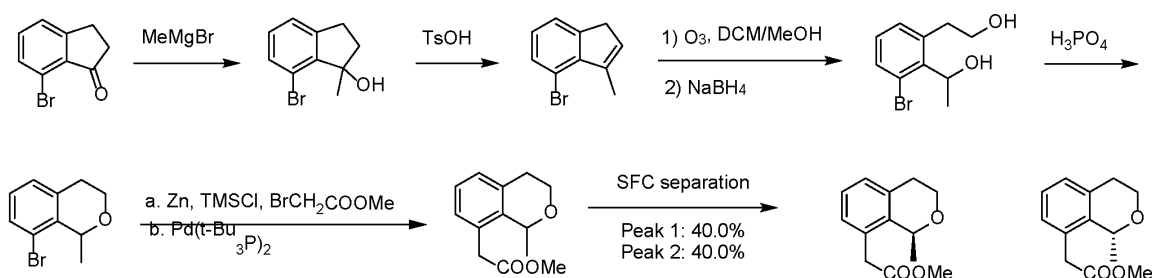
[000292] By a similar procedure as described above in steps 5 and 6 starting from 8-bromo-1-methylisochromane (SFC separation conditions: (column: ChiralPak IH, 250 x 50 mm, 10 μm ; mobile phase: $[\text{CO}_2\text{-Heptane: IPA} = 1:1(0.1\% \text{NH}_3\text{H}_2\text{O})]$; B%: 11%, isocratic elution mode)) were prepared two compounds. **Peak 1**, arbitrarily assigned as (R)-2-(1-methylisochroman-8-yl)acetate, was obtained as a yellow oil. **Peak 2**, arbitrarily assigned as methyl (S)-2-(1-methylisochroman-8-yl)acetate was obtained as a yellow oil. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.19 - 7.14$ (m, 1H), 7.13 - 7.09 (m, 1H), 7.05 (d, $J = 7.2$ Hz, 1H), 5.11 (q, $J = 6.6$ Hz, 1H), 4.13 - 4.06 (m, 1H), 3.86 - 3.80 (m, 1H), 3.71 (s, 3H), 3.67 - 3.60 (m, 1H), 3.58 - 3.51 (m, 1H), 2.97 - 2.90 (m, 1H), 2.84 - 2.76 (m, 1H), 1.49 (d, $J = 6.6$ Hz, 3H).

[000293] By similar procedures as described above in steps 5, 6 and 7 starting from (3R,4S)-5-bromo-3,4,7-trimethylisochromane (SFC separation conditions: column: DAICEL

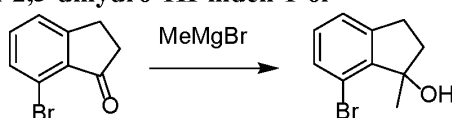
CHIRALPAK AD (250 mm * 50 mm, 10 μ m); mobile phase: [CO₂-i-PrOH (0.1% NH₃·H₂O)]; B%: 11%-11%, 2 min) were prepared two compounds. **Peak 1**, arbitrarily assigned as tert-butyl 2-bromo-2-((3R,4S)-3,4,7-trimethylisochroman-5-yl)acetate, was obtained as a yellow oil. **Peak 2**, arbitrarily assigned as tert-butyl 2-bromo-2-((3S,4R)-3,4,7-trimethylisochroman-5-yl)acetate was obtained as a yellow oil.

[000294] By similar procedures as described above in steps 5, 6 and 7 starting from 5-bromo-7-fluoro-4-methylisochromane (SFC separation conditions: column: DAICEL CHIRALPAK IC (250 mm * 30 mm, 10 μ m); mobile phase: [CO₂-i-PrOH (0.1% NH₃·H₂O)]; 18% B isocratic elution mode) were prepared two compounds. **Peak 1**, arbitrarily assigned as methyl 2-bromo-2-((S)-7-fluoro-4-methylisochroman-5-yl)acetate, was obtained as a yellow oil. **Peak 2**, arbitrarily assigned as methyl 2-bromo-2-((R)-7-fluoro-4-methylisochroman-5-yl)acetate was obtained as a yellow oil.

Preparation of methyl (S)-2-(1-methylisochroman-8-yl)acetate and methyl (R)-2-(1-methylisochroman-8-yl)acetate



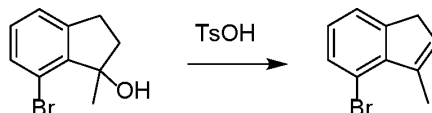
Step 1: 7-bromo-1-methyl-2,3-dihydro-1H-inden-1-ol



[000295] To a solution of MeMgBr (3 M, 157.94 mL, 5 *eq*) was added 7-bromo-2,3-dihydro-1H-inden-1-one (20 g, 94.76 mmol, 1 *eq*) in THF (200 mL) at 0°C under N₂. The mixture was stirred at 0°C for 2 hrs. TLC (Petroleum ether/ethyl acetate = 5/1, R_f = 0.35) indicated one new spot was formed and 7-bromo-2,3-dihydro-1H-inden-1-one was consumed completely. The reaction mixture was quenched by aq. NH₄Cl (500 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (400 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 0/1). 7-Bromo-1-methyl-2,3-dihydro-1H-inden-1-ol (88.29% yield) was obtained as a yellow

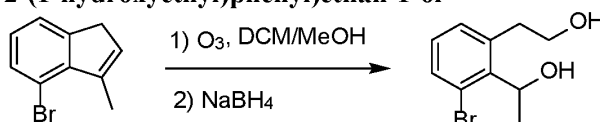
oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.35 (d, J = 7.8 Hz, 1H), 7.19 - 7.14 (m, 1H), 7.11 - 7.06 (m, 1H), 2.97 - 2.91 (m, 1H), 2.82 (t, J = 8.8 Hz, 1H), 2.27 (dd, J = 5.4, 8.7 Hz, 2H), 1.64 (s, 3H).

Step 2: 4-bromo-3-methyl-1H-indene

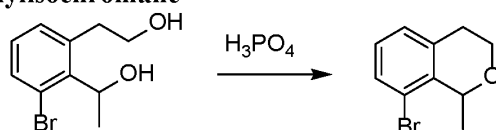


[000296] To a solution of 7-bromo-1-methyl-2,3-dihydro-1H-inden-1-ol (19 g, 83.66 mmol, 1 *eq*) in toluene (150 mL) was added TsOH (288.14 mg, 1.67 mmol, 0.02 *eq*) at 20°C. The mixture was stirred at 135°C for 2 hrs. TLC (Petroleum ether/ethyl acetate = 3/1, R_f = 0.85) indicated one new spot was formed and 7-bromo-1-methyl-2,3-dihydro-1H-inden-1-ol was consumed completely. The reaction mixture was quenched by H_2O (300 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 1/0 to 0/1). 4-Bromo-3-methyl-1H-indene (97.18% yield) was obtained as a colorless solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.47 - 7.35 (m, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.33 - 6.20 (m, 1H), 3.30 (t, J = 2.2 Hz, 2H), 2.43 (q, J = 2.2 Hz, 3H).

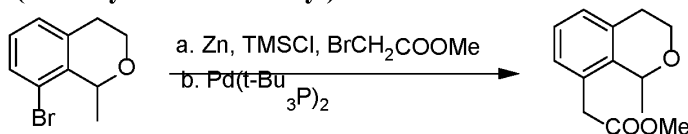
Step 3: 2-(3-bromo-2-(1-hydroxyethyl)phenyl)ethan-1-ol



[000297] To a solution of 4-bromo-3-methyl-1H-indene (10 g, 47.83 mmol, 1 *eq*) in DCM (100 mL) and MeOH (20 mL) was added O_3 (11.48 g, 239.14 mmol, 5 *eq*) at -70°C. The mixture was stirred at -70°C for 0.5 hrs. NaBH_4 (2.35 g, 62.18 mmol, 1.3 *eq*) was added at -70°C. The mixture was stirred at 15°C for 2 hrs. TLC (Petroleum ether/ethyl acetate = 5/1, R_f = 0.25) indicated one new spot was formed and 4-bromo-3-methyl-1H-indene was consumed completely. The reaction mixture was quenched by NH_4Cl (200 mL) and extracted with CH_2Cl_2 (100 mL x 3). The combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was used for next step and without purification. 2-(3-Bromo-2-(1-hydroxyethyl)phenyl)ethan-1-ol (6.4 g, crude) was obtained as a white solid.

Step 4: 8-bromo-1-methylisochromane

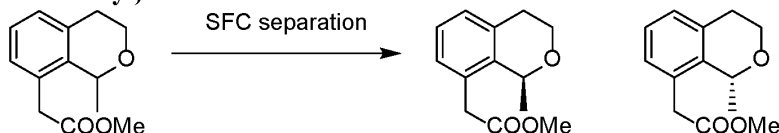
[000298] To a solution of 2-(3-bromo-2-(1-hydroxyethyl)phenyl)ethan-1-ol (6.2 g, 25.29 mmol, 1 *eq*) in CH_3CN (60 mL) was added H_3PO_4 (26.04 g, 265.73 mmol, 15.50 mL, 10.51 *eq*) at 20°C under N_2 . The mixture was stirred at 80°C for 12 hrs. TLC (Petroleum ether/ethyl acetate = 3/1, $R_f = 0.5$) indicated one new spot was formed and 2-(3-bromo-2-(1-hydroxyethyl)phenyl)ethan-1-ol remained. The reaction mixture was quenched by H_2O (200 mL) and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (200 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 1/0 to 0/1). 8-Bromo-1-methylisochromane (52.23% yield) was obtained as colorless oil.

Step 5: methyl 2-(1-methylisochroman-8-yl)acetate

[000299] A mixture of Zn (15.39 g, 235.33 mmol, 1.2 *eq*) in THF (196.11 mL) was added TMSCl (2.13 g, 19.61 mmol, 2.49 mL, 0.1 *eq*) at 20°C , and then stirred at 20°C for 0.5 hrs. $\text{BrCH}_2\text{COOt-Bu}$ (30 g, 196.11 mmol, 18.52 mL, 1 *eq*) was dropwise added at 20°C and then stirred at 20°C for 12 hrs. To a solution of 8-bromo-1-methylisochromane (3 g, 13.21 mmol, 1 *eq*) in THF (25 mL) was added $(\text{Pd t-Bu}_3\text{P})_2$ (675.11 mg, 1.32 mmol, 0.1 *eq*) and the above mixture (1 M, 39.63 mL, 3 *eq*) at 25°C under N_2 . The mixture was stirred at 80°C for 1 hr. TLC (Petroleum ether/ethyl acetate = 2/1, $R_f = 0.26$) indicated 8-bromo-1-methylisochromane was consumed completely and one new spot formed. The reaction mixture was filtered and the filter cake was washed with ethyl acetate. Then the reaction mixture was quenched by addition H_2O (20 mL) at 20°C , and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether/ethyl acetate = 1/0 to 0/1). Methyl 2-(1-methylisochroman-8-yl)acetate (68.73% yield) was obtained as a white solid. ^1H NMR (400 MHz, CDCl_3) δ = 7.19 - 7.13 (m, 1H), 7.13 - 7.09 (m, 1H), 7.05 (d, $J = 7.4$ Hz, 1H), 5.11 (q, $J = 6.6$ Hz, 1H), 4.12 - 4.07 (m,

1H), 3.86 - 3.80 (m, 1H), 3.70 (s, 3H), 3.66 - 3.60 (m, 1H), 3.57 - 3.51 (m, 1H), 3.00 - 2.89 (m, 1H), 2.82 - 2.73 (m, 1H), 1.49 (d, $J = 6.5$ Hz, 3H).

Step 6: methyl (S)-2-(1-methylisochroman-8-yl)acetate and methyl (R)-2-(1-methylisochroman-8-yl)acetate

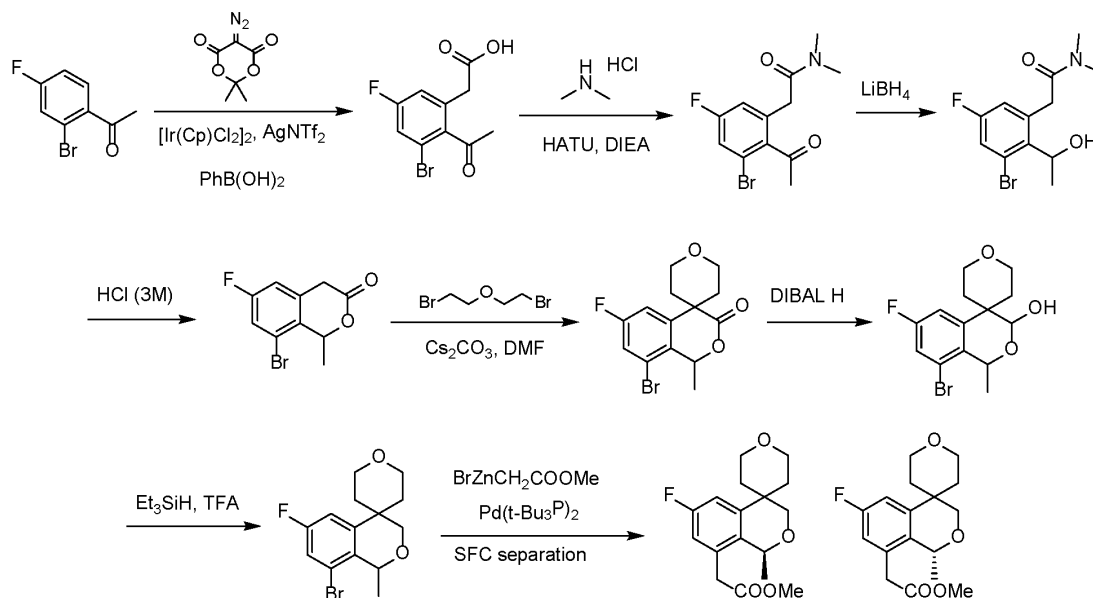


[000300] Methyl 2-(1-methylisochroman-8-yl)acetate was separated by SFC (column: DAICEL CHIRALCEL OJ (250mm*50mm, 10um); mobile phase: [Heptane-EtOH]; B%:20%, isocratic elution mode) to give two peaks ($R_{t1} = 2.93$ min & $R_{t2} = 3.44$ min).

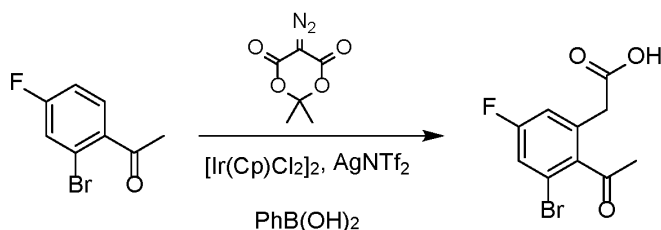
[000301] Peak 1 (40.00% yield) was obtained as a yellow oil and arbitrarily assigned as methyl (S)-2-(1-methylisochroman-8-yl)acetate. ^1H NMR (400 MHz, CHLOROFORM- d) δ = 7.19 - 7.14 (m, 1H), 7.13 - 7.09 (m, 1H), 7.05 (d, $J = 7.3$ Hz, 1H), 5.11 (q, $J = 6.5$ Hz, 1H), 4.11 (dd, $J = 4.4, 8.6, 11.4$ Hz, 1H), 3.87 - 3.80 (m, 1H), 3.71 (s, 3H), 3.66 - 3.60 (m, 1H), 3.58 - 3.51 (m, 1H), 2.99 - 2.90 (m, 1H), 2.83 - 2.75 (m, 1H), 1.49 (d, $J = 6.5$ Hz, 3H).

[000302] Peak 2 (40.00% yield) was obtained as a yellow oil and arbitrarily assigned as methyl (R)-2-(1-methylisochroman-8-yl)acetate. ^1H NMR (400 MHz, CHLOROFORM- d) δ = 7.19 - 7.14 (m, 1H), 7.13 - 7.08 (m, 1H), 7.05 (d, $J = 7.4$ Hz, 1H), 5.11 (q, $J = 6.5$ Hz, 1H), 4.11 (ddd, $J = 4.5, 8.6, 11.4$ Hz, 1H), 3.83 (td, $J = 5.0, 11.3$ Hz, 1H), 3.71 (s, 3H), 3.66 - 3.61 (m, 1H), 3.58 - 3.50 (m, 1H), 2.99 - 2.89 (m, 1H), 2.84 - 2.75 (m, 1H), 1.49 (d, $J = 6.5$ Hz, 3H).

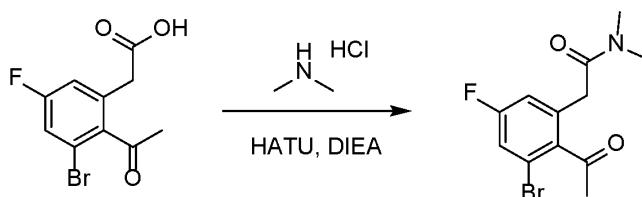
Preparation of methyl 2-(6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)acetate



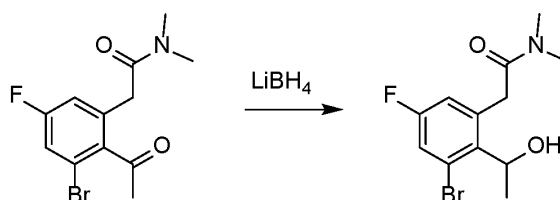
Step 1: 2-(2-acetyl-3-bromo-5-fluorophenyl)acetic acid



[000303] A mixture of 1-(2-bromo-4-fluorophenyl)ethan-1-one (8.50 g, 39.16 mmol, 1 *eq*), 5-diazo-2,2-dimethyl-1,3-dioxane-4,6-dione (9.99 g, 58.75 mmol, 1.5 *eq*), [Ir(Cp)Cl₂]₂ (315.97 mg, 391.64 μmol, 0.01 *eq*), AgNTf₂ (258.33 mg, 665.79 μmol, 0.017 *eq*), PhB(OH)₂ (4.78 g, 39.16 mmol, 1 *eq*) in H₂O (170 mL) was stirred for 16 hrs at 80°C. LCMS showed 66% of starting material was remained and ~16% with desired Mass was detected. Water (10 mL) was added, the mixture was extracted with ethyl acetate (10 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by flash silica gel chromatography (Biotage®; 40 g SepaFlash® Silica Flash Column, Eluent of 0~10% Ethyl acetate/Petroleum ether gradient @ 80 mL/min) to give 2-(2-acetyl-3-bromo-5-fluorophenyl)acetic acid (9.3% yield) as a white solid. LCMS: [M+1] = 275.0. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.27 (dd, J = 2.3, 7.8 Hz, 1H), 7.00 (dd, J = 2.3, 8.8 Hz, 1H), 3.62 (s, 2H), 2.59 (s, 3H).

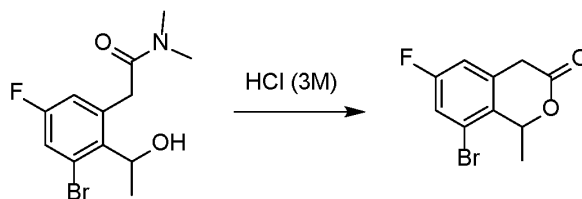
Step 2: 2-(2-acetyl-3-bromo-5-fluorophenyl)-N,N-dimethylacetamide

[000304] To a solution of 2-(2-acetyl-3-bromo-5-fluorophenyl)acetic acid (1.91 g, 6.96 mmol, 1 *eq*) in DCM (25 mL) was added N-methylmethanamine;hydrochloride (1.30 g, 16.00 mmol, 2.3 *eq*), DIEA (3.15 g, 24.35 mmol, 4.24 mL, 3.5 *eq*), DMAP (1.44 g, 11.83 mmol, 1.7 *eq*), HATU (4.76 g, 12.52 mmol, 1.8 *eq*), the mixture was stirred at 25°C for 16 hrs. LCMS showed ~30.9 % desired mass. Water (30 mL) was added, the mixture was extracted with DCM (30 mL x 2). The combined organic layers were washed brine (30 mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, 20gSepaFlash® Silica Flash Column, Eluent of 0~30% Petroleum ether gradient /Ethyl acetate @ 120mL/min) to give product 2-(2-acetyl-3-bromo-5-fluorophenyl)-N,N-dimethylacetamide (66.6% yield) as a yellow oil. LCMS: [M+1] = 302.0.

Step 3: 2-(3-bromo-5-fluoro-2-(1-hydroxyethyl)phenyl)-N,N-dimethylacetamide

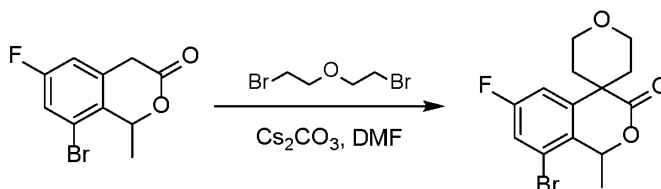
[000305] To a solution of 2-(2-acetyl-3-bromo-5-fluorophenyl)-N,N-dimethylacetamide (1.4 g, 4.63 mmol, 1 *eq*) in THF (20 mL) was added LiBH₄ (2 M, 4.63 mL, 2 *eq*) in 0°C, the mixture was stirred at 25°C for 12 hrs. LCMS showed ~ 66% desired mass. The mixture was poured into ice water (20 mL), the mixture was extracted with ethyl acetate (20 mL x 2). The combined organic layers were washed with brine (20 mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to give a residue to give 2-(3-bromo-5-fluoro-2-(1-hydroxyethyl)phenyl)-N,N-dimethylacetamide (1.1 g, crude) as a yellow oil. LCMS: [M+1] = 286.0.

Step 4: 8-bromo-6-fluoro-1-methylisochroman-3-one



[000306] To a solution of 2-(3-bromo-5-fluoro-2-(1-hydroxyethyl)phenyl)-N,N-dimethylacetamide (1.1 g, 3.62 mmol, 1 *eq*) in THF (12 mL) was added HCl (3 M, 1.21 mL, 1 *eq*), the mixture was stirred at 90°C for 2 hrs. LCMS showed ~54 % desired mass. Water (15 mL) was added, the mixture was extracted with ethyl acetate (15 mL x2). The combined organic layers were washed with brine (15 mL x 2), dried over Na₂SO₄ and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, 20g SepaFlash® Silica Flash Column, Eluent of 0~30%Petroleum ether gradient /Ethyl acetate @ 120mL/min) to give 8-bromo-6-fluoro-1-methylisochroman-3-one (59.7% yield) as a yellow oil. LCMS: [M+1] = 259.0. ¹H NMR (400 MHz, CHLOROFORM-d) δ = 7.20 - 7.18 (m, 1H), 6.84 (br d, J = 8.1 Hz, 1H), 5.73 (q, J = 6.9 Hz, 1H), 3.71 - 3.61 (m, 2H), 1.55 (d, J = 6.9 Hz, 3H).

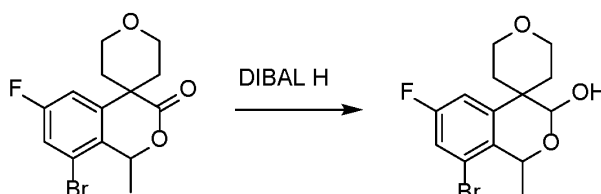
Step 5: 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-3-one



[000307] To a solution of Cs₂CO₃ (6.41 g, 19.69 mmol, 3 *eq*) in DMF (10 mL) was added 8-bromo-6-fluoro-1-methylisochroman-3-one (1.7 g, 6.56 mmol, 1 *eq*) in DMF (10 mL) at 20°C under N₂. The mixture was stirred at 20°C for 0.5 hrs. 1-bromo-2-(2-bromoethoxy)ethane (6.09 g, 26.25 mmol, 3.30 mL, 4 *eq*) was added at 20°C under N₂. The mixture was stirred at 20°C for 12 hr. LCMS showed one peak with desired mass was detected. The reaction mixture was quenched by H₂O (100 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (100 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 0/1) to give 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-3-one

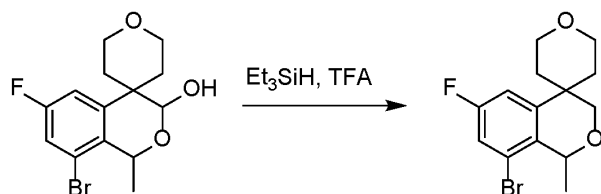
(69.4% yield) as colorless oil. LCMS: $[M+1] = 329.1$. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 7.31$ (dd, $J = 2.4, 7.5$ Hz, 1H), 7.24 (dd, $J = 2.3, 10.1$ Hz, 1H), 5.76 (q, $J = 6.6$ Hz, 1H), 4.50 (dt, $J = 2.5, 11.6$ Hz, 1H), $4.05 - 3.86$ (m, 3H), 2.34 (ddd, $J = 5.6, 11.6, 13.9$ Hz, 1H), $2.04 - 1.90$ (m, 3H), 1.72 (d, $J = 6.8$ Hz, 3H).

Step 6: 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-3-ol



[000308] To a solution of 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-3-one (1.5 g, 4.56 mmol, 1 *eq*) in CH_2Cl_2 (20 mL) was added DIBAL-H (1 M, 5.92 mL, 1.3 *eq*) at 0°C under N_2 . The mixture was stirred at 0°C for 1 hr. TLC (petroleum ether/ethyl acetate = 3/1, $R_f = 0.25$) indicated one new spot was formed. The reaction mixture was added aq.HCl (1M, 50 mL), it was stirred for 30 mins, then extracted with DCM (30 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 1/0 to 0/1) to give 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-3-ol (800 mg, 2.42 mmol, 53.0%) as a white solid. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 7.25 - 7.15$ (m, 2H), $5.77 - 5.46$ (m, 1H), 5.11 (q, $J = 6.4$ Hz, 1H), $4.01 - 3.77$ (m, 4H), $2.29 - 2.06$ (m, 2H), $1.82 - 1.59$ (m, 5H).

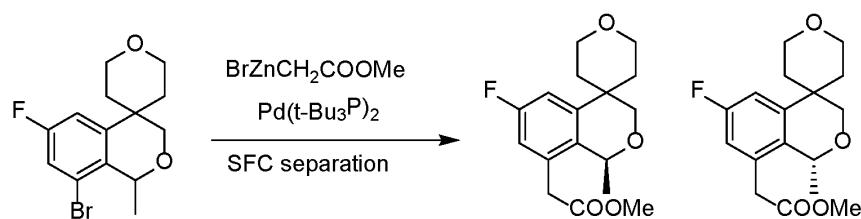
Step 7: 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]



[000309] To a solution of 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-3-ol (700 mg, 2.11 mmol, 1 *eq*) in DCM (14 mL) was added Et_3SiH (1.47 g, 12.68 mmol, 2.03 mL, 6 *eq*) and TFA (2.17 g, 19.02 mmol, 1.41 mL, 9 *eq*) at 20°C under N_2 . The mixture was stirred at 50°C for 24 hrs. TLC (Plate 1, petroleum

ether/ethyl acetate = 3/1, R_f = 0.5) indicated one new spot was formed. The reaction mixture was quenched by H_2O (30 mL) and extracted with DCM (10 mL x 3). The combined organic layers were washed with brine (20 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 1/0 to 0/1) to give 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran] (1.1 g, crude) as a white solid. 1H NMR (400 MHz, $CHCl_3$ -d) δ = 7.20 - 7.13 (m, 2H), 5.04 (q, J = 6.4 Hz, 1H), 4.10 (d, J = 12.1 Hz, 1H), 3.97 - 3.87 (m, 3H), 3.75 - 3.67 (m, 1H), 3.58 (dt, J = 2.1, 12.4 Hz, 1H), 2.23 (dt, J = 5.1, 13.3 Hz, 1H), 1.90 - 1.81 (m, 1H), 1.77 - 1.70 (m, 1H), 1.60 (d, J = 6.4 Hz, 3H), 1.56 (br d, J = 4.8 Hz, 1H).

Step 8: methyl 2-(6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)acetate



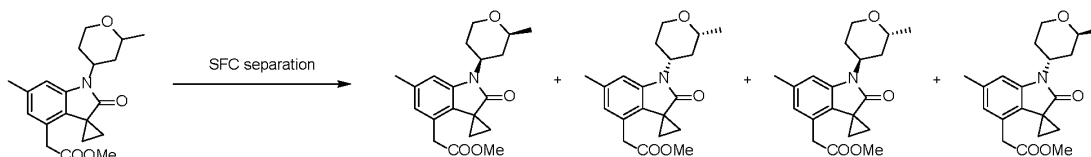
[000310] A mixture of give 8-bromo-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran] (1.0 g, 3.17 mmol, 1 *eq*) in THF (5 mL) was added $Pd(t-Bu_3P)_2$ (162.15 mg, 317.28 μ mol, 0.1 *eq*) at 25°C. $BrZnCH_2COOMe$ (1 M, 6.98 mL, 2.2 *eq*) was added into the reaction. The reaction was stirred at 80°C for 3 hrs. TLC (Petroleum ether: Ethyl acetate = 2:1) showed the starting material (R_f = 0.50) was consumed and a new spot (R_f = 0.30) observed. The mixture was filtered and H_2O was added to the filtrate. The mixture was filtered and the layers were separated and the aqueous phase was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography (Petroleum ether/Ethyl acetate = 2/1). The product was further separated by SFC (condition: column: DAICEL CHIRALPAK AD (250mm*30mm, 10 μ m); mobile phase: $[CO_2-EtOH]$; B%: 15%, isocratic elution mode).

[000311] **Peak 1** (15.3% yield) was obtained as a yellow oil and arbitrarily assigned as methyl (S)-2-(6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)acetate. 1H NMR (400 MHz, $CHCl_3$ -d) δ = 7.10 (dd, J = 2.6, 10.3 Hz, 1H), 6.87

(dd, $J = 2.6, 9.1$ Hz, 1H), 5.07 (q, $J = 6.5$ Hz, 1H), 4.06 - 3.95 (m, 2H), 3.93 - 3.83 (m, 2H), 3.73 (s, 3H), 3.75 - 3.66 (m, 1H), 3.64 - 3.48 (m, 3H), 2.21 (dt, $J = 5.1, 13.3$ Hz, 1H), 1.92 (dt, $J = 5.1, 13.3$ Hz, 1H), 1.76 - 1.50 (m, 4H), 1.49 (d, $J = 6.5$ Hz, 3H).

[000312] Peak 2 (15.3% yield) was obtained as a yellow oil and arbitrarily assigned as methyl (R)-2-(6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)acetate. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 7.09$ (dd, $J = 2.6, 10.3$ Hz, 1H), 6.87 (dd, $J = 2.5, 9.1$ Hz, 1H), 5.07 (q, $J = 6.5$ Hz, 1H), 4.00 (q, $J = 12.0$ Hz, 2H), 3.95 - 3.84 (m, 2H), 3.80 - 3.67 (m, 4H), 3.64 - 3.47 (m, 3H), 2.21 (dt, $J = 5.2, 13.4$ Hz, 1H), 1.92 (dt, $J = 5.1, 13.2$ Hz, 1H), 1.74 - 1.59 (m, 2H), 1.48 (d, $J = 6.5$ Hz, 3H).

Separation of isomers of methyl 2-(6'-methyl-1'-(2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate



[000313] Methyl 2-(6'-methyl-1'-(2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (4.8 g, 16.15 mmol, 1 *eq*) was separated by SFC (column: DAICEL CHIRALPAK IC (250 mm*50 mm, 10 μm); mobile phase: [CO_2 -MeOH (0.1% $\text{NH}_3\text{H}_2\text{O}$)]; B%:35%, isocratic elution mode and column: REGIS (s,s) WHELK-O1 (250 mm*50 mm, 10 μm); mobile phase: [CO_2 -IPA]; B%:25%, isocratic elution mode) to give 4 isomers.

[000314] Peak 1, arbitrarily assigned as methyl 2-(6'-methyl-1'-((2S,4S)-2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (13.00% yield), was obtained as a yellow oil. SFC: $R_t = 2.228$ min. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 6.92$ (s, 1H), 6.74 (s, 1H), 4.66 - 4.45 (m, 1H), 4.15 (dd, $J = 3.8, 11.9$ Hz, 1H), 3.71 (s, 3H), 3.65 - 3.52 (m, 2H), 3.35 (s, 2H), 2.50 (dq, $J = 4.7, 12.6$ Hz, 1H), 2.38 (s, 3H), 2.25 - 2.11 (m, 1H), 1.89 - 1.85 (m, 2H), 1.75 (td, $J = 2.0, 12.6$ Hz, 1H), 1.68 (br d, $J = 2.4$ Hz, 1H), 1.61 (br s, 2H), 1.28 (d, $J = 6.2$ Hz, 3H).

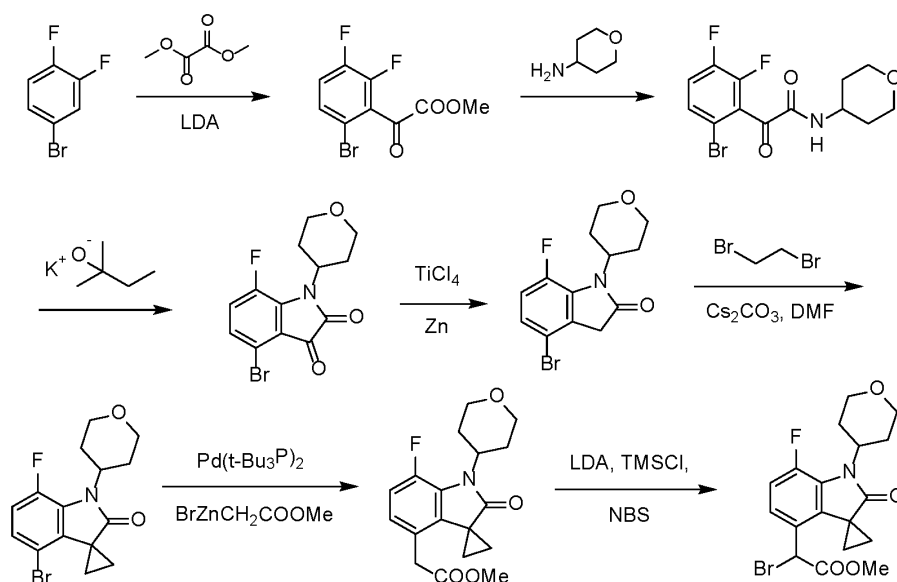
[000315] Peak 2, arbitrarily assigned as methyl 2-(6'-methyl-1'-((2R,4R)-2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (13.00% yield), was obtained as a yellow oil. SFC: $R_t = 2.450$ min. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 6.92$ (s, 1H), 6.74 (s, 1H), 4.57 (tdd, $J = 4.3, 8.3, 12.6$ Hz, 1H), 4.15

(dd, $J = 4.5, 11.1$ Hz, 1H), 3.71 (s, 3H), 3.65 - 3.55 (m, 2H), 3.35 (s, 2H), 2.50 (dq, $J = 4.8, 12.6$ Hz, 1H), 2.38 (s, 3H), 2.26 - 2.11 (m, 1H), 1.91 - 1.82 (m, 2H), 1.75 (td, $J = 2.0, 12.7$ Hz, 1H), 1.68 (br d, $J = 2.0$ Hz, 1H), 1.65 - 1.61 (m, 2H), 1.28 (d, $J = 6.2$ Hz, 3H).

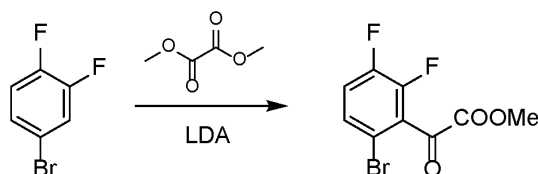
[000316] Peak 3, arbitrarily assigned as methyl 2-(6'-methyl-1'-((2R,4S)-2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (31.7% yield), was obtained as a yellow oil. SFC: $R_t = 2.794$ min. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 6.91$ (s, 1H), 6.75 (s, 1H), 4.79 - 4.68 (m, 1H), 4.40 - 4.32 (m, 1H), 3.92 - 3.86 (m, 2H), 3.71 (s, 3H), 3.35 (s, 2H), 2.70 - 2.61 (m, 1H), 2.56 - 2.45 (m, 1H), 2.38 (s, 3H), 1.89 - 1.83 (m, 2H), 1.77 - 1.70 (m, 1H), 1.65 - 1.57 (m, 3H), 1.39 (d, $J = 6.9$ Hz, 3H).

[000317] Peak 4, arbitrarily assigned as methyl 2-(6'-methyl-1'-((2S,4R)-2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (33.33% yield), was obtained as a yellow oil. SFC: $R_t = 3.106$ min. ^1H NMR (400 MHz, CHLOROFORM- d) $\delta = 6.91$ (s, 1H), 6.75 (s, 1H), 4.87 - 4.61 (m, 1H), 4.44 - 4.28 (m, 1H), 3.93 - 3.82 (m, 2H), 3.71 (s, 3H), 3.35 (s, 2H), 2.70 - 2.60 (m, 1H), 2.56 - 2.44 (m, 1H), 2.38 (s, 3H), 1.88 - 1.82 (m, 2H), 1.77 - 1.68 (m, 1H), 1.65 - 1.57 (m, 3H), 1.39 (d, $J = 6.8$ Hz, 3H).

Preparation of methyl 2-bromo-2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate

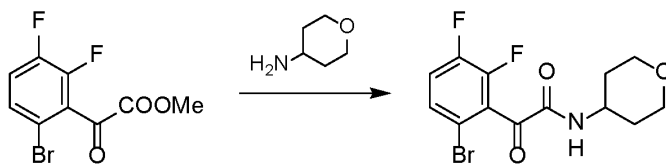


Step 1: methyl 2-(6-bromo-2,3-difluorophenyl)-2-oxoacetate



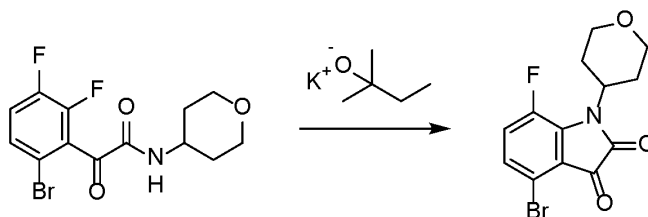
[000318] To a solution of 4-bromo-1,2-difluorobenzene (10 g, 51.82 mmol, 1 eq) in THF (100 mL) was added LDA (2 M, 25.91 mL, 1 eq) dropwise at -70 °C under an atmosphere of N₂. The reaction mixture was allowed to stir at -70 °C for 0.5 hrs. To this mixture was added a solution of dimethyl oxalate (6.12 g, 51.82 mmol, 1 eq) in THF (50 mL) at -70 °C. The reaction mixture was allowed to stir at -70 °C for 1 hr. The reaction was quenched by the addition of aq. NH₄Cl (200 mL) and extracted with ethyl acetate (200 mL x 2). The organic solutions were combined, washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. Methyl 2-(6-bromo-2,3-difluorophenyl)-2-oxoacetate (8.7 g, crude) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.40 (ddd, *J* = 1.8, 3.9, 8.9 Hz, 1H), 7.27 - 7.20 (m, 1H), 3.98 (s, 3H).

Step 2: 2-(6-bromo-2,3-difluorophenyl)-2-oxo-N-(tetrahydro-2H-pyran-4-yl)acetamide



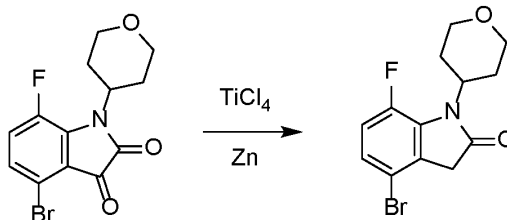
[000319] To methyl 2-(6-bromo-2,3-difluorophenyl)-2-oxoacetate (8.7 g, 31.18 mmol, 1 eq) in MeOH (100 mL) was added tetrahydro-2H-pyran-4-amine (4.73 g, 46.77 mmol, 1.5 eq) at 25 °C under an atmosphere of N₂. The reaction mixture was allowed to stir at 25 °C for 16 hrs under an atmosphere of N₂. The mixture was concentrated under reduced pressure. The crude product was triturated with petroleum ether/ethyl acetate (5/1). 2-(6-bromo-2,3-difluorophenyl)-2-oxo-N-(tetrahydro-2H-pyran-4-yl)acetamide (73.70% yield) was obtained as a yellow oil. LCMS [M+1] = 348.0. ¹H NMR (400 MHz, CDCl₃) δ = 7.36 (ddd, *J* = 1.8, 3.9, 8.9 Hz, 1H), 7.26 - 7.14 (m, 1H), 6.88 (br d, *J* = 6.4 Hz, 1H), 4.05 - 3.94 (m, 3H), 3.56 - 3.49 (m, 2H), 2.05 - 1.92 (m, 2H), 1.67 - 1.58 (m, 2H).

Step 3: 4-bromo-7-fluoro-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione



[000320] To a solution of 2-(6-bromo-2,3-difluorophenyl)-2-oxo-N-(tetrahydro-2H-pyran-4-yl)acetamide (8 g, 22.98 mmol, 1 eq) in toluene (100 mL) was added potassium 2-methylbutan-2-olate (1 M, 34.47 mL, 1.5 eq) at 0 °C under an atmosphere of N₂. The mixture was allowed to stir at 25 °C for 1 hr. The reaction was quenched by the addition of cold aq. HCl (1 M, 100 mL) and extracted with ethyl acetate (100 mL x 2). The organic solutions were combined, washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 4-bromo-7-fluoro-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione (66.31% yield) as a yellow solid. LCMS [M+1] = 328.0. ¹H NMR (400 MHz, CDCl₃) δ = 7.25 (s, 1H), 7.23 (d, J = 2.5 Hz, 1H), 4.63 - 4.54 (m, 1H), 4.13 (dd, J = 4.8, 11.7 Hz, 2H), 3.54 - 3.49 (m, 2H), 2.55 - 2.46 (m, 2H), 1.75 (br dd, J = 2.4, 12.3 Hz, 2H).

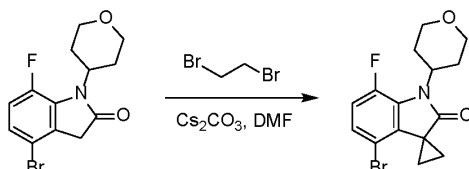
Step 4: 4-bromo-7-fluoro-1-(tetrahydro-2H-pyran-4-yl)indolin-2-one



[000321] Two batches were carried out in parallel. To a mixture of Zn (1.4 g, 21.41 mmol, 4.68 eq) in THF (20 mL) was added TiCl₄ (2.60 g, 13.71 mmol, 1.5 mL, 3 eq) dropwise at 0 °C under an atmosphere of N₂. The mixture was allowed to stir at 80 °C for 2 hrs. A solution of 4-bromo-7-fluoro-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione (1.5 g, 4.57 mmol, 1 eq) in THF (20 mL) was added at 20 °C and the mixture was allowed to stir at 20 °C for 2 hrs. The reaction was quenched by the addition of saturated aq. NaHCO₃ (100 mL). The mixture was filtered and the filtrate was extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (100 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 3/1). 4-bromo-7-fluoro-1-(tetrahydro-2H-pyran-4-yl)indolin-2-one (69.63% yield) was obtained from the combined batches as a yellow oil. LCMS [M+1] =

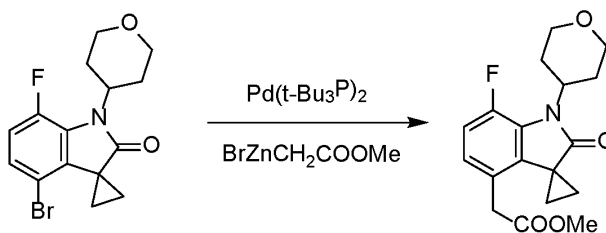
314.0. ^1H NMR (400 MHz, CDCl_3) δ = 7.13 (dd, J = 3.7, 8.9 Hz, 1H), 6.97 (dd, J = 8.9, 11.8 Hz, 1H), 4.73 - 4.62 (m, 1H), 4.11 (dd, J = 4.9, 11.6 Hz, 2H), 3.55 - 3.48 (m, 4H), 2.50 - 2.39 (m, 2H), 1.66 (br dd, J = 2.4, 12.3 Hz, 2H).

Step 5: 4'-bromo-7'-fluoro-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



[000322] To a solution of 4-bromo-7-fluoro-1-(tetrahydro-2H-pyran-4-yl)indolin-2-one (2.1 g, 6.68 mmol, 1 eq) in DMF (30 mL) was added Cs_2CO_3 (6.53 g, 20.05 mmol, 3 eq) and 1,2-dibromoethane (6.28 g, 33.42 mmol, 2.52 mL, 5 eq). The mixture was allowed to stir at 35°C for 12 hrs. The reaction was quenched by the addition of H_2O (100 mL) at 0°C and extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, washed with brine (50 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 1/0 to 3/1). 4'-bromo-7'-fluoro-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (87.95% yield) was obtained as a yellow solid. LCMS $[\text{M}+1] = 340.0$. ^1H NMR (400 MHz, CDCl_3) δ = 7.07 (dd, J = 4.0, 8.9 Hz, 1H), 6.90 (dd, J = 8.9, 11.8 Hz, 1H), 4.81 - 4.69 (m, 1H), 4.11 (dd, J = 4.8, 11.5 Hz, 2H), 3.52 (br t, J = 11.9 Hz, 2H), 2.58 - 2.46 (m, 2H), 2.41 (q, J = 3.9 Hz, 2H), 1.72 - 1.65 (m, 2H), 1.61 - 1.58 (m, 2H).

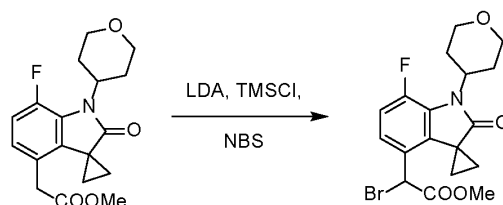
Step 6: methyl 2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate



[000323] To a solution of 4'-bromo-7'-fluoro-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (1.2 g, 3.53 mmol, 1 eq) in THF (10 mL) was added $\text{Pd}(\text{t-Bu}_3\text{P})_2$ (90.14 mg, 176.37 μmol , 0.05 eq) and $\text{BrZnCH}_2\text{COOMe}$ (1 M, 10.58 mL, 3 eq) at 20°C and the reaction was allowed to stir at 80°C for 2 hrs under an atmosphere of N_2 . The

reaction was quenched by the addition of H₂O (30 mL) at 0 °C and filtered. The filtrate was extracted with ethyl acetate (30 mL x 3). The organic solutions were combined, washed with brine (30 mL x 3), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 3/1). Methyl 2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (19.56% yield) was obtained as a yellow oil. LCMS Rt = 0.445 min, [M+1] = 334.3. ¹H NMR (400 MHz, CDCl₃) δ = 6.99 (dd, J = 8.6, 12.0 Hz, 1H), 6.94 - 6.86 (m, 1H), 4.86 - 4.63 (m, 1H), 4.13 - 4.08 (m, 2H), 3.71 (s, 3H), 3.56 - 3.50 (m, 2H), 3.35 (s, 2H), 2.60 - 2.46 (m, 2H), 2.00 - 1.89 (m, 2H), 1.72 - 1.65 (m, 4H).

Step 7: methyl 2-bromo-2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate

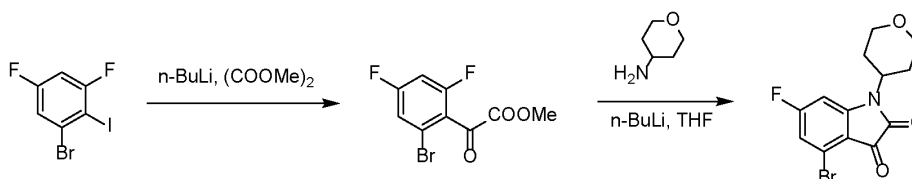


[000324] To a solution of methyl 2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (180 mg, 539.97 μmol, 1 eq) in THF (5 mL) was added LDA (2 M, 269.98 μL, 1 eq) at -70 °C under an atmosphere of N₂. After 0.5 hrs, TMSCl (70.40 mg, 647.96 μmol, 82.24 μL, 1.2 eq) was added and the mixture was allowed to stir at -70 °C for 0.5hrs. NBS (288.32 mg, 1.62 mmol, 3 eq) in THF (5 mL) was added. The mixture was allowed to stir at -70 °C for 0.5 hrs. The reaction was quenched by the addition of saturated aqueous NH₄Cl (30 mL) and extracted with ethyl acetate (30 mL x 2). The organic solutions were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 3/1). Methyl 2-bromo-2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate (8.40% yield) was obtained as a yellow oil. LCMS [M+1] = 412.0. ¹H NMR (400 MHz, CDCl₃) δ = 7.40 (dd, J = 4.2, 8.9 Hz, 1H), 7.07 (dd, J = 8.9, 11.9 Hz, 1H), 4.95 (s, 1H), 4.77 - 4.72 (m, 1H), 4.11 - 4.08 (m, 2H), 3.80 (s, 3H), 3.52 (s, 2H), 2.52 (br d, J = 7.9 Hz, 2H), 2.02 - 1.91 (m, 2H), 1.73 - 1.67 (m, 4H).

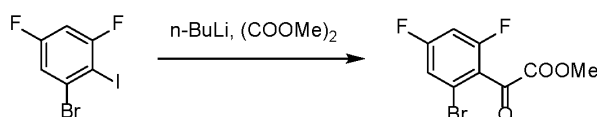
[000325] Methyl 2-bromo-2-(6'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate was prepared from 4-bromo-6-fluoro-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione following procedures similar to steps 4, 5, 6 and

7 above in the synthesis of methyl 2-bromo-2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetate. ^1H NMR (400 MHz, CDCl_3) δ = 7.11 (dd, J = 2.3, 10.3 Hz, 1H), 6.89 (dd, J = 2.1, 9.0 Hz, 1H), 4.94 (d, J = 1.4 Hz, 1H), 4.51 (tt, J = 4.4, 12.6 Hz, 1H), 4.13 (d, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.53 (dt, J = 1.8, 12.0 Hz, 2H), 2.56 - 2.45 (m, 2H), 1.78 (br d, J = 2.3 Hz, 2H), 1.72 - 1.67 (m, 2H), 1.29 - 1.25 (m, 2H).

Preparation of 4-bromo-6-fluoro-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione

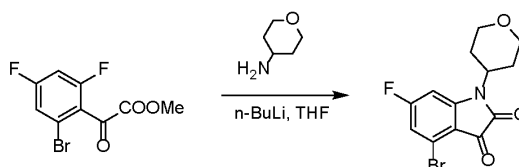


Step 1: methyl 2-(2-bromo-4,6-difluorophenyl)-2-oxoacetate



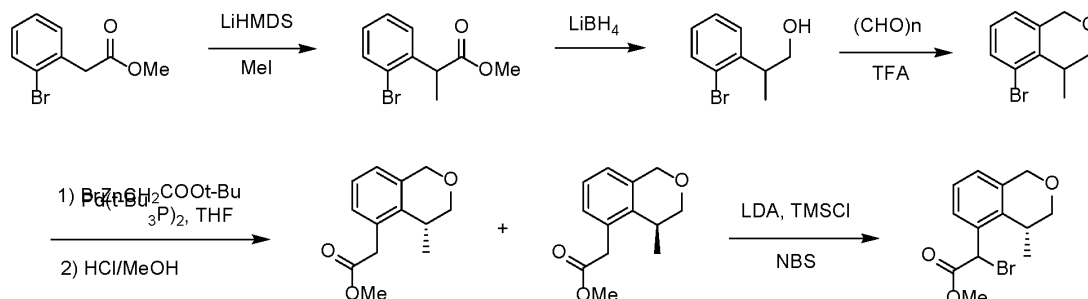
[000326] To a solution of 1-bromo-3,5-difluoro-2-iodobenzene (26 g, 81.53 mmol, 1 eq) in toluene (400 mL) was added $n\text{-BuLi}$ (2.5 M, 24.46 mL, 0.75 eq) dropwise at -70°C under an atmosphere of N_2 . The reaction mixture was allowed to stir at -70°C for 0.5 hrs. Then to the reaction mixture was added a solution of dimethyl oxalate (19.26 g, 163.07 mmol, 2 eq) in toluene (500 mL) at -70°C . The reaction mixture was allowed to stir at -70°C for 1 hr. The reaction was quenched by the addition of aq. NH_4Cl (400 mL) and the mixture was extracted with ethyl acetate (100 mL $\times$ 2). The organic solutions were combined, washed with brine (200 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 1/0 to 2/1). Three batches were carried out in parallel. Methyl 2-(2-bromo-4,6-difluorophenyl)-2-oxoacetate (70.33% yield) was obtained as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.25 (td, J = 1.9, 7.8 Hz, 1H), 6.92 (ddd, J = 2.3, 8.4, 9.6 Hz, 1H), 3.96 (s, 3H).

Step 2: 4-bromo-6-fluoro-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione

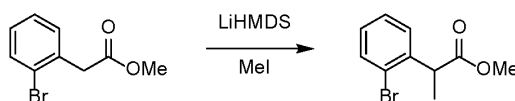


[000327] To a solution of tetrahydro-2H-pyran-4-amine (3.99 g, 39.42 mmol, 1.1 *eq*) in THF (50 mL) was added *n*-BuLi (2.5 M, 14.34 mL, 1 *eq*) at 0 °C under an atmosphere of N₂. The reaction was allowed to stir at 0 °C for 0.5 hrs. The reaction mixture was added to a solution of methyl 2-(2-bromo-4,6-difluorophenyl)-2-oxoacetate (10 g, 35.84 mmol, 1 *eq*) in THF (50 mL) at 0 °C under an atmosphere of N₂. The mixture was allowed to stir at 25 °C for 0.5 hrs. The reaction was quenched with aq. 2 M HCl (100 mL) and extracted with ethyl acetate (100 mL x2). The organic solutions were combined, washed with brine (50mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was triturated with petroleum ether/ethyl acetate (3/1). 4-bromo-6-fluoro-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione (42.52% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.00 (dd, *J* = 1.2, 8.6 Hz, 1H), 6.83 (dd, *J* = 1.2, 8.9 Hz, 1H), 4.36 (tt, *J* = 4.3, 12.3 Hz, 1H), 4.15 (br dd, *J* = 4.4, 11.7 Hz, 2H), 3.52 (br t, *J* = 11.5 Hz, 2H), 2.45 (dq, *J* = 4.6, 12.5 Hz, 2H), 1.74 (br dd, *J* = 2.2, 12.5 Hz, 2H)

Preparation of methyl 2-bromo-2-((*R*)-4-methylisochroman-5-yl)acetate



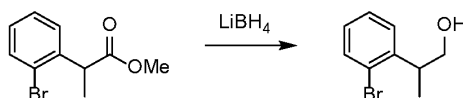
Step 1: methyl 2-(2-bromophenyl)propanoate



[000328] To a solution of methyl 2-(2-bromophenyl)acetate (50 g, 218.27 mmol, 1 *eq*) in THF (100 mL) was added LiHMDS (1 M, 240.10 mL, 1.1 *eq*) dropwise at 0 °C under an atmosphere of N₂ and the reaction was allowed to stir at 0 °C for 1 hr. MeI (30.98 g, 218.27 mmol, 13.59 mL, 1 *eq*) was added dropwise at 0 °C under an atmosphere of N₂. The mixture was allowed to stir at 20 °C for 1 hr. The reaction was quenched by the addition of NH₄Cl (500 mL) and extracted with ethyl acetate (200 mL x 3). The organic solutions were combined, washed with brine (100 mL x 3), dried over Na₂SO₄, filtered and concentrated under

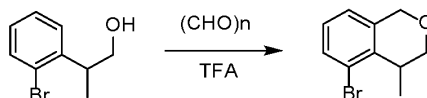
reduced pressure. Methyl 2-(2-bromophenyl)propanoate (60 g, crude) was obtained as a yellow oil. ^1H NMR (400 MHz, CDCl_3) δ = 7.57 (d, J = 8.2 Hz, 1H), 7.35 - 7.27 (m, 2H), 7.16 - 7.10 (m, 1H), 4.24 (q, J = 7.2 Hz, 1H), 3.69 (s, 3H), 1.50 (d, J = 7.2 Hz, 3H)

Step 2: 2-(2-bromophenyl)propan-1-ol



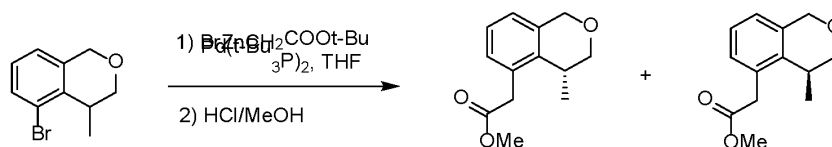
[000329] Two reactions were carried out in parallel. To a solution of LiBH_4 (8.04 g, 368.86 mmol, 2.99 *eq*) in THF (100 mL) was added a solution of methyl 2-(2-bromophenyl)propanoate (30 g, 123.41 mmol, 1 *eq*) in THF (100 mL) at 0 °C. The mixture was allowed to stir at 20 °C for 12 hrs. The mixture was diluted with H_2O (500 mL) and extracted with ethyl acetate (200 mL x 3). The organic solutions were combined, washed with brine (200 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/1 to 10/1). 2-(2-bromophenyl)propan-1-ol (37 g, 172.02 mmol, 78.72% yield over 2 steps) as colorless oil. LCMS R_t = 0.869, $[\text{M}-18+1]$ = 197.1. ^1H NMR (400 MHz, CDCl_3) δ = 7.56 (d, J = 7.9 Hz, 1H), 7.32 - 7.27 (m, 1H), 7.26 (d, J = 6.8 Hz, 1H), 7.10 - 7.04 (m, 1H), 3.82 - 3.75 (m, 1H), 3.72 - 3.66 (m, 1H), 3.54 - 3.46 (m, 1H), 1.28 (d, J = 7.0 Hz, 3H).

Step 3: 5-bromo-4-methylisochromane



[000330] A solution of 2-(2-bromophenyl)propan-1-ol (17 g, 79.04 mmol, 1 *eq*) and $(\text{HCHO})_n$ (7.83 g, 86.94 mmol, 1.1 *eq*) in TFA (100 mL) was allowed to stir at 100 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H_2O (200 mL) and extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (200 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The mixture was further purified by prep-HPLC (column: Phenomenex luna C18 250*150mm*15um; mobile phase: [water (TFA)-ACN]; B%: 30%-60%, 20min). 5-bromo-4-methylisochromane (44.57% yield) was obtained as a yellow oil. LCMS R_t = 1.031, $[\text{M}-18+1]$ = 209.0. ^1H NMR (400 MHz, CDCl_3) δ = 7.43 (d, J = 7.9 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 6.98 - 6.92 (m, 1H), 4.87 - 4.79 (m, 1H), 4.76 - 4.67 (m, 1H), 4.00 - 3.93 (m, 1H), 3.80 (dd, J = 2.8, 11.3 Hz, 1H), 3.02 - 2.92 (m, 1H), 1.39 (d, J = 6.9 Hz, 3H).

Step 4: methyl (R)-2-(4-methylisochroman-5-yl)acetate and methyl (S)-2-(4-methylisochroman-5-yl)acetate

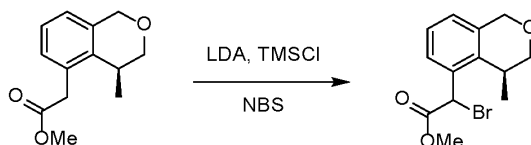


[000331] To a solution of 5-bromo-4-methylisochroman (6 g, 26.42 mmol, 1 *eq*) and Pd(*t*-Bu₃P)₂ (1.35 g, 2.64 mmol, 0.1 *eq*) in THF (60 mL) was added BrZnCH₂COOt-Bu (1.0 M, 60 mL, 2.27 *eq*) at 20 °C under an atmosphere of N₂. The mixture was allowed to stir at 80 °C for 2 hrs. The reaction mixture was diluted with H₂O (200 mL) and filtered, then extracted with ethyl acetate (100 mL x 2). The organic solutions were combined, washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was poured into HCl/MeOH (100 mL) at 20 °C. The mixture was allowed to stir at 50 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure. The residue was diluted with H₂O (50 mL) and extracted with ethyl acetate (20 mL x 3). The organic solutions were combined, washed with brine (20 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 10/1). The racemate (5 g) was obtained as a yellow oil. The racemate was separated by SFC (column: DAICEL CHIRALPAK AD (250mm*50mm, 10um); mobile phase: [0.1%NH₃H₂O IPA]; B%: 11%-11%, 1.6min.

[000332] Peak 1, arbitrarily assigned as methyl (S)-2-(4-methylisochroman-5-yl)acetate (30.93% yield) was obtained as colorless oil. LCMS [M-18+1] = 203.1. SFC Rt = 1.134. ¹H NMR (400 MHz, CDCl₃) δ = 7.20 - 7.12 (m, 2H), 6.95 - 6.89 (m, 1H), 4.89 - 4.74 (m, 2H), 3.97 - 3.91 (m, 1H), 3.85 - 3.80 (m, 1H), 3.76 - 3.72 (m, 1H), 3.71 (s, 3H), 3.65 - 3.60 (m, 1H), 2.93 - 2.85 (m, 1H), 1.33 (d, J = 7.0 Hz, 3H).

[000333] Peak 2, arbitrarily assigned as methyl (R)-2-(4-methylisochroman-5-yl)acetate (25.78% yield) was obtained as colorless oil. LCMS [M-18+1] = 203.1. SFC Rt = 1.330. ¹H NMR (400 MHz, CDCl₃) δ = 7.18 - 7.11 (m, 2H), 6.94 - 6.89 (m, 1H), 4.89 - 4.73 (m, 2H), 3.97 - 3.91 (m, 1H), 3.87 - 3.79 (m, 1H), 3.76 - 3.72 (m, 1H), 3.71 (s, 3H), 3.66 - 3.59 (m, 1H), 2.94 - 2.84 (m, 1H), 1.33 (d, J = 7.0 Hz, 3H).

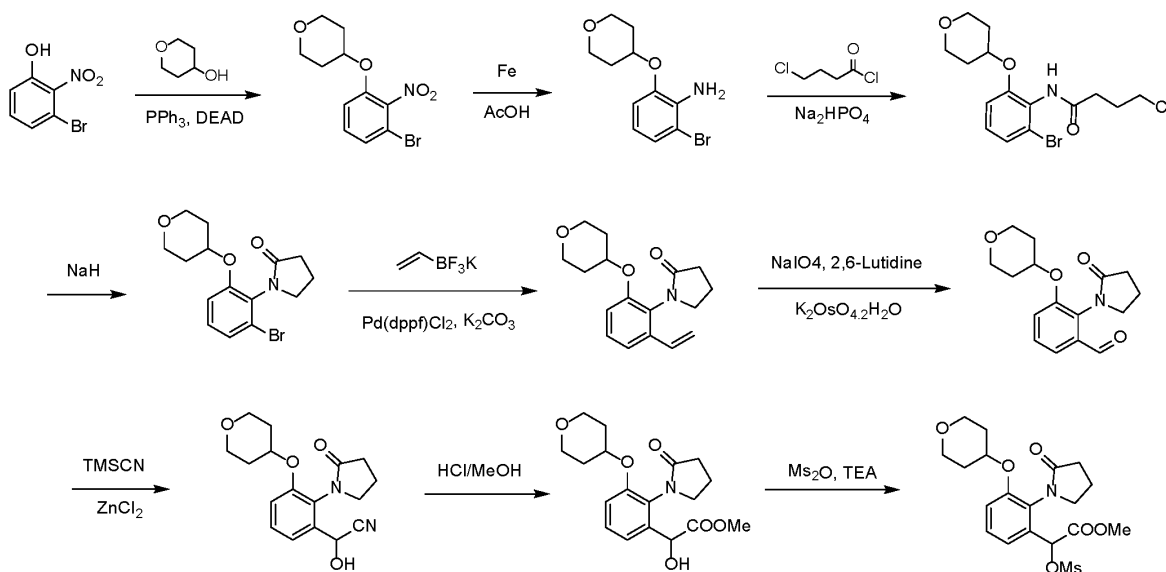
Step 5: methyl 2-bromo-2-((S)-4-methylisochroman-5-yl)acetate

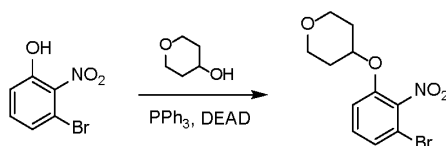


[000334] To a solution of methyl (S)-2-(4-methylisochroman-5-yl)acetate (500.00 mg, 2.27 mmol, 1 *eq*) in THF (10 mL) was added LDA (2 M, 1.70 mL, 1.5 *eq*) at -60 °C and the mixture was allowed to stir at -60 °C for 30 min. TMSCl (394.58 mg, 3.63 mmol, 460.96 μ L, 1.6 *eq*) was added at -60 °C and the mixture was allowed to stir at -60 °C for 0.5 hrs. A solution of NBS (484.82 mg, 2.72 mmol, 1.2 *eq*) in THF (5 mL) was added at -60 °C. The mixture was allowed to stir at -60 °C for 1 hr. The residue was diluted with NH₄Cl (20 mL) and extracted with ethyl acetate (10 mL x 3). The organic solutions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 20/1). Methyl 2-bromo-2-((S)-4-methylisochroman-5-yl)acetate (29.45% yield) was obtained as a yellow oil.

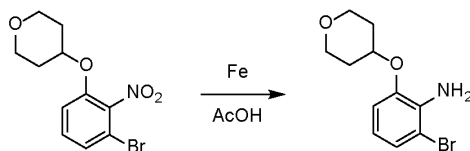
[000335] By a similar procedure starting from arbitrarily assigned methyl (R)-2-(4-methylisochroman-5-yl)acetate was prepared methyl 2-bromo-2-((S)-4-methylisochroman-5-yl)acetate.

Preparation of methyl 2-((methylsulfonyl)oxy)-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetate



Step 1: 4-(3-bromo-2-nitrophenoxy)tetrahydro-2H-pyran

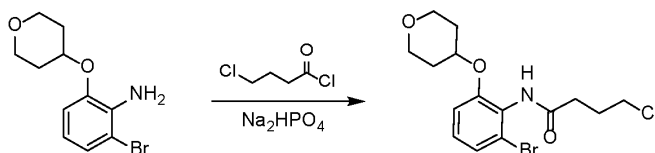
[000336] To a solution of 3-bromo-2-nitrophenol (13 g, 59.63 mmol, 1 *eq*) in toluene (200 mL) was added DIAD (18.09 g, 89.45 mmol, 17.34 mL, 1.5 *eq*), tetrahydro-2H-pyran-4-ol (7.31 g, 71.56 mmol, 7.15 mL, 1.2 *eq*) and PPh₃ (18.77 g, 71.56 mmol, 1.2 *eq*). The mixture was allowed to stir at 100 °C for 2 hrs. The reaction was quenched by the addition of H₂O (20 mL) at 20 °C and extracted with ethyl acetate (10 mL x 3). The organic solutions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 0/1). 4-(3-bromo-2-nitrophenoxy)tetrahydro-2H-pyran (23 g, 53.29 mmol, 89.37% yield, 70% purity) was obtained as colorless oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.30 - 7.27 (m, 1H), 7.25 - 7.20 (m, 1H), 7.00 (dd, *J* = 1.3, 8.3 Hz, 1H), 4.64 (tt, *J* = 3.5, 7.0 Hz, 1H), 3.90 (ddd, *J* = 3.5, 7.6, 11.5 Hz, 2H), 3.64 - 3.56 (m, 2H), 2.05 - 1.99 (m, 2H), 1.83 (ddd, *J* = 3.6, 6.9, 13.5 Hz, 2H).

Step 2: 2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)aniline

[000337] To a solution of 4-(3-bromo-2-nitrophenoxy)tetrahydro-2H-pyran (20 g, 66.20 mmol, 1 *eq*) in ethyl acetate (180 mL) and H₂O (20 mL) was added AcOH (48.14 g, 801.67 mmol, 45.89 mL, 12.11 *eq*) at 25 °C. The mixture was allowed to stir at 50 °C. Fe (18.48 g, 330.99 mmol, 5 *eq*) was added at 50 °C. The mixture was allowed to stir at 80 °C for 2 hrs. The reaction was quenched by the addition of aq. NaOH (10 mL) at 20 °C and the mixture was extracted with ethyl acetate (10 mL x 3). The organic solutions were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 1/0 to 0/1). 2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)aniline (18 g, 49.61 mmol, 74.94% yield, 75% purity) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.06 (dd, *J* = 0.8, 8.2 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.60 - 6.53 (m, 1H), 6.39 (br s, 2H), 4.49 (tt, *J* = 3.9, 8.0

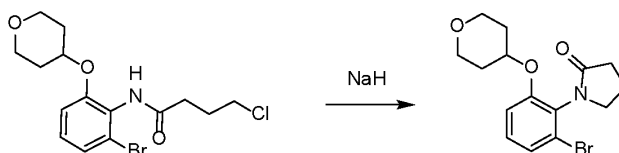
Hz, 1H), 4.02 - 3.96 (m, 2H), 3.59 (ddd, $J = 3.2, 8.6, 11.7$ Hz, 2H), 2.08 - 2.04 (m, 2H), 1.83 (tdd, $J = 4.2, 8.6, 12.9$ Hz, 2H).

Step 3: N-(2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-chlorobutanamide

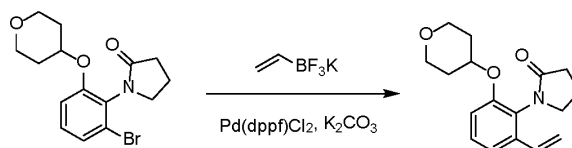


[000338] To a solution of 2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)aniline (9 g, 33.07 mmol, 1 *eq*) and Na_2HPO_4 (9.39 g, 66.14 mmol, 9.39 mL, 2 *eq*) in CHCl_3 (90 mL) was added 4-chlorobutanoyl chloride (5.60 g, 39.69 mmol, 4.44 mL, 1.2 *eq*) at 25 °C and the mixture was allowed to stir at 25 °C for 2 hrs. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. N-(2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-chlorobutanamide (12 g, crude) was obtained as a yellow oil. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.24$ (br d, $J = 9.5$ Hz, 1H), 7.12 (br t, $J = 6.4$ Hz, 1H), 6.90 (br d, $J = 8.1$ Hz, 1H), 6.37 (br s, 2H), 4.51 (dt, $J = 3.9, 7.6$ Hz, 1H), 3.99 - 3.90 (m, 2H), 3.60 - 3.54 (m, 2H), 2.16 - 2.06 (m, 4H), 2.04 - 1.98 (m, 2H), 1.85 - 1.75 (m, 2H).

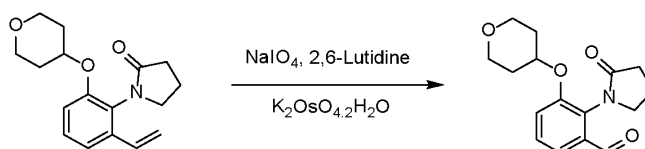
Step 4: 1-(2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)pyrrolidin-2-one



[000339] To a solution of NaH (1.17 g, 29.20 mmol, 60% purity, 1.1 *eq*) in DMF (50 mL) was added N-(2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-4-chlorobutanamide (10 g, 26.55 mmol, 1 *eq*) in DMF (50 mL) at 0 °C and the mixture was allowed to stir at 25 °C for 12 hrs. The reaction was quenched by the addition of sat. NH_4Cl (50 mL) and the mixture was extracted with ethyl acetate (50 mL x 2). The organic solutions were combined, washed with brine (30 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate=1/0 to 0/1). 1-(2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)pyrrolidin-2-one (7 g, 16.46 mmol, 62.00% yield, 80% purity) was obtained as a yellow oil. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.25 - 7.19$ (m, 1H), 7.13 (t, $J = 8.2$ Hz, 1H), 6.89 (d, $J = 8.2$ Hz, 1H), 4.99 - 4.95 (m, 1H), 4.52 (tt, $J = 3.5, 7.0$ Hz, 1H), 4.35 (s, 1H), 3.96 - 3.87 (m, 2H), 3.59 (dddd, $J = 3.8, 7.5, 11.4, 18.5$ Hz, 2H), 2.63 - 2.51 (m, 2H), 2.27 - 2.23 (m, 2H), 2.00 (td, $J = 3.4, 6.9$ Hz, 2H), 1.82 - 1.75 (m, 2H).

Step 5: 1-(2-((tetrahydro-2H-pyran-4-yl)oxy)-6-vinylphenyl)pyrrolidin-2-one

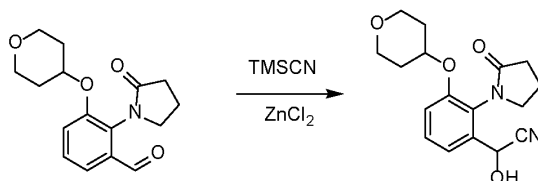
[000340] To a solution of 1-(2-bromo-6-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)pyrrolidin-2-one (3.5 g, 10.29 mmol, 1 *eq*) in dioxane (40 mL) and H₂O (4 mL) was added K₂CO₃ (4.27 g, 30.86 mmol, 3 *eq*), Pd(dppf)Cl₂ (1.51 g, 2.06 mmol, 0.2 *eq*) and trifluoro(vinyl)-λ⁴-borane, potassium salt (4.13 g, 30.86 mmol, 3 *eq*). The mixture was allowed to stir at 100 °C for 12 hrs. The reaction was quenched by the addition of H₂O (30 mL) at 20 °C and extracted with ethyl acetate (15 mL x 3). The organic solutions were combined, washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 0/1). 1-(2-((tetrahydro-2H-pyran-4-yl)oxy)-6-vinylphenyl)pyrrolidin-2-one (47.36% yield) was obtained as a brown oil. LCMS [M+1] = 288.1. ¹H NMR (400 MHz, CDCl₃) δ = 7.26 - 7.20 (m, 2H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.71 (dd, *J* = 11.1, 17.6 Hz, 1H), 5.76 (d, *J* = 17.5 Hz, 1H), 5.34 (d, *J* = 11.0 Hz, 1H), 4.53 (tt, *J* = 3.5, 7.0 Hz, 1H), 3.96 - 3.89 (m, 2H), 3.83 - 3.76 (m, 1H), 3.65 - 3.50 (m, 3H), 2.61 - 2.54 (m, 2H), 2.24 (quin, *J* = 7.5 Hz, 2H), 2.05 - 1.95 (m, 2H), 1.84 - 1.76 (m, 2H).

Step 6: 2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)benzaldehyde

[000341] To a solution of 1-(2-((tetrahydro-2H-pyran-4-yl)oxy)-6-vinylphenyl)pyrrolidin-2-one (1.4 g, 4.87 mmol, 1 *eq*) and 2,6-lutidine (1.04 g, 9.74 mmol, 1.13 mL, 2 *eq*) in THF (20 mL) and H₂O (10 mL) was added K₂OsO₄·2H₂O (179.51 mg, 487.21 μmol, 0.1 *eq*) and NaIO₄ (4.17 g, 19.49 mmol, 1.08 mL, 4 *eq*) at 0 °C. The mixture was allowed to stir at 25 °C for 0.5 hrs. The reaction mixture was filtered and the filtrate was diluted with sat. Na₂SO₃ (20 mL) and extracted with ethyl acetate (10 mL x 3). The organic solutions were combined, washed with brine (15 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 0/1). 2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)benzaldehyde (950 mg, 2.63 mmol, 53.92% yield, 80% purity) was obtained as a yellow oil. ¹H NMR (400 MHz,

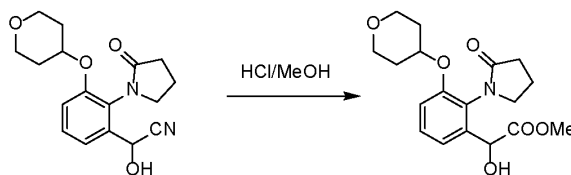
CDCl_3) δ = 10.03 (s, 1H), 7.54 (dd, J = 1.1, 7.7 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.26 - 7.20 (m, 1H), 4.61 - 4.55 (m, 1H), 4.03 - 3.91 (m, 3H), 3.67 - 3.57 (m, 3H), 2.66 - 2.53 (m, 2H), 2.34 - 2.25 (m, 2H), 2.12 - 2.04 (m, 2H), 1.83 (br d, J = 7.6 Hz, 2H).

Step 7: 2-hydroxy-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetonitrile



[000342] To a solution of 2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)benzaldehyde (950 mg, 3.28 mmol, 1 *eq*) in DCM (10 mL) was added TMSCN (488.62 mg, 4.93 mmol, 616.16 μL , 1.5 *eq*) and ZnCl_2 (104.81 mg, 328.35 μmol , 0.1 *eq*). The reaction mixture was allowed to stir at 25 °C for 12 hrs. The reaction mixture was filtered and the filtrate was diluted with H_2O (10 mL) and extracted with ethyl acetate (10 mL x 3). The organic solutions were combined, washed with brine (10 mL x 2), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 2-hydroxy-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetonitrile (1.5 g, crude) as a yellow oil. LCMS $[\text{M}+1] = 389.2$.

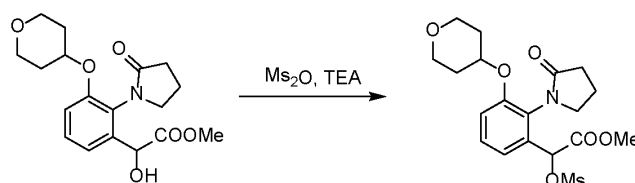
Step 8: methyl 2-hydroxy-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetate



[000343] A solution of 2-hydroxy-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetonitrile (1.3 g, 2.01 mmol, 1 *eq*) in HCl/MeOH (6 M, 334.59 μL , 1 *eq*) was allowed to stir at 30 °C for 24 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: $[\text{H}_2\text{O}$ (0.1%TFA)-ACN]; gradient: 20%-40% B over 8.0 min). methyl 2-hydroxy-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetate (57.03% yield) was obtained as a yellow oil. LCMS $[\text{M}+1] = 350.1$. ^1H NMR (400 MHz, CDCl_3) δ = 7.36 (t, J = 8.1 Hz, 1H), 7.08 (d, J = 7.0 Hz, 1H), 6.97 (d, J = 8.2

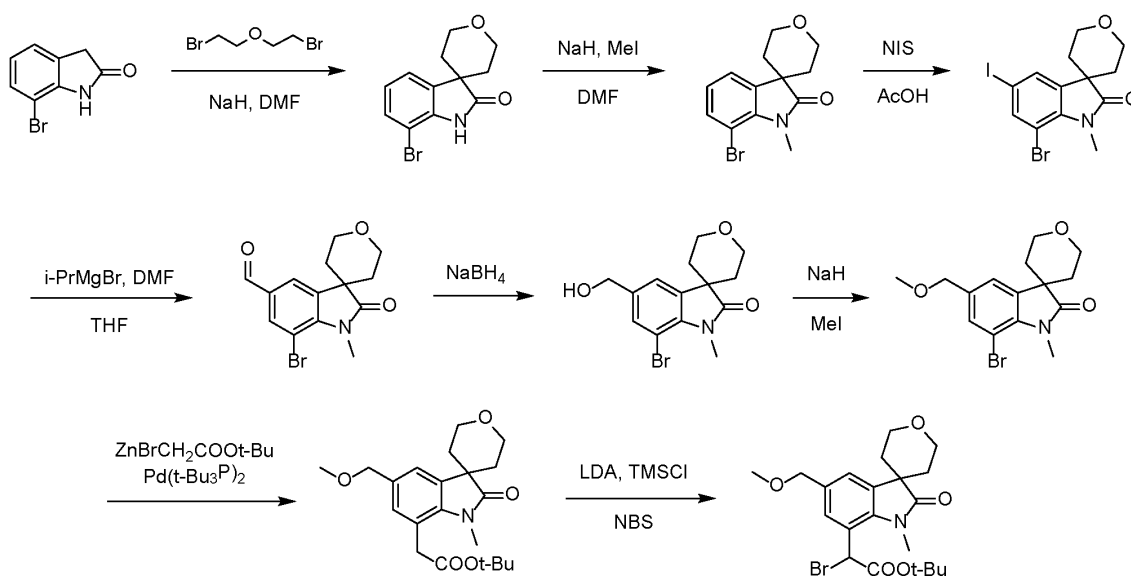
Hz, 1H), 5.16 (s, 1H), 4.60 - 4.53 (m, 1H), 3.95 - 3.69 (m, 9H), 2.72 - 2.61 (m, 2H), 2.33 - 2.22 (m, 2H), 2.13 - 1.98 (m, 2H), 1.80 (ddd, $J = 3.5, 7.3, 13.6$ Hz, 2H).

Step 9: methyl 2-((methylsulfonyl)oxy)-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetate

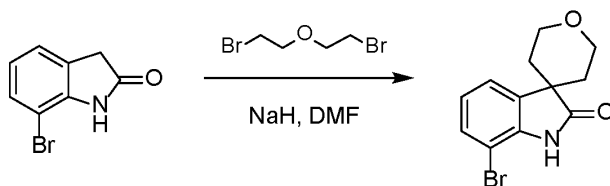


[000344] To a solution of methyl 2-hydroxy-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetate (150 mg, 429.34 μmol , 1 *eq*) in DCM (3 mL) was added TEA (130.33 mg, 1.29 mmol, 179.27 μL , 3 *eq*) and Ms_2O (224.37 mg, 1.29 mmol, 3 *eq*) at 0 °C. The mixture was allowed to stir at 0 °C for 15 min. The reaction was quenched by the addition of NaHCO_3 (aq) (2 mL) at 20 °C and extracted with DCM (2 mL x 3). The organic solutions were combined, washed with brine (3 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. methyl 2-((methylsulfonyl)oxy)-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetate (170 mg, crude) was obtained as a yellow oil. LCMS $[\text{M}+1] = 428.1$.

Preparation of tert-butyl 2-bromo-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate

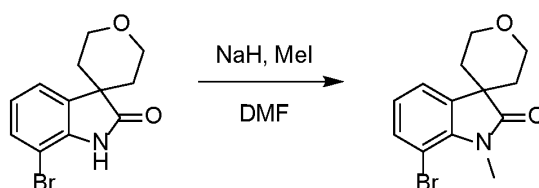


Step 1: 7-bromo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



[000345] Three parallel reactions were carried out. To a mixture of NaH (14.15 g, 353.70 mmol, 60% purity, 5 *eq.*) in DMF (450 mL) was added a solution of 7-bromoindolin-2-one (15 g, 70.74 mmol, 1 *eq.*) in DMF (450 mL) at 0 °C under an atmosphere of N₂. The reaction was allowed to stir at 0 °C for 1 hr. 1-bromo-2-(2-bromoethoxy)ethane (24.61 g, 106.11 mmol, 13.30 mL, 1.5 *eq.*) was added at 0 °C. The reaction mixture was allowed to warm to 25 °C and was allowed to stir at 25 °C for 15 hrs. The three parallel reactions were combined. The reaction was quenched by the addition of H₂O (3000 mL) and filtered. The filter cake was washed with water (600 mL x 3) and dried in vacuum to give 7-bromo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (50 g, 120.46 mmol, 56.76% yield, crude) as a red solid. LCMS [M+1] = 282.1.

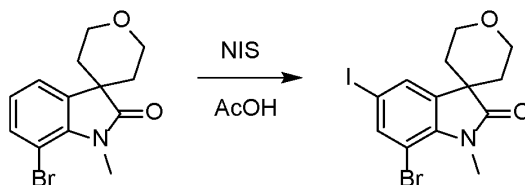
Step 2: 7-bromo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



[000346] Two parallel reactions were carried out. To a solution of 7-bromo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (12 g, 42.53 mmol, 1 *eq.*) in DMF (160 mL) was added NaH (3.40 g, 85.07 mmol, 60% purity, 2 *eq.*) at 0 °C under an atmosphere of N₂. The reaction mixture was allowed to stir at 0 °C under an atmosphere of N₂ for 0.5 hrs. MeI (12.07 g, 85.07 mmol, 5.30 mL, 2 *eq.*) was added dropwise to the reaction mixture at 0 °C. The reaction mixture was allowed to warm to 25 °C and stir for 2 hrs. The two reaction mixtures were combined and quenched by the addition of sat. NH₄Cl (500 mL) at 0 °C. The mixture was extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1). 7-bromo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (35.72% yield) was obtained as a white solid. LCMS [M+1] = 675.4. ¹H NMR (400 MHz, CDCl₃) δ = 7.40 (dd, *J* = 0.8, 8.3 Hz, 1H), 7.23 (dd, *J* = 0.8, 7.4 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 4.32 -

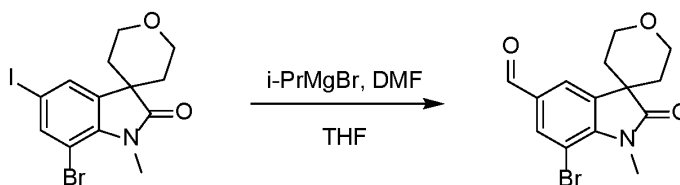
4.26 (m, 2H), 3.93 - 3.88 (m, 2H), 3.60 (s, 3H), 1.95 - 1.88 (m, 2H), 1.76 (br d, $J = 13.9$ Hz, 2H).

Step 3: 7-bromo-5-iodo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



[000347] Two parallel reactions were carried out. To a solution of 7-bromo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (5 g, 16.88 mmol, 1 *eq.*) in AcOH (50 mL) was added NIS (9.5 g, 42.21 mmol, 2.5 *eq.*) at 25 °C under an atmosphere of N₂. The reaction mixture was heated to 50 °C and allowed to stir for 16 hrs. The two reactions mixtures were combined, quenched by the addition of sat. NaHCO₃ (200 mL) and extracted with ethyl acetate (30 mL x 3). The organic solutions were combined, washed with brine (30 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/0 to 90/10). 7-bromo-5-iodo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (70.17% yield) was obtained as a white solid. LCMS $[M+1] = 421.7$. ¹H NMR (400 MHz, CDCl₃) $\delta = 7.73$ (d, $J = 1.5$ Hz, 1H), 7.47 (d, $J = 1.5$ Hz, 1H), 4.29 - 4.23 (m, 2H), 3.91 - 3.86 (m, 2H), 3.56 (s, 3H), 1.93 - 1.86 (m, 2H), 1.76 - 1.71 (m, 2H).

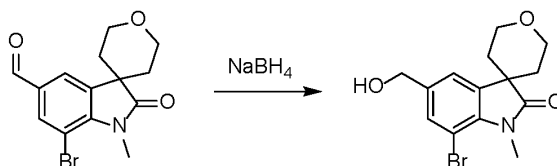
Step 4: 7-bromo-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-5-carbaldehyde



[000348] Two parallel reactions were carried out. To a solution of 7-bromo-5-iodo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (5 g, 11.85 mmol, 1 *eq.*) in THF (50 mL) was added i-PrMgBr (1 M, 17.77 mL, 1.5 *eq.*) dropwise at 0 °C under an atmosphere of N₂. The reaction mixture was allowed to stir at 0 °C for 0.5 hrs. To the reaction mixture was added DMF (8.66 g, 118.47 mmol, 9.12 mL, 10 *eq.*) at 0 °C. The reaction mixture was warmed to 25 °C and allowed to stir at 25 °C for 2 hrs. The two reaction mixtures were

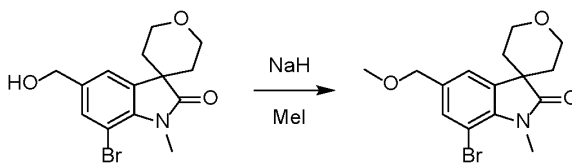
combined, quenched by the addition of sat. NH_4Cl (200 mL) at 20 °C and extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, washed with brine (50 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/0 to 80/20). 7-bromo-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-5-carbaldehyde (78.12% yield) was obtained as a yellow solid. LCMS $[\text{M}+1] = 323.8$. ^1H NMR (400 MHz, CDCl_3) $\delta = 9.86$ (s, 1H), 7.93 (d, $J = 1.3$ Hz, 1H), 7.75 (d, $J = 1.3$ Hz, 1H), 4.27 (t, $J = 9.8$ Hz, 2H), 3.95 - 3.91 (m, 2H), 3.65 (s, 3H), 1.99 - 1.94 (m, 2H), 1.77 (br d, $J = 13.9$ Hz, 2H).

Step 5: 7-bromo-5-(hydroxymethyl)-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



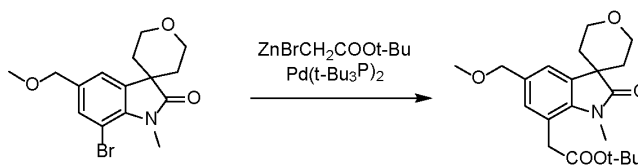
[000349] Two parallel reactions were carried out. To a solution of 7-bromo-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-5-carbaldehyde (3 g, 9.25 mmol, 1 eq.) in THF (30 mL) was added NaBH_4 (350.12 mg, 9.25 mmol, 1 eq.) at 0 °C under an atmosphere of N_2 . The reaction mixture was warmed to 25 °C and allowed to stir for 2 hrs. The two reaction mixtures were combined, quenched by the addition of water (250 mL) at 25 °C and extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, washed with brine (50 mL x 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 100/0 to 70/30). 7-bromo-5-(hydroxymethyl)-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (82.82% yield) was obtained as a yellow solid. LCMS $[\text{M}+1] = 325.9$. ^1H NMR (400 MHz, CDCl_3) $\delta = 7.36$ (s, 1H), 7.21 (s, 1H), 4.57 (s, 2H), 4.26 - 4.20 (m, 2H), 3.88 - 3.84 (m, 2H), 3.53 (s, 3H), 1.90 - 1.84 (m, 2H), 1.70 (br d, $J = 13.9$ Hz, 2H).

Step 6: 7-bromo-5-(methoxymethyl)-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



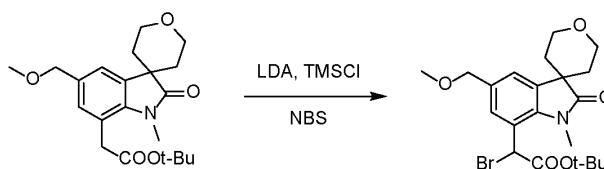
[000350] To a solution of 7-bromo-5-(hydroxymethyl)-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (5 g, 15.33 mmol, 1 *eq.*) in THF (100 mL) was added NaH (919.64 mg, 22.99 mmol, 60% purity, 1.5 *eq.*) at 0 °C under an atmosphere of N₂. The reaction mixture was allowed to stir at 0 °C for 0.5 hrs. To the reaction mixture was added MeI (3.26 g, 22.99 mmol, 1.43 mL, 1.5 *eq.*) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 2 hrs. The reaction mixture was quenched by the addition of sat. NH₄Cl (200 mL) at 25 °C and extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/0 to 80/20). 7-bromo-5-(methoxymethyl)-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (92.04% yield) was obtained as a yellow solid. LCMS [M+1] = 340.0.

Step 7: tert-butyl 2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate



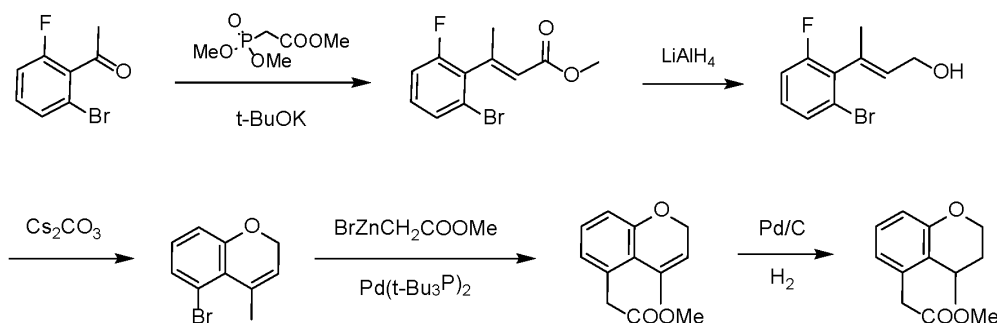
[000351] To a solution of 7-bromo-5-(methoxymethyl)-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (4.8 g, 14.11 mmol, 1 *eq.*) in THF (50 mL) was added Pd(t-Bu₃P)₃ (721.04 mg, 1.41 mmol, 0.1 *eq.*) and ZnBrCH₂COOt-Bu (1 M, 28.22 mL, 2 *eq.*) at 25 °C under an atmosphere of N₂. The reaction mixture was heated to 80 °C and allowed to stir at 80 °C for 2 hrs. The reaction was quenched by the addition of water (150 mL) at 25 °C and filtered. The filtered cake was washed with ethyl acetate (20 mL x 3) and then with 1 N HCl (500 mL). The filtrate was extracted with ethyl acetate (20 mL x 3). The organic solutions were combined, washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/0 to 80/20). tert-butyl 2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate (84.95% yield) was obtained as a yellow solid. LCMS [M+1] = 376.3. ¹HNMR (400 MHz, CDCl₃) δ = 7.22 (s, 1H), 7.04 (s, 1H), 4.41 (s, 2H), 4.32 - 4.26 (m, 2H), 3.94 - 3.89 (m, 2H), 3.80 (s, 2H), 3.44 (s, 3H), 3.40 (s, 3H), 1.96 - 1.90 (m, 2H), 1.75 (br d, J = 13.9 Hz, 2H), 1.45 (s, 9H).

Step 8: tert-butyl 2-bromo-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate

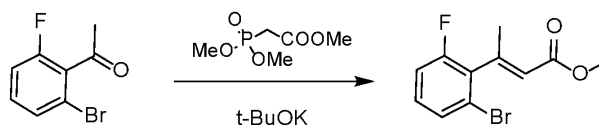


[000352] To a solution of tert-butyl 2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate (1 g, 2.66 mmol, 1 eq.) in THF (10 mL) was added LDA (2 M, 1.60 mL, 1.2 eq.) dropwise at -70 °C under an atmosphere of N₂. The reaction mixture was allowed to stir at -70 °C for 0.5 hrs. To the reaction mixture was added TMSCl (434.04 mg, 4.00 mmol, 507.05 uL, 1.5 eq.) at -70 °C. The reaction mixture was allowed to stir at -70 °C for 0.5 hrs. To the reaction mixture was added the solution of NBS (711.07 mg, 4.00 mmol, 1.5 eq.) in THF (8 mL) at -70 °C. The reaction mixture was allowed to stir at -70 °C for 1 hr. The reaction was quenched by the addition of sat. NH₄Cl (50 mL) at 25 °C and extracted with ethyl acetate (10 mL x 3). The organic solutions were combined, washed with brine (10 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/0 to 75/25). tert-butyl 2-bromo-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate (24.79% yield) was obtained as yellow oil. LCMS [M+1] = 454.0. ¹H NMR (400 MHz, CDCl₃) δ = 7.53 (s, 1H), 7.28 (br s, 1H), 6.00 (s, 1H), 4.42 (s, 2H), 4.30 - 4.27 (m, 2H), 3.93 - 3.90 (m, 2H), 3.59 (s, 3H), 3.40 (s, 3H), 1.96 - 1.92 (m, 2H), 1.78 - 1.75 (m, 2H), 1.49 (s, 9H).

Preparation of methyl 2-(4-methylchroman-5-yl)acetate

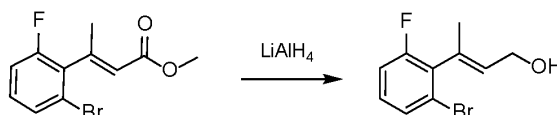


Step 1: methyl (E)-3-(2-bromo-6-fluorophenyl)but-2-enoate



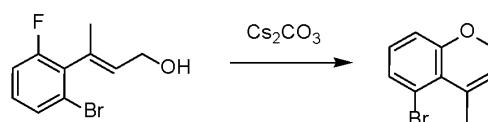
[000353] To a solution of methyl 2-(dimethoxyphosphoryl)acetate (15.10 g, 82.94 mmol, 11.95 mL, 1.2 eq) in THF (150 mL) was added t-BuOK (1 M, 82.94 mL, 1.2 eq) at 0 °C. The mixture was allowed to stir at 0 °C for 0.5 hrs. 1-(2-bromo-6-fluorophenyl)ethan-1-one (15 g, 69.11 mmol, 1 eq) in THF (150 mL) was added at 0 °C and the mixture was allowed to stir at 0 °C for 1.5 hrs, then at 50 °C for 14 hrs. The reaction was quenched by the addition of H₂O (300 mL) and ethyl acetate (50 mL) was added. The organic solution was separated and the aqueous solution was extracted with ethyl acetate (50 mL x 2). The organic solutions were combined, washed with brine (100 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 10/1, TLC: Petroleum ether/ethyl acetate = 10/1, R_f = 0.56). methyl (E)-3-(2-bromo-6-fluorophenyl)but-2-enoate (20 g, crude) was obtained as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.17 - 7.14 (m, 1H), 7.09 - 7.05 (m, 1H), 6.98 - 6.96 (m, 1H), 6.01 (d, *J* = 1.5 Hz, 1H), 3.66 (s, 3H), 2.47 (d, *J* = 1.1 Hz, 3H).

Step 2: (E)-3-(2-bromo-6-fluorophenyl)but-2-en-1-ol



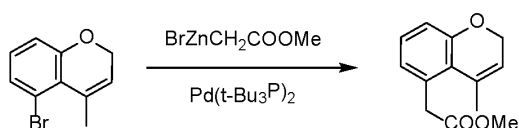
[000354] Two reactions were carried out in parallel. To a solution of methyl (E)-3-(2-bromo-6-fluorophenyl)but-2-enoate (11 g, 40.28 mmol, 1 eq) in THF (120 mL) at 0 °C, under an atmosphere of nitrogen, was added LiAlH₄ (2.5 M, 24.17 mL, 1.5 eq). The reaction mixture was allowed to stir at 20 °C for 2 hrs. To the reaction mixture was added H₂O (2.5 mL) and NaOH (15%, 2.5 mL). The mixture was further diluted with H₂O (500 mL) and extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. (E)-3-(2-bromo-6-fluorophenyl)but-2-en-1-ol (50.65% yield) was obtained as yellow oil.

Step 3: 5-bromo-4-methyl-2H-chromene



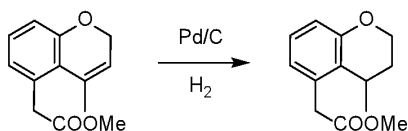
[000355] To a solution of (E)-3-(2-bromo-6-fluorophenyl)but-2-en-1-ol (15 g, 61.20 mmol, 1 *eq*) in DMF (180 mL) was added Cs₂CO₃ (59.82 g, 183.61 mmol, 3 *eq*) at 20 °C. The mixture was allowed to stir at 80 °C for 16 hrs. The reaction was quenched by the addition of H₂O (400 mL) and ethyl acetate (200 mL) was added. The organic solution was separated and the aqueous solution was extracted with ethyl acetate (200 mL x 3). The organic solutions were combined, washed with brine (400 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 10/1). 5-bromo-4-methyl-2H-chromene (19.54% yield) was obtained as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.20 (dd, *J* = 1.3, 7.9 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.87 (dd, *J* = 1.3, 8.1 Hz, 1H), 5.82 (ddd, *J* = 1.5, 3.1, 6.0 Hz, 1H), 4.48 (qd, *J* = 1.4, 4.5 Hz, 2H), 2.37 (q, *J* = 1.5 Hz, 3H).

Step 4: methyl 2-(4-methyl-2H-chromen-5-yl)acetate



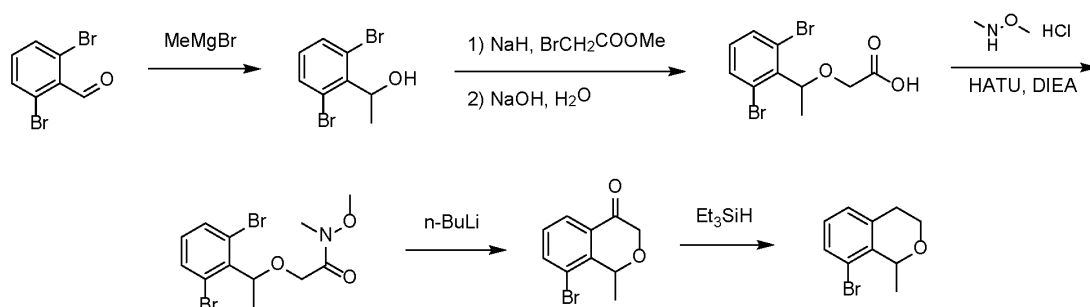
[000356] A suspension of 5-bromo-4-methyl-2H-chromene (200 mg, 888.57 μmol, 1 *eq*), BrZnCH₂COOMe (1 M, 4.44 mL, 5 *eq*) and Pd(t-Bu₃P)₂ (22.71 mg, 44.43 μmol, 0.05 *eq*) in THF (250 mL) was allowed to stir at 70 °C for 2 hrs under an atmosphere of N₂. Water (5 mL) was added and the mixture was filtrated. The filtrate was extracted with ethyl acetate (5 mL x 2). The organic solutions were combined, washed with brine (5 mL x 2), dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, 25g Sepa Flash ® Silica Flash Column, Eluent of 0~20% Petroleum ethergradient/ Ethyl acetate@ 120 mL/ min). methyl 2-(4-methyl-2H-chromen-5-yl)acetate (85.94% yield) was obtained as yellow oil. LCMS [M+1] = 219.1. ¹H NMR (400 MHz, CDCl₃) δ = 7.10 (t, *J* = 7.8 Hz, 1H), 6.87 (dd, *J* = 1.1, 8.1 Hz, 1H), 6.80 (dd, *J* = 0.8, 7.6 Hz, 1H), 5.76 (ddd, *J* = 1.4, 3.2, 5.9 Hz, 1H), 4.48 - 4.44 (m, 2H), 3.87 - 3.85 (m, 2H), 3.73 - 3.70 (m, 3H), 2.16 (d, *J* = 1.4 Hz, 3H).

Step 5: methyl 2-(4-methylchroman-5-yl)acetate

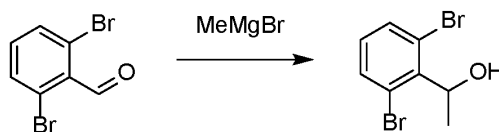


[000357] A solution of methyl 2-(4-methyl-2H-chromen-5-yl)acetate (2 g, 9.16 mmol, 1 *eq*) and Pd/C (20.00 g, 18.79 mmol, 1.88 mL, 10% purity, 2.05 *eq*) in MeOH (30 mL) was allowed to stir at 30 °C under H₂ (15 psi) for 12 hrs. The mixture was filtered and the filtrate was concentrated under reduced pressure to give methyl 2-(4-methylchroman-5-yl)acetate (1.7 g, 84.22%) as yellow oil. LCMS [M+1] = 221.2.

Preparation of 8-bromo-1-methylisochromane

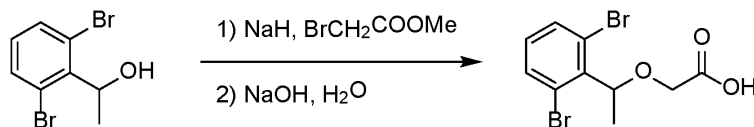


Step 1: 1-(2,6-dibromophenyl)ethan-1-ol



[000358] MeMgBr (3 M, 142.09 mL, 1.5 *eq*) was added dropwise to a solution of 2,6-dibromobenzaldehyde (75 g, 284.18 mmol, 1 *eq*) in THF (1000 mL) at 0 °C. The mixture was allowed to stir at 0-10 °C for 2 hrs. The reaction mixture was added dropwise into sat. NH₄Cl (1000 mL) at 0 °C under an atmosphere of N₂ and the mixture was extracted with ethyl acetate (200 mL x 2). The organic solutions were combined, washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 1-(2,6-dibromophenyl)ethan-1-ol (94.97% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.55 (d, *J* = 8.0 Hz, 2H), 6.97 (t, *J* = 8.0 Hz, 1H), 5.57 (q, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 6.8 Hz, 3H).

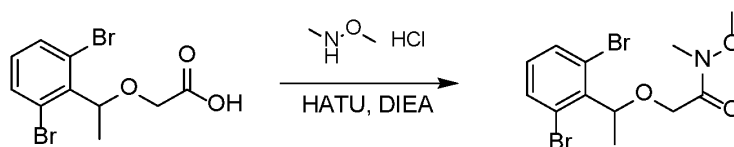
Step 2: 2-(1-(2,6-dibromophenyl)ethoxy)acetic acid



[000359] To a solution of 1-(2,6-dibromophenyl)ethan-1-ol (36 g, 128.59 mmol, 1 *eq*) in THF (400 mL) was added NaH (10.29 g, 257.18 mmol, 60% purity, 2 *eq*) at 0 °C under an atmosphere of N₂. The mixture was allowed to stir at 0 °C for 0.5 hrs. BrCH₂COOMe (39.34

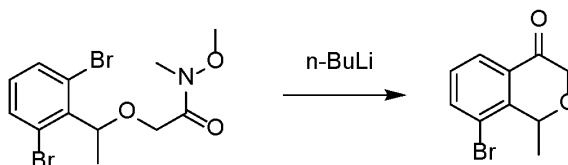
g, 257.18 mmol, 24.35 mL, 2 *eq*) was added at 0 °C and the solution was allowed to stir at 20 °C for 1 hr. H₂O (200 mL) and NaOH (10.29 g, 257.18 mmol, 2 *eq*) were added into the reaction mixture and the mixture was allowed to stir at 20 °C for 2 hrs. The mixture was extracted with EtOAc (200 mL x 3). The aqueous solution was adjusted to pH = 3 by the addition of HCl (1M) and extracted with DCM (200 mL x 3). The organic solutions were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 2-(1-(2,6-dibromophenyl)ethoxy)acetic acid (98.93% yield) as a white solid. ¹H NMR (400 MHz, CD₃OD) δ = 7.63 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 8.0 Hz, 1H), 5.51 - 5.42 (m, 1H), 3.94 (d, *J* = 16.5 Hz, 1H), 3.70 (d, *J* = 16.6 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 3H).

Step 3: 2-(1-(2,6-dibromophenyl)ethoxy)-N-methoxy-N-methylacetamide



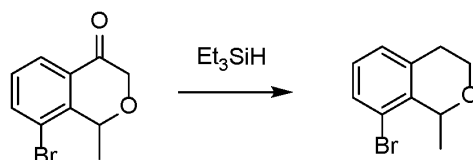
[000360] A mixture of 2-(1-(2,6-dibromophenyl)ethoxy)acetic acid (96 g, 284.03 mmol, 1 *eq*) and HATU (118.80 g, 312.43 mmol, 1.1 *eq*) in DCM (1000 mL) was allowed to stir at 20 °C for 1 hr. DIEA (110.13 g, 852.09 mmol, 148.42 mL, 3 *eq*) and N,O-dimethylhydroxylamine hydrochloride (33.25 g, 340.84 mmol, 1.2 *eq*) were added to the mixture. The reaction was allowed to stir at 20 °C for 15 hrs. The reaction mixture was quenched by the addition of H₂O (1000mL) and extracted with ethyl acetate (200 mL x 3). The organic solutions were combined, washed with brine (200 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 3/1 to 1/1). 2-(1-(2,6-dibromophenyl)ethoxy)-N-methoxy-N-methylacetamide (85.93% yield) was obtained as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.57 (d, *J* = 8.1 Hz, 2H), 6.99 (t, *J* = 7.9 Hz, 1H), 5.45 (q, *J* = 6.7 Hz, 1H), 4.20 (br d, *J* = 15.6 Hz, 1H), 3.94 (d, *J* = 15.8 Hz, 1H), 3.59 (s, 3H), 3.19 (s, 3H), 1.68 (d, *J* = 6.7 Hz, 3H).

Step 4: 8-bromo-1-methylisochroman-4-one



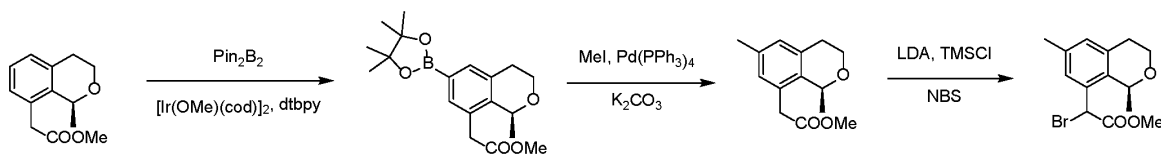
[000361] To a solution of 2-(1-(2,6-dibromophenyl)ethoxy)-N-methoxy-N-methylacetamide (51 g, 133.84 mmol, 1 *eq*) in THF (300 mL) was added n-BuLi (2.5 M, 53.53 mL, 1 *eq*) at -70 °C and the solution was allowed to stir at -70 °C for 2 hrs under an atmosphere of N₂. The reaction mixture was quenched by the addition of sat. NH₄Cl (300 mL) at 0 °C, and extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 5/1). 8-bromo-1-methylisochroman-4-one (74.38% yield) was obtained as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 8.02 (dd, *J* = 0.9, 7.8 Hz, 1H), 7.77 (dd, *J* = 1.2, 7.9 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 5.34 - 5.30 (m, 1H), 4.64 (d, *J* = 18.3 Hz, 1H), 4.37 (d, *J* = 18.1 Hz, 1H), 1.67 (d, *J* = 6.8 Hz, 3H).

Step 5: 8-bromo-1-methylisochromane

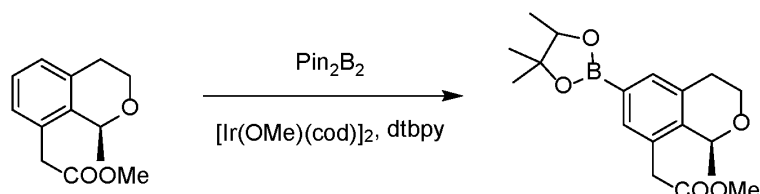


[000362] To a solution of 8-bromo-1-methylisochroman-4-one (38.5 g, 159.70 mmol, 1 *eq*) in TFA (300 mL) was added Et₃SiH (92.85 g, 798.49 mmol, 127.54 mL, 5 *eq*) at 20 °C under an atmosphere of N₂ and the solution was allowed to stir at 50 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (20 mL) and sat. NaHCO₃ (100 mL). The aqueous solution was extracted with ethyl acetate (20 mL x 2). The organic solutions were combined, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 5/1) to give 8-bromo-1-methylisochromane (82.72% yield) as a white solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.39 (dd, *J* = 0.6, 7.6 Hz, 1H), 7.05 (td, *J* = 7.2, 14.9 Hz, 2H), 5.06 (q, *J* = 6.5 Hz, 1H), 4.11 (ddd, *J* = 4.3, 9.4, 11.5 Hz, 1H), 3.86 (ddd, *J* = 3.8, 5.9, 11.5 Hz, 1H), 2.99 - 2.90 (m, 1H), 2.78 - 2.72 (m, 1H), 1.59 (d, *J* = 6.5 Hz, 3H).

Preparation of methyl 2-bromo-2-((S)-1,6-dimethylisochroman-8-yl)acetate

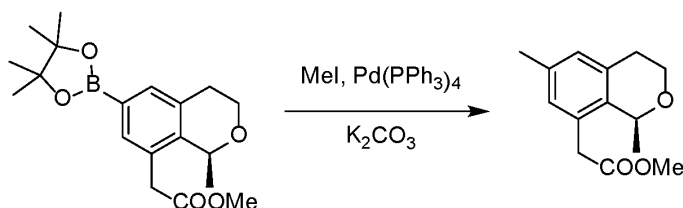


Step 1: methyl (S)-2-(1-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isochroman-8-yl)acetate



[000363] To a solution of arbitrarily assigned methyl (S)-2-(1-methylisochroman-8-yl)acetate (1.5 g, 6.81 mmol, 1 eq) in dioxane (20 mL) was added Pin₂B₂ (3.46 g, 13.62 mmol, 2 eq) and dtbpy (109.67 mg, 408.60 μmol, 0.06 eq) and [Ir(OMe)(cod)]₂ (135.42 mg, 204.30 μmol, 0.03 eq) at 20 °C under an atmosphere of N₂. The mixture was allowed to stir at 100 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 5/1) to give methyl (S)-2-(1,6-dimethylisochroman-8-yl)acetate (3 g, crude) as yellow oil. LCMS [M+1] = 235.1. ¹H NMR (400 MHz, CDCl₃) δ = 7.51 (s, 2H), 5.15 - 5.08 (m, 1H), 4.15 - 4.06 (m, 1H), 3.83 (dd, *J* = 5.0, 10.9 Hz, 1H), 3.71 - 3.69 (m, 3H), 3.65 - 3.61 (m, 1H), 3.60 - 3.55 (m, 1H), 2.93 (br dd, *J* = 5.8, 7.8 Hz, 1H), 2.85 - 2.76 (m, 1H), 1.47 (d, *J* = 6.5 Hz, 3H), 1.34 (s, 12H).

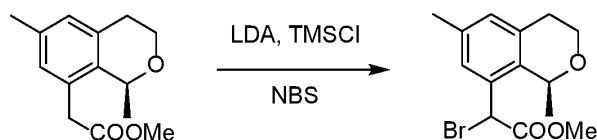
Step 2: methyl (S)-2-(1,6-dimethylisochroman-8-yl)acetate



[000364] To a solution of methyl (S)-2-(1,6-dimethylisochroman-8-yl)acetate (3 g, 8.66 mmol, 1 eq) in toluene (50 mL), EtOH (20 mL) and H₂O (20 mL) were added Pd(PPh₃)₄ (500.64 mg, 433.24 μmol, 0.05 eq), K₂CO₃ (3.59 g, 25.99 mmol, 3 eq) and MeI (6.15 g, 43.32 mmol, 2.70 mL, 5 eq) in turn at 20 °C under an atmosphere of N₂. The reaction mixture was heated to 100 °C and allowed to stir at 100 °C for 16 hrs. The reaction was quenched with water (200 mL) at 20 °C and extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (100 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1 to 5/1) to give methyl (S)-2-(1,6-dimethylisochroman-8-yl)acetate (1 g, 3.41 mmol, 39.41% yield, 80% purity) as a yellow oil. LCMS [M+1] = 235.1 ¹H NMR

(400 MHz, CDCl_3) δ = 6.93 (br s, 1H), 6.87 (s, 1H), 5.08 (q, J = 6.5 Hz, 1H), 4.13 - 4.05 (m, 1H), 3.81 (td, J = 5.1, 10.8 Hz, 1H), 3.71 (s, 3H), 3.63 - 3.57 (m, 1H), 3.53 - 3.48 (m, 1H), 2.94 - 2.84 (m, 1H), 2.79 - 2.70 (m, 1H), 2.30 (s, 3H), 1.47 (br d, J = 6.5 Hz, 3H).

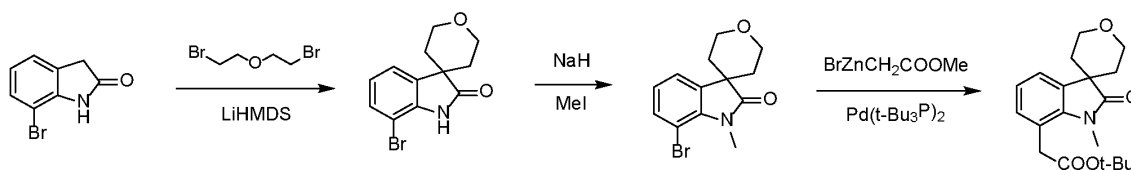
Step 3: methyl 2-bromo-2-((S)-1,6-dimethylisochroman-8-yl)acetate



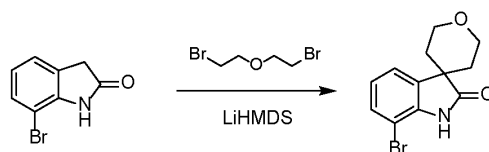
[000365] To a solution of methyl (S)-2-(1,6-dimethylisochroman-8-yl)acetate (0.5 g, 2.13 mmol, 1 eq) in THF (5 mL) was added LDA (2 M, 3.20 mL, 3 eq) at -60°C and the mixture was allowed to stir at -60°C for 30 min. TMSCl (765.10 mg, 7.04 mmol, 893.81 μL , 3.3 eq) was added at -60°C and the mixture was allowed to stir at -60°C for 0.5 hrs. A solution of NBS (569.74 mg, 3.20 mmol, 1.5 eq) in THF (5 mL) was added at -60°C . The mixture was allowed to stir at 60°C for 1 hr. The reaction was diluted with sat. NH_4Cl (50 mL) and extracted with ethyl acetate (20 mL x 3). The organic solutions were combined, washed with brine (50 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 10/1 to 5/1) to give methyl 2-bromo-2-((S)-1,6-dimethylisochroman-8-yl)acetate (0.46 g, 734.39 μmol , 34.41% yield, 50% purity) as yellow oil.

[000366] By a similar method starting from arbitrarily assigned methyl (R)-2-(1-methylisochroman-8-yl)acetate was prepared arbitrarily assigned methyl 2-bromo-2-((R)-1,6-dimethylisochroman-8-yl)acetate.

Preparation of tert-butyl 2-(1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate

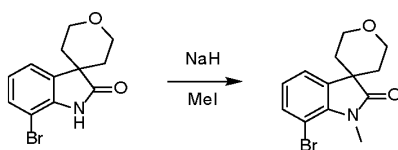


Step 1: 7-bromo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



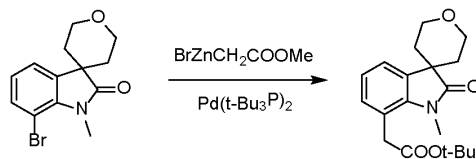
[000367] Four parallel reactions were carried out. To a solution of 7-bromoindolin-2-one (5 g, 23.58 mmol, 1 eq) in THF (100 mL) was added LiHMDS (1 M, 117.90 mL, 5 eq) at -70 °C, then the mixture was allowed to stir at -70 °C for 0.5 hrs. Then 1-bromo-2-(2-bromoethoxy)ethane (8.20 g, 35.37 mmol, 4.43 mL, 1.5 eq) was added at -70 °C. The reaction was allowed to stir at 25 °C for 16 hrs. The reaction was quenched by the addition of H₂O (500 mL) and ethyl acetate (200 mL) was added. The organic solution was separated and the aqueous solution was extracted with ethyl acetate (200 mL x 3). The organic solutions were combined, washed with brine (500 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 3/1). 7-bromo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (29.69% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.37 (d, *J* = 8.3 Hz, 1H), 7.29 (s, 1H), 6.97 (t, *J* = 7.9 Hz, 1H), 4.24 (td, *J* = 6.2, 11.9 Hz, 2H), 3.92 (td, *J* = 4.7, 11.8 Hz, 2H), 1.96 - 1.86 (m, 4H).

Step 2: 7-bromo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one



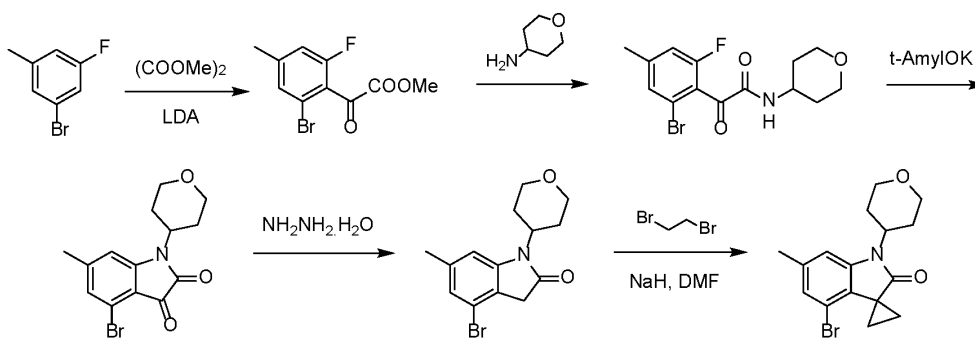
[000368] To a solution of 7-bromo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (5.4 g, 19.14 mmol, 1 eq) in DMF (55 mL) was added NaH (765.52 mg, 19.14 mmol, 60% purity, 1 eq) at 0 °C. The mixture was allowed to stir at 0 °C for 30 min and then MeI (5.43 g, 38.28 mmol, 2.38 mL, 2 eq) was added at 0 °C. The mixture was allowed to stir at 20 °C for 16 hrs. The mixture was quenched by the addition of sat. NH₄Cl (200 mL) and ethyl acetate (100 mL) was added. The organic and aqueous solutions were separated and the aqueous solution was extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 10/1). 7-bromo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (89.97% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.39 (dd, *J* = 1.1, 8.2 Hz, 1H), 7.22 (dd, *J* = 1.0, 7.4 Hz, 1H), 6.96 - 6.89 (m, 1H), 4.29 (ddd, *J* = 2.9, 10.4, 11.6 Hz, 2H), 3.90 (td, *J* = 4.3, 11.8 Hz, 2H), 3.59 (s, 3H), 1.97 - 1.88 (m, 2H), 1.80 - 1.72 (m, 2H).

Step 3: tert-butyl 2-(1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate

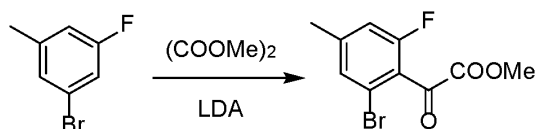


[000369] To a solution of 7-bromo-1-methyl-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-2-one (6.5 g, 21.95 mmol, 1 *eq*) in THF (65 mL) was added BrZnCH₂COOt-Bu (1 M, 43.90 mL, 2 *eq*) and Pd(t-Bu₃P)₂ (1.12 g, 2.19 mmol, 0.1 *eq*) at 20 °C. The mixture was allowed to stir at 80 °C for 2 hrs. The mixture was quenched by the addition of H₂O and filtered. The filtrate was extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (100 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 5/1). tert-butyl 2-(1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate (89.36% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.23 (dd, *J* = 1.4, 7.1 Hz, 1H), 7.09 - 7.01 (m, 2H), 4.38 - 4.21 (m, 2H), 3.92 (td, *J* = 4.3, 11.7 Hz, 2H), 3.81 (s, 2H), 3.46 (s, 3H), 1.94 (ddd, *J* = 4.4, 10.0, 14.1 Hz, 2H), 1.77 (br d, *J* = 13.9 Hz, 2H), 1.45 (s, 9H).

Preparation of 4'-bromo-6'-methyl-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



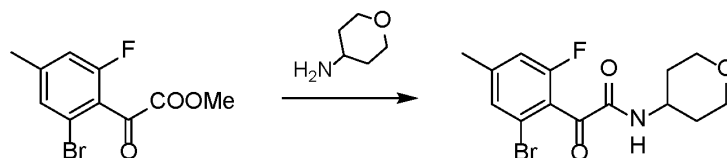
Step 1: methyl 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxoacetate



[000370] To a solution of 1-bromo-3-fluoro-5-methylbenzene (50 g, 264.52 mmol, 1 *eq*) in THF (500 mL) was added LDA (2 M, 158.71 mL, 1.2 *eq*) dropwise at -70 °C under an atmosphere of N₂. The reaction mixture was allowed to stir at -70 °C for 0.5 hrs. To the

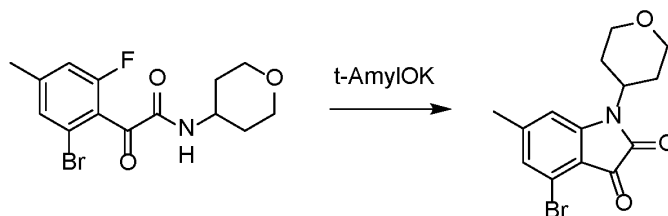
reaction mixture was added a solution of dimethyl oxalate (40.61 g, 343.87 mmol, 1.3 *eq*) in THF (500 mL) at -70 °C under an atmosphere of N₂. The reaction mixture was allowed to stir at -70 °C under N₂ for 2 hrs. The reaction was quenched by the addition of aq. NH₄Cl (500 mL) and extracted with EtOAc (200 mL x 3). The organic solutions were combined, washed with brine (500 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 5/1). Methyl 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxoacetate (90.71% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.28 (s, 1H), 6.95 (d, *J* = 10.3 Hz, 1H), 3.94 (s, 3H), 2.40 (s, 3H).

Step 2: 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxo-N-(tetrahydro-2H-pyran-4-yl)acetamide



[000371] To a mixture of methyl 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxoacetate (30 g, 109.06 mmol, 1 *eq*) in MeOH (300 mL) was added tetrahydro-2H-pyran-4-amine (12.13 g, 119.97 mmol, 1.1 *eq*) dropwise at 0 °C. The mixture was allowed to stir at 25 °C for 16 hrs. The reaction mixture was filtered and concentrated under reduced. The crude product was triturated with MeOH at 20 °C for 30 min. 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxo-N-(tetrahydro-2H-pyran-4-yl)acetamide (71.28% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.26-7.21 (m, 1H), 6.93 (d, *J* = 9.5 Hz, 1H), 6.85 (br d, *J* = 6.7 Hz, 1H), 4.13-3.97 (m, 3H), 3.51 (dt, *J* = 2.1, 11.7 Hz, 2H), 2.38 (s, 3H), 2.04-1.94 (m, 2H), 1.70-1.55 (m, 2H).

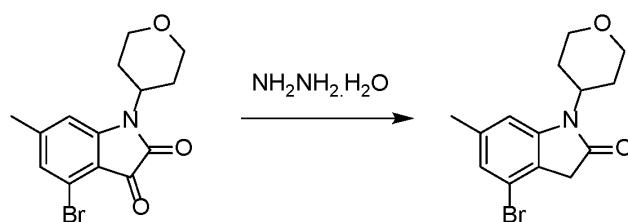
Step 3: 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione



[000372] To a mixture of 2-(2-bromo-6-fluoro-4-methylphenyl)-2-oxo-N-(tetrahydro-2H-pyran-4-yl)acetamide (10 g, 27.76 mmol, 1 *eq*) in toluene (100 mL) was added dropwise a

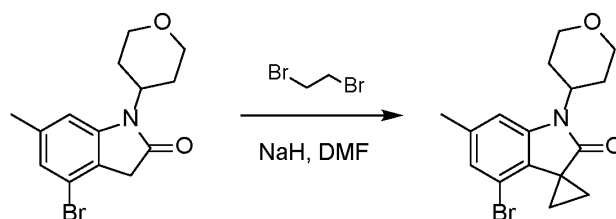
solution of t-AmylOK (4.56 g, 36.09 mmol, 5.24 mL, 1.3 *eq*) in toluene (50 mL) at 0 °C. The reaction was allowed to stir at 0 °C for 2 hrs and then quenched by the addition of HCl (1 M, 200 mL). The mixture was extracted with EtOAc (100 mL x 3). The organic solutions were combined, dried over Na₂SO₄, filtered and concentrated. The crude product was triturated by Petroleum ether : Ethyl acetate (2/1, 50 mL). The mixture was filtered and the filtrate was concentrated to dryness to give 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione (94.44% yield) as a red solid.

Step 4: 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-4-yl)indolin-2-one



[000373] To a solution of 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-4-yl)indoline-2,3-dione (24 g, 74.04 mmol, 1 *eq*) in glycol (250 mL) was added NH₂NH₂.H₂O (51.60 g, 1.03 mol, 50 mL, 13.92 *eq*) at 25 °C under an atmosphere of N₂. The mixture was allowed to stir at 130 °C for 4 hrs. The reaction mixture was concentrated under reduced pressure and quenched by the addition of H₂O (300 mL). The mixture was extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (100 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was used directly without further purification. 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-4-yl)indolin-2-one (25 g, crude) was obtained as a yellow solid. LCMS: [M+1] = 312.0.

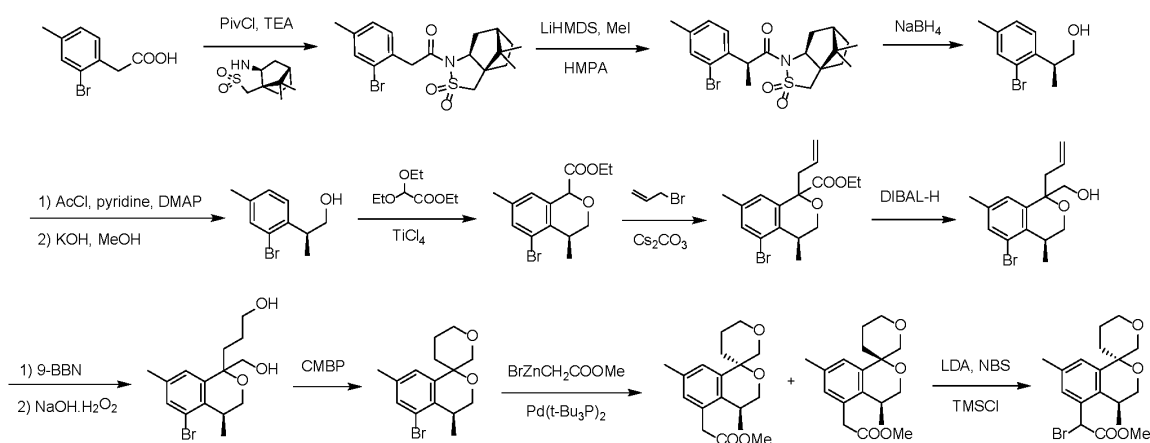
Step 5: 4'-bromo-6'-methyl-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one



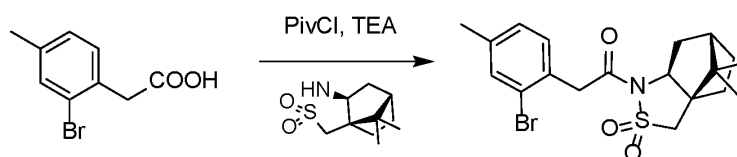
[000374] To a solution of 4-bromo-6-methyl-1-(tetrahydro-2H-pyran-4-yl)indolin-2-one (22.69 g, 73.15 mmol, 1 *eq*) in DMF (250 mL) was added NaH (14.63 g, 365.75 mmol, 60% purity, 5 *eq*) at 0 °C under an atmosphere of N₂. The solution was allowed to stir at 0 °C for

0.5 hrs, then 1,2-dibromoethane (68.71 g, 365.75 mmol, 27.59 mL, 5 *eq*) was added to the solution at 0 °C and the solution was allowed to stir at 20 °C for 2 hrs. The reaction was quenched by the addition of sat. NH₄Cl (300 mL) and extracted with EtOAc (100 mL x 3). The organic solutions were combined, washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated to give the crude product. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 2/1). 4'-bromo-6'-methyl-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-2'-one (60.99% yield) was obtained as a yellow solid.

Preparation of methyl 2-bromo-2-((1S,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetate



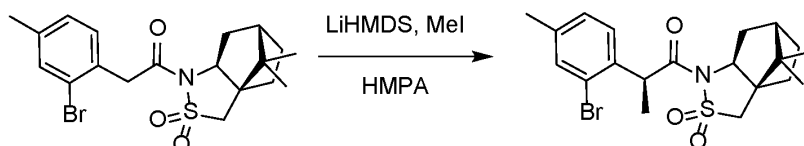
Step 1: 2-(2-bromo-4-methylphenyl)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)ethan-1-one



[000375] To a solution of 2-(2-bromo-4-methylphenyl)acetic acid (40 g, 174.62 mmol, 1 *eq*), (3aR,6S,7aS)-8,8-dimethylhexahydro-3H-3a,6-methanobenzo[c]isothiazole 2,2-dioxide (37.60 g, 174.62 mmol, 1 *eq*) and TEA (35.34 g, 349.24 mmol, 48.61 mL, 2 *eq*) in toluene (400 mL) was added PivCl (84.22 g, 698.48 mmol, 85.94 mL, 4 *eq*) in toluene (20 mL) dropwise at 80°C. The mixture was allowed to stir at 110°C for 16 hrs. The reaction was quenched by the addition of H₂O (1 L) at 0°C and extracted with ethyl acetate (300 mL x 3). The organic

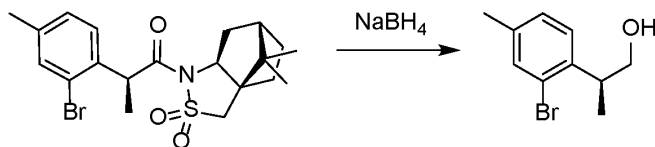
solutions were combined, washed with brine (300 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1). 2-(2-bromo-4-methylphenyl)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)ethan-1-one (150 g, crude) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.40 (s, 1H), 7.15 - 7.12 (m, 1H), 7.10 - 7.06 (m, 1H), 4.29 (d, *J* = 17.3 Hz, 1H), 4.05 (d, *J* = 17.3 Hz, 1H), 3.92 (dd, *J* = 4.9, 7.8 Hz, 1H), 3.52 (q, *J* = 13.8 Hz, 2H), 2.34 - 2.29 (m, 3H), 2.24 - 2.13 (m, 1H), 2.07 - 2.00 (m, 1H), 1.95 - 1.86 (m, 3H), 1.46 - 1.40 (m, 1H), 1.38 - 1.31 (m, 1H), 1.25 - 1.21 (m, 3H), 0.99 (s, 3H).

Step 2: (S)-2-(2-bromo-4-methylphenyl)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)propan-1-one



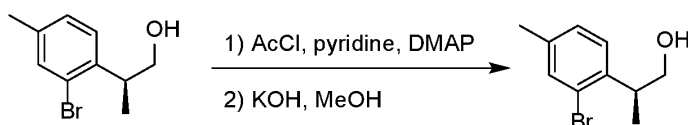
[000376] Four batches were carried out in parallel. To a solution of 2-(2-bromo-4-methylphenyl)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)ethan-1-one (38 g, 89.13 mmol, 1 *eq*) in THF (400 mL) was added LiHMDS (1 M, 98.04 mL, 1.1 *eq*) under an atmosphere of N₂ at -78°C and the mixture was allowed to stir for 30 min. HMPA (79.86 g, 445.63 mmol, 77.98 mL, 5 *eq*) and MeI (63.25 g, 445.63 mmol, 27.74 mL, 5 *eq*) were added at -78°C. The reaction was allowed to stir at -78°C for 2 hrs. The reaction was quenched by aq.NH₄Cl (800 mL) slowly and extracted with ethyl acetate (300 mL x 3). The organic solutions were combined, washed with brine (300 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate=100/1 to 3/1). (S)-2-(2-bromo-4-methylphenyl)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)propan-1-one (120 g, 78.39%) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.41 (d, *J* = 1.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.12 - 7.07 (m, 1H), 4.73 (q, *J* = 7.0 Hz, 1H), 3.91 (dd, *J* = 5.2, 7.4 Hz, 1H), 3.52 - 3.39 (m, 2H), 2.30 (s, 3H), 2.17 - 2.07 (m, 2H), 1.93 - 1.85 (m, 3H), 1.55 (d, *J* = 7.0 Hz, 3H), 1.46 - 1.38 (m, 1H), 1.37 - 1.31 (m, 1H), 1.19 (s, 3H), 0.98 (s, 3H).

Step 3: (S)-2-(2-bromo-4-methylphenyl)propan-1-ol



[000377] Three batches were carried out in parallel. To a solution of (S)-2-(2-bromo-4-methylphenyl)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidotetrahydro-3H-3a,6-methanobenzo[c]isothiazol-1(4H)-yl)propan-1-one (20 g, 45.41 mmol, 1 eq) in THF (150 mL) was added NaBH₄ (3.81 g, 100.65 mmol, 2.22 eq) in H₂O (12 mL) at 25°C and the mixture was allowed to stir at 25°C for 16 hrs. The reaction was quenched by the slow addition of ice water (200 mL), adjusted to pH = 6, and extracted with ethyl acetate (200 mL x 2). The organic solutions were combined, washed with brine (300 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The batches were combined and purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1). (S)-2-(2-bromo-4-methylphenyl)propan-1-ol (66 g, crude) was obtained as a yellow oil.

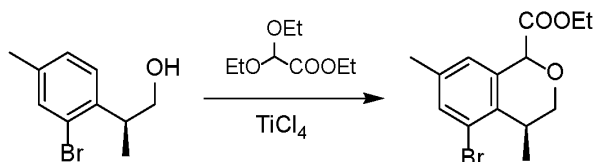
Step 4: (S)-2-(2-bromo-4-methylphenyl)propan-1-ol



[000378] To a solution of (S)-2-(2-bromo-4-methylphenyl)propan-1-ol (64 g, 279.34 mmol, 1 eq) in DCM (600 mL) was added DMAP (1.71 g, 13.97 mmol, 0.05 eq), pyridine (38.67 g, 488.84 mmol, 39.46 mL, 1.75 eq) and AcCl (32.89 g, 419.01 mmol, 29.79 mL, 1.5 eq) at 0 °C under an atmosphere of N₂ and the solution was allowed to stir at 20 °C for 2 hrs. The reaction was quenched by the addition of H₂O (500 mL) at 0 °C and extracted with DCM (500 mL x 3). The organic solutions were combined, washed with brine (600 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1). [(2S)-2-(2-bromo-4-methyl-phenyl) propyl] acetate (66.01% yield) was obtained as a yellow oil. To a solution of [(2S)-2-(2-bromo-4-methyl-phenyl)propyl] acetate (50 g, 184.40 mmol, 1 eq) in H₂O (120 mL), THF (600 mL) and MeOH (29.54 g, 922.00 mmol, 37.31 mL, 5 eq) was added KOH (8.28 g, 147.52 mmol, 0.8 eq) at 25 °C under an atmosphere of N₂ and the solution was allowed to stir at 50°C for 6 hrs. KOH (4.14 g, 73.76 mmol, 0.4 eq) in H₂O (20 mL) was added to the mixture at 25°C and the solution was allowed to stir at 50°C for 16 hrs. The mixture was extracted with MTBE (200 mL x 3). The organic solutions were combined, washed with brine

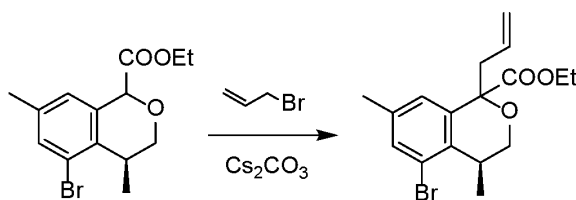
(200 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. (S)-2-(2-bromo-4-methylphenyl)propan-1-ol (40 g, 174.59 mmol, 62.50% yield over 2 steps) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.42 (s, 1H), 7.20 - 7.06 (m, 2H), 3.83 - 3.64 (m, 2H), 3.48 (sxt, *J* = 6.7 Hz, 1H), 2.31 (s, 3H), 1.28 (d, *J* = 7.0 Hz, 3H).

Step 5: ethyl (4S)-5-bromo-4,7-dimethylisochromane-1-carboxylate



[000379] Two batches were carried out in parallel. To a solution of (S)-2-(2-bromo-4-methylphenyl)propan-1-ol (22.9 g, 99.95 mmol, 1 *eq*) and ethyl 2,2-diethoxyacetate (52.84 g, 299.85 mmol, 53.64 mL, 3 *eq*) in DCE (230 mL) was added TiCl₄ (75.83 g, 399.80 mmol, 4 *eq*) at 0 °C under an atmosphere of N₂ and the reaction was allowed to stir at 50 °C for 16 hrs. The reaction was quenched by the addition of H₂O (500 mL) at 0 °C and extracted with DCM (100 mL x 3). The organic solutions were combined, washed with brine (200 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate=100/1 to 3/1). Ethyl (4S)-5-bromo-4,7-dimethylisochromane-1-carboxylate (68 g, crude) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.34 (s, 1H), 7.12 (s, 1H), 5.31 (s, 1H), 4.30 - 4.23 (m, 2H), 4.06 - 4.01 (m, 1H), 3.80 (dd, *J* = 2.4, 11.1 Hz, 1H), 2.97 (q, *J* = 6.6 Hz, 1H), 2.29 (s, 3H), 1.46 - 1.43 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H).

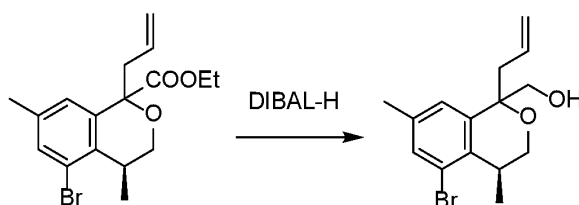
Step 6: ethyl (4S)-1-allyl-5-bromo-4,7-dimethylisochromane-1-carboxylate



[000380] Two batches were carried out in parallel. To a solution of ethyl (4S)-5-bromo-4,7-dimethylisochromane-1-carboxylate (34 g, 108.56 mmol, 1 *eq*) and 3-bromoprop-1-ene (17.07 g, 141.13 mmol, 1.3 *eq*) in DMF (350 mL) was added Cs₂CO₃ (70.74 g, 217.12 mmol, 2 *eq*) at 20 °C under an atmosphere of N₂. The mixture was allowed to stir at 50 °C for 12 hrs. Water (1 L) was added and the mixture was extracted with ethyl acetate (1 L x 2). The organic solutions were combined, washed with brine (1.5 L x 2), dried over Na₂SO₄, and concentrated

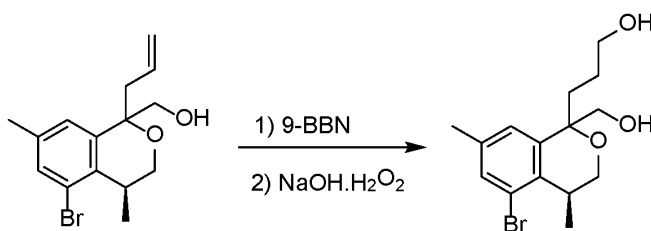
under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 10/1). ethyl (4S)-1-allyl-5-bromo-4,7-dimethylisochromane-1-carboxylate (61.28% yield) was obtained as a yellow oil.

Step 7: ((4S)-1-allyl-5-bromo-4,7-dimethylisochroman-1-yl)methanol



[000381] To a solution of ethyl (4S)-1-allyl-5-bromo-4,7-dimethylisochromane-1-carboxylate (21.3 g, 60.30 mmol, 1 *eq*) in toluene (200 mL) was added DIBAL-H (1 M, 180.89 mL, 3 *eq*) at 0°C under an atmosphere of N₂. The reaction was allowed to stir at 25 °C for 1 hr. The reaction was quenched by the addition of HCl aqueous solution (1 M) to pH = 3 at 0°C. The mixture was extracted with ethyl acetate (300 mL x 2). The organic solutions were combined, washed with brine (300 mL X 3), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 1/1). ((4S)-1-allyl-5-bromo-4,7-dimethylisochroman-1-yl)methanol was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.31 (s, 1H), 6.91 (s, 1H), 5.93 - 5.55 (m, 1H), 5.17 - 4.95 (m, 2H), 4.08 - 3.94 (m, 1H), 3.89 - 3.71 (m, 3H), 3.01 - 2.70 (m, 2H), 2.61 - 2.44 (m, 1H), 2.33 - 2.28 (m, 3H), 1.36 (d, *J* = 6.9 Hz, 3H).

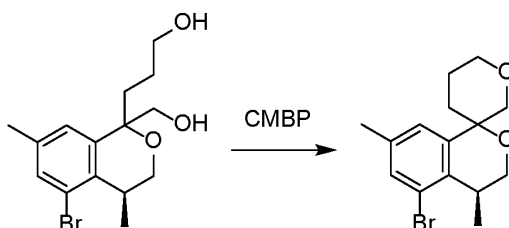
Step 8: 3-((4S)-5-bromo-1-(hydroxymethyl)-4,7-dimethylisochroman-1-yl)propan-1-ol



[000382] Two batches were carried out in parallel. To a mixture of ((4S)-1-allyl-5-bromo-4,7-dimethylisochroman-1-yl)methanol (18.6 g, 59.77 mmol, 1 *eq*) in THF (100 mL) was added 9-BBN (0.5 M, 358.60 mL, 3 *eq*) at 20°C under an atmosphere of N₂. The reaction mixture was allowed to stir at 20°C for 2 hrs. To the mixture was added NaOH (4 M, 211.10 mL, 14.13 *eq*) and H₂O₂ (94.87 g, 836.84 mmol, 80.40 mL, 30% purity, 14.00 *eq*) at 0°C under an atmosphere of N₂. The mixture was allowed to stir at 0°C for 1 hr. The reaction was

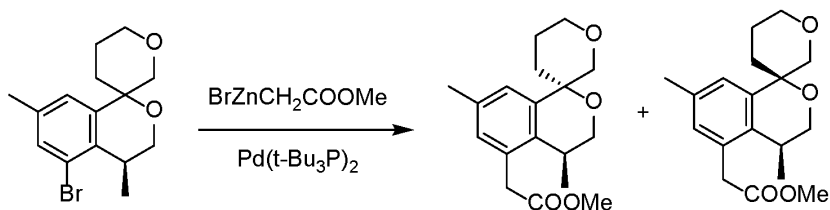
quenched by the addition of aq. Na₂SO₃ (300 mL) and extracted with ethyl acetate (300 mL x 2). The organic solutions were combined, washed with brine and dried over Na₂SO₄. After filtration, the volatile materials were removed under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 0/1). 3-((4S)-5-bromo-1-(hydroxymethyl)-4,7-dimethylisochroman-1-yl)propan-1-ol (52 g, crude) was obtained as a yellow oil.

Step 9: (4S)-5-bromo-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]



[000383] Two batches were carried out in parallel. To a solution of 3-((4S)-5-bromo-1-(hydroxymethyl)-4,7-dimethylisochroman-1-yl)propan-1-ol (24 g, 72.90 mmol, 1 *eq*) in toluene (240 mL) was added CMBP (35.19 g, 145.80 mmol, 2 *eq*) at 20 °C under an atmosphere of N₂ and the solution was allowed to stir at 120 °C for 2 hrs. The reaction was quenched by the addition of H₂O (700 mL) at 0 °C and extracted with ethyl acetate (300 mL x 3). The organic solutions were combined, washed with brine (300 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate=100/1 to 1/1). (4S)-5-bromo-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] (23.5 g, crude) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.30 (s, 1H), 6.91 - 6.86 (m, 1H), 4.08 (br dd, *J* = 4.4, 11.4 Hz, 1H), 4.00 (dd, *J* = 2.3, 12.4 Hz, 1H), 3.93 - 3.81 (m, 1H), 3.77 - 3.64 (m, 1H), 3.59 - 3.48 (m, 1H), 3.37 (d, *J* = 12.5 Hz, 1H), 3.00 - 2.91 (m, 1H), 2.31 (s, 3H), 2.25 - 2.14 (m, 1H), 2.06 - 1.90 (m, 2H), 1.59 - 1.49 (m, 1H), 1.36 (d, *J* = 6.9 Hz, 3H).

Step 10: methyl 2-((1S,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetate and methyl 2-((1R,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetate

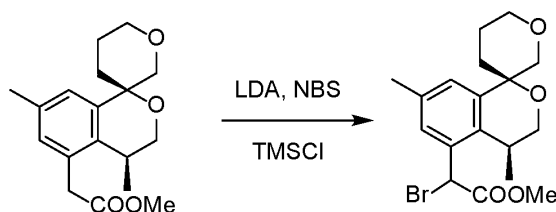


[000384] Two batches were carried out in parallel. To a solution of (4S)-5-bromo-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran] (14.5 g, 46.59 mmol, 1 eq) in THF (140 mL) was added Pd(t-Bu₃P)₂ (2.38 g, 4.66 mmol, 0.1 eq) and BrZnCH₂COOMe (1 M, 69.89 mL, 1.5 eq) at 2 °C under an atmosphere of N₂ and the reaction was allowed to stir at 80 °C for 2 hrs. The reaction was quenched by the addition of H₂O (50 mL), filtered and extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, washed with brine (50 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1) to give a mixture of stereoisomers (56.41% yield). The stereoisomers were separated by SFC (column: ChiralPak IH, 250 * 50 mm, 10 µm; mobile phase: [CO₂ - IPA]; B%:30%, isocratic elution mode).

[000385] Peak 1, arbitrarily assigned as methyl 2-((1S,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetate, was obtained (20.63% yield) as a white solid. SFC R_{t1} = 1.394 min.

[000386] Peak 2, arbitrarily assigned as methyl 2-((1R,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetate, was obtained (51.88% yield) as a white solid. SFC R_{t2} = 2.557 min

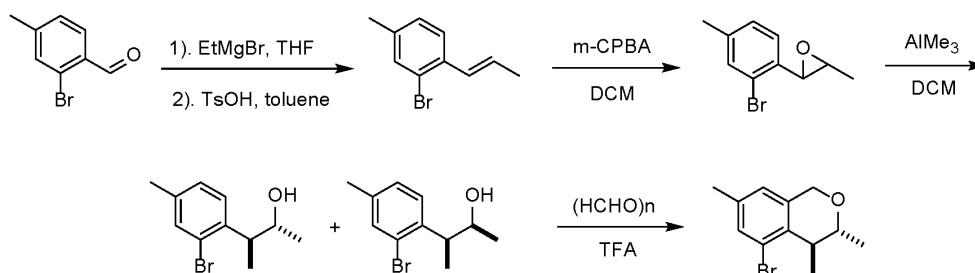
Step 11: methyl 2-bromo-2-((1R,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetate



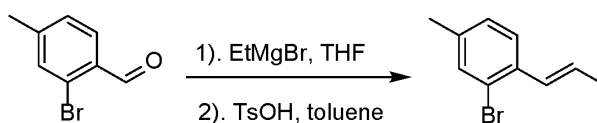
[000387] To a solution of arbitrarily assigned methyl 2-((1R,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetate (9.3 g, 30.55 mmol, 1 eq) in THF (100 mL) was added LDA (2 M, 45.83 mL, 3 eq) at -70 °C under an atmosphere of N₂. After 30 min,

TMSCl (9.96 g, 91.66 mmol, 11.63 mL, 3 eq) was added, the mixture was allowed to stir at -70 °C for 30 min. Then NBS (16.31 g, 91.66 mmol, 3 eq) in THF (30 mL) was added. The mixture was allowed to stir at -70 °C for 30 min. The reaction was quenched by the addition of saturated aqueous NH₄Cl (200 mL) and extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 3/1). methyl 2-bromo-2-((1R,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetate (95.64% yield) was obtained as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.55 - 7.37 (m, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), 5.67 (d, *J* = 11.2 Hz, 1H), 4.10 - 3.98 (m, 2H), 3.96 - 3.76 (m, 5H), 3.57 - 3.49 (m, 1H), 3.40 (dd, *J* = 9.7, 12.4 Hz, 1H), 2.97 - 2.82 (m, 1H), 2.34 (d, *J* = 4.6 Hz, 3H), 2.29 - 2.17 (m, 1H), 2.04 - 1.94 (m, 2H), 1.53 (br d, *J* = 13.5 Hz, 1H), 1.45 - 1.40 (m, 3H).

Preparation of (3R,4S)-5-bromo-3,4,7-trimethylisochromane



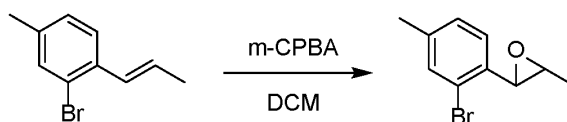
Step 1: (E)-2-bromo-4-methyl-1-(prop-1-en-1-yl)benzene



[000388] To a solution of 2-bromo-4-methylbenzaldehyde (90.0 g, 452.16 mmol, 1.0 *eq.*) in THF (900 mL) was added EtMgBr (3.0 M, 301.44 mL, 2.0 *eq.*) at 0°C. The mixture was allowed to stir under an atmosphere of nitrogen at 0°C for 0.5 hrs and then at 25°C for 1 hr. The reaction was quenched by the addition of sat. aq. NH₄Cl (900 mL) and extracted with ethyl acetate (500 mL x 2). The organic solutions were combined, washed with brine (500 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by silica gel chromatography (SiO₂, Petroleum ether/Ethyl acetate = 0/100 to 70/30) to give the crude product (80 g) as yellow oil. The crude product (15.0 g, 65.47 mmol, 1 *eq.*) was

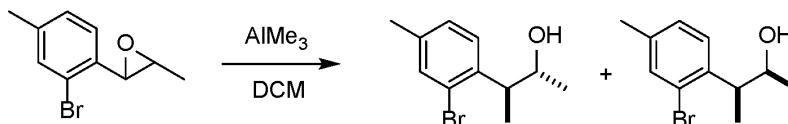
dissolved in toluene (150 mL). Then TsOH·H₂O (37.4 g, 196.41 mmol, 3.0 *eq.*) was added at 25°C under an atmosphere of N₂. The mixture was heated to 80 °C and allowed to stir at 80°C under an atmosphere of N₂ for 12 hrs. The reaction was quenched by the addition of H₂O (150 mL) and the mixture was extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (100 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give (E)-2-bromo-4-methyl-1-(prop-1-en-1-yl)benzene (15 g, crude) as yellow oil, which was used for the next step directly without purification. ¹H NMR (400 MHz, CDCl₃) δ = 7.37 (d, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 8.1 Hz, 1H), 6.71 (dd, *J* = 1.4, 15.6 Hz, 1H), 6.15 (dd, *J* = 6.8, 15.6 Hz, 1H), 2.31 (s, 3H), 1.92 (dd, *J* = 1.7, 6.7 Hz, 3H).

Step 2: 2-(2-bromo-4-methylphenyl)-3-methyloxirane



[000389] To a solution of (E)-2-bromo-4-methyl-1-(prop-1-en-1-yl)benzene (40.0 g, 189.49 mmol, 1.0 *eq.*) in DCM (400 mL) was added m-CPBA (65.4 g, 322.13 mmol, 85% purity, 1.7 *eq.*) at 20°C. The mixture was allowed to stir at 20°C for 6 hrs. The reaction was quenched by the addition of sat. aq. Na₂SO₃ (400 mL) and then DCM (200 mL) was added. The organic solution was separated and the aqueous solution was extracted with DCM (200 mL x 3). The organic solutions were combined, washed with brine (100 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue, which was purified by silica gel chromatography (SiO₂, Petroleum ether/Ethyl acetate = 0/100 to 10/90) to give 2-(2-bromo-4-methylphenyl)-3-methyloxirane (66.23% yield) as yellow oil.

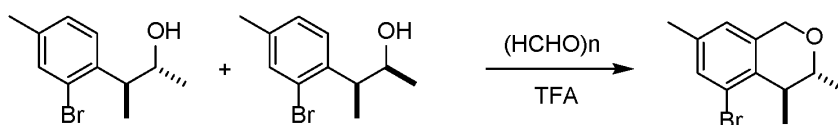
Step 3: (2R,3S)-3-(2-bromo-4-methylphenyl)butan-2-ol and (2S,3S)-3-(2-bromo-4-methylphenyl)butan-2-ol



[000390] To a solution of 2-(2-bromo-4-methylphenyl)-3-methyloxirane (36.0 g, 158.52 mmol, 1.0 *eq.*) in DCM (400 mL) was added AlMe₃ (1.0 M, 317.04 mL, 2.0 *eq.*) at -70°C under an atmosphere of N₂. Then the reaction mixture was allowed to warm to 20°C and stir at 20°C under an atmosphere of N₂ for 12 hrs. The mixture was poured into ice water (350 mL) and extracted with DCM (350 mL x 2). The organic solutions were combined, washed with H₂O

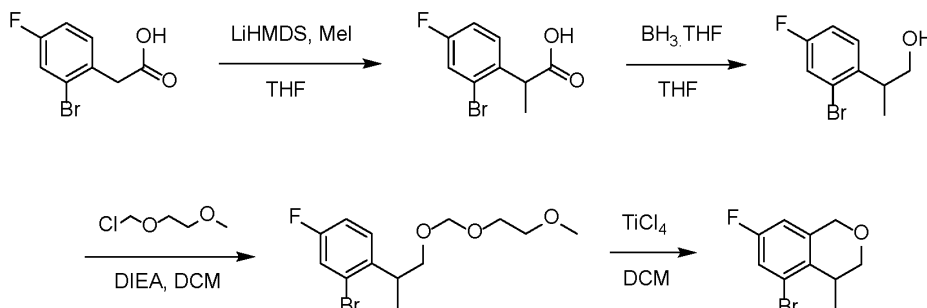
(350 mL x 2) and brine (350 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by silica gel chromatography (SiO₂, Petroleum ether/Ethyl acetate = 100/0 to 10/90) to give a mixture of (2R,3S)-3-(2-bromo-4-methylphenyl)butan-2-ol and (2S,3S)-3-(2-bromo-4-methylphenyl)butan-2-ol (36.0 g, crude) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.41 (s, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.16 - 7.07 (m, 1H), 3.98 (qd, *J* = 6.1, 12.6 Hz, 1H), 3.38 - 3.24 (m, 1H), 2.31 (s, 3H), 1.26 - 1.21 (m, 6H).

Step 4: (3R,4S)-5-bromo-3,4,7-trimethylisochromane

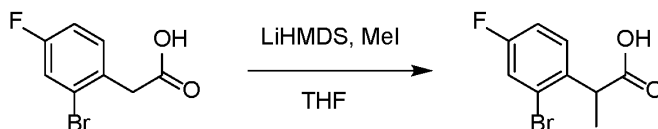


[000391] To a mixture of (2R,3S)-3-(2-bromo-4-methylphenyl)butan-2-ol and (2S,3S)-3-(2-bromo-4-methylphenyl)butan-2-ol (36.0 g, 148.07 mmol, 1.0 *eq.*) in TFA (360 mL) was added (HCHO)_n (40.0 g, 444.19 mmol, 3.0 *eq.*) at 20°C. The mixture was allowed to stir at 50 °C for 16 hrs. The mixture was diluted by the addition of iced water (300 mL) and adjusted to pH = 7-8 by the addition of sat. aq. NaHCO₃ aqueous at 0 °C. The mixture was extracted with ethyl acetate (200 mL x 3). The organic solutions were combined, washed with brine (200 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by prep-HPLC (column: Welch Xtimate C18 250 * 100 mm # 10 um; mobile phase: [H₂O (0.01%TFA)-ACN]; B%: 60% - 88%, 20.000 min) to give (3R,4S)-5-bromo-3,4,7-trimethylisochromane (74.45% yield) as yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.28 (s, 1H), 6.77 (s, 1H), 4.76 - 4.62 (m, 2H), 4.00 (dq, *J* = 2.3, 6.6 Hz, 1H), 2.77 (dq, *J* = 2.0, 6.8 Hz, 1H), 2.28 (s, 3H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.6 Hz, 3H).

Preparation of 5-bromo-7-fluoro-4-methylisochromane

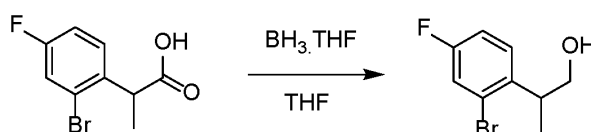


Step 1: 2-(2-bromo-4-fluorophenyl)propanoic acid



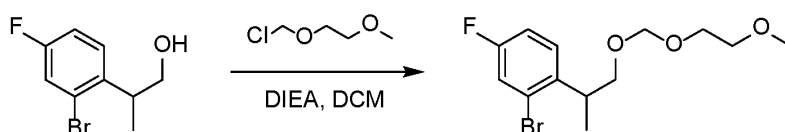
[000392] To a solution of 2-(2-bromo-4-fluorophenyl)acetic acid (5 g, 21.46 mmol, 1 *eq*) in THF (100 mL) was added LiHMDS (1 M, 47.20 mL, 2.2 *eq*) at 0 °C under an atmosphere of N₂. The mixture was allowed to stir at 0 °C for 0.5 hrs and then MeI (6.09 g, 42.91 mmol, 2.67 mL, 2 *eq*) was added at 0 °C. The mixture was allowed to stir and warm to 20 °C over 1.5 hrs. The mixture was diluted with NH₄Cl solution (200 mL) and extracted with ethyl acetate (100 mL x 3). The organic solutions were combined, washed with brine (100 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 5/1 to 3/1). 2-(2-bromo-4-fluorophenyl)propanoic acid (84.89% yield) was obtained as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ = 7.37 - 7.31 (m, 2H), 7.05 (dt, *J* = 2.6, 8.3 Hz, 1H), 4.25 (q, *J* = 7.3 Hz, 1H), 1.52 (d, *J* = 7.3 Hz, 3H).

Step 2: 2-(2-bromo-4-fluorophenyl)propan-1-ol



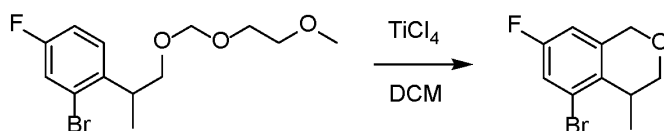
[000393] To a solution of 2-(2-bromo-4-fluorophenyl)propanoic acid (12 g, 48.57 mmol, 1 *eq*) in THF (140 mL) was added BH₃·THF (1 M, 145.71 mL, 3 *eq*) at 0 °C under an atmosphere of N₂. The mixture was allowed to stir at 20 °C for 2 hrs. MeOH (20 mL) was added dropwise at 0 °C followed by 1M aq. HCl solution (50 mL) and the mixture was allowed to stir for 30 min. The mixture was poured into 10% aq Na₂CO₃ solution (300 mL) and extracted twice with ethyl acetate (200 mL each). The organic solutions were combined, washed with brine (100 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 100/1 to 10/1). 2-(2-bromo-4-fluorophenyl)propan-1-ol (88.33% yield) was obtained as yellow oil.

Step 3: 2-bromo-4-fluoro-1-(1-((2-methoxyethoxy)methoxy)propan-2-yl)benzene



[000394] To a solution of 2-(2-bromo-4-fluorophenyl)propan-1-ol (1 g, 4.29 mmol, 1 *eq*) in DCM (20 mL) was added DIEA (1.66 g, 12.87 mmol, 2.24 mL, 3 *eq*) at 0 °C. 1-(chloromethoxy)-2-methoxyethane (1.07 g, 8.58 mmol, 979.72 μ L, 2 *eq*) was added at 20 °C under an atmosphere of N₂. The mixture was allowed to stir at 20 °C for 16 hrs. The reaction was quenched by the addition of water (50 mL) at 20 °C. The mixture was extracted with ethyl acetate (30 mL x 2). The organic solutions were combined, washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 10/1). 2-bromo-4-fluoro-1-(1-((2-methoxyethoxy)methoxy)propan-2-yl)benzene (87.08% yield) was obtained as yellow oil. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ = 7.33 - 7.29 (m, 1H), 7.27 - 7.24 (m, 1H), 7.05 - 6.98 (m, 1H), 4.70 (s, 2H), 3.76 - 3.70 (m, 1H), 3.64 - 3.58 (m, 3H), 3.55 - 3.50 (m, 3H), 3.39 (s, 3H), 1.27 (d, *J* = 6.8 Hz, 3H)

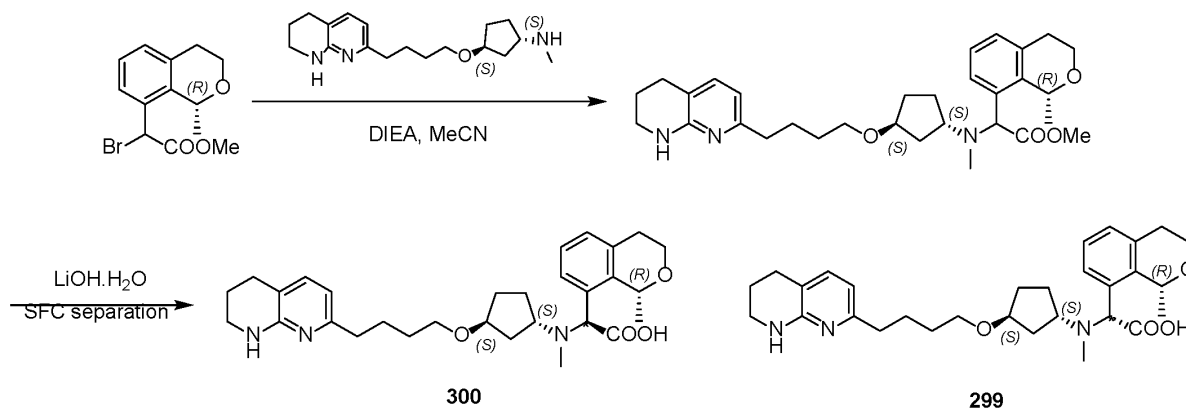
Step 4: 5-bromo-7-fluoro-4-methylisochromane



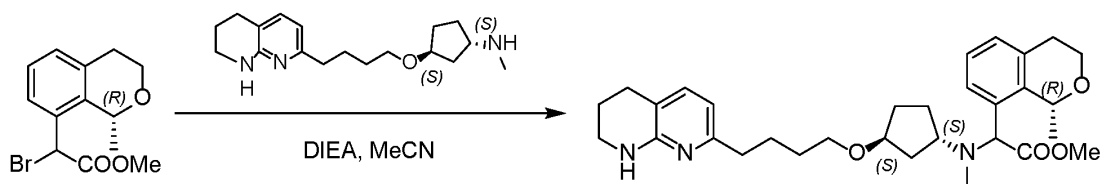
[000395] To a solution of 2-bromo-4-fluoro-1-(1-((2-methoxyethoxy)methoxy)propan-2-yl)benzene (5.9 g, 18.37 mmol, 1 *eq*) in DCM (20 mL) was added TiCl₄ (2.13 g, 11.21 mmol, 3 *eq*) at 0 °C. The mixture was allowed to stir at 40 °C for 16 hrs. The reaction was quenched by the addition of saturated aqueous NaHCO₃ (50 mL). Ethyl acetate (50 mL) was added to the mixture. The organic solution was separated and the aqueous solution was extracted with ethyl acetate (50 mL x 3). The organic solutions were combined, washed with brine (50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 100/1 to 10/1). 5-Bromo-7-fluoro-4-methylisochromane (71.08% yield) was obtained as brown oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.20 (dd, *J* = 1.9, 8.1 Hz, 1H), 6.69 (br d, *J* = 7.1 Hz, 1H), 4.82 - 4.76 (m, 1H), 4.70 - 4.63 (m, 1H), 3.97 (d, *J* = 11.2 Hz, 1H), 3.76 (dd, *J* = 2.3, 11.2 Hz, 1H), 2.97 - 2.87 (m, 1H), 1.35 (d, *J* = 6.8 Hz, 3H).

Final Compounds

General Example of Alkylation and Hydrolysis: Preparation of 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((R)-1-methylisochroman-8-yl)acetic acid (Compounds 300 and 299)

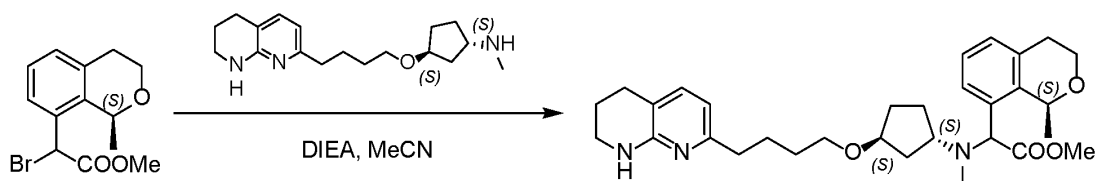


Step 1 (arbitrary stereochemistry): methyl 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((R)-1-methylisochroman-8-yl)acetate



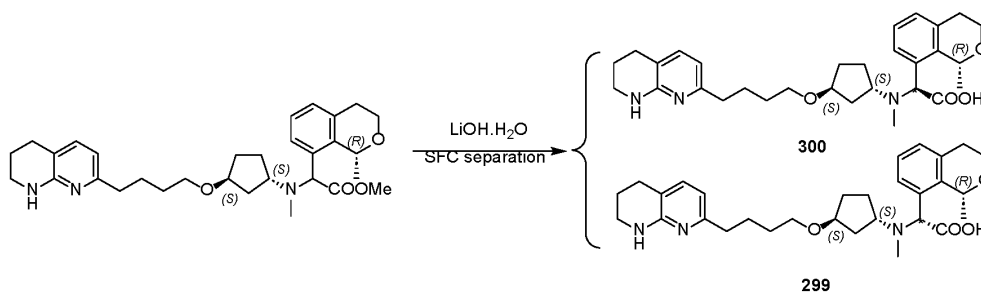
[000396] To a solution of (1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine (200 mg, 659.11 μmol , 1 *eq*) in MeCN (4 mL) was added DIEA (255.55 mg, 1.98 mmol, 344.41 μL , 3 *eq*) and methyl 2-bromo-2-((R)-1-methylisochroman-8-yl)acetate (197.18 mg, 659.11 μmol , 1 *eq*) at 25°C under N₂. The mixture was stirred at 80 °C for 12 hrs. LCMS showed (1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine was consumed completely and one main peak with desired mass was detected. The reaction mixture was quenched by addition H₂O (20 mL) at 20 °C, and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 1/0 to 0/1). Methyl 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((R)-1-methylisochroman-8-yl)acetate (78.52% yield) was obtained as a yellow oil. LCMS: [M+1] = 528.1.

Step 1 (absolute stereochemistry): methyl 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-1-methylisochroman-8-yl)acetate



[000397] To a solution of (1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine (200 mg, 659.11 μmol , 1 *eq*) in MeCN (4 mL) was added DIEA (255.55 mg, 1.98 mmol, 344.41 μL , 3 *eq*) and methyl 2-bromo-2-((R)-1-methylisochroman-8-yl)acetate (197.18 mg, 659.11 μmol , 1 *eq*) at 25°C under N₂. The mixture was stirred at 80 °C for 12 hrs. LCMS showed (1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine was consumed completely and one main peak with desired mass was detected. The reaction mixture was quenched by addition H₂O (20 mL) at 20 °C, and extracted with ethyl acetate (10 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether/ethyl acetate = 1/0 to 0/1). Methyl 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-1-methylisochroman-8-yl)acetate (78.52% yield) was obtained as a yellow oil. LCMS: [M+1] = 528.1.

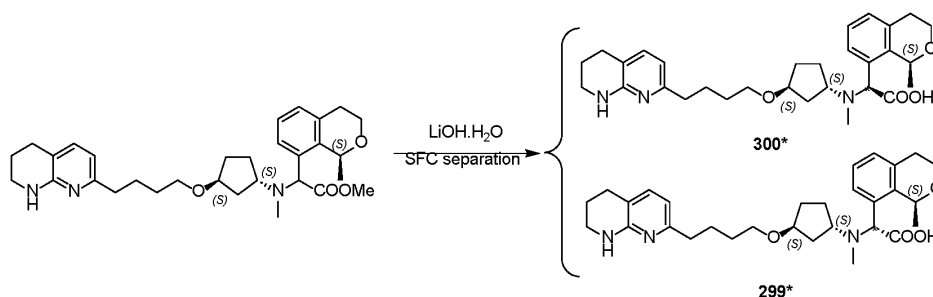
Step 2 (arbitrary stereochemistry): 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((R)-1-methylisochroman-8-yl)acetic acid (Compounds 300 and 299)



[000398] To a solution of methyl 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((R)-1-methylisochroman-8-yl)acetate (250 mg, 479.21 μmol , 1 *eq*) in DCM (3 mL) in dioxane (4 mL) and H₂O (4 mL) was added LiOH.H₂O (60.32 mg, 1.44 mmol, 3 *eq*) at 25°C. The mixture was stirred at 35°C for 12 hrs.

LCMS ($R_t = 1.193$ min, $[M+1] = 508.3$, 96.78%) showed methyl 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((R)-1-methylisochroman-8-yl)acetate was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: $[NH_4HCO_3-ACN]$; gradient: 25%-55% B over 8.0 min). The residue was separated by SFC (column: REGIS (s, s) WHELK-O1 (250mm*30mm, 5um); mobile phase: $[CO_2-MeOH (0.1\%NH_3H_2O)]$; B%:50%, isocratic elution mode) to give two peaks.

Step 2 (absolute stereochemistry): 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid (Compounds 300* and 299*)

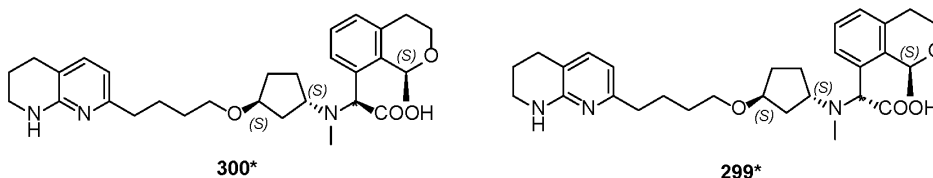


[000399] To a solution of methyl 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-1-methylisochroman-8-yl)acetate (250 mg, 479.21 μ mol, 1 *eq*) in DCM (3 mL) in dioxane (4 mL) and H_2O (4 mL) was added $LiOH \cdot H_2O$ (60.32 mg, 1.44 mmol, 3 *eq*) at 25°C. The mixture was stirred at 35°C for 12 hrs. LCMS ($R_t = 1.193$ min, $[M+1] = 508.3$, 96.78%) showed methyl 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-1-methylisochroman-8-yl)acetate was consumed completely and one main peak with desired mass was detected. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: $[NH_4HCO_3-ACN]$; gradient: 25%-55% B over 8.0 min). The residue was separated by SFC (column: REGIS (s, s) WHELK-O1 (250mm*30mm, 5um); mobile phase: $[CO_2-MeOH (0.1\%NH_3H_2O)]$; B%:50%, isocratic elution mode) to give two peaks.

[000400] Compound 300 (peak 1), arbitrarily assigned as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((R)-1-methylisochroman-8-yl)acetic acid, (81.45% yield) was obtained as a white solid. LCMS: $[M+1] = 508.3$. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.62$ (d, $J = 7.4$ Hz, 1H), 7.23 - 7.12 (m, 3H), 6.37 (d, $J = 7.3$ Hz, 1H), 5.27 (q, $J = 6.5$ Hz, 1H), 4.58 (s, 1H), 4.16 (ddd, $J = 4.6, 9.0, 11.5$ Hz, 1H), 3.96 (br s, 1H), 3.89 - 3.75 (m, 2H), 3.38 (td, $J = 5.8, 8.9$ Hz, 4H), 3.32 - 3.31 (m, 1H), 2.97 - 2.88 (m, 1H), 2.84 - 2.76 (m, 1H), 2.71 (t, $J = 6.3$ Hz, 2H), 2.59 - 2.49 (m, 2H), 2.47 (s, 3H), 2.10 (br dd, $J = 7.3, 13.4$ Hz, 1H), 2.01 - 1.90 (m, 2H), 1.90 - 1.81 (m, 4H), 1.71 (d, $J = 6.7$ Hz, 3H), 1.66 - 1.58 (m, 2H), 1.56 - 1.48 (m, 2H).

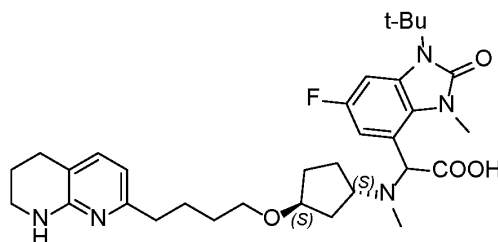
[000401] Compound 299 (peak 2), arbitrarily assigned as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((R)-1-methylisochroman-8-yl)acetic acid, (13.66% yield) was obtained as a white solid. LCMS: $[M+1] = 508.3$. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.55$ (d, $J = 7.9$ Hz, 1H), 7.26 - 7.19 (m, 2H), 7.12 (br d, $J = 7.3$ Hz, 1H), 6.40 (d, $J = 7.3$ Hz, 1H), 5.59 - 5.51 (m, 1H), 4.55 (s, 1H), 4.18 - 4.05 (m, 2H), 3.96 (br s, 1H), 3.84 - 3.79 (m, 1H), 3.43 (br t, $J = 6.1$ Hz, 2H), 3.38 (br d, $J = 5.4$ Hz, 2H), 2.97 - 2.90 (m, 1H), 2.83 - 2.76 (m, 1H), 2.72 (br t, $J = 6.3$ Hz, 2H), 2.68 - 2.60 (m, 1H), 2.56 - 2.51 (m, 1H), 2.40 (s, 3H), 2.20 - 2.12 (m, 1H), 2.09 - 1.99 (m, 2H), 1.91 - 1.81 (m, 4H), 1.78 - 1.64 (m, 4H), 1.60 (d, $J = 6.6$ Hz, 3H), 1.58 - 1.56 (m, 1H).

[000402] When the General Method of Alkylation and Hydrolysis was carried out, the stereochemistry of the starting materials was arbitrarily assigned. Someone skilled in the art will recognize that if the stereochemistry of the starting materials are later determined to be different, the stereochemistry of intermediates and final products may also be determined to be different than those drawn in the scheme. In this example, further analysis led to the reassignment of **299** as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid (Compound 299*), and of **300** as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid (Compound 300*).



[000403] Additional Compounds were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents and using appropriate purification and separation conditions:

Preparation of 2-(1-(tert-butyl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl-amino)acetic acid (Compounds 102 and 101)



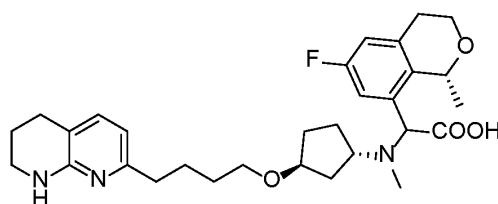
[000404] Isomers of 2-(1-(tert-butyl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl-amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by reversed-phase HPLC (column: Phenomenex Gemini - NX 80 * 40 mm * 3 μ m; mobile phase: [H₂O (10 mM NH₄HCO₃) - ACN]; gradient: 25% - 45% B over 8.0 min) and separated by SFC (column: DAICEL CHIRALPAK IG (250 mm * 30 mm, 10 μ m); mobile phase: [CO₂ - IPA (0.1% NH₃H₂O)]; B%: 45%, isocratic elution mode.

[000405] **Compound 102** (peak 1), arbitrarily assigned (S)-2-(1-(tert-butyl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl-amino)acetic acid (87.5 mg, 148.96 μ mol, 32.09% yield, 99.03% purity) was obtained as a white solid. LCMS: [M+1] = 582.4. ¹H NMR (400 MHz, METHANOL-*d*₄) δ = 7.37 - 7.31 (m, 2H), 7.29 (dd, *J* = 2.4, 11.1 Hz, 1H), 6.46 (d, *J* = 7.4 Hz, 1H), 5.09 (s, 1H), 3.99 - 3.94 (m, 1H), 3.86 (br s, 1H), 3.78 (s, 3H), 3.48 - 3.41 (m, 4H), 2.75 (t, *J* = 6.2 Hz, 2H), 2.73 - 2.66 (m, 1H), 2.63 - 2.55 (m, 1H), 2.39 (s, 3H), 2.28 (br dd, *J* = 6.3, 12.7 Hz, 1H), 2.04 - 1.94 (m, 2H), 1.93 - 1.88 (m, 2H), 1.85 - 1.78 (m, 1H), 1.78 (s, 9H), 1.71 - 1.61 (m, 4H), 1.61 - 1.51 (m, 2H).

[000406] **Compound 101** (peak 2), arbitrarily assigned (R)-2-(1-(tert-butyl)-6-fluoro-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl-amino)acetic acid (83.5 mg, 140.94

umol, 30.37% yield, 98.18% purity) was obtained as a white solid. LCMS: $[M+1] = 582.4$. ^1H NMR (400 MHz, METHANOL- d_4) $\delta = 7.37 - 7.29$ (m, 2H), 7.26 (dd, $J = 2.5, 10.9$ Hz, 1H), 6.43 (d, $J = 7.3$ Hz, 1H), 5.07 (s, 1H), 4.13 - 3.98 (m, 1H), 3.97 - 3.92 (m, 1H), 3.77 - 3.75 (m, 3H), 3.43 - 3.35 (m, 4H), 2.76 - 2.72 (m, 2H), 2.72 - 2.65 (m, 1H), 2.58 - 2.51 (m, 1H), 2.45 - 2.34 (m, 3H), 2.15 - 2.06 (m, 1H), 2.03 - 1.95 (m, 2H), 1.88 (dd, $J = 5.2, 6.4$ Hz, 2H), 1.82 - 1.78 (m, 1H), 1.77 (s, 9H), 1.76 - 1.63 (m, 4H), 1.61 - 1.55 (m, 2H).

Preparation of 2-((R)-6-fluoro-1-methylisochroman-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 152 and 151)



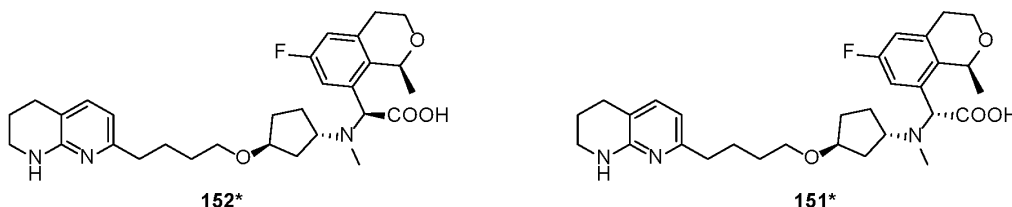
[000407] Isomers of 2-((R)-6-fluoro-1-methylisochroman-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Phenomenex luna C18 100 * 40 mm * 5 μm ; mobile phase: $[\text{H}_2\text{O}$ (0.2% FA)-ACN]; gradient: 10%-45% B over 8.0 min) and separated by SFC (column: DAICEL CHIRALPAK AD (250 mm * 30 mm, 10 μm); mobile phase: $[\text{CO}_2\text{-EtOH}$ (0.1% $\text{NH}_3\text{H}_2\text{O}$)]); B%: 30%, isocratic elution mode).

[000408] **Compound 152** (peak 1), arbitrarily assigned as (S)-2-((R)-6-fluoro-1-methylisochroman-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (122.7 mg, 233.42 μmol , 68.17% yield, 100% purity) was obtained as a white solid. LCMS: $[M+1] = 526.3$. ^1H NMR (400 MHz, METHANOL- d_4) $\delta = 7.46$ (dd, $J = 2.7, 10.3$ Hz, 1H), 7.26 (d, $J = 7.4$ Hz, 1H), 6.91 (dd, $J = 2.4, 8.8$ Hz, 1H), 6.41 (d, $J = 7.4$ Hz, 1H), 5.30 (q, $J = 6.5$ Hz, 1H), 4.54 (d, $J = 1.0$ Hz, 1H), 4.15 (ddd, $J = 4.6, 9.2, 11.5$ Hz, 1H), 3.96 (br s, 1H), 3.79 (ddd, $J = 3.8, 6.2, 11.5$ Hz, 2H), 3.45 - 3.36 (m, 4H), 3.00 - 2.89 (m, 1H), 2.85 - 2.76 (m, 1H), 2.73 (t, $J = 6.3$ Hz, 2H), 2.67 - 2.59 (m, 1H), 2.57 - 2.48 (m, 1H), 2.38 (s, 3H), 2.18 (br dd, $J = 6.9, 13.3$ Hz, 1H), 2.00 - 1.86 (m, 4H), 1.81 - 1.70 (m, 3H), 1.67 (d, $J = 6.6$ Hz, 4H), 1.65 - 1.48 (m, 3H).

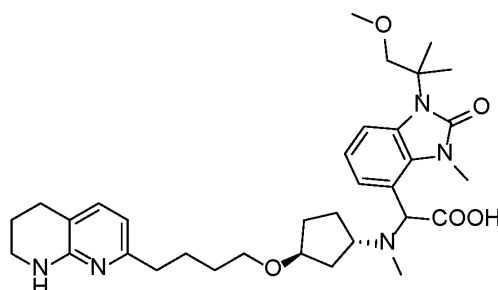
[000409] **Compound 151** (peak 2), arbitrarily assigned as (R)-2-((R)-6-fluoro-1-methylisochroman-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-

yl)butoxy)cyclopentyl)amino)acetic acid (25.2 mg, 46.19 μmol , 13.49% yield, 96.342% purity) was obtained as a white solid. LCMS: $[M+1] = 526.3$. ^1H NMR (400 MHz, METHANOL- d_4) $\delta = 7.41$ (dd, $J = 2.6, 10.5$ Hz, 1H), 7.34 (d, $J = 7.3$ Hz, 1H), 6.84 (dd, $J = 2.4, 8.8$ Hz, 1H), 6.44 (d, $J = 7.4$ Hz, 1H), 5.55 (q, $J = 6.5$ Hz, 1H), 4.48 (s, 1H), 4.16 - 4.02 (m, 2H), 3.93 (br s, 1H), 3.81 (ddd, $J = 3.8, 6.3, 11.4$ Hz, 1H), 3.49 - 3.43 (m, 2H), 3.40 - 3.36 (m, 2H), 2.99 - 2.90 (m, 1H), 2.82 - 2.71 (m, 4H), 2.59 - 2.52 (m, 1H), 2.28 (s, 3H), 2.15 (br dd, $J = 6.1, 12.7$ Hz, 1H), 2.04 - 1.93 (m, 2H), 1.91 - 1.86 (m, 2H), 1.80 - 1.65 (m, 5H), 1.60 (d, $J = 6.5$ Hz, 5H).

[000410] When the General Method of Alkylation and Hydrolysis was carried out, the stereochemistry of the starting materials was arbitrarily assigned. Someone skilled in the art will recognize that if the stereochemistry of the starting materials are later determined to be different, the stereochemistry of intermediates and final products may also be determined to be different than those drawn in the scheme. In this example, further analysis led to the reassignment of **151** (R)-2-((S)-6-fluoro-1-methylisochroman-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compound 151*), and of **152** as (S)-2-((S)-6-fluoro-1-methylisochroman-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compound 152*).



Preparation of 2-(1-(1-methoxy-2-methylpropan-2-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 292 and 291)



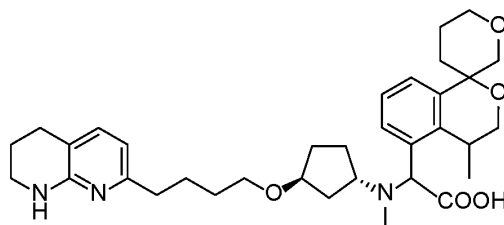
[000411] Isomers of 2-(1-(1-methoxy-2-methylpropan-2-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-

yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 μ m; mobile phase: $[\text{NH}_4\text{HCO}_3\text{-ACN}]$; gradient: 25%-65% B over 8.0 min) and separated by SFC (column: REGIS (s, s) WHELK-O1 (250 mm * 30 mm, 5 μ m); mobile phase: $[\text{CO}_2\text{-EtOH (0.1\% NH}_3\text{H}_2\text{O)}]$; B%:50%, isocratic elution mode).

[000412] Compound 292 (peak 1), arbitrarily assigned (S)-2-(1-(1-methoxy-2-methylpropan-2-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (58.92% yield) was obtained as a white solid. LCMS: $[\text{M}+1] = 594.2$. $^1\text{H NMR}$ (400 MHz, $\text{METHANOL-}d_4$) $\delta = 7.51$ (d, $J = 8.3$ Hz, 1H), 7.43 (d, $J = 8.0$ Hz, 1H), 7.26 (d, $J = 7.4$ Hz, 1H), 7.03 (t, $J = 8.1$ Hz, 1H), 6.41 (d, $J = 7.3$ Hz, 1H), 5.16 (s, 1H), 3.96 (br s, 1H), 3.93 - 3.82 (m, 3H), 3.80 (s, 3H), 3.40 (s, 4H), 3.29 (s, 3H), 2.73 (t, $J = 6.3$ Hz, 2H), 2.63 - 2.52 (m, 2H), 2.50 (s, 3H), 2.21 (br dd, $J = 6.8, 12.9$ Hz, 1H), 2.01 - 1.93 (m, 2H), 1.92 - 1.82 (m, 3H), 1.77 (d, $J = 3.6$ Hz, 7H), 1.73 - 1.63 (m, 3H), 1.58 - 1.50 (m, 2H).

[000413] Compound 291 (peak 2), arbitrarily assigned (R)-2-(1-(1-methoxy-2-methylpropan-2-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (53.78% yield) was obtained as a white solid. LCMS: $[\text{M}+1] = 594.2$. $^1\text{H NMR}$ (400 MHz, $\text{METHANOL-}d_4$) $\delta = 7.52$ (d, $J = 7.6$ Hz, 1H), 7.42 (d, $J = 7.4$ Hz, 1H), 7.23 (d, $J = 7.4$ Hz, 1H), 7.06 (t, $J = 8.1$ Hz, 1H), 6.38 (d, $J = 7.3$ Hz, 1H), 5.14 (s, 1H), 4.04 - 3.97 (m, 1H), 3.94 (br d, $J = 2.0$ Hz, 1H), 3.90 - 3.83 (m, 2H), 3.78 (s, 3H), 3.40 - 3.32 (m, 4H), 3.29 (s, 3H), 2.71 (t, $J = 6.2$ Hz, 2H), 2.61 - 2.51 (m, 2H), 2.48 (s, 3H), 2.07 - 1.97 (m, 3H), 1.90 - 1.81 (m, 4H), 1.77 (d, $J = 3.5$ Hz, 6H), 1.73 - 1.61 (m, 3H), 1.56 - 1.49 (m, 2H).

Preparation of 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetic acid (Compounds 112 and 111)



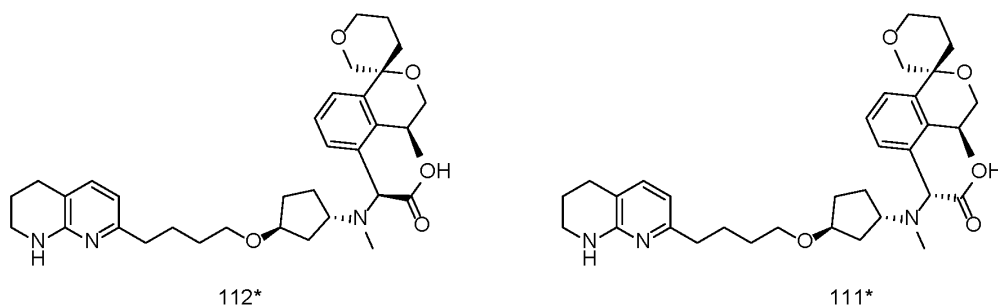
[000414] Isomers of 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((1S,4S)-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents and purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 10%-50% B over 8.0 min).

[000415] **Compound 112** (peak 1), arbitrarily assigned as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((1S,4S)-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetic acid (189.6 mg, 325.38 μmol, 45.85% yield, 99.15% purity) was obtained as a white solid. LCMS: [M+1] = 578.4. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.66 (dd, J = 1.5, 7.4 Hz, 1H), 7.31-7.24 (m, 2H), 7.19 (d, J = 7.4 Hz, 1H), 6.38 (d, J = 7.3 Hz, 1H), 4.76 (s, 1H), 4.02-3.90 (m, 5H), 3.80 (d, J = 11.4 Hz, 1H), 3.63-3.55 (m, 1H), 3.47 (d, J = 12.4 Hz, 1H), 3.39 (dt, J = 3.2, 5.7 Hz, 4H), 3.04-2.96 (m, 1H), 2.71 (t, J = 6.3 Hz, 2H), 2.53 (q, J = 7.3 Hz, 2H), 2.49-2.42 (m, 3H), 2.24-2.09 (m, 3H), 2.05-1.92 (m, 2H), 1.92-1.83 (m, 5H), 1.73-1.68 (m, 1H), 1.67-1.59 (m, 2H), 1.56-1.50 (m, 6H).

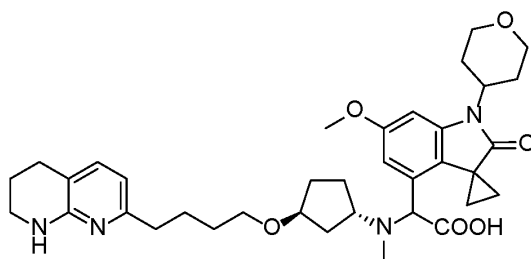
[000416] **Compound 111** (peak 2), arbitrarily assigned as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((1S,4S)-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetic acid (40.1 mg, 67.52 μmol, 9.51% yield, 97.28% purity), was obtained as a white solid. LCMS: [M+1] = 578.4. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.59 (dd, J = 3.3, 5.9 Hz, 1H), 7.28-7.25 (m, 2H), 7.22 (d, J = 7.4 Hz, 1H), 6.39 (d, J = 7.4 Hz, 1H), 4.72 (s, 1H), 4.16-4.09 (m, 1H), 3.99-3.93 (m, 4H), 3.78 (d, J = 11.3 Hz, 1H), 3.62-3.56 (m, 1H), 3.48 (d, J = 12.4 Hz, 1H), 3.44-3.40 (m, 2H), 3.37 (s, 2H), 2.71 (t, J = 6.3 Hz, 2H), 2.64-2.58 (m, 1H), 2.56-2.51 (m, 1H), 2.41 (br s, 3H), 2.20-2.14

(m, 2H), 2.13-2.05 (m, 2H), 2.04-1.98 (m, 1H), 1.93-1.84 (m, 5H), 1.75-1.65 (m, 3H), 1.60-1.49 (m, 4H), 1.41 (d, J = 6.9 Hz, 3H).

[000417] When the General Method of Alkylation and Hydrolysis was carried out, the stereochemistry of the starting materials was arbitrarily assigned. Someone skilled in the art will recognize that if the stereochemistry of the starting materials are later determined to be different, the stereochemistry of intermediates and final products may also be determined to be different than those drawn in the scheme. In this example, further analysis led to the reassignment of **111** as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((1R,4S)-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetic acid (Compound 111*), and of **112** as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((1R,4S)-4-methyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)acetic acid (Compound 112*).



Preparation of 2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 60 and 59)



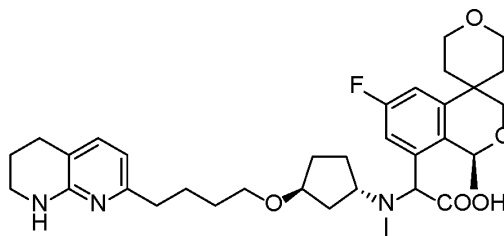
[000418] Isomers of 2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [H₂O (10 mM

NH₄HCO₃)-ACN]; gradient: 25%-55% B over 8.0 min) and separated by SFC (column: DAICEL CHIRALPAK IG (250 mm * 30 mm, 10 μ m); mobile phase: [CO₂-IPA (0.1% NH₃H₂O)]; B%:50%, isocratic elution mode).

[000419] Compound 60 (peak 1), arbitrarily assigned as (S)-2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (42.63% yield) was obtained as a white solid. LCMS: [M+1] = 633.4. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.27 (d, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 2.1 Hz, 1H), 6.83 (d, *J* = 2.3 Hz, 1H), 6.41 (d, *J* = 7.4 Hz, 1H), 4.39 (tt, *J* = 4.1, 12.1 Hz, 1H), 4.06 (dd, *J* = 4.3, 11.4 Hz, 2H), 4.00 - 3.89 (m, 3H), 3.84 (s, 3H), 3.59 - 3.51 (m, 2H), 3.40 (q, *J* = 6.3 Hz, 4H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.65 - 2.47 (m, 5H), 2.36 (s, 3H), 2.11 (br dd, *J* = 6.7, 12.9 Hz, 1H), 2.05 - 1.86 (m, 5H), 1.78 - 1.62 (m, 7H), 1.59 - 1.51 (m, 4H).

[000420] Compound 59 (peak 2), arbitrarily assigned as (R)-2-(6'-methoxy-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (39.30% yield) was obtained as a white solid. LCMS: [M+1] = 633.4. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.27 (d, *J* = 7.4 Hz, 1H), 7.03 (d, *J* = 2.1 Hz, 1H), 6.83 (d, *J* = 2.1 Hz, 1H), 6.40 (d, *J* = 7.4 Hz, 1H), 4.39 (tt, *J* = 4.2, 12.1 Hz, 1H), 4.09 - 4.01 (m, 3H), 3.94 (br s, 1H), 3.90 (s, 1H), 3.84 (s, 3H), 3.56 (br t, *J* = 11.6 Hz, 2H), 3.42 - 3.35 (m, 4H), 2.72 (t, *J* = 6.3 Hz, 2H), 2.66 - 2.44 (m, 5H), 2.35 (s, 3H), 2.10 (br dd, *J* = 6.3, 12.7 Hz, 1H), 2.02 - 1.92 (m, 3H), 1.87 (br dd, *J* = 5.1, 5.9 Hz, 2H), 1.82 - 1.68 (m, 4H), 1.67 - 1.55 (m, 7H).

Preparation of 2-((S)-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 96 and 95)



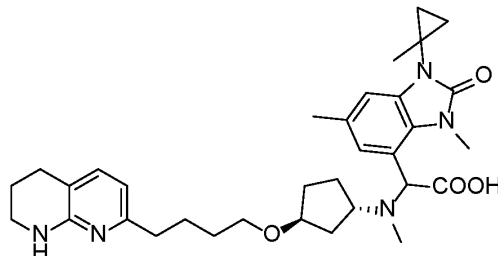
[000421] Isomers of 2-((S)-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)-amino)acetic acid were prepared according to the General Example of

Alkylation and Hydrolysis, substituting the appropriate reagents and purified by prep-HPLC (TFA condition; column: 3_Phenomenex Luna C18 75*30mm*3um; mobile phase: [H₂O](0.1% TFA)-ACN]; gradient: 10%-30% B over 10.0 min).

[000422] Compound 96 (peak 1), arbitrarily assigned as (S)-2-((S)-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (44.7% yield) was obtained as a white solid. LCMS: [M+1] = 596.3. ¹H NMR (400 MHz, MeOD-d₄) δ = 7.57 (d, *J* = 7.3 Hz, 1H), 7.44 (d, *J* = 9.8 Hz, 2H), 6.58 (d, *J* = 7.4 Hz, 1H), 5.23 (q, *J* = 6.5 Hz, 1H), 4.95 - 4.89 (m, 1H), 4.18 - 4.13 (m, 1H), 4.08 - 4.04 (m, 1H), 4.02 (br s, 1H), 3.90 - 3.81 (m, 2H), 3.79 - 3.70 (m, 1H), 3.62 (br t, *J* = 11.5 Hz, 1H), 3.51 - 3.47 (m, 2H), 3.47 - 3.36 (m, 2H), 3.31 (td, *J* = 1.6, 3.2 Hz, 3H), 2.81 (t, *J* = 6.1 Hz, 2H), 2.79 - 2.61 (m, 3H), 2.58 (br d, *J* = 1.6 Hz, 2H), 2.31 - 2.31 (m, 1H), 2.31 - 2.22 (m, 1H), 2.21 - 1.85 (m, 8H), 1.81 (br s, 1H), 1.68 - 1.51 (m, 4H)

[000423] Compound 95 (peak 2), arbitrarily assigned as (R)-2-((S)-6-fluoro-1-methyl-2',3',5',6'-tetrahydrospiro[isochromane-4,4'-pyran]-8-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (9.1% yield) was obtained as a white solid. LCMS: [M+1] = 596.3. ¹H NMR (400 MHz, MeOD-d₄) δ = 7.53 (d, *J* = 7.4 Hz, 1H), 7.41 (dd, *J* = 2.5, 10.3 Hz, 1H), 7.32 (dd, *J* = 2.5, 9.4 Hz, 1H), 6.57 (d, *J* = 7.3 Hz, 1H), 5.47 (d, *J* = 6.6 Hz, 1H), 4.83 (s, 1H), 4.59 - 4.40 (m, 1H), 4.25 (d, *J* = 12.3 Hz, 1H), 4.04 (br t, *J* = 4.5 Hz, 1H), 3.99 (d, *J* = 12.3 Hz, 1H), 3.90 - 3.84 (m, 2H), 3.83 - 3.74 (m, 1H), 3.69 - 3.60 (m, 1H), 3.59 - 3.54 (m, 1H), 3.53 - 3.47 (m, 1H), 3.41 (br dd, *J* = 3.9, 6.1 Hz, 2H), 2.91 - 2.81 (m, 1H), 2.78 (br t, *J* = 6.1 Hz, 2H), 2.69 - 2.58 (m, 1H), 2.58 - 2.47 (m, 3H), 2.40 (br dd, *J* = 5.7, 11.9 Hz, 1H), 2.35 - 2.26 (m, 1H), 2.35 - 2.16 (m, 2H), 1.85 - 1.85 (m, 1H), 1.93 - 1.84 (m, 1H), 1.84 - 1.83 (m, 1H), 1.92 - 1.83 (m, 3H), 1.82 (br s, 1H), 1.80 (br s, 1H), 1.70 (br s, 1H), 1.58 (br d, *J* = 13.8 Hz, 1H).

Preparation of 2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 274 and 273)



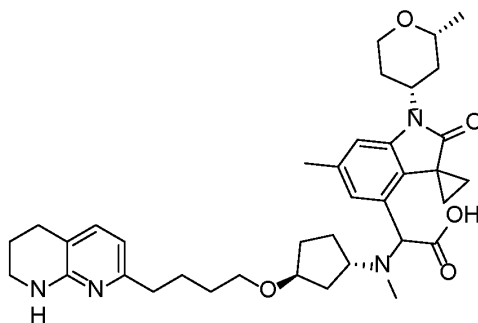
[000424] Isomers of 2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Phenomenex luna C18 100*40mm*3 um;mobile phase: [H₂O(0.1%TFA)-ACN];gradient:1%-30% B over 8.0 min) and separated by SFC (column: REGIS (s,s) WHELK-O1 (250 mm*30 mm, 5 um);mobile phase: [CO₂-IPA(0.1% NH₃H₂O)];B%:50%, isocratic elution mode).

[000425] **Compound 274** (peak 1), arbitrarily assigned as (S)-2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (46.20% yield) was obtained as a white solid. LCMS: [M+1] = 576.3. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.29 (s, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.15 (s, 1H), 6.40 (d, J = 7.3 Hz, 1H), 5.06 (s, 1H), 4.04 - 3.92 (m, 2H), 3.76 (s, 3H), 3.40 (t, J = 5.9 Hz, 4H), 2.73 (t, J = 6.2 Hz, 2H), 2.64 - 2.54 (m, 2H), 2.49 (s, 3H), 2.40 (s, 3H), 2.20 (br dd, J = 7.2, 13.1 Hz, 1H), 1.97 (dt, J = 5.7, 11.9 Hz, 2H), 1.91 - 1.86 (m, 2H), 1.84 - 1.74 (m, 2H), 1.72 - 1.62 (m, 3H), 1.58 - 1.52 (m, 2H), 1.45 (s, 3H), 1.12 - 1.05 (m, 2H), 1.04 - 0.98 (m, 2H).

[000426] **Compound 273** (peak 2), arbitrarily assigned as (R)-2-(3,6-dimethyl-1-(1-methylcyclopropyl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (53.10% yield) was obtained as a white solid. LCMS: [M+1] = 576.2. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.32 - 7.22 (m, 2H), 7.17 (d, J = 0.6 Hz, 1H), 6.41 (d, J = 7.3 Hz, 1H), 5.06 (s, 1H), 4.20 - 4.04 (m, 1H), 3.96 (br s, 1H), 3.74 (s, 3H), 3.45 - 3.34 (m, 4H), 2.72 (t, J = 6.2 Hz, 2H), 2.68 -

2.61 (m, 1H), 2.56 - 2.47 (m, 3H), 2.41 (s, 3H), 2.12 - 1.95 (m, 3H), 1.91 - 1.80 (m, 4H), 1.79 - 1.69 (m, 2H), 1.69 - 1.47 (m, 4H), 1.45 (s, 3H), 1.12 - 1.06 (m, 2H), 1.05 - 0.99 (m, 2H).

Preparation of 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-1'-((2R,4R)-2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid (Compounds 70 and 69)



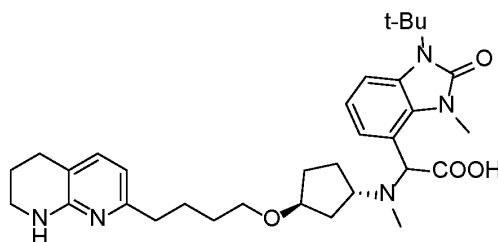
[000427] Isomers of 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-1'-((2R,4R)-2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents and purified by prep-HPLC (column: Phenomenex Luna C18 75*30 mm*3 um; mobile phase: [H₂O (0.1%TFA)-ACN]; gradient: 20%-40% B over 8.0 min).

[000428] **Compound 70** (peak 1), arbitrarily assigned as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-1'-((2R,4R)-2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid (42.39% yield), was obtained as a white solid. LCMS: [M+1] = 631.3. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.56 (d, *J* = 7.3 Hz, 1H), 7.23 (d, *J* = 4.5 Hz, 2H), 6.58 (d, *J* = 7.3 Hz, 1H), 4.47 (tt, *J* = 4.0, 12.2 Hz, 1H), 4.28 - 4.16 (m, 1H), 4.16 - 4.00 (m, 3H), 3.66 - 3.57 (m, 2H), 3.56 - 3.32 (m, 5H), 2.80 (br t, *J* = 6.2 Hz, 2H), 2.76 - 2.64 (m, 2H), 2.53 (dt, *J* = 4.8, 12.5 Hz, 3H), 2.44 (s, 3H), 2.38 - 2.31 (m, 1H), 2.27 - 2.02 (m, 4H), 1.99 - 1.89 (m, 5H), 1.84 - 1.70 (m, 5H), 1.69 - 1.56 (m, 4H), 1.24 (d, *J* = 6.1 Hz, 3H).

[000429] **Compound 69** (peak 2), arbitrarily assigned as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-1'-((2R,4R)-2-methyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid (28.91% yield), was obtained as a white solid. LCMS: [M+1] = 631.3. ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.53 (d, *J* = 7.3 Hz, 1H), 7.22 (s, 1H), 7.15 (s, 1H), 6.57 (d, *J* = 7.3 Hz, 1H), 4.56 - 4.34 (m, 2H), 4.22 - 4.12 (m, 1H), 4.11 - 4.02 (m, 2H), 3.67 - 3.59 (m,

2H), 3.57 - 3.46 (m, 2H), 3.44 - 3.38 (m, 2H), 2.79 (br t, $J = 6.2$ Hz, 3H), 2.70 - 2.56 (m, 2H), 2.55 - 2.47 (m, 3H), 2.44 (s, 3H), 2.37 - 2.26 (m, 2H), 2.22 (br d, $J = 11.3$ Hz, 1H), 2.16 - 2.04 (m, 2H), 1.96 - 1.80 (m, 7H), 1.77 - 1.63 (m, 7H), 1.24 (d, $J = 6.1$ Hz, 3H).

Preparation of 2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 344 and 343)



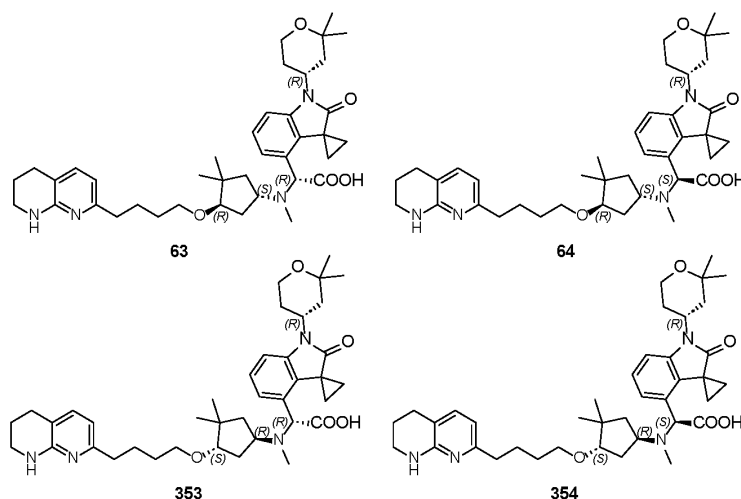
[000430] Isomers of 2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Phenomenex Luna C18 75 * 30 mm * 3 μ m; mobile phase: [TFA-ACN]; B%: 5%-35%, 8.00 min) and separated by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm,10 μ m);mobile phase: [0.1% $\text{NH}_3\text{H}_2\text{O}$ ETOH];B%: 50%-50%,15min).

[000431] **Compound 344** (peak 1), arbitrarily assigned as (S)-2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (0.056 g, 99.34 μ mol, 16.20%), was obtained as a white solid. LCMS: $[\text{M}+1] = 564.4$. ^1H NMR (400 MHz, METHANOL- d_4) $\delta =$ 7.54 (br dd, $J = 2.2, 8.2$ Hz, 1H), 7.43 (br dd, $J = 2.1, 7.9$ Hz, 1H), 7.26 (br d, $J = 7.1$ Hz, 1H), 7.04 (dt, $J = 2.8, 8.1$ Hz, 1H), 6.41 (br dd, $J = 2.7, 7.3$ Hz, 1H), 5.18 - 5.13 (m, 1H), 3.96 (br s, 2H), 3.82 - 3.76 (m, 3H), 3.40 (br d, $J = 2.6$ Hz, 3H), 2.73 (br s, 2H), 2.65 - 2.52 (m, 3H), 2.50 (br d, $J = 2.5$ Hz, 3H), 2.24 - 2.18 (m, 1H), 1.89 (br s, 6H), 1.80 - 1.75 (m, 9H), 1.72 - 1.63 (m, 3H), 1.54 (br s, 2H).

[000432] **Compound 343** (peak 2), arbitrarily assigned as (R)-2-(1-(tert-butyl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (0.060 g, 10.64 μ mol, 17.36%), was obtained as a white solid. LCMS: $[\text{M}+1] = 564.4$. ^1H NMR (400 MHz, METHANOL- d_4) $\delta =$ 7.56 (d, $J = 7.9$ Hz, 1H), 7.42 (d, $J = 7.9$ Hz, 1H), 7.23 (d, $J = 7.3$ Hz, 1H), 7.08 (t, $J = 8.1$ Hz,

1H), 6.38 (d, J = 7.3 Hz, 1H), 5.14 (s, 1H), 4.03 - 3.93 (m, 2H), 3.77 (s, 3H), 3.39 - 3.35 (m, 3H), 2.72 (t, J = 6.3 Hz, 2H), 2.67 - 2.52 (m, 3H), 2.49 (br s, 3H), 2.06 - 1.94 (m, 4H), 1.89 - 1.85 (m, 3H), 1.78 (s, 9H), 1.72 - 1.62 (m, 3H), 1.56 - 1.50 (m, 2H).

Preparation of Isomers of 2-((3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(1'-((R)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid (Compounds 63, 64, 353, and 354)



[000433] Isomers of 2-((3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(1'-((R)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 20%-70% B over 8.0 min). The residue was further separated by SFC (column: DAICEL CHIRALPAK) to afford pure **353** (51.4 mg) and mixture of **354** & **63** & **64** (200 mg). The mixture of **354** & **63** & **64** (200 mg) was further separated by SFC (column: DAICEL CHIRALCEL OX (250 mm * 30 mm, 10 um); mobile phase: [CO₂-EtOH: CAN = 1:1 (0.1% NH₃H₂O)]; B%:55%, isocratic elution mode) to afford pure **354** (34.25 mg crude) and a mixture of **63** & **64** (120 mg). The isolated **354** was further purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 25%-75% B over 8.0 min) to afford **354** (25.2 mg). The mixture of **63** & **64** (120 mg) was further separated by SFC (column: DAICEL CHIRALCEL OX (250 mm * 30 mm, 10 um); mobile phase: [CO₂-EtOH: CAN = 1:1 (0.1% NH₃H₂O)]; B%:55%, isocratic elution mode) to afford **63** (33.1 mg) & **64**. **64** was further purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10um;

mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 25%-75% B over 8.0 min) to afford **64** (24.1 mg).

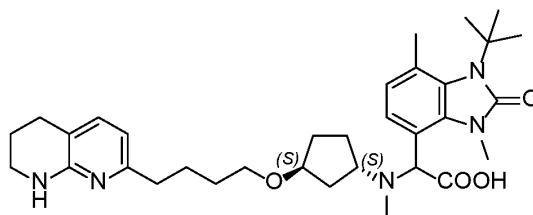
[000434] Compound 353 (peak 1, 450 mg, 682.99 μ mol, 11.28%), arbitrarily assigned as (R)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(1'-((R)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 659.4, 98.79%; SFC R_t = 1.317, 92.58%; ¹H NMR (400 MHz, METHANOL-d₄) δ = 7.41 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 7.4 Hz, 2H), 6.40 (d, *J* = 7.3 Hz, 1H), 4.64 (ddd, *J* = 4.4, 8.3, 12.6 Hz, 1H), 4.17 - 4.06 (m, 1H), 3.88 - 3.83 (m, 3H), 3.43 - 3.36 (m, 4H), 2.72 (t, *J* = 6.3 Hz, 2H), 2.59 (s, 1H), 2.58 - 2.50 (m, 3H), 2.41 - 2.34 (m, 4H), 2.20 - 2.13 (m, 1H), 2.07 - 2.02 (m, 1H), 1.98 (br s, 1H), 1.90 - 1.85 (m, 2H), 1.76 - 1.56 (m, 11H), 1.37 (s, 3H), 1.28 (s, 3H), 1.09 (s, 3H), 0.94 (s, 3H).

[000435] Compound 354 (peak 2, 25.3 mg, 36.58 μ mol, 5.47%), arbitrarily assigned as (S)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(1'-((R)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 659.4, 97.69%; SFC R_t = 4.937, 98.42%; ¹H NMR (400 MHz, CD₃OD) δ = 7.42 - 7.37 (m, 1H), 7.35 - 7.26 (m, 3H), 6.43 (d, *J* = 7.3 Hz, 1H), 4.70 - 4.62 (m, 1H), 4.28 - 4.16 (m, 1H), 3.91 (s, 1H), 3.86 (br d, *J* = 8.0 Hz, 2H), 3.51 - 3.35 (m, 6H), 2.75 - 2.65 (m, 3H), 2.58 - 2.50 (m, 3H), 2.42 - 2.38 (m, 3H), 2.20 - 2.13 (m, 1H), 2.05 - 1.98 (m, 2H), 1.90 - 1.85 (m, 2H), 1.80 - 1.73 (m, 2H), 1.70 - 1.59 (m, 8H), 1.37 (s, 3H), 1.28 (s, 3H), 1.10 (s, 3H), 0.97 (s, 3H).

[000436] Compound 64 (peak 3, 24.1 mg, 36.58 μ mol, 5.26%), arbitrarily assigned as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(1'-((R)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 659.4, 98.19%; SFC R_t = 1.653, 100%; ¹H NMR (400 MHz, CD₃OD) δ = 7.42 (dd, *J* = 1.1, 7.7 Hz, 1H), 7.31 - 7.23 (m, 3H), 6.41 (d, *J* = 7.3 Hz, 1H), 4.69 - 4.60 (m, 1H), 4.05 - 3.95 (m, 2H), 3.89 - 3.83 (m, 2H), 3.52 - 3.47 (m, 1H), 3.43 - 3.37 (m, 4H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.64 - 2.50 (m, 4H), 2.41 (s, 3H), 2.38 (s, 1H), 2.17 - 2.07 (m, 2H), 2.05 - 1.99 (m, 1H), 1.91 - 1.85 (m, 2H), 1.75 - 1.55 (m, 10H), 1.37 (s, 3H), 1.28 (s, 3H), 1.08 (s, 3H), 0.93 (s, 3H).

[000437] Compound 63 (peak 4, 33.1 mg, 48.83 μ mol, 7.15%), arbitrarily assigned as (R)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(1'-((R)-2,2-dimethyltetrahydro-2H-pyran-4-yl)-2'-oxospiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid, was obtained as a white solid. LCMS $[M+1] = 659.4$, 97.19%; SFC $R_t = 2.288$, 97.72%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.42$ (d, $J = 7.4$ Hz, 1H), 7.32 - 7.24 (m, 3H), 6.42 (d, $J = 7.3$ Hz, 1H), 4.64 (ddd, $J = 4.1, 8.5, 12.5$ Hz, 1H), 4.07 - 3.98 (m, 1H), 3.96 (s, 1H), 3.88 - 3.84 (m, 2H), 3.49 (br d, $J = 5.9$ Hz, 1H), 3.43 - 3.37 (m, 4H), 2.72 (t, $J = 6.3$ Hz, 2H), 2.64 - 2.52 (m, 4H), 2.41 (s, 3H), 2.39 - 2.33 (m, 1H), 2.16 - 2.07 (m, 2H), 2.05 - 1.99 (m, 1H), 1.91 - 1.85 (m, 2H), 1.73 - 1.54 (m, 10H), 1.37 (s, 3H), 1.28 (s, 3H), 1.08 (s, 3H), 0.93 (s, 3H).

Preparation of 2-(1-(tert-butyl)-3,7-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 357 and 358)



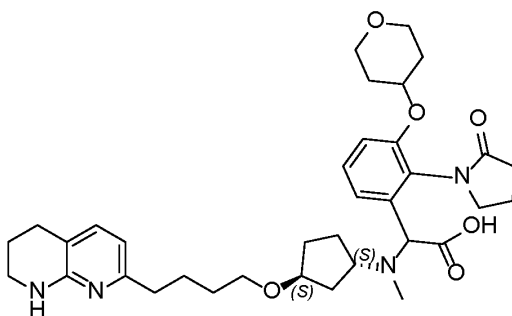
[000438] Isomers of 2-(1-(tert-butyl)-3,7-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Waters Xbridge BEH C 18 100 * 30 mm * 10 μ m; mobile phase: $[\text{H}_2\text{O}$ (10 mM NH_4HCO_3)-ACN]; gradient: 20%-50% B over 8.0 min). The racemate was further separated by SFC (column: DAICEL CHIRALPAK IG (250 mm * 30 mm, 10 μ m); mobile phase: $[\text{CO}_2$ -EtOH (0.1% $\text{NH}_3\text{H}_2\text{O}$)]); B%:50%, isocratic elution mode).

[000439] Compound 357 (peak 1), arbitrarily assigned as (S)-2-(1-(tert-butyl)-3,7-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained as a white solid (20.49% yield). LCMS $[M+1] = 578.2$, 99%; SFC $R_t = 0.833$, 100.00%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.36$ (d, $J = 8.4$ Hz, 1H), 7.24 (d, $J = 7.3$ Hz, 1H), 6.92 (d, $J = 8.4$ Hz, 1H), 6.40 (d, $J = 7.4$ Hz, 1H), 5.15 (s, 1H), 4.04 - 3.83 (m, 2H), 3.75 (s, 3H), 3.42 - 3.37 (m, 4H), 2.73 (t, $J = 6.3$ Hz, 2H), 2.64 (s, 3H), 2.55 (br dd, $J = 6.6, 8.4$ Hz, 2H), 2.51 (s, 3H), 2.19

(br dd, $J = 6.8, 13.2$ Hz, 1H), 2.00 - 1.80 (m, 5H), 1.74 (s, 9H), 1.73 - 1.57 (m, 4H), 1.57 - 1.48 (m, 2H).

[000440] Compound 358 (peak 2), arbitrarily assigned as (R)-2-(1-(tert-butyl)-3,7-dimethyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained as a white solid (49 mg, 83.11 μ mol, 20.91%). LCMS $[M+1] = 578.2$, 98%; SFC $R_t = 1.287$, 100.00%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.35$ (d, $J = 8.4$ Hz, 1H), 7.21 (d, $J = 7.4$ Hz, 1H), 6.95 (d, $J = 8.4$ Hz, 1H), 6.37 (d, $J = 7.3$ Hz, 1H), 5.13 (s, 1H), 3.95 (br s, 2H), 3.74 (s, 3H), 3.41 - 3.33 (m, 4H), 2.71 (t, $J = 6.2$ Hz, 2H), 2.64 (s, 3H), 2.62 - 2.41 (m, 5H), 2.07 - 1.92 (m, 3H), 1.91 - 1.81 (m, 4H), 1.74 (s, 9H), 1.71 - 1.55 (m, 3H), 1.55 - 1.45 (m, 2H).

Preparation of 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetic acid (Compounds 359 and 360)



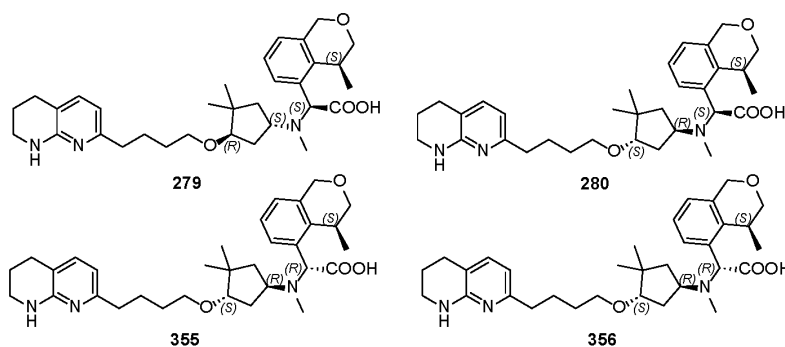
[000441] Isomers of 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10 μ m; mobile phase: $[\text{H}_2\text{O} (10\text{mM } \text{NH}_4\text{HCO}_3)\text{-ACN}]$; gradient: 20%-50% B over 8.0 min) to give two peaks. Then peak 2 was purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3 μ m; mobile phase: $[\text{H}_2\text{O} (0.1\% \text{TFA})\text{-ACN}]$; gradient: 15%-35% B over 8.0 min).

[000442] Compound 359 (peak 1), arbitrarily assigned as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetic acid, was obtained as a white solid (60.4 mg, 94.38 μ mol, 39.94%). LCMS $[M+1] = 621.4$, 97.20%; SFC $R_t = 1.246$ min, 95.40%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.42 - 7.36$ (m, 1H), 7.32 - 7.27 (m, 1H), 7.18 - 7.13 (m, 2H),

6.37 (d, $J = 7.4$ Hz, 1H), 4.67 (tt, $J = 3.6, 7.2$ Hz, 1H), 4.52 (d, $J = 5.4$ Hz, 1H), 3.97 (br d, $J = 3.2$ Hz, 2H), 3.95 - 3.84 (m, 3H), 3.84 - 3.76 (m, 1H), 3.68 - 3.56 (m, 2H), 3.42 - 3.36 (m, 4H), 2.70 (t, $J = 6.3$ Hz, 2H), 2.58 (td, $J = 4.1, 8.4$ Hz, 2H), 2.55 - 2.50 (m, 2H), 2.47 (s, 3H), 2.41 - 2.32 (m, 1H), 2.31 - 2.25 (m, 1H), 2.16 (br s, 1H), 2.12 - 2.04 (m, 2H), 2.02 - 1.94 (m, 2H), 1.92 - 1.82 (m, 3H), 1.80 - 1.70 (m, 4H), 1.69 - 1.63 (m, 2H), 1.58 - 1.51 (m, 2H).

[000443] **Compound 360** (peak 2), arbitrarily assigned as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(2-(2-oxopyrrolidin-1-yl)-3-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)acetic acid, was obtained as a white solid (5.5 mg, 8.68 μ mol, 3.67%). LCMS $[M+1] = 621.4$, 97.89%; SFC $R_t = 1.242$ min, 98.43%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.64$ (d, $J = 7.9$ Hz, 1H), 7.59 (d, $J = 7.4$ Hz, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.45 - 7.37 (m, 1H), 6.62 (d, $J = 7.4$ Hz, 1H), 5.49 (q, $J = 6.2$ Hz, 1H), 4.97 (br s, 1H), 4.90 (br s, 1H), 4.21 (d, $J = 12.0$ Hz, 1H), 4.06 (br d, $J = 12.4$ Hz, 1H), 3.98 - 3.90 (m, 1H), 3.73 (br dd, $J = 3.5, 12.6$ Hz, 1H), 3.69 - 3.60 (m, 1H), 3.58 (br t, $J = 5.9$ Hz, 3H), 3.50 (br d, $J = 5.6$ Hz, 2H), 2.82 (t, $J = 6.2$ Hz, 2H), 2.73 (t, $J = 7.6$ Hz, 2H), 2.57 (br s, 2H), 2.11 (d, $J = 14.3$ Hz, 1H), 1.98 - 1.93 (m, 2H), 1.87 - 1.71 (m, 7H), 1.68 - 1.61 (m, 6H), 1.57 - 1.47 (m, 2H), 1.29 (d, $J = 14.8$ Hz, 6H), 1.15 - 1.07 (m, 4H), 0.96 (br s, 3H).

Preparation of Isomers of 2-((3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid (Compounds 279, 280, 355 and 356)



[000444] Isomers of 2-((3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Waters Xbridge BEH C18 250 * 50 mm * 10 μ m; mobile phase: $[\text{H}_2\text{O} (10\text{mM } \text{NH}_4\text{HCO}_3)\text{-ACN}]$; gradient: 20% - 60% B over 10.0 min) to give a white solid (74.11% yield). This solid was further separated by chiral SFC

(column: Daicel ChiralPak IG (250 * 30 mm, 10 μ m); mobile phase: [CO₂-IPA (0.1% NH₃H₂O)]; B%: 50%, isocratic elution mode) to give peak 1, a mixture of peak 2 & peak 3, and peak 4. The mixture of peak 2 & peak 3 was further separated by SFC (column: DAICEL CHIRALPAK IG (250 mm * 30 mm, 10 μ m); mobile phase: [CO₂-MeOH (0.1%NH₃H₂O)]; B%: 50%, isocratic elution mode).

[000445] Compound 355 (peak 1), arbitrarily assigned as (R)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid, was obtained as a white solid (54.2 mg, 92.69 μ mol, 6.18%). LCMS [M+1] = 536.4, 91.62%; ¹H NMR (400 MHz, CD₃OD) δ = 7.54 (d, J = 7.8 Hz, 1H), 7.25 - 7.15 (m, 2H), 7.01 (d, J = 7.5 Hz, 1H), 6.39 (d, J = 7.3 Hz, 1H), 4.82 (br s, 1H), 4.76 (s, 1H), 4.66 (s, 1H), 4.14 (br t, J = 8.6 Hz, 1H), 3.94 (d, J = 11.1 Hz, 1H), 3.79 (dd, J = 2.0, 11.1 Hz, 1H), 3.54 - 3.46 (m, 2H), 3.40 - 3.35 (m, 3H), 2.71 (br t, J = 6.1 Hz, 2H), 2.56 (br dd, J = 8.4, 16.0 Hz, 3H), 2.46 (s, 3H), 2.26 - 2.17 (m, 1H), 2.12 - 2.05 (m, 1H), 1.91 - 1.85 (m, 3H), 1.78 - 1.67 (m, 3H), 1.61 - 1.56 (m, 2H), 1.41 (d, J = 7.0 Hz, 3H), 1.11 (s, 3H), 0.96 (s, 3H).; SFC Rt = 0.411, de = 100.00%.

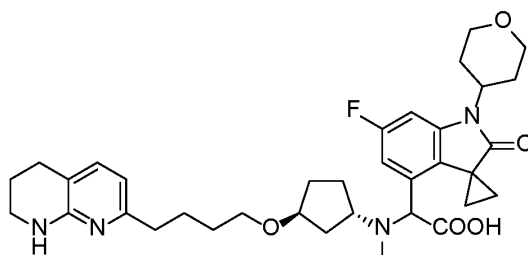
[000446] Compound 280 (peak 2), arbitrarily assigned as (S)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid, was obtained as a white solid (138.4 mg, 258.35 μ mol, 15.78%). LCMS [M+1] = 536.2, 100.00%; ¹H NMR (400 MHz, CD₃OD) δ = 7.53 (d, J = 7.8 Hz, 1H), 7.26 - 7.17 (m, 2H), 7.02 (d, J = 7.6 Hz, 1H), 6.39 (d, J = 7.3 Hz, 1H), 4.82 (s, 1H), 4.78 - 4.72 (m, 1H), 4.65 (s, 1H), 4.24 (br t, J = 8.4 Hz, 1H), 3.94 (d, J = 11.0 Hz, 1H), 3.79 (dd, J = 2.1, 11.1 Hz, 1H), 3.54 - 3.41 (m, 3H), 3.40 - 3.33 (m, 3H), 2.71 (t, J = 6.3 Hz, 2H), 2.62 - 2.51 (m, 2H), 2.47 (s, 3H), 2.30 (td, J = 7.0, 14.1 Hz, 1H), 2.12 - 2.03 (m, 1H), 1.94 - 1.84 (m, 3H), 1.76 - 1.65 (m, 3H), 1.63 - 1.56 (m, 2H), 1.38 (d, J = 7.0 Hz, 3H), 1.12 (s, 3H), 0.96 (s, 3H).; SFC Rt = 0.564, de = 100%.

[000447] Compound 279 (peak 3), arbitrarily assigned as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid, was obtained as a white solid (28.7 mg, 53.57 μ mol, 3.27%). LCMS [M+1] = 536.2, 100%; ¹H NMR (400 MHz, CD₃OD) δ = 7.62 (d, J = 7.6 Hz, 1H), 7.25 - 7.13 (m, 2H), 7.05 (d, J = 7.5 Hz, 1H), 6.37 (d, J = 7.4 Hz, 1H), 4.85 - 4.79 (m, 1H), 4.76 - 4.71 (m, 1H), 4.68 (s, 1H), 3.98 (d, J = 11.0 Hz, 2H), 3.82 (dd, J = 2.3, 11.2 Hz, 1H), 3.52 - 3.42 (m, 2H), 3.41 - 3.35 (m, 3H), 3.00 (q, J = 6.6 Hz, 1H), 2.71 (t, J = 6.3 Hz, 2H),

2.57 - 2.43 (m, 5H), 2.22 (td, $J = 7.2, 14.0$ Hz, 1H), 2.02 - 1.93 (m, 1H), 1.91 - 1.85 (m, 2H), 1.79 - 1.70 (m, 2H), 1.70 - 1.62 (m, 2H), 1.62 - 1.53 (m, 2H), 1.51 (d, $J = 6.9$ Hz, 3H), 1.09 (s, 3H), 0.90 (s, 3H).; SFC $R_t = 0.759$, de = 100%.

[000448] Compound 356 (peak 4), arbitrarily assigned as (R)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid, was obtained as a white solid (180.3 mg, 336.56 μ mol, 20.56%). LCMS $[M+1] = 536.2$, 100%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.60$ (d, $J = 7.8$ Hz, 1H), 7.24 (t, $J = 7.7$ Hz, 1H), 7.18 (d, $J = 7.3$ Hz, 1H), 7.06 (d, $J = 7.5$ Hz, 1H), 6.38 (d, $J = 7.3$ Hz, 1H), 4.82 (s, 1H), 4.76 - 4.71 (m, 1H), 4.67 (s, 1H), 4.09 (br s, 1H), 3.96 (d, $J = 11.1$ Hz, 1H), 3.81 (dd, $J = 2.1, 11.1$ Hz, 1H), 3.50 - 3.36 (m, 5H), 2.99 - 2.90 (m, 1H), 2.71 (t, $J = 6.2$ Hz, 2H), 2.59 - 2.51 (m, 2H), 2.51 - 2.38 (m, 3H), 2.27 (td, $J = 7.0, 14.1$ Hz, 1H), 1.94 (br d, $J = 5.6$ Hz, 1H), 1.91 - 1.83 (m, 3H), 1.74 - 1.63 (m, 3H), 1.61 - 1.54 (m, 2H), 1.51 (d, $J = 6.9$ Hz, 3H), 1.11 (s, 3H), 0.92 (s, 3H).; SFC $R_t = 1.109$, de = 94.74%.

Preparation of 2-(6'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 365 and 366)



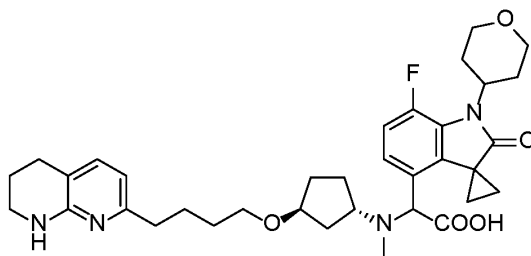
[000449] Isomers of 2-(6'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3 μ m; mobile phase: $[\text{H}_2\text{O}$ (0.1%TFA)-ACN]; gradient: 20%-40% B over 8.0 min).

[000450] Compound 365 (peak 1), arbitrarily assigned as (S)-2-(6'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained as a white solid. LCMS $[M+1] = 621.3$, 99.72%; SFC $R_t = 0.687$ min, 98.74%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.55$ (d, $J = 7.4$ Hz, 1H), 7.25 (dd, $J = 2.1, 9.3$ Hz, 1H), 7.18 (br d, $J = 10.4$

Hz, 1H), 6.58 (d, $J = 7.4$ Hz, 1H), 4.40 (tt, $J = 4.1, 12.1$ Hz, 1H), 4.24 - 4.13 (m, 2H), 4.10 - 4.04 (m, 3H), 3.56 (br t, $J = 11.4$ Hz, 2H), 3.51 - 3.46 (m, 3H), 3.44 - 3.39 (m, 1H), 2.80 (t, $J = 6.2$ Hz, 2H), 2.70 (dt, $J = 7.3, 14.9$ Hz, 2H), 2.64 - 2.52 (m, 5H), 2.43 - 2.36 (m, 1H), 2.20 - 2.10 (m, 2H), 2.09 - 2.02 (m, 1H), 1.99 - 1.91 (m, 5H), 1.84 - 1.76 (m, 2H), 1.74 - 1.66 (m, 5H), 1.62 - 1.55 (m, 2H).

[000451] Compound 366 (peak 2), arbitrarily assigned as (R)-2-(6'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained as a white solid. LCMS $[M+1] = 621.3$, 100.00%; SFC $R_t = 2.002$ min, 95.10%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.53$ (d, $J = 7.4$ Hz, 1H), 7.25 (dd, $J = 2.2, 9.3$ Hz, 1H), 7.09 (dd, $J = 2.1, 10.3$ Hz, 1H), 6.57 (d, $J = 7.3$ Hz, 1H), 4.49 - 4.35 (m, 2H), 4.16 (s, 1H), 4.11 - 4.03 (m, 3H), 3.57 (br t, $J = 11.5$ Hz, 2H), 3.50 (br dd, $J = 5.4, 10.9$ Hz, 2H), 3.42 (br t, $J = 5.6$ Hz, 2H), 2.79 (br t, $J = 6.1$ Hz, 3H), 2.70 - 2.57 (m, 3H), 2.55 (br s, 3H), 2.39 - 2.26 (m, 2H), 2.20 - 2.06 (m, 2H), 1.94 - 1.89 (m, 4H), 1.85 (br d, $J = 7.4$ Hz, 2H), 1.81 - 1.72 (m, 2H), 1.71 - 1.58 (m, 6H).

Preparation of 2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 367 and 368)



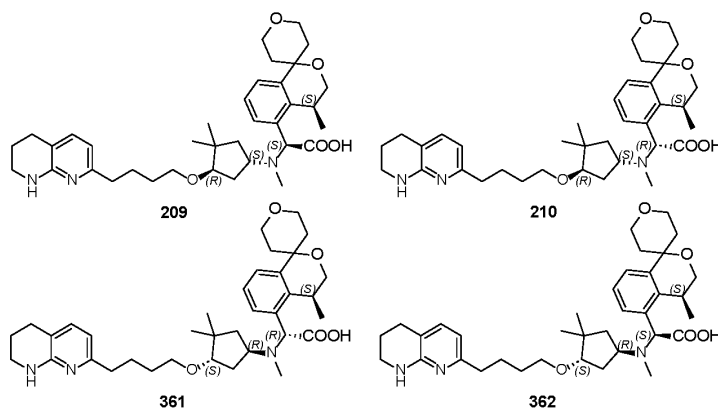
[000452] Isomers of 2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents and purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 μm ; mobile phase: $[\text{H}_2\text{O}$ (10 mM NH_4HCO_3) - ACN]; gradient: 25% - 55% B over 8.0 min). The product was further separated by SFC (column: DAICEL CHIRALPAK IG (250 mm * 30 mm, 10 μm); mobile phase: $[\text{CO}_2$ - EtOH (0.1% $\text{NH}_3\text{H}_2\text{O}$)]); B%: 50%, isocratic elution mode.

[000453] Compound 367 (peak 1), arbitrarily assigned as (S)-2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-

(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained. LCMS [M+1] = 621.4, 99.53%; SFC R_t = 1.896 min, 100%; ^1H NMR (400 MHz, CD_3OD) δ = 7.51 (dd, J = 4.5, 8.9 Hz, 1H), 7.34 (d, J = 7.4 Hz, 1H), 7.10 (dd, J = 8.9, 12.3 Hz, 1H), 6.45 (d, J = 7.3 Hz, 1H), 4.78 - 4.72 (m, 1H), 4.07 (br dd, J = 4.4, 11.5 Hz, 2H), 3.97 (s, 2H), 3.90 - 3.77 (m, 1H), 3.52 (br t, J = 12.0 Hz, 2H), 3.46 - 3.39 (m, 4H), 2.74 (br t, J = 6.3 Hz, 2H), 2.72 - 2.62 (m, 2H), 2.61 - 2.50 (m, 3H), 2.28 (s, 4H), 2.17 (br dd, J = 6.4, 12.5 Hz, 1H), 2.01 - 1.93 (m, 2H), 1.92 - 1.86 (m, 2H), 1.77 - 1.65 (m, 9H), 1.60 - 1.54 (m, 2H).

[000454] Compound 368 (peak 2), arbitrarily assigned as (R)-2-(7'-fluoro-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained LCMS [M+1] = 621.4, 95.62%; SFC R_t = 2.174 min, 94.92%; ^1H NMR (400 MHz, CD_3OD) δ = 7.46 (dd, J = 4.4, 8.9 Hz, 1H), 7.31 (br d, J = 7.0 Hz, 1H), 7.12 (dd, J = 9.0, 12.3 Hz, 1H), 6.43 (d, J = 7.4 Hz, 1H), 4.79 - 4.70 (m, 1H), 4.07 (br dd, J = 4.3, 11.4 Hz, 2H), 4.02 (br d, J = 5.8 Hz, 1H), 3.93 (br s, 1H), 3.89 (s, 1H), 3.52 (br t, J = 11.9 Hz, 2H), 3.44 - 3.36 (m, 4H), 2.75 - 2.72 (m, 2H), 2.64 (br dd, J = 4.1, 9.0 Hz, 2H), 2.59 - 2.49 (m, 3H), 2.30 - 2.14 (m, 4H), 2.13 - 2.06 (m, 1H), 2.02 - 1.90 (m, 2H), 1.89 - 1.84 (m, 2H), 1.79 - 1.64 (m, 9H), 1.62 - 1.57 (m, 2H)

Preparation of 2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methyl-2',3',5',6'-tetrahydrospirofiso chromane-1,4'-pyran]-5-yl)acetic acid and 2-(((1R,4S)-3,3-dimethyl-4-(42-Preparation of Isomers of ((3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methyl-2',3',5',6'-tetrahydrospirofiso chromane-1,4'-pyran]-5-yl)acetic acid (Compounds 209, 210, 361 and 362)



[000455] Isomers of 2-((3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [H₂O (0.1%TFA)-ACN]; gradient: 20%-50% B over 8.0 min). The resulting solid was further purified by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm, 10um); mobile phase: [CO₂-IPA (0.1%NH₃H₂O)]; B%:55%, isocratic elution mode).

[000456] **Compound 361** (peak 1), arbitrarily assigned as (R)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 606.3, 90%; SFC Rt = 0.960, 100%; ¹H NMR (400 MHz, CD₃OD) δ = 7.56 (br d, *J* = 7.3 Hz, 1H), 7.27 - 7.22 (m, 2H), 7.18 (br d, *J* = 7.3 Hz, 1H), 6.39 (d, *J* = 7.3 Hz, 1H), 4.67 (br s, 1H), 3.95 (br s, 2H), 3.89 - 3.84 (m, 2H), 3.79 (br s, 1H), 3.54 - 3.51 (m, 1H), 3.46 (br dd, *J* = 5.3, 11.3 Hz, 2H), 3.40 - 3.35 (m, 4H), 2.71 (br s, 2H), 2.56 (br d, *J* = 7.9 Hz, 2H), 2.43 (s, 3H), 2.24 - 2.19 (m, 2H), 2.10 - 2.03 (m, 2H), 1.93 - 1.87 (m, 5H), 1.73 - 1.67 (m, 3H), 1.61 - 1.57 (m, 3H), 1.41 (d, *J* = 6.9 Hz, 3H), 1.10 (s, 3H), 0.96 (s, 3H).

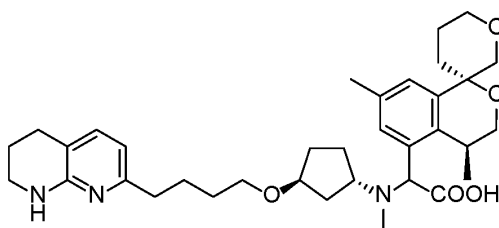
[000457] **Compound 210** (peak 2), arbitrarily assigned as (R)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 606.3, 98.3%; SFC Rt = 0.960, 100%; ¹H NMR (400 MHz, CD₃OD) δ = 7.54 (br d, *J* = 6.5 Hz, 1H), 7.32 - 7.27 (m, 1H), 7.27 - 7.24 (m, 1H), 7.20 (br d, *J* = 7.3 Hz, 1H), 6.39 (d, *J* = 7.3 Hz, 1H), 4.67 (s, 1H), 3.96 - 3.89 (m, 2H), 3.84 (br dd, *J* = 3.8, 13.2 Hz, 2H), 3.80 (br s, 1H), 3.52 - 3.41 (m, 4H), 3.40 - 3.35 (m, 3H), 2.71 (br t, *J* = 6.1 Hz, 2H), 2.60 - 2.53 (m, 2H), 2.45 (br s, 3H), 2.26 (br dd, *J* = 5.8, 18.4 Hz, 2H), 2.11 - 2.05 (m, 1H), 1.94 - 1.86 (m, 5H), 1.70 (br dd, *J* = 9.8, 12.7 Hz, 3H), 1.64 - 1.56 (m, 4H), 1.39 (d, *J* = 6.9 Hz, 3H), 1.12 (s, 3H), 0.97 (s, 3H).

[000458] **Compound 209** (peak 3), arbitrarily assigned as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 606.3, 95.4%; SFC Rt = 0.960, 100%; ¹H NMR (400 MHz, CD₃OD) δ = 7.64 - 7.61 (m, 1H), 7.27 (d, *J* = 4.4 Hz, 2H), 7.17 (d, *J* = 7.4 Hz, 1H), 6.37 (d, *J* =

7.3 Hz, 1H), 4.71 (s, 1H), 3.91 (br d, $J = 9.0$ Hz, 2H), 3.84 (br s, 2H), 3.80 - 3.77 (m, 1H), 3.49 - 3.41 (m, 3H), 3.41 - 3.36 (m, 4H), 2.98 (br d, $J = 6.8$ Hz, 2H), 2.71 (br t, $J = 6.2$ Hz, 2H), 2.56 - 2.52 (m, 2H), 2.50 (br s, 3H), 2.21 (br dd, $J = 5.2, 12.7$ Hz, 2H), 1.92 - 1.86 (m, 5H), 1.72 (br d, $J = 8.1$ Hz, 2H), 1.65 (br d, $J = 8.0$ Hz, 3H), 1.52 (br d, $J = 6.9$ Hz, 3H), 1.08 (s, 3H), 0.89 (s, 3H).

[000459] Compound 362 (peak 4), arbitrarily assigned as (S)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methyl-2',3',5',6'-tetrahydrospiro[isochromane-1,4'-pyran]-5-yl)acetic acid, was obtained as a white solid. LCMS $[M+1] = 606.3$, 100%; SFC $R_t = 1.149$, 95.7%; ^1H NMR (400 MHz, CD_3OD) $\delta = 7.57 - 7.51$ (m, 2H), 7.42 - 7.37 (m, 2H), 6.59 (d, $J = 7.4$ Hz, 1H), 4.77 - 4.26 (m, 1H), 4.00 - 3.87 (m, 3H), 3.87 - 3.74 (m, 4H), 3.56 - 3.49 (m, 2H), 3.48 - 3.43 (m, 3H), 2.92 (br d, $J = 6.3$ Hz, 1H), 2.80 (br t, $J = 6.1$ Hz, 3H), 2.76 - 2.54 (m, 2H), 2.44 - 2.35 (m, 1H), 2.26 (dt, $J = 5.3, 12.9$ Hz, 3H), 1.98 - 1.89 (m, 5H), 1.89 - 1.73 (m, 3H), 1.72 - 1.62 (m, 4H), 1.51 (d, $J = 6.9$ Hz, 3H), 1.13 (s, 3H), 1.01 (br s, 3H).

Preparation of (R)-2-((1S,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid and (S)-2-((1S,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 1 and 2)



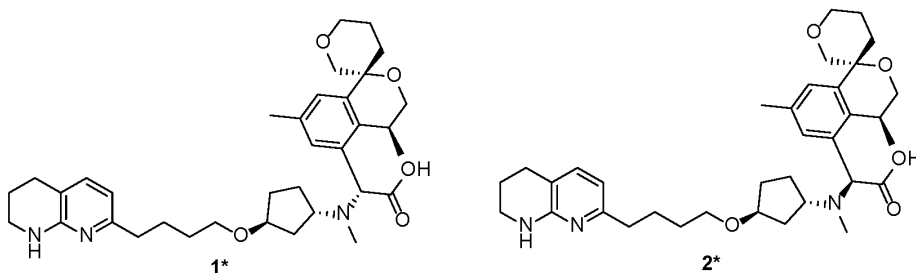
[000460] Isomers of arbitrarily assigned 2-((1S,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, and were purified by prep-HPLC (column: Phenomenex luna C18 250 * 150 mm * 15 μm ; mobile phase: $[\text{H}_2\text{O} (0.1\% \text{TFA}) - \text{ACN}]$; gradient: 5% - 35% B over 20.0 min).

[000461] Compound 2 (peak 1), arbitrarily assigned as (S)-2-((1S,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-

tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (98.30% purity), was obtained as a white solid.

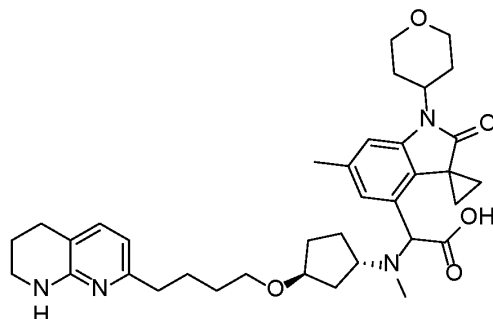
[000462] Compound 1 (peak 2), arbitrarily assigned as (R)-2-((1S,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained as a yellow solid.

[000463] When synthesis was carried out, the stereochemistry of the starting materials was arbitrarily assigned. Someone skilled in the art will recognize that if the stereochemistry of the starting materials are later determined to be different, the stereochemistry of intermediates and final products may also be determined to be different than those drawn in the scheme. In this example, further analysis led to the reassignment of **2** as (S)-2-((1R,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compound 2*), and of **1** as (R)-2-((1R,4S)-4,7-dimethyl-5',6'-dihydro-2'H,4'H-spiro[isochromane-1,3'-pyran]-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compound 1*).



Preparation of (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid and (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-2'-oxo-1'-

(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid (Compounds 155 and 156)



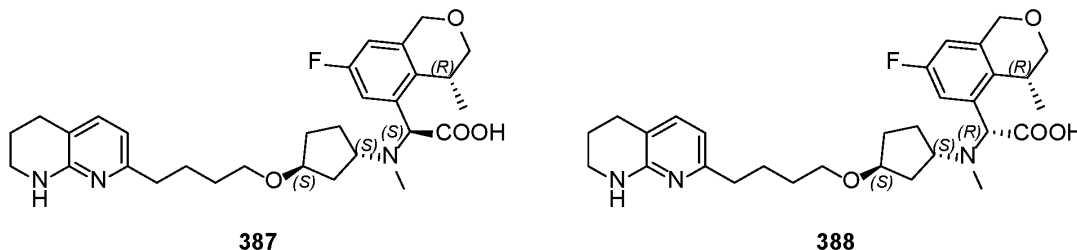
[000464] Isomers of arbitrarily assigned 2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, and were purified by prep-HPLC (column: Phenomenex luna C18 250*150mm*15um; mobile phase: [H₂O (0.2%FA)-ACN]; gradient: 26%-55% B over 20.0 min). The products were separated by SFC (column: DAICEL CHIRALPAK IK (250 mm * 25 mm, 10 um); mobile phase: [CO₂ – EtOH (0.1%NH₃H₂O)]; B%:60%, isocratic elution mode).

[000465] **Compound 156** (peak 1), arbitrarily assigned as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid was obtained as a white solid.

[000466] **Compound 155** (peak 2) was arbitrarily assigned as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-(6'-methyl-2'-oxo-1'-(tetrahydro-2H-pyran-4-yl)spiro[cyclopropane-1,3'-indolin]-4'-yl)acetic acid.

Preparation of (S)-2-((R)-7-fluoro-4-methylisochroman-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid and (R)-2-

((R)-7-fluoro-4-methylisochroman-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 387 and 388)



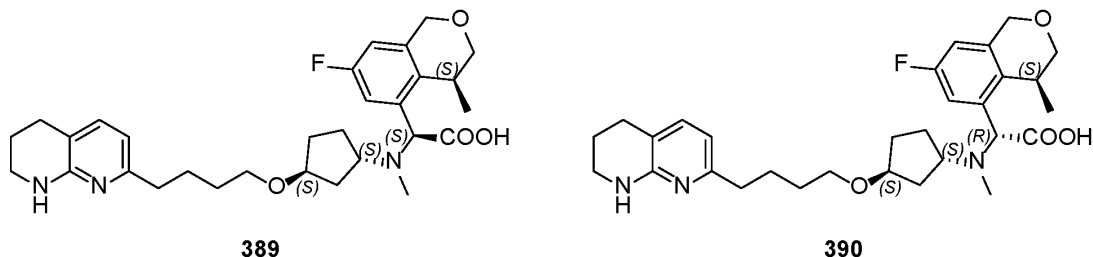
[000467] Compounds **387** and **388** were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 um; mobile phase: [H₂O (10 mM NH₄HCO₃)-ACN]; gradient: 20%-50% B over 8.0 min) and separated by SFC (column: ChiralPak IH, 250 * 30 mm, 1.0 um; mobile phase: [CO₂-IPA (0.1% NH₃H₂O)]; B%:28%, isocratic elution mode)..

[000468] **Compound 387** (peak 1), arbitrarily assigned as (S)-2-((R)-7-fluoro-4-methylisochroman-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained (17 mg, 30.81 μmol) as a white solid. LCMS [M+1]⁺= 526.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.44 (dd, *J* = 2.2, 10.3 Hz, 1H), 7.31 (br d, *J* = 7.5 Hz, 1H), 6.79 - 6.65 (m, 1H), 6.44 (d, *J* = 7.3 Hz, 1H), 4.81 (s, 1H), 4.74 - 4.69 (m, 1H), 4.63 (s, 1H), 4.01 - 3.90 (m, 3H), 3.79 - 3.73 (m, 1H), 3.56 - 3.36 (m, 5H), 2.75 - 2.68 (m, 3H), 2.58 - 2.51 (m, 1H), 2.33 (s, 3H), 2.22 (br d, *J* = 6.2 Hz, 1H), 1.97 (br d, *J* = 3.7 Hz, 2H), 1.91 - 1.85 (m, 2H), 1.79 - 1.65 (m, 5H), 1.61 - 1.55 (m, 2H), 1.38 (d, *J* = 7.0 Hz, 3H).

[000469] **Compound 388** (peak 2), arbitrarily assigned as (R)-2-((R)-7-fluoro-4-methylisochroman-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained (64.9 mg, 123.47 μmol) as a white solid. LCMS [M+1]⁺= 526.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.41 (dd, *J* = 2.6, 10.1 Hz, 1H), 7.22 (d, *J* = 7.3 Hz, 1H), 6.81 (dd, *J* = 2.4, 8.5 Hz, 1H), 6.39 (d, *J* = 7.2 Hz, 1H), 4.81 (s, 1H), 4.70 (br d, *J* = 12.3 Hz, 2H), 3.94 (br d, *J* = 10.6 Hz, 3H), 3.77 (dd, *J* = 2.0, 11.2 Hz, 1H), 3.42 - 3.35 (m, 4H), 3.07 - 2.92 (m, 1H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.65 - 2.50 (m, 2H), 2.49 - 2.26 (m, 3H), 2.09 - 1.94 (m, 3H), 1.93 - 1.85 (m, 3H), 1.84 - 1.77 (m, 1H), 1.74 - 1.60 (m, 3H), 1.55 (br s, 2H), 1.49 (d, *J* = 6.8 Hz, 3H).

Preparation of (S)-2-((S)-7-fluoro-4-methylisochroman-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid and (R)-2-

((S)-7-fluoro-4-methylisochroman-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 389 and 390)

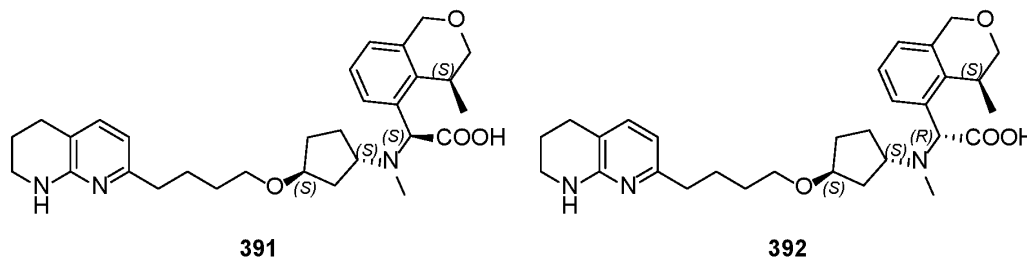


[000470] Compounds **389** and **390** were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: DAICEL CHIRALCEL OZ 250 * 25 mm I.D. 10 μ m; mobile phase: [CO₂-MeOH (0.1% NH₃H₂O)]; B%:55%, isocratic elution mode) and separated by SFC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 μ m; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 20%-50% B over 8.0 min).

[000471] **Compound 389** (peak 1), arbitrarily assigned as (S)-2-((S)-7-fluoro-4-methylisochroman-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained (74.3 mg, 135.70 μ mol) as a white solid. LCMS [M+1]⁺= 526.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.47 (dd, J = 2.6, 10.4 Hz, 1H), 7.25 (d, J = 7.3 Hz, 1H), 6.81 (dd, J = 2.5, 8.6 Hz, 1H), 6.41 (d, J = 7.4 Hz, 1H), 4.81 (s, 2H), 4.68 (s, 2H), 3.98 (br s, 1H), 3.96 - 3.93 (m, 1H), 3.92 - 3.82 (m, 1H), 3.78 (dd, J = 2.3, 11.2 Hz, 1H), 3.45 - 3.38 (m, 4H), 3.05 (br d, J = 6.8 Hz, 1H), 2.74 (t, J = 6.2 Hz, 2H), 2.65 - 2.51 (m, 2H), 2.42 (s, 3H), 2.21 (br dd, J = 7.1, 13.2 Hz, 1H), 1.94 (br d, J = 3.1 Hz, 2H), 1.90 (br dd, J = 5.2, 6.1 Hz, 2H), 1.82 - 1.78 (m, 1H), 1.75 - 1.68 (m, 2H), 1.60 - 1.52 (m, 2H), 1.48 (d, J = 7.0 Hz, 3H), 1.16 (d, J = 6.1 Hz, 1H).

[000472] **Compound 390** (peak 2), arbitrarily assigned as (R)-2-((S)-7-fluoro-4-methylisochroman-5-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained (20.7 mg, 37.73 μ mol) as a white solid. LCMS [M+1]⁺= 526.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.40 (dd, J = 2.6, 10.3 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 6.78 - 6.69 (m, 1H), 6.43 (d, J = 7.4 Hz, 1H), 4.74 (s, 2H), 4.69 - 4.58 (m, 2H), 4.16 - 4.06 (m, 1H), 3.97 - 3.92 (m, 2H), 3.78 (dd, J = 2.2, 11.1 Hz, 1H), 3.45 (dt, J = 2.3, 5.8 Hz, 2H), 3.40 - 3.36 (m, 3H), 2.73 (br t, J = 6.2 Hz, 3H), 2.59 - 2.53 (m, 1H), 2.17 (br dd, J = 6.9, 11.8 Hz, 1H), 2.03 - 1.96 (m, 2H), 1.93 - 1.84 (m, 3H), 1.83 - 1.68 (m, 5H), 1.62 - 1.57 (m, 2H), 1.38 (d, J = 7.0 Hz, 3H), 1.29 (s, 1H).

Preparation of (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid and (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid (Compounds 391 and 392)



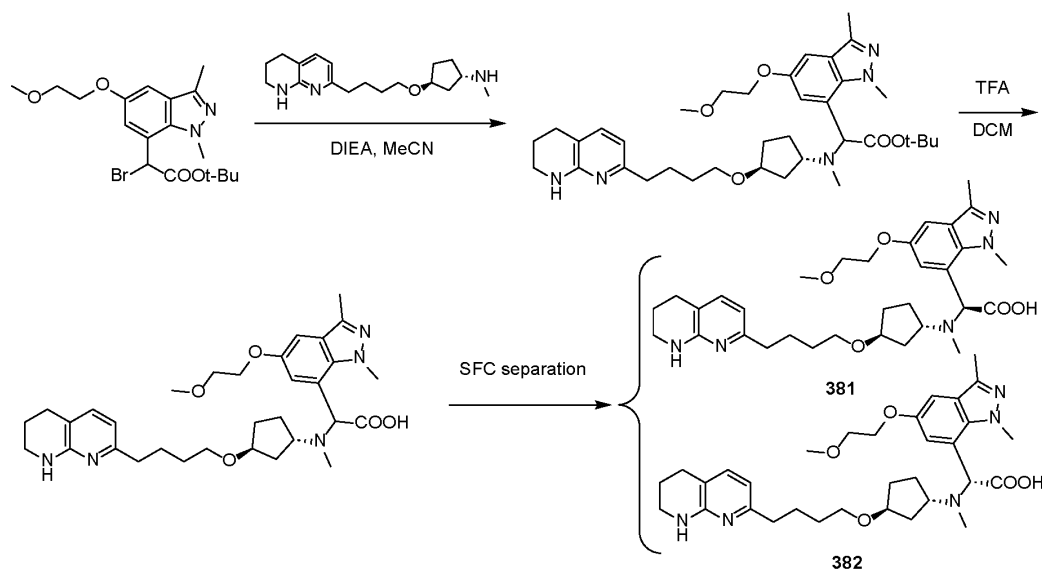
[000473] Compounds **391** and **392** were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30 mm * 10 um; mobile phase: [water (NH₄HCO₃)-ACN]; B%: 25%-50%, 8 min) and separated by SFC (column: (s, s) WHELK-O1 (250 mm * 30 mm, 5 um); mobile phase: [0.1% NH₃H₂O IPA]; B%: 50%-50%, 8 min).

[000474] **Compound 391** (peak 1), arbitrarily assigned as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid, was obtained (165.1 mg, 323.96 umol) as a white solid. LCMS [M+1] = 508.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.63 (d, *J* = 7.8 Hz, 1H), 7.24 - 7.17 (m, 2H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.37 (d, *J* = 7.4 Hz, 1H), 4.81 (s, 1H), 4.75 - 4.69 (m, 2H), 3.96 (br d, *J* = 11.4 Hz, 3H), 3.80 (dd, *J* = 2.4, 11.1 Hz, 1H), 3.41 - 3.36 (m, 4H), 3.00 (br d, *J* = 7.0 Hz, 1H), 2.71 (t, *J* = 6.3 Hz, 2H), 2.57 - 2.45 (m, 5H), 2.13 (br dd, *J* = 7.4, 13.3 Hz, 1H), 2.00 - 1.81 (m, 6H), 1.74 - 1.59 (m, 3H), 1.56 - 1.49 (m, 5H).

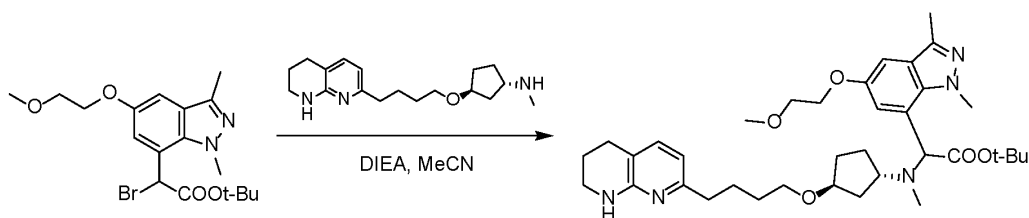
[000475] **Compound 392** (peak 2), arbitrarily assigned as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((S)-4-methylisochroman-5-yl)acetic acid, was obtained (48.2 mg, 94.53 umol) as a white solid. LCMS [M+1] = 508.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.55 (d, *J* = 7.6 Hz, 1H), 7.26 - 7.18 (m, 2H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.39 (d, *J* = 7.3 Hz, 1H), 4.82 (s, 1H), 4.77 - 4.71 (m, 2H), 4.19 - 4.08 (m, 1H), 4.01 - 3.93 (m, 2H), 3.80 (dd, *J* = 2.3, 11.1 Hz, 1H), 3.44 - 3.35 (m, 5H), 2.71 (t, *J* = 6.3 Hz, 2H), 2.63 - 2.43 (m, 5H), 2.19 (br dd, *J* = 6.9, 13.3 Hz, 1H), 2.10 - 1.80 (m, 6H), 1.76 - 1.62 (m, 3H), 1.59 - 1.51 (m, 2H), 1.39 (d, *J* = 6.9 Hz, 3H).

Preparation of (S)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid and

(R)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 381 and 382)



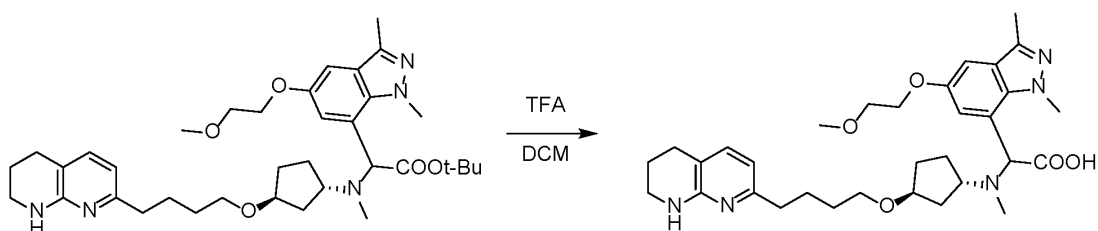
Step 1: (S)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid



[000476] To a solution of tert-butyl 2-bromo-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)acetate (0.25 g, 604.88 μmol , 1 eq) and (1S,3S)-N-methyl-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentan-1-amine (183.55 mg, 604.88 μmol , 1 eq) in MeCN (2 mL) was added DIEA (312.71 mg, 2.42 mmol, 421.44 μL , 4 eq) and 4A MS (0.1 g, 604.88 μmol , 1 eq) at 20°C. The mixture was allowed to stir at 50°C for 2hrs. The reaction was quenched by the addition of H₂O (30 mL), and the mixture was extracted with ethyl acetate (10 mLx3). The organic solutions were combined, washed with brine (20 mLx3), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether/Ethyl acetate=4/3 to 0/1) to give (S)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-

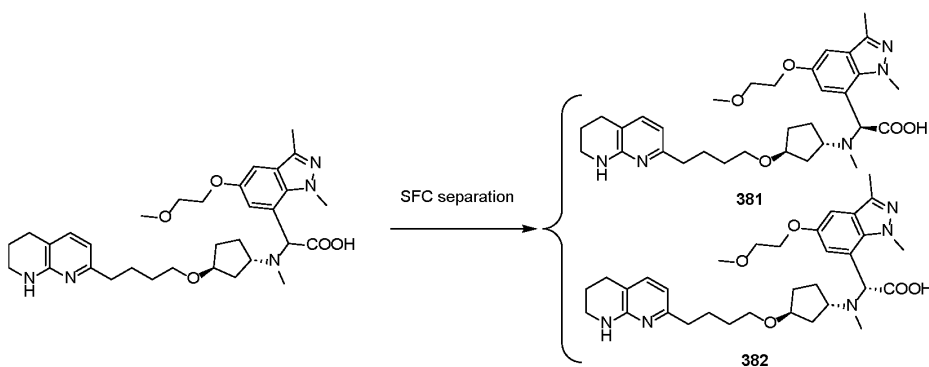
1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (0.4 g, 545.43 μ mol, 90.17% yield, 86.7% purity) as yellow oil. LCMS $[M+1] = 636.4$.

Step 2: 2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid



[000477] To a solution of (S)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (0.4 g, 629.09 μ mol, 1 eq) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 21.40 eq) at 20°C. The mixture was allowed to stir at 35°C for 16 hr and then concentrated under reduced pressure to remove solvent. The mixture was purified by pre-HPLC (column: Phenomenex Luna C18 75*30mm*3 μ m; mobile phase: $[H_2O$ (0.1%TFA)-ACN]; gradient: 10%-40% B over 8.0 min) to give 2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (82.26% yield) as a white solid. LCMS: $[M+1] = 580.35$.

Step 3: (S)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid and (R)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 381 and 382)

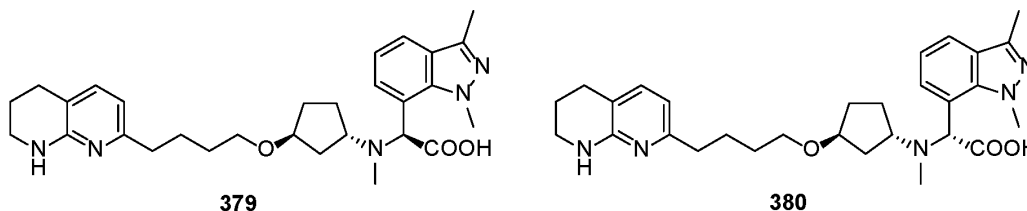


[000478] 2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (0.3 g, 517.48 μ mol) was separated by SFC (column: ChiralPak IH, 250*30mm, 10 μ m; mobile phase: [CO₂-EtOH (0.1% NH₃H₂O)]; B%:27%, isocratic elution mode).

[000479] **381** (Peak 1), arbitrarily assigned as (S)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained as a white solid (68 mg, 117.30 μ mol). LCMS [M+1] = 580.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.51 (d, J = 2.3 Hz, 1H), 7.36 (br d, J = 7.3 Hz, 1H), 7.10 (d, J = 2.3 Hz, 1H), 6.46 (d, J = 7.4 Hz, 1H), 5.15 (s, 1H), 4.35 (s, 3H), 4.16 (br d, J = 4.5 Hz, 2H), 3.96 (br s, 1H), 3.77 (dd, J = 3.8, 5.3 Hz, 3H), 3.45 (br d, J = 2.4 Hz, 3H), 3.43 (s, 3H), 2.76 (br t, J = 6.1 Hz, 2H), 2.62 - 2.56 (m, 1H), 2.48 (s, 3H), 2.41 (s, 3H), 2.39 - 2.34 (m, 1H), 2.06 - 1.99 (m, 1H), 1.99 - 1.86 (m, 4H), 1.83 - 1.77 (m, 1H), 1.73 - 1.54 (m, 7H).

[000480] **382** (Peak 2), arbitrarily assigned as (R)-2-(5-(2-methoxyethoxy)-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained as a white solid (67.7 mg, 116.78 μ mol). LCMS [M+1] = 580.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.40 (d, J = 2.3 Hz, 1H), 7.18 (d, J = 7.3 Hz, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.30 (d, J = 7.3 Hz, 1H), 5.00 (s, 1H), 4.23 (s, 3H), 4.07 - 4.01 (m, 2H), 3.95 - 3.86 (m, 1H), 3.82 (br s, 1H), 3.66 (dd, J = 3.8, 5.3 Hz, 2H), 3.32 (s, 3H), 3.29 - 3.24 (m, 3H), 2.62 (br t, J = 6.1 Hz, 2H), 2.58 - 2.50 (m, 1H), 2.46 - 2.40 (m, 1H), 2.37 (s, 3H), 2.34 (br s, 3H), 2.00 - 1.86 (m, 3H), 1.83 - 1.76 (m, 2H), 1.75 - 1.61 (m, 3H), 1.61 - 1.46 (m, 3H), 1.45 - 1.37 (m, 2H).

Preparation of (S)-2-(1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid and (R)-2-(1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 379 and 380)

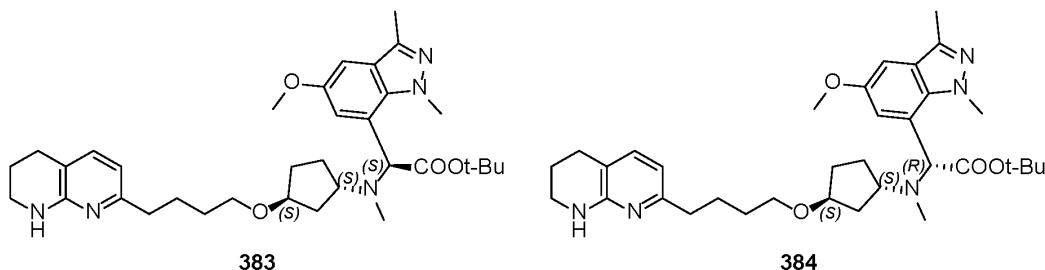


[000481] Compounds **379** and **380** were prepared starting from the appropriate starting material using procedures similar to those described for the preparation of compounds **381** and **382**. The final compounds were purified by prep-HPLC (column: Phenomenex Luna C 18 75 * 30 mm * 3 um; mobile phase: [H₂O (0.1%TFA)-ACN]; gradient: 1%-25% B over 8.0 min) to give two peaks. **Peak 1** was further purified by prep-HPLC (column: REGIS(s, s) WHELK-O1 (250 mm * 30 mm, 5 um); mobile phase: [CO₂-EtOH (0.1% NH₃H₂O)]; B%: 50%, isocratic elution mode). **Peak 2** was further purified by prep-HPLC (column: REGIS (s, s) WHELK-O1 (250 mm * 30 mm, 5 um); mobile phase: [CO₂- EtOH (0.1% NH₃H₂O)]; B%:50%, isocratic elution mode).

[000482] Peak 1, Compound **379**, arbitrarily assigned as (S)-2-(1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)-amino)acetic acid (16.33% yield), was obtained as a white solid. LCMS: [M+1] = 506.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.76 (d, *J* = 7.3 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 7.3 Hz, 1H), 5.23 (s, 1H), 4.40 (s, 3H), 3.97 (br s, 1H), 3.89 - 3.80 (m, 1H), 3.49 - 3.38 (m, 6H), 2.75 (br t, *J* = 6.3 Hz, 2H), 2.71 - 2.65 (m, 1H), 2.61 - 2.55 (m, 1H), 2.52 (s, 3H), 2.44 (s, 3H), 2.33 (br dd, *J* = 6.5, 12.9 Hz, 1H), 2.04 - 1.98 (m, 1H), 1.93 - 1.89 (m, 2H), 1.80 - 1.73 (m, 2H), 1.68 - 1.63 (m, 2H), 1.61 - 1.54 (m, 2H).

[000483] Peak 2, Compound **380**, arbitrarily assigned as (R)-2-(1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)-amino)acetic acid (23.9 mg, 47.27 umol, 15.93%), was obtained as a white solid. LCMS: [M+1] = 506.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.78 - 7.73 (m, 1H), 7.70 (br d, *J* = 8.1 Hz, 1H), 7.27 (br d, *J* = 7.3 Hz, 1H), 7.17 (br t, *J* = 7.5 Hz, 1H), 6.40 (br d, *J* = 7.1 Hz, 1H), 5.20 (br s, 1H), 4.38 (s, 3H), 4.05 - 3.98 (m, 1H), 3.93 (br s, 1H), 3.44 - 3.34 (m, 6H), 2.73 (br t, *J* = 6.1 Hz, 2H), 2.69 - 2.55 (m, 2H), 2.51 (s, 3H), 2.46 (br s, 3H), 2.07 - 2.00 (m, 2H), 1.90 - 1.78 (m, 4H), 1.70 - 1.62 (m, 2H), 1.56 - 1.45 (m, 2H).

Preparation of (S)-2-(5-methoxy-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid and (R)-2-(5-methoxy-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid (Compounds 383 and 384)



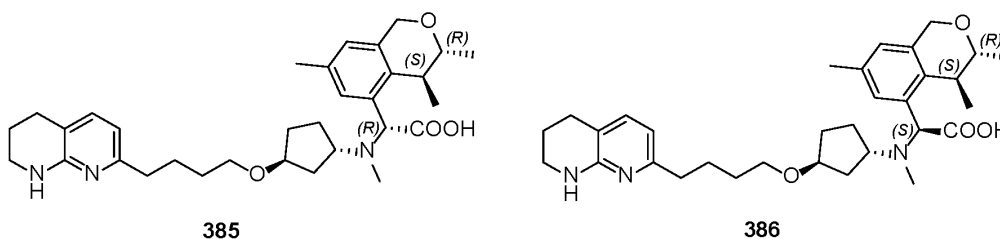
Compounds **383** and **384** were prepared starting from the appropriate starting material using procedures similar to those described for the preparation of compounds **381** and **382**. The final compounds were purified by prep-HPLC column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 μ m; mobile phase: [H₂O (0.05% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; gradient: 10%-40% B over 8.0 min) by prep-HPLC column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 μ m; mobile phase: [H₂O (0.05% NH₃H₂O + 10 mM NH₄HCO₃)-ACN]; gradient: 10%-40% B over 8.0 min).

[000484] Peak 1, Compound **383**, arbitrarily assigned as (S)-2-(5-methoxy-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained (63.8 mg, 119.10 μ mol) as a white solid. LCMS [M+1] = 536.2. ¹H NMR (400 MHz, CD₃OD) δ = 7.47 (d, *J* = 2.1 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.41 (d, *J* = 7.3 Hz, 1H), 5.10 (s, 1H), 4.33 (s, 3H), 4.01 (br dd, *J* = 3.0, 7.4 Hz, 1H), 3.92 (br s, 1H), 3.84 (s, 3H), 3.39 - 3.35 (m, 3H), 2.72 (t, *J* = 6.2 Hz, 2H), 2.66 - 2.60 (m, 1H), 2.56 - 2.51 (m, 1H), 2.48 (s, 3H), 2.43 (br s, 3H), 2.12 - 1.96 (m, 3H), 1.96 - 1.80 (m, 3H), 1.79 - 1.58 (m, 5H), 1.56 - 1.48 (m, 2H).

[000485] Peak 2, Compound **384**, arbitrarily assigned as (R)-2-(5-methoxy-1,3-dimethyl-1H-indazol-7-yl)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)acetic acid, was obtained (65.1 mg, 121.53 μ mol) as a white solid. LCMS [M+1] = 536.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.49 (d, *J* = 2.3 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 6.48 (d, *J* = 7.3 Hz, 1H), 5.16 (s, 1H), 4.37 (s, 3H), 3.98 (br s, 1H), 3.84 (s, 3H), 3.81 - 3.84 (m, 1H), 3.48 - 3.44 (m, 3H), 2.80 - 2.74 (m, 2H), 2.72 (br dd, *J* = 5.5, 9.4 Hz, 1H), 2.63 - 2.53 (m, 1H), 2.50 (s, 3H), 2.43 (s, 3H), 2.39 - 2.32 (m, 1H), 2.09 - 2.01 (m, 1H), 1.99 - 1.90 (m, 3H), 1.87 - 1.70 (m, 3H), 1.68 - 1.56 (m, 5H).

Preparation of (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((3R,4S)-3,4,7-trimethylisochroman-5-yl)acetic acid and (S)-

2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((3R,4S)-3,4,7-trimethylisochroman-5-yl)acetic acid (Compounds 385 and 386)

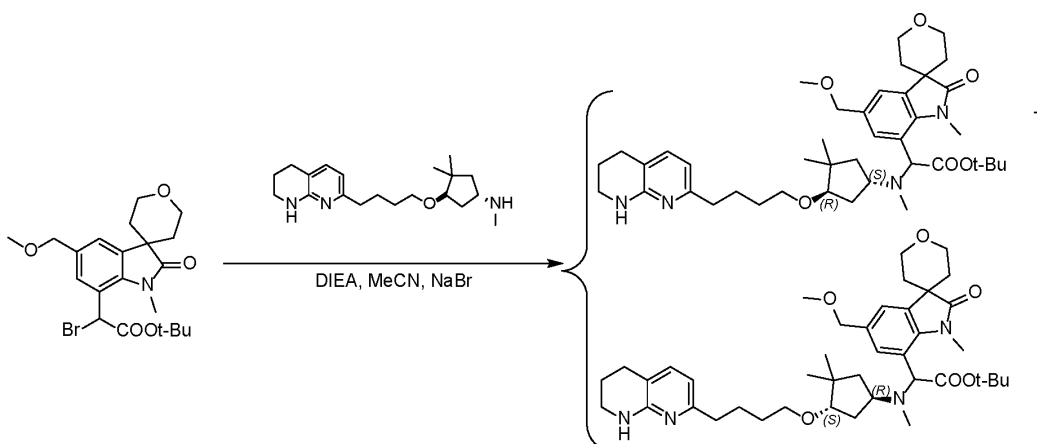


[000486] Compounds **385** and **386** were prepared starting from the appropriate starting material using procedures similar to those described for the preparation of compounds **381** and **382**. The final compounds were purified by prep-HPLC (column: Phenomenex Luna 80 * 30 mm * 3 μ m; mobile phase: [water (TFA)-ACN]; B%: 5%-35%, 8 min) and separated by SFC (column: Daicel Chiral Pak IG (250 * 30 mm, 10 μ m); mobile phase: [CO₂-MeOH (0.1% NH₃H₂O)]; 45% B isocratic elution mode).

[000487] Peak 1, Compound **385**, arbitrarily assigned as (R)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((3R,4S)-3,4,7-trimethylisochroman-5-yl)acetic acid, was obtained (43.5 mg, 80.50 μ mol) as a white solid. LCMS [M+1] = 536.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.42 (s, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 6.82 (s, 1H), 6.37 (d, *J* = 7.4 Hz, 1H), 4.71 (d, *J* = 3.8 Hz, 2H), 4.60 (s, 1H), 4.08 - 4.00 (m, 2H), 3.99 - 3.95 (m, 1H), 3.41 - 3.35 (m, 4H), 3.22 (br d, *J* = 6.8 Hz, 1H), 2.70 (t, *J* = 6.3 Hz, 2H), 2.57 - 2.48 (m, 2H), 2.47 - 2.42 (m, 3H), 2.29 (s, 3H), 2.14 - 1.92 (m, 4H), 1.91 - 1.75 (m, 4H), 1.69 - 1.63 (m, 2H), 1.58 - 1.52 (m, 2H), 1.33 (d, *J* = 7.0 Hz, 3H), 1.16 (d, *J* = 6.6 Hz, 3H).

[000488] Peak 2, Compound **386**, arbitrarily assigned as (S)-2-(methyl((1S,3S)-3-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)amino)-2-((3R,4S)-3,4,7-trimethylisochroman-5-yl)acetic acid, was obtained (108.5 mg, 202.11 μ mol) as a white solid. LCMS [M+1] = 536.3. ¹H NMR (400 MHz, CD₃OD) δ = 7.50 (s, 1H), 7.17 (d, *J* = 7.3 Hz, 1H), 6.88 (s, 1H), 6.36 (d, *J* = 7.3 Hz, 1H), 4.71 - 4.66 (m, 3H), 4.04 - 3.96 (m, 2H), 3.88 (br s, 1H), 3.41 - 3.35 (m, 4H), 2.81 (q, *J* = 6.6 Hz, 1H), 2.71 (t, *J* = 6.3 Hz, 2H), 2.54 - 2.45 (m, 5H), 2.28 (s, 3H), 2.11 - 1.97 (m, 2H), 1.94 - 1.84 (m, 5H), 1.74 - 1.67 (m, 1H), 1.64 - 1.57 (m, 2H), 1.55 - 1.49 (m, 2H), 1.45 (d, *J* = 7.0 Hz, 3H), 1.20 (d, *J* = 6.6 Hz, 3H).

Preparation of tert-butyl 2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate and tert-butyl 2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate



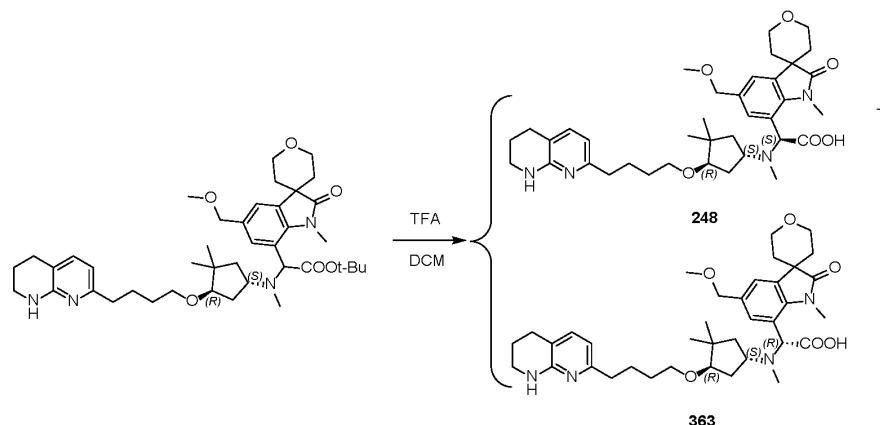
[000489] Isomers of were prepared according to Step 1 of the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents, purified by flash silica gel chromatography (Biotage®; 4 g SepaFlash® Silica Flash Column, Eluent of 0 ~ 10% MeOH/Ethyl acetate gradient @ 20 mL/min). The residue was separated by SFC (column: REGIS (s, s) WHELK-O1 (250 mm * 30 mm, 5 um); mobile phase: [CO₂ - MeOH (0.1% NH₃H₂O)]; B%: 50%, isocratic elution mode).

[000490] **Peak 1**, arbitrarily assigned as tert-butyl 2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate, was obtained as yellow oil.

[000491] **Peak 2**, arbitrarily assigned as tert-butyl 2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate, was obtained as a yellow oil.

Preparation of as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetic acid and (R)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(5-

(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetic acid (Compounds 248 and 363)



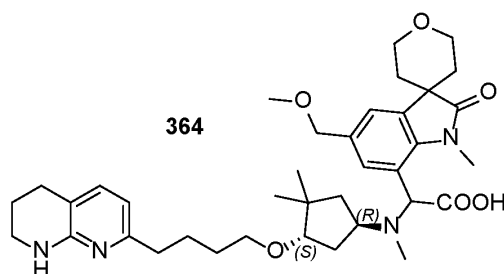
[000492] To a solution of tert-butyl 2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methylamino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetate (200 mg, 283.71 μ mol, 1 eq) in DCM (3 mL) was added TFA (1.54 g, 13.46 mmol, 1 mL, 47.45 eq) at 25 °C. The reaction mixture was allowed to stir at 25 °C for 16 hrs. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (column: Phenomenex luna C18 100 * 40 mm * 5 μ m; mobile phase: [H₂O (0.2% FA) - ACN]; gradient: 15% - 40% B over 8.0 min). The product was separated by SFC (column: DAICEL CHIRALCEL OD (250 mm * 30 mm, 10 μ m); mobile phase: [CO₂ - IPA (0.1% NH₃H₂O)]; B%: 50%, isocratic elution mode. SFC: Rt1 = 1.365 min, 56.20% Rt2 = 1.737 min, 38.79%) to give two peaks.

[000493] **Compound 248** (peak 1), arbitrarily assigned as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methylamino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetic acid, was obtained as a white solid (25.85% yield). LCMS [M+1] = 649.4. SFC Rt = 1.328 min. ¹H NMR (400 MHz, CD₃OD) δ = 7.60 (s, 1H), 7.48 - 7.36 (m, 1H), 7.35 - 7.22 (m, 1H), 6.43 (d, J = 7.3 Hz, 1H), 5.10 (s, 1H), 4.43 (s, 2H), 4.30 - 4.15 (m, 3H), 3.89 (dt, J = 3.9, 7.6 Hz, 2H), 3.62 (s, 3H), 3.49 - 3.38 (m, 5H), 3.37 (s, 3H), 2.73 (t, J = 6.2 Hz, 2H), 2.67 - 2.61 (m, 1H), 2.60 - 2.54 (m, 1H), 2.51 (br s, 3H), 2.24 - 2.17 (m, 1H), 2.04 - 1.82 (m, 6H), 1.75 - 1.67 (m, 4H), 1.66 - 1.51 (m, 3H), 1.09 (s, 3H), 0.95 (s, 3H).

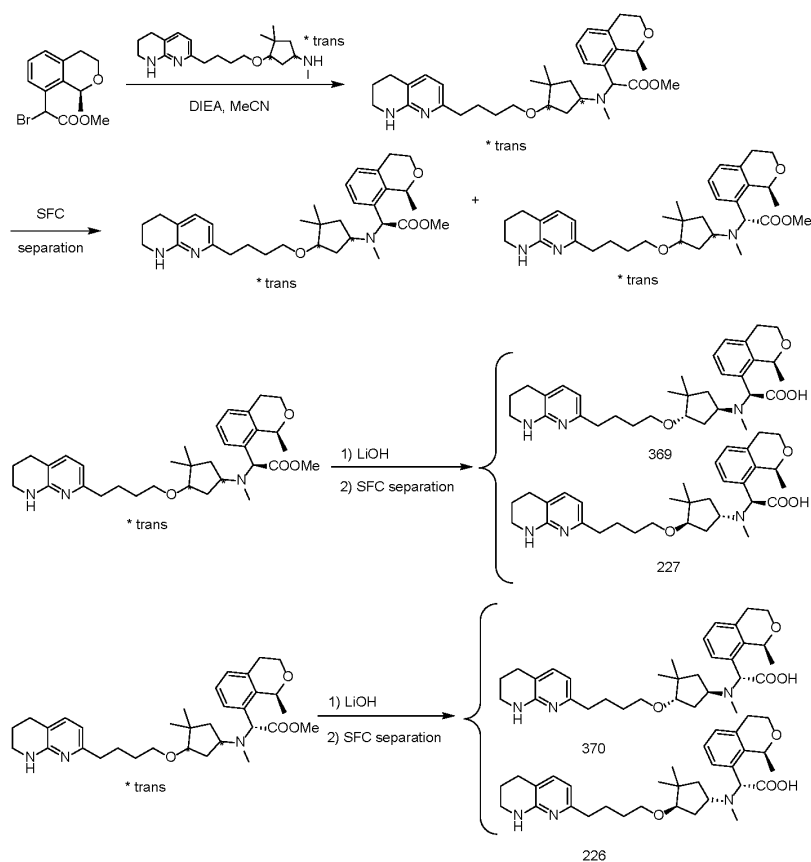
[000494] **Compound 363** (peak 2), arbitrarily assigned as (R)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methylamino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetic

acid, was obtained as a white solid (18.55% yield). LCMS $[M+1] = 649.4$. SFC $R_t = 1.675$ min. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.51$ (s, 1H), 7.34 - 7.25 (m, 1H), 7.15 (d, $J = 7.3$ Hz, 1H), 6.31 (d, $J = 7.3$ Hz, 1H), 4.99 (s, 1H), 4.32 (s, 2H), 4.20 - 4.10 (m, 2H), 3.85 - 3.75 (m, 3H), 3.55 (s, 3H), 3.39 - 3.35 (m, 1H), 3.30 (t, $J = 5.6$ Hz, 4H), 3.26 (s, 3H), 2.63 (t, $J = 6.2$ Hz, 2H), 2.52 - 2.41 (m, 5H), 2.08 - 2.00 (m, 1H), 1.97 - 1.91 (m, 1H), 1.86 - 1.76 (m, 4H), 1.66 - 1.54 (m, 6H), 1.49 - 1.41 (m, 2H), 0.97 (s, 3H), 0.77 (s, 3H).

Preparation of 2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-(5-(methoxymethyl)-1-methyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)acetic acid (Compounds 364)



[000495] Compounds **364** were prepared starting from the appropriate starting material using a procedure similar to that described for the preparation of compounds **248** and **363** and purified by prep-HPLC (column: Phenomenex luna C18 100 * 40 mm * 5 μm ; mobile phase: $[\text{H}_2\text{O}$ (0.2% FA) - ACN]; gradient: 25% - 55% B over 8.0 min. Compounds **364** were obtained as a white solid. LCMS $[M+1] = 649.4$. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.61$ (d, $J = 12.8$ Hz, 1H), 7.43 (dd, $J = 1.3, 9.8$ Hz, 1H), 7.35 (dd, $J = 7.3, 15.6$ Hz, 1H), 6.47 (t, $J = 7.4$ Hz, 1H), 5.15 (d, $J = 6.0$ Hz, 1H), 4.44 (d, $J = 4.5$ Hz, 2H), 4.25 (dq, $J = 2.6, 11.1$ Hz, 2H), 3.94 - 3.86 (m, 2H), 3.64 (d, $J = 14.3$ Hz, 3H), 3.52 - 3.44 (m, 2H), 3.44 - 3.40 (m, 3H), 3.38 (d, $J = 4.1$ Hz, 3H), 2.75 (br t, $J = 6.1$ Hz, 2H), 2.72 - 2.62 (m, 1H), 2.59 (s, 2H), 2.52 (br s, 1H), 2.23 - 2.05 (m, 2H), 1.97 - 1.86 (m, 4H), 1.76 - 1.58 (m, 7H), 1.30 (d, $J = 6.5$ Hz, 3H), 1.12 - 1.07 (m, 3H), 0.99 (s, 1H), 0.90 (s, 1H).

Preparation of Compounds 226, 227, 369 and 370

[000496] Isomers of (RS)-2-(((1RS,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents. The intermediates after alkylation were purified by column chromatography (SiO₂, petroleum ether/ethyl acetate = 1/0 to 0/1) and then separated by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm, 10um); mobile phase: [CO₂-EtOH (0.1%NH₃ H₂O)]; B%:40%, isocratic elution mode) to give 2 product mixtures. Each product mixture following SFC separation was separately subjected to hydrolysis and purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8.0 min) to give two product mixtures.

[000497] The product of hydrolysis of SFC peak 1, arbitrarily assigned as (S)-2-(((1RS,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid, was

purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8.0 min) and separated by SFC (column: REGIS (s, s) WHELK-O1 (250mm*30mm, 5um); mobile phase: [CO₂-EtOH (0.1%NH₃H₂O)]; B%:50%, isocratic elution mode) to give two compounds.

[000498] Compound 369 (peak 1), arbitrarily assigned as (S)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 536.3. SFC R_t = 1.753 min. ¹H NMR (400 MHz, CD₃OD) δ = 7.60 (d, J = 7.6 Hz, 1H), 7.27 - 7.20 (m, 1H), 7.16 (dd, J = 3.6, 7.3 Hz, 2H), 6.37 (d, J = 7.3 Hz, 1H), 5.22 (q, J = 6.6 Hz, 1H), 4.50 (s, 1H), 4.17 (ddd, J = 4.8, 9.1, 11.4 Hz, 1H), 4.03 - 3.85 (m, 1H), 3.81 (ddd, J = 4.1, 6.1, 11.4 Hz, 1H), 3.50 - 3.36 (m, 5H), 2.99 - 2.88 (m, 1H), 2.85 - 2.77 (m, 1H), 2.71 (t, J = 6.3 Hz, 2H), 2.58 - 2.35 (m, 5H), 2.25 (td, J = 7.0, 14.1 Hz, 1H), 1.95 - 1.84 (m, 3H), 1.80 (br dd, J = 8.8, 12.9 Hz, 1H), 1.73 - 1.63 (m, 6H), 1.59 - 1.51 (m, 2H), 1.09 (s, 3H), 0.89 (s, 3H).

[000499] Compound 227 (peak 2), arbitrarily assigned as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 536.3. SFC R_t = 1.955 min. ¹H NMR (400 MHz, CD₃OD) δ = 7.63 (d, J = 7.4 Hz, 1H), 7.28 - 7.16 (m, 3H), 6.39 (d, J = 7.4 Hz, 1H), 5.29 (q, J = 6.5 Hz, 1H), 4.55 (s, 1H), 4.19 (ddd, J = 4.7, 8.8, 11.5 Hz, 1H), 3.99 - 3.86 (m, 1H), 3.86 - 3.80 (m, 1H), 3.53 - 3.39 (m, 5H), 3.01 - 2.91 (m, 1H), 2.88 - 2.80 (m, 1H), 2.73 (t, J = 6.2 Hz, 2H), 2.59 - 2.46 (m, 5H), 2.20 (td, J = 7.1, 14.1 Hz, 1H), 2.01 - 1.93 (m, 1H), 1.93 - 1.88 (m, 2H), 1.77 - 1.63 (m, 7H), 1.62 - 1.54 (m, 2H), 1.10 (s, 3H), 0.89 (s, 3H).

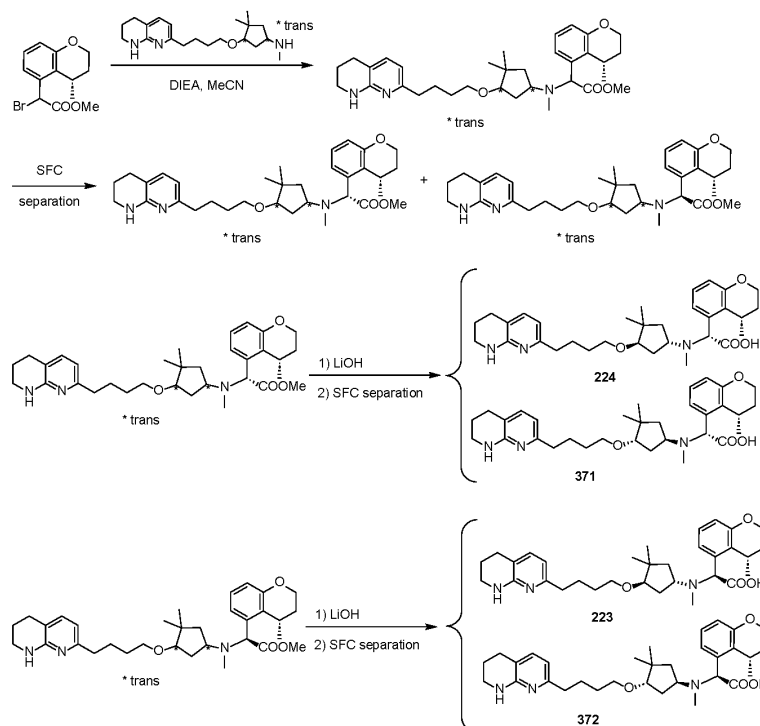
[000500] The product of hydrolysis of SFC peak 2, arbitrarily assigned as (R)-2-(((1RS,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid, was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8.0 min) and separated by SFC (column: REGIS (s, s) WHELK-O1 (250mm*30mm, 5um); mobile phase: [CO₂-EtOH (0.1%NH₃H₂O)]; B%:50%, isocratic elution mode) to give two compounds.

[000501] Compound 370 (peak 1), arbitrarily assigned as (R)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid, was obtained as white solid. LCMS [M+1] = 536.3. SFC R_t

= 1.489 min. ^1H NMR (400 MHz, CD_3OD) δ = 7.54 (d, J = 7.6 Hz, 1H), 7.29 - 7.17 (m, 2H), 7.16 - 7.08 (m, 1H), 6.41 (d, J = 7.3 Hz, 1H), 5.52 (q, J = 6.4 Hz, 1H), 4.53 (s, 1H), 4.19 - 4.04 (m, 2H), 3.85 - 3.76 (m, 1H), 3.57 - 3.50 (m, 1H), 3.47 - 3.37 (m, 4H), 2.99 - 2.90 (m, 1H), 2.85 - 2.77 (m, 1H), 2.72 (t, J = 6.2 Hz, 2H), 2.67 - 2.54 (m, 2H), 2.43 (s, 3H), 2.22 - 2.10 (m, 2H), 1.88 (td, J = 5.9, 11.3 Hz, 3H), 1.78 - 1.67 (m, 3H), 1.64 - 1.57 (m, 5H), 1.09 (s, 3H), 0.97 (s, 3H).

[000502] Compound 226 (peak 2), arbitrarily assigned as (R)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1-methylisochroman-8-yl)acetic acid, was obtained as a white solid. LCMS $[M+1] = 536.3$. SFC $R_t = 1.792$ min. ^1H NMR (400 MHz, CD_3OD) δ = 7.52 (br d, J = 7.5 Hz, 1H), 7.25 - 7.17 (m, 2H), 7.13 (br d, J = 7.4 Hz, 1H), 6.40 (d, J = 7.4 Hz, 1H), 5.53 (q, J = 6.5 Hz, 1H), 4.49 (s, 1H), 4.24 - 4.09 (m, 2H), 3.86 - 3.76 (m, 1H), 3.55 - 3.48 (m, 1H), 3.46 - 3.40 (m, 2H), 3.39 - 3.35 (m, 2H), 2.99 - 2.89 (m, 1H), 2.79 (td, J = 4.1, 16.5 Hz, 1H), 2.71 (br t, J = 6.1 Hz, 2H), 2.65 - 2.52 (m, 2H), 2.44 (s, 3H), 2.24 (td, J = 7.1, 13.9 Hz, 1H), 2.06 (br d, J = 4.5 Hz, 1H), 1.92 - 1.84 (m, 3H), 1.79 - 1.65 (m, 3H), 1.63 - 1.56 (m, 5H), 1.11 (s, 3H), 0.96 (s, 3H).

Preparation of Compounds 223, 224, 371 and 372



[000503] Isomers of (RS)-2-(((1SR,4RS)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylchroman-5-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents. The intermediates after alkylation were purified by SFC (column: REGIS(S, S) WHELK-O1 (250 mm*25 mm, 10 μ m); mobile phase: [CO₂-IPA (0.1%NH₃H₂O)]; B%:43%, isocratic elution mode to give 2 product mixtures. Each product following SFC separation was separately subjected to hydrolysis and purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 μ m; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8.0 min) to give two products.

[000504] The product of hydrolysis of alkylation SFC peak 1, arbitrarily assigned as (R)-2-(((1RS,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylchroman-5-yl)acetic acid, was purified by by SFC (column: REGIS (s,s) WHELK-O1 (250 mm*30 mm, 5 μ m); mobile phase: [CO₂-IPA(0.1%NH₃H₂O)]; B%:50%, isocratic elution mode) to give two compounds.

[000505] **Compound 224** (peak 1), arbitrarily assigned as (R)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylchroman-5-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 536.3. SFC R_t = 0.998 min. ¹H NMR (400 MHz, CD₃OD) δ = 7.25 (br d, *J* = 7.8 Hz, 1H), 7.17 (br d, *J* = 7.3 Hz, 1H), 7.10 (br t, *J* = 7.9 Hz, 1H), 6.80 (br d, *J* = 8.0 Hz, 1H), 6.38 (d, *J* = 7.3 Hz, 1H), 4.68 (s, 1H), 4.26 (br d, *J* = 8.0 Hz, 2H), 4.10 - 3.90 (m, 1H), 3.49 - 3.42 (m, 2H), 3.41 - 3.37 (m, 3H), 3.19 (br s, 1H), 2.71 (br t, *J* = 6.1 Hz, 2H), 2.59 - 2.46 (m, 5H), 2.26 - 2.18 (m, 1H), 2.12 - 1.97 (m, 2H), 1.90 - 1.84 (m, 3H), 1.78 - 1.71 (m, 2H), 1.70 - 1.63 (m, 2H), 1.59 - 1.53 (m, 2H), 1.49 (br d, *J* = 7.0 Hz, 3H), 1.10 (s, 3H), 0.90 (s, 3H).

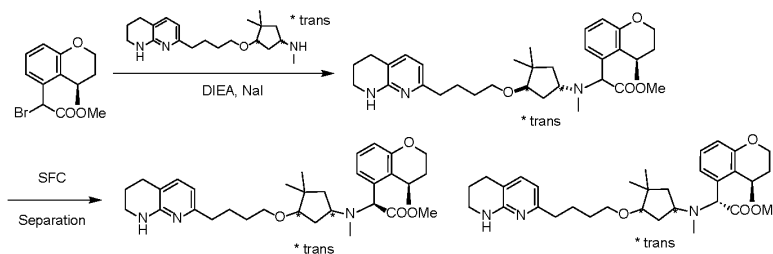
[000506] **Compound 371** (peak 2), arbitrarily assigned as (R)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylchroman-5-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 536.3. SFC R_t = 1.506 min. ¹H NMR (400 MHz, CD₃OD) δ = 7.24 (br d, *J* = 7.6 Hz, 1H), 7.18 - 7.07 (m, 2H), 6.80 (br d, *J* = 8.0 Hz, 1H), 6.37 (d, *J* = 7.4 Hz, 1H), 4.66 (s, 1H), 4.25 (br d, *J* = 8.1 Hz, 2H), 4.17 - 3.89 (m, 1H), 3.48 - 3.42 (m, 2H), 3.41 - 3.34 (m, 3H), 3.14 (br s, 1H), 2.70 (br t, *J* = 6.1 Hz, 2H), 2.56 - 2.43 (m, 4H), 2.34 - 2.26 (m, 1H), 2.11 - 2.03 (m, 1H), 1.94 - 1.77 (m, 5H), 1.74 - 1.64 (m, 3H), 1.60 - 1.53 (m, 2H), 1.48 (br d, *J* = 7.0 Hz, 3H), 1.37 - 1.26 (m, 1H), 1.11 (s, 3H), 0.91 (br s, 3H)

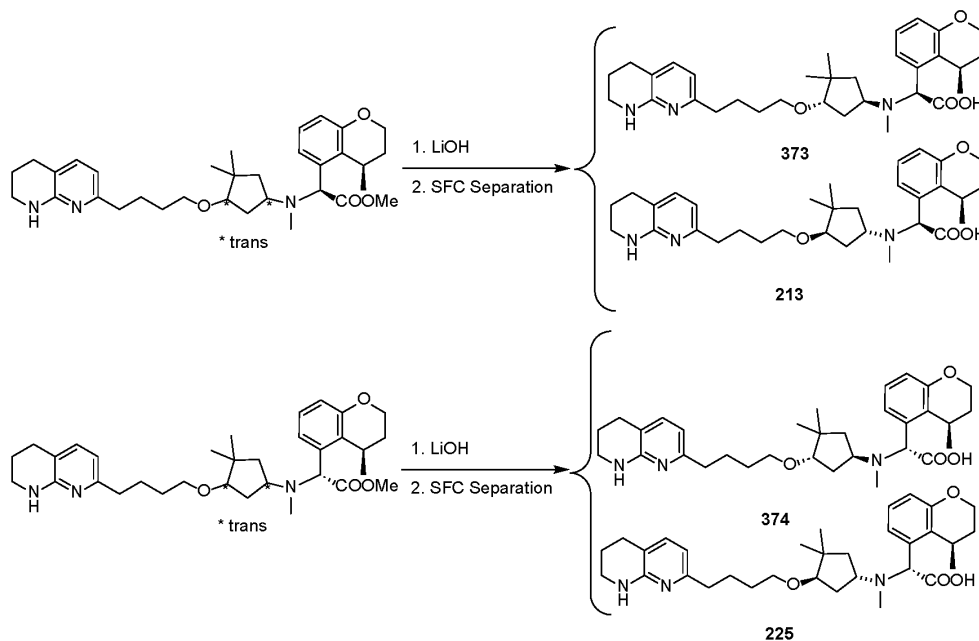
[000507] The product of hydrolysis of alkylation SFC peak 2, arbitrarily assigned as (S)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylchroman-5-yl)acetic acid, was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30 mm*10 μ m; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 30%-60% B over 8.0 min) and separated by SFC (column: REGIS (s,s) WHELK-O1 (250 mm*30 mm, 5 μ m); mobile phase: [CO₂-IPA(0.1%NH₃H₂O)]; B%:50%, isocratic elution mode) to give two compounds.

[000508] **Compound 223** (peak 1), arbitrarily assigned as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylchroman-5-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 536.3. SFC R_t = 1.821 min. ¹H NMR (400 MHz, CD₃OD) δ = 7.20 - 7.13 (m, 2H), 7.13 - 7.06 (m, 1H), 6.83 - 6.72 (m, 1H), 6.38 (d, *J* = 7.3 Hz, 1H), 4.67 (s, 1H), 4.26 (br d, *J* = 8.0 Hz, 2H), 4.22 - 4.12 (m, 1H), 3.59 - 3.47 (m, 3H), 3.45 - 3.40 (m, 1H), 3.40 - 3.36 (m, 2H), 2.72 - 2.68 (m, 2H), 2.58 - 2.52 (m, 2H), 2.50 (s, 3H), 2.24 (td, *J* = 6.8, 13.8 Hz, 1H), 2.12 - 2.02 (m, 2H), 1.96 - 1.82 (m, 4H), 1.76 - 1.62 (m, 3H), 1.61 - 1.54 (m, 2H), 1.37 (d, *J* = 7.0 Hz, 3H), 1.11 (s, 3H), 0.96 (s, 3H).

[000509] **Compound 372** (peak 2), arbitrarily assigned as (S)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-4-methylchroman-5-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 536.3. SFC R_t = 2.183 min. ¹H NMR (400 MHz, CD₃OD) δ = 7.20 - 7.09 (m, 3H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.38 (d, *J* = 7.3 Hz, 1H), 4.64 (s, 1H), 4.28 - 4.20 (m, 3H), 3.55 - 3.41 (m, 4H), 3.39 - 3.36 (m, 2H), 2.70 (br t, *J* = 6.1 Hz, 2H), 2.59 - 2.52 (m, 2H), 2.49 (br s, 3H), 2.31 (td, *J* = 6.9, 14.0 Hz, 1H), 2.12 - 2.03 (m, 2H), 1.93 - 1.85 (m, 3H), 1.81 (br d, *J* = 13.8 Hz, 1H), 1.75 - 1.67 (m, 3H), 1.61 - 1.56 (m, 2H), 1.34 (br d, *J* = 7.0 Hz, 3H), 1.12 (s, 3H), 0.96 (s, 3H).

Preparation of Compounds 213, 225, 373 and 374





[000510] Isomers of (RS)-2-(((1RS,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((R)-4-methylchroman-5-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents. The intermediates after alkylation were purified by column chromatography (SiO₂, 12g Sepa Flash® Silica Flash Column, Eluent of 0~80% Petroleum ethergradient/ Ethyl acetate@ 120 mL/min) and then separated by SFC (column: DAICEL CHIRALPAK IC (250 mm * 30 mm, 10 μm); mobile phase: [CO₂-IPA (0.1%NH₃H₂O)]; B%:60%, isocratic elution mode) to give 2 product mixtures. Each product following SFC separation was separately subjected to hydrolysis to give two products.

[000511] The product of hydrolysis of alkylation SFC peak 1, arbitrarily assigned as (S)-2-(((1RS,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((R)-4-methylchroman-5-yl)acetic acid, was purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150 * 40 mm * 10 μm; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 35%-65% B over 8.0 min) and separated by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm, 10μm); mobile phase: [CO₂-MeOH (0.1%NH₃H₂O)]; B%:40%, isocratic elution mode) to give two compounds.

[000512] **Compound 373** (peak 1,), arbitrarily assigned as (S)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((R)-4-methylchroman-5-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 536.3. SFC

$R_{t1} = 1.224$ min. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.31 - 7.20$ (m, 1H), $7.17 - 7.09$ (m, 2H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.37 (d, $J = 7.3$ Hz, 1H), 4.66 (s, 1H), $4.28 - 4.22$ (m, 2H), 4.05 (br d, $J = 6.1$ Hz, 1H), $3.48 - 3.35$ (m, 5H), 3.14 (br d, $J = 1.5$ Hz, 1H), 2.70 (t, $J = 6.3$ Hz, 2H), $2.63 - 2.34$ (m, 5H), 2.29 (td, $J = 7.0, 14.1$ Hz, 1H), $2.12 - 2.03$ (m, 1H), $1.98 - 1.77$ (m, 5H), $1.74 - 1.63$ (m, 3H), $1.60 - 1.53$ (m, 2H), 1.48 (d, $J = 7.0$ Hz, 3H), 1.11 (s, 3H), 0.91 (br s, 3H).

[000513] Compound 213 (peak 2), arbitrarily assigned as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((R)-4-methylchroman-5-yl)acetic acid, was obtained as a white solid. LCMS $[\text{M}+1] = 536.3$. SFC $R_{t1} = 1.642$ min. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.26$ (d, $J = 7.6$ Hz, 1H), 7.20 (d, $J = 7.3$ Hz, 1H), 7.11 (t, $J = 7.9$ Hz, 1H), 6.80 (d, $J = 8.0$ Hz, 1H), 6.39 (d, $J = 7.3$ Hz, 1H), 4.69 (s, 1H), $4.29 - 4.24$ (m, 2H), 4.03 (br s, 1H), $3.53 - 3.47$ (m, 1H), 3.44 (br d, $J = 6.5$ Hz, 1H), $3.42 - 3.36$ (m, 3H), $3.22 - 3.14$ (m, 1H), 2.71 (t, $J = 6.3$ Hz, 2H), $2.59 - 2.45$ (m, 5H), $2.27 - 2.18$ (m, 1H), $2.13 - 2.06$ (m, 1H), $2.03 - 1.96$ (m, 1H), $1.92 - 1.85$ (m, 3H), $1.78 - 1.72$ (m, 2H), $1.71 - 1.64$ (m, 2H), $1.60 - 1.53$ (m, 2H), 1.49 (d, $J = 7.0$ Hz, 3H), 1.10 (s, 3H), 0.91 (s, 3H).

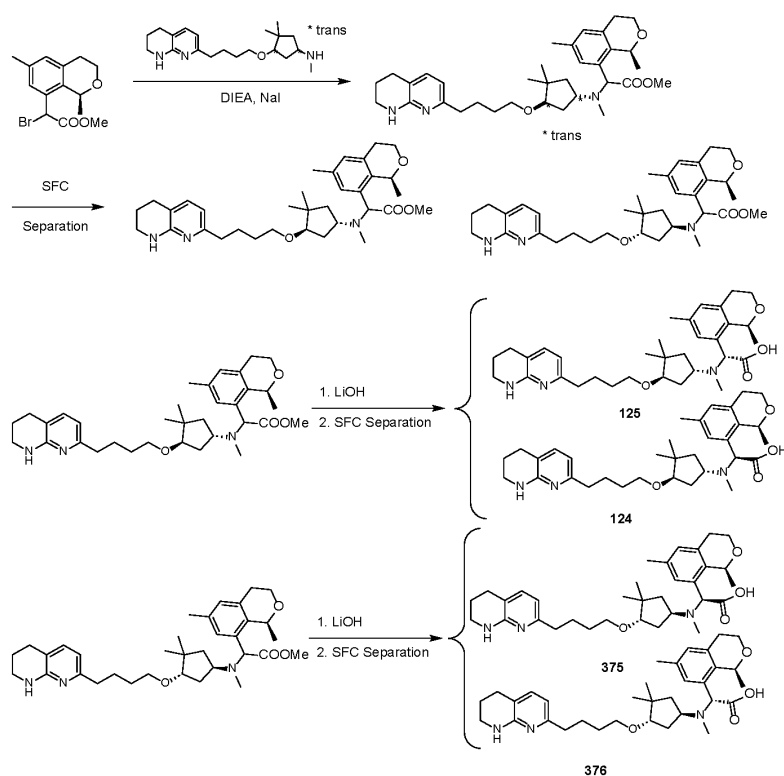
[000514] The product of hydrolysis of alkylation SFC peak 2, arbitrarily assigned as (R)-2-(((1RS,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((R)-4-methylchroman-5-yl)acetic acid, was purified by prep-HPLC (column: Waters Xbridge BEH C18 100 * 30 mm * 10 μm ; mobile phase: $[\text{H}_2\text{O}$ (10mM NH_4HCO_3)-ACN]; gradient: 30%-60% B over 8.0 min) and separated by SFC (column: REGIS (s,s) WHELK-O1 (250 mm * 30 mm, 5 μm); mobile phase: $[\text{CO}_2$ -IPA(0.1% $\text{NH}_3\text{H}_2\text{O}$)]; $\text{B}\%$:50%, isocratic elution mode) to give two compounds.

[000515] Compound 374 (peak 1), arbitrarily assigned as (R)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((R)-4-methylchroman-5-yl)acetic acid, was obtained as a white solid. LCMS $[\text{M}+1] = 536.3$. SFC $R_{t1} = 1.658$ min. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.17$ (br d, $J = 8.0$ Hz, 2H), $7.12 - 7.07$ (m, 1H), 6.76 (d, $J = 8.3$ Hz, 1H), 6.38 (d, $J = 7.4$ Hz, 1H), 4.67 (s, 1H), $4.28 - 4.23$ (m, 2H), $4.20 - 4.12$ (m, 1H), $3.59 - 3.51$ (m, 2H), $3.50 - 3.47$ (m, 1H), $3.45 - 3.40$ (m, 1H), $3.39 - 3.36$ (m, 2H), 2.70 (t, $J = 6.2$ Hz, 2H), $2.58 - 2.52$ (m, 2H), 2.50 (s, 3H), $2.28 - 2.21$ (m, 1H), $2.12 - 2.04$ (m, 2H), $1.93 - 1.82$ (m, 4H), $1.76 - 1.65$ (m, 3H), $1.61 - 1.56$ (m, 2H), 1.37 (d, $J = 7.0$ Hz, 3H), 1.11 (s, 3H), 0.96 (s, 3H).

[000516] Compound 225 (peak 2), arbitrarily assigned as (R)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((R)-4-

methylchroman-5-yl)acetic acid, was obtained as a white solid. LCMS $[M+1] = 536.3$. SFC $R_{t1} = 2.091$ min. ^1H NMR (400 MHz, CD_3OD) $\delta = 7.22 - 7.16$ (m, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 6.77 (d, $J = 8.0$ Hz, 1H), 6.39 (d, $J = 7.4$ Hz, 1H), 4.64 (s, 1H), 4.28 (s, 2H), 4.22 (br d, $J = 2.6$ Hz, 1H), 3.59 - 3.52 (m, 2H), 3.51 - 3.48 (m, 1H), 3.46 - 3.42 (m, 1H), 3.41 - 3.38 (m, 2H), 2.72 (t, $J = 6.3$ Hz, 2H), 2.57 (br d, $J = 7.9$ Hz, 2H), 2.53 - 2.46 (m, 3H), 2.36 - 2.29 (m, 1H), 2.12 - 2.04 (m, 2H), 1.95 - 1.83 (m, 4H), 1.76 - 1.69 (m, 3H), 1.63 - 1.57 (m, 2H), 1.36 (d, $J = 7.0$ Hz, 3H), 1.14 (s, 3H), 0.97 (s, 3H).

Preparation of Compounds 124, 125, 375 and 376



[000517] Isomers of 2-(((1R,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1,6-dimethylisochroman-8-yl)acetic acid were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents. The intermediates after alkylation were purified by column chromatography (SiO_2 , petroleum ether/ethyl acetate = 1/1 to 0/1) and then separated by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm, 10 μm); mobile phase: $[\text{CO}_2\text{-MeOH}$ (0.1% $\text{NH}_3\text{H}_2\text{O}$)] B%:45%, isocratic elution mode) to give 2 product mixtures. Each product mixture following SFC separation of the alkylation products was separately subjected to

hydrolysis and purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um; mobile phase: [H₂O (0.1%TFA)-ACN]; gradient: 20%-45% B over 8.0 min).

[000518] The product of hydrolysis of alkylation SFC peak 1, arbitrarily assigned as 2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1,6-dimethylisochroman-8-yl)acetic acid, was separated by SFC (column: DAICEL CHIRALPAK IG (250mm*30mm,10um);mobile phase: [CO₂-MeOH(0.1%NH₃H₂O)];B%:45%, isocratic elution mode) to give two compounds.

[000519] Compound 125 (peak 1), arbitrarily assigned as (R)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1,6-dimethylisochroman-8-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 550.4. SFC Rt = 1.552. ¹H NMR (400 MHz, CD₃OD) δ = 7.43 (s, 1H), 7.16 (d, J = 7.3 Hz, 1H), 7.00 (s, 1H), 6.37 (d, J = 7.3 Hz, 1H), 5.16 (q, J = 6.5 Hz, 1H), 4.47 (s, 1H), 4.14 (ddd, J = 4.6, 9.0, 11.5 Hz, 1H), 4.09 - 3.83 (m, 1H), 3.82 - 3.76 (m, 1H), 3.49 - 3.40 (m, 2H), 3.40 - 3.35 (m, 3H), 2.94 - 2.85 (m, 1H), 2.81 - 2.74 (m, 1H), 2.71 (t, J = 6.3 Hz, 2H), 2.51 (dt, J = 7.0, 13.1 Hz, 4H), 2.29 (s, 3H), 2.27 - 2.22 (m, 1H), 2.00 - 1.90 (m, 1H), 1.90 - 1.85 (m, 2H), 1.85 - 1.78 (m, 1H), 1.73 - 1.57 (m, 7H), 1.57 - 1.48 (m, 2H), 1.10 (s, 3H), 0.90 (s, 3H).

[000520] Compound 124 (peak 2), arbitrarily assigned as (S)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1,6-dimethylisochroman-8-yl)acetic acid, was further purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H₂O(10mM NH₄HCO₃)-ACN];gradient:30%-60% B over 8.0 min) and was obtained as a white solid. LCMS [M+1] = 550.4. SFC Rt = 1.776. ¹H NMR (400 MHz, CD₃OD) δ = 7.44 (s, 1H), 7.16 (d, J = 7.4 Hz, 1H), 7.00 (s, 1H), 6.37 (d, J = 7.4 Hz, 1H), 5.21 (q, J = 6.7 Hz, 1H), 4.49 (s, 1H), 4.15 (ddd, J = 4.6, 8.8, 11.5 Hz, 1H), 3.90 (br dd, J = 2.3, 4.4 Hz, 1H), 3.82 - 3.76 (m, 1H), 3.48 - 3.41 (m, 2H), 3.40 - 3.36 (m, 3H), 2.93 - 2.85 (m, 1H), 2.80 - 2.74 (m, 1H), 2.70 (t, J = 6.3 Hz, 2H), 2.57 - 2.46 (m, 5H), 2.28 (s, 3H), 2.19 (td, J = 6.8, 13.9 Hz, 1H), 1.99 - 1.91 (m, 1H), 1.90 - 1.85 (m, 2H), 1.73 (br d, J = 9.4 Hz, 2H), 1.68 (d, J = 6.6 Hz, 5H), 1.58 - 1.52 (m, 2H), 1.09 (s, 3H), 0.87 (s, 3H).

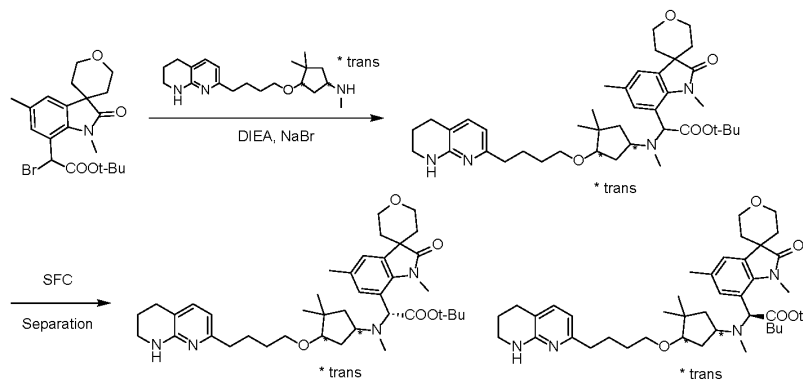
[000521] The product of hydrolysis of alkylation SFC peak 2, arbitrarily assigned as 2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1,6-dimethylisochroman-8-yl)acetic acid, was

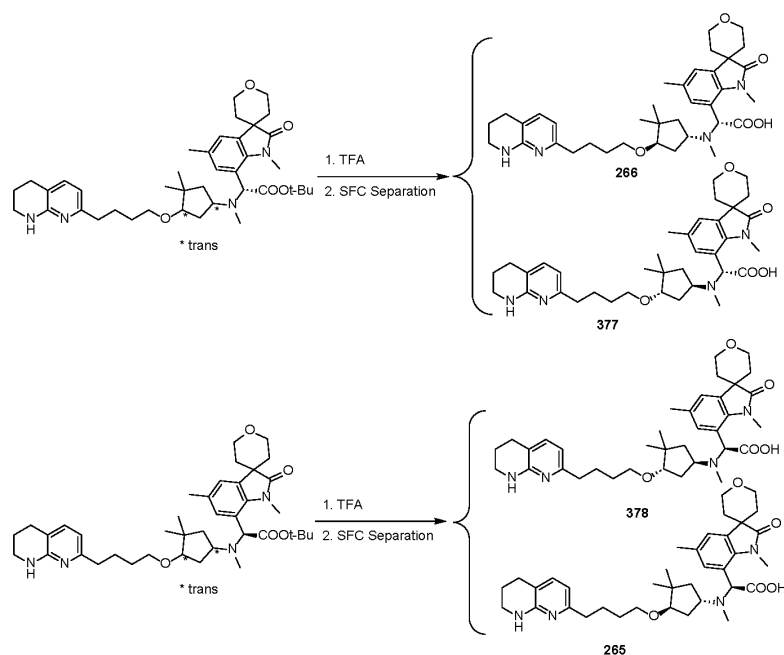
separated by SFC (column: REGIS (s,s) WHELK-O1 (250mm*30mm,5um);mobile phase: [CO₂-MeOH(0.1%NH₃H₂O)];B%:50%, isocratic elution mode) to give two compounds.

[000522] Compound 375 (peak 1), arbitrarily assigned as (S)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1,6-dimethylisochroman-8-yl)acetic acid, was further purified by prep-HPLC (column: Waters Xbridge Prep OBD C18 150*40mm*10um;mobile phase: [H₂O(10mM NH₄HCO₃)-ACN];gradient:35%-65% B over 8.0 min) and was obtained as a white solid. LCMS [M+1] = 550.4. SFC Rt = 1.611. ¹H NMR (400 MHz, CD₃OD) δ = 7.36 (s, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 6.96 (s, 1H), 6.40 (d, *J* = 7.4 Hz, 1H), 5.47 (q, *J* = 6.3 Hz, 1H), 4.50 (s, 1H), 4.16 - 4.07 (m, 2H), 3.81 - 3.75 (m, 1H), 3.55 - 3.50 (m, 1H), 3.48 - 3.41 (m, 2H), 3.40 - 3.33 (m, 3H), 2.92 - 2.84 (m, 1H), 2.78 - 2.69 (m, 3H), 2.62 - 2.53 (m, 2H), 2.45 (s, 3H), 2.29 (s, 3H), 2.19 - 2.08 (m, 2H), 1.92 - 1.85 (m, 3H), 1.76 - 1.68 (m, 3H), 1.59 (d, *J* = 6.5 Hz, 4H), 1.10 (s, 3H), 0.96 (s, 3H).

[000523] Compound 376 (peak 2), arbitrarily assigned as (R)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)-2-((S)-1,6-dimethylisochroman-8-yl)acetic acid, was obtained as a white solid. LCMS [M+1] = 550.4. SFC Rt = 2.044. ¹H NMR (400 MHz, CD₃OD) δ = 7.36 (s, 1H), 7.21 (d, *J* = 7.3 Hz, 1H), 6.96 (s, 1H), 6.40 (d, *J* = 7.3 Hz, 1H), 5.47 (q, *J* = 6.5 Hz, 1H), 4.45 (s, 1H), 4.23 - 4.14 (m, 1H), 4.10 (ddd, *J* = 4.6, 9.2, 11.4 Hz, 1H), 3.82 - 3.76 (m, 1H), 3.53 - 3.48 (m, 1H), 3.46 - 3.41 (m, 2H), 3.39 - 3.35 (m, 2H), 2.94 - 2.85 (m, 1H), 2.78 - 2.69 (m, 3H), 2.61 (br d, *J* = 8.3 Hz, 1H), 2.58 - 2.52 (m, 1H), 2.44 (s, 3H), 2.29 (s, 3H), 2.27 - 2.21 (m, 1H), 2.10 - 2.01 (m, 1H), 1.91 - 1.84 (m, 3H), 1.79 - 1.72 (m, 1H), 1.71 - 1.65 (m, 2H), 1.60 (br d, *J* = 7.3 Hz, 1H), 1.56 (d, *J* = 6.6 Hz, 3H), 1.11 (s, 3H), 0.96 (s, 3H).

Preparation of Compounds 265, 266, 377 and 378





[000524] Compounds **265**, **266**, **377** and **378** were prepared according to the General Example of Alkylation and Hydrolysis, substituting the appropriate reagents as shown. The intermediates after alkylation were separated by SFC (column: REGIS(S,S)WHELK-O1(250mm*25mm,10um); mobile phase: [CO₂-IPA(0.1% NH₃ H₂O)]; B%: 62%, isocratic elution mode) to give 2 product mixtures. Each product following SFC separation was separately subjected to hydrolysis and purified by prep-HPLC (column: Phenomenex Luna C18 75*30mm*3um;mobile phase: [H₂O(0.1%TFA)-ACN]; gradient:10%-40% B over 8.0 min) to give two product mixtures.

[000525] The products of hydrolysis of alkylation SFC peak 1, arbitrarily assigned as (R)-2-(1,5-dimethyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)-2-(((1R,4SR)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methylamino)acetic acid, were separated by SFC (column: DAICEL CHIRALCEL OD (250mm*30mm,10um); mobile phase: [CO₂-EtOH(0.1%NH₃H₂O)]; B%:50%, isocratic elution mode) to give two compounds.

[000526] **Compound 266** (peak 1), arbitrarily assigned as (R)-2-(1,5-dimethyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methylamino)acetic acid, was obtained as a white solid. LCMS [M+1]= 619.4. SFC R_t = 1.222min. ¹H NMR (400 MHz, CD₃OD) δ = 7.43 (s, 1H), 7.31 - 7.10 (m, 2H), 6.41 (d, J = 7.4 Hz, 1H), 5.06 (s, 1H), 4.37 - 4.10 (m, 3H),

3.92 - 3.83 (m, 2H), 3.60 (s, 3H), 3.45 - 3.35 (m, 5H), 2.73 (t, J = 6.3 Hz, 2H), 2.63 - 2.50 (m, 4H), 2.34 (s, 3H), 2.27 - 2.18 (m, 1H), 1.95 - 1.86 (m, 4H), 1.84 - 1.77 (m, 1H), 1.74 - 1.62 (m, 5H), 1.57 (br d, J = 6.0 Hz, 2H), 1.09 (s, 3H), 0.94 (s, 3H).

[000527] Compound 377 (peak 2), arbitrarily assigned as (R)-2-(1,5-dimethyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)acetic acid, was obtained as a white solid. LCMS [M+1] = 619.4. SFC R_t = 1.748min. ^1H NMR (400 MHz, CD_3OD) δ = 7.43 (s, 1H), 7.28 - 7.12 (m, 2H), 6.39 (d, J = 7.4 Hz, 1H), 5.04 (s, 1H), 4.28 - 4.19 (m, 2H), 3.89 (br dd, J = 5.5, 11.3 Hz, 3H), 3.62 (s, 3H), 3.51 - 3.45 (m, 2H), 3.42 - 3.38 (m, 4H), 3.15 - 3.10 (m, 1H), 2.72 (t, J = 6.2 Hz, 2H), 2.59 - 2.55 (m, 3H), 2.32 (s, 3H), 2.22 - 2.13 (m, 1H), 2.05 - 1.96 (m, 1H), 1.92 - 1.87 (m, 3H), 1.70 - 1.63 (m, 5H), 1.59 - 1.52 (m, 2H), 1.07 (s, 3H), 0.86 (s, 3H).

[000528] The products of hydrolysis of SFC peak 2, arbitrarily assigned as (S)-2-(1,5-dimethyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)acetic acid, were separated by SFC (column: DAICEL CHIRALPAK AD (250mm*30mm,10um);mobile phase: [CO_2 -EtOH(0.1% $\text{NH}_3\text{H}_2\text{O}$)]; $\text{B}\%$:15%, isocratic elution mode) to give two compounds.

[000529] Compound 378 (peak 1), arbitrarily assigned as (S)-2-(1,5-dimethyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)-2-(((1R,4S)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)acetic acid, was obtained as a white solid. LCMS [M+1] = 619.4. SFC R_t = 1.126min. ^1H NMR (400 MHz, CD_3OD) δ = 7.43 (s, 1H), 7.31 - 7.10 (m, 2H), 6.41 (d, J = 7.4 Hz, 1H), 5.06 (s, 1H), 4.37 - 4.10 (m, 3H), 3.92 - 3.83 (m, 2H), 3.60 (s, 3H), 3.45 - 3.35 (m, 5H), 2.73 (t, J = 6.3 Hz, 2H), 2.63 - 2.50 (m, 4H), 2.34 (s, 3H), 2.27 - 2.18 (m, 1H), 1.95 - 1.86 (m, 4H), 1.84 - 1.77 (m, 1H), 1.74 - 1.62 (m, 5H), 1.57 (br d, J = 6.0 Hz, 2H), 1.09 (s, 3H), 0.94 (s, 3H).

[000530] Compound 265 (peak 2), arbitrarily assigned as (S)-2-(1,5-dimethyl-2-oxo-2',3',5',6'-tetrahydrospiro[indoline-3,4'-pyran]-7-yl)-2-(((1S,4R)-3,3-dimethyl-4-(4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)butoxy)cyclopentyl)(methyl)amino)acetic acid, was obtained as a white solid. LCMS [M+1] = 619.3. SFC R_t = 1.173min. ^1H NMR (400 MHz, CD_3OD) δ = 7.43 (s, 1H), 7.28 - 7.12 (m, 2H), 6.39 (d, J = 7.4 Hz, 1H), 5.04 (s, 1H), 4.28 - 4.19 (m, 2H), 3.89 (br dd, J = 5.5, 11.3 Hz, 3H), 3.62 (s, 3H), 3.51 - 3.45 (m, 2H), 3.42 - 3.38 (m, 4H), 3.15 -

3.10 (m, 1H), 2.72 (t, J = 6.2 Hz, 2H), 2.59 - 2.55 (m, 3H), 2.32 (s, 3H), 2.22 - 2.13 (m, 1H), 2.05 - 1.96 (m, 1H), 1.92 - 1.87 (m, 3H), 1.70 - 1.63 (m, 5H), 1.59 - 1.52 (m, 2H), 1.07 (s, 3H), 0.86 (s, 3H).

[000531] Additional compounds of the invention were prepared using synthetic routes similar to those described above, substituting the appropriate reagents, purification and separation conditions.

Assay Conditions

[000532] Fluorescence Polarization (FP) assays with the fluorescein-labeled, disulfide-cyclized peptide ACRGDGWCG. In the assay, 6.5 nM of integrin $\alpha 5\beta 1$ 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. The assays were run 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.

[000533] IC₅₀ values of Tables 1 and 2 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

<i>Compound</i>	<i>$\alpha 5\beta 1$ IC₅₀</i>		<i>Compound</i>	<i>$\alpha 5\beta 1$ IC₅₀</i>		<i>Compound</i>	<i>$\alpha 5\beta 1$ IC₅₀</i>
1	B		120	C		239	A
2	A		121	B		240	B
3	C		122	C		241	A
4	B		123	C		242	C
5	B		124	A		243	A
6	C		125	C		244	C
7	C		126	B		245	C
8	B		127	C		246	A
9	C		128	C		247	C
10	B		129	B		248	C
11	B		130	A		249	A

<i>Compound</i>	<i>a5b1 IC₅₀</i>		<i>Compound</i>	<i>a5b1 IC₅₀</i>		<i>Compound</i>	<i>a5b1 IC₅₀</i>
12	B		131	B		250	B
13	C		132	A		251	A
14	B		133	B		252	C
15	B		134	B		253	C
16	A		135	B		254	A
17	B		136	A		255	A
18	B		137	A		256	B
19	B		138	C		257	B
20	A		139	B		258	C
21	C		140	B		259	C
22	B		141	B		260	A
23	B		142	B		261	A
24	B		143	B		262	C
25	C		144	A		263	C
26	A		145	C		264	A
27	B		146	C		265	A
28	B		147	B		266	C
29	C		148	C		267	A
30	C		149	C		268	C
31	C		150	C		269	B
32	B		151	C		270	B
33	C		152	A		271	A
34	C		153	C		272	C
35	C		154	B		273	B
36	C		155	C		274	A
37	B		156	A		275	C
38	A		157	C		276	A
39	C		158	C		277	B
40	A		159	B		278	A
41	C		160	A		279	A
42	A		161	C		280	B
43	B		162	B		281	C
44	A		163	C		282	B
45	B		164	C		283	A
46	A		165	B		284	C
47	C		166	A		285	C
48	B		167	C		286	C
49	A		168	A		287	A
50	C		169	C		288	C
51	B		170	A		289	B
52	C		171	A		290	A
53	B		172	B		291	B
54	A		173	C		292	A
55	B		174	B		293	C

<i>Compound</i>	<i>a5b1 IC₅₀</i>		<i>Compound</i>	<i>a5b1 IC₅₀</i>		<i>Compound</i>	<i>a5b1 IC₅₀</i>
56	A		175	C		294	A
57	B		176	A		295	C
58	B		177	C		296	B
59	C		178	A		297	C
60	A		179	B		298	B
61	C		180	C		299	B
62	C		181	B		300	A
63	C		182	B		301	A
64	A		183	A		302	C
65	B		184	C		303	B
66	A		185	C		304	C
67	B		186	B		305	C
68	A		187	C		306	B
69	C		188	B		307	C
70	B		189	B		308	A
71	C		190	A		309	C
72	B		191	C		310	B
73	C		192	B		311	A
74	B		193	B		312	C
75	C		194	B		313	B
76	B		195	A		314	A
77	C		196	C		315	C
78	B		197	C		316	B
79	C		198	B		317	C
80	B		199	C		318	B
81	B		200	A		319	C
82	A		201	C		320	C
83	C		202	C		321	A
84	A		203	A		322	C
85	C		204	C		323	A
86	A		205	B		324	C
87	C		206	C		325	C
88	A		207	A		326	B
89	B		208	C		327	A
90	B		209	A		328	C
91	B		210	B		329	A
92	A		211	B		330	C
93	C		212	B		331	C
94	C		213	A		332	B
95	B		214	B		333	A
96	A		215	A		334	C
97	C		216	C		335	B
98	C		217	C		336	A
99	C		218	A		337	A

<i>Compound</i>	<i>a5b1 IC₅₀</i>		<i>Compound</i>	<i>a5b1 IC₅₀</i>		<i>Compound</i>	<i>a5b1 IC₅₀</i>
100	A		219	C		338	B
101	B		220	B		339	B
102	A		221	A		340	A
103	C		222	C		341	C
104	B		223	C		342	A
105	A		224	C		343	B
106	B		225	B		344	A
107	C		226	B		345	B
108	B		227	A		346	A
109	C		228	C		347	C
110	B		229	A		348	A
111	B		230	C		349	B
112	A		231	C		350	A
113	A		232	B		351	C
114	B		233	A		352	A
115	A		234	B			
116	C		235	A			
117	A		236	A			
118	C		237	C			
119	B		238	C			

Table 2. Potency Data Table

<i>Compound</i>	<i>a5b1 IC₅₀</i>		<i>Compound</i>	<i>a5b1 IC₅₀</i>		<i>Compound</i>	<i>a5b1 IC₅₀</i>
353	B		367	A		381	A
354	B		368	B		382	C
355	C		369	B		383	A
356	B		370	C		384	B
357	A		371	C		385	A
358	C		372	C		386	C
359	B		373	B		387	B
360	B		374	C		388	C
361	C		375	B		389	A
362	B		376	C		390	B
363	C		377	C		391	A
364	A		378	B		392	B
365	A		379	A			
366	B		380	B			

[000534] 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.

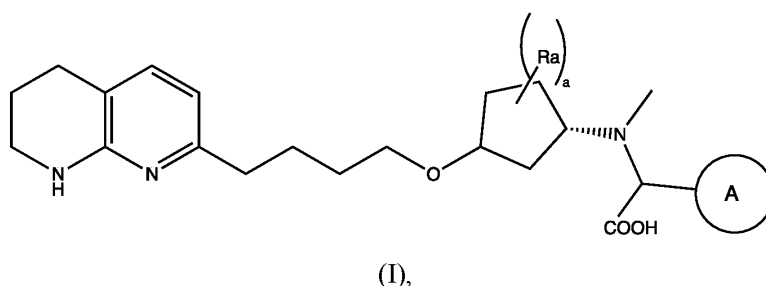
[000535] All references, patents or applications, U.S. or foreign, cited in the application are hereby incorporated by reference as if written herein in their entireties. Where any inconsistencies arise, material literally disclosed herein controls.

[000536] 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.

[000537] 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.

Enumerated Embodiments

Embodiment 1: In one aspect, the invention features a compound of Formula (I), or a pharmaceutically acceptable salt thereof:



wherein:

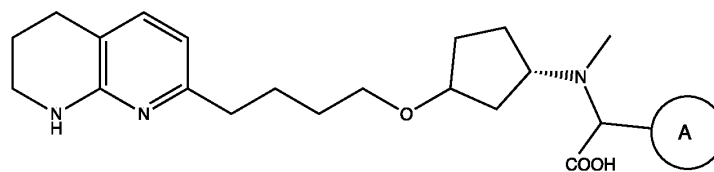


is a 3- to 15-member heterocyclyl ring structure optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆alkyloxy, a 3-8 member heterocyclyl ring structure, an aryl, or a 5- to 6-member heteroaryl, wherein the C₁₋₆ alkyl, the C₁₋₆alkyloxy, the 3-8 member heterocyclyl ring structure, the aryl, or the 5- to 6-member heteroaryl are optionally substituted with one or more halogen, C₁₋₄alkyloxy, or C₁₋₆ alkyl optionally substituted with one or more halogen;

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

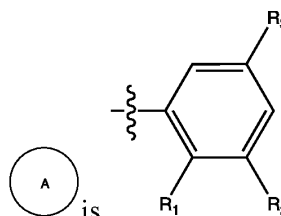
R_a is C₁₋₆ alkyl.

Embodiment 2: The compound of Embodiment 1, wherein the compound is a compound of Formula (I-A), or a pharmaceutically acceptable salt thereof.



(IA)

Embodiment 3: The compound of any one of Embodiments 1-2, wherein  is phenyl or a 6-member heteroaryl.



Embodiment 4: The compound of Embodiment 3, wherein  is

R_1 is C_{1-4} alkoxy; and R_2 is C_{1-4} alkyl optionally substituted with one or more halogen; or

R_1 and R_2 together form a fused 5- to 8-member heterocycloalkyl ring, a fused 5- to 6-member heteroaryl ring, a fused 7- to 15-member spirocyclic heterocycloalkyl ring system, wherein the fused ring is optionally substituted with halogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, or a 4- to 8-member heterocycloalkyl ring, wherein the C_{1-4} alkyl, the C_{3-6} cycloalkyl, or the 4- to 8-member heterocycloalkyl ring is optionally substituted with one or more halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

R_3 is C_{1-4} alkyl optionally substituted with one or more halogen;

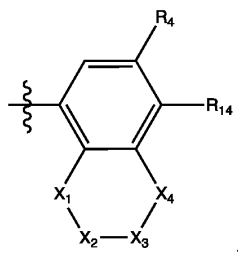
Embodiment 5: The compound of Embodiment 4, wherein

R_1 is methoxy;

R_2 is fluoro; and

R_3 is C_{1-4} alkyl optionally substituted with one or more fluoro.

Embodiment 6: The compound of Embodiment 4, wherein  is



wherein

R₄ and R₁₄ are each independently H, halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

X₁ is CR_{5a}R_{5b} or NR_{5c}

R_{5a} is H or a C₁₋₄ alkyl optionally substituted with one or more halogen, and R_{5b} is a C₁₋₄ alkyl or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen; or

R_{5a} and R_{5b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a spirocyclic C₃₋₆ cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 6-member spirocyclic heterocycloalkyl or a C₃₋₆ spirocyclic cycloalkyl optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{5c} is a C₁₋₄ alkyl or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen;

X₂ is CR_{6a}R_{6b}, -CH₂CR_{6a}R_{6b}, C=O, O or NR_{6c};

R_{6a} and R_{6b} are each independently H, a C₁₋₄ alkyl, a 5- to 6-member heteroaryl, a 6-member aryl, a C₃₋₇ cycloalkyl, or a 4- to 7-member heterocycloalkyl, wherein the C₁₋₄ alkyl, the 5- to 6-member heteroaryl, the 6-member aryl, the C₃₋₈ cycloalkyl, or the 4- to 7-member heterocycloalkyl is each optionally substituted with one or more halogen or C₁₋₄ alkyl;

R_{6c} is C₁₋₄ alkyl optionally substituted with one or more halogen

X₃ is a direct bond, CR_{7a}R_{7b}, O or NR_{7c};

R_{7a} and R_{7b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{7c} is a C₁₋₄ alkyl optionally substituted with one or more halogen;

X₄ is CR_{8a}R_{8b} or NR_{8c}

R_{8a} is H and R_{8b} is halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{8a} and R_{8b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a C₃₋₆ cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 8-member spirocyclic heterocycloalkyl or a C₃₋₇ spirocyclic cycloalkyl optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen; and

R_{8c} is H, C₁₋₄ alkyl, a 4- to 8-member heterocycloalkyl, or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl, the 4- to 8-member heterocycloalkyl, or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen;

provided that no two of both X₂ and X₃ comprise O or N heteroatoms and no two of X₃ and X₄ comprise O or N heteroatoms.

Embodiment 7: The compound of Embodiment 6, wherein

R₁₄ is H; and

X₁ is CR_{5a}R_{5b} and R_{5a} is H, and R_{5b} is methyl or cyclopropyl.

Embodiment 8: The compound of any one of Embodiments 6-7, wherein

R₄ is H, fluoro, or methyl;

X₁ is CR_{5a}R_{5b} and R_{5a} is H, and R_{5b} is methyl;

X₂ is O and X₃ is CR_{7a}R_{7b} and R_{7a} and R_{7b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen; or

X₃ is O and X₂ is CR_{6a}R_{7b} and R_{6a} and R_{6b} are each independently H; and

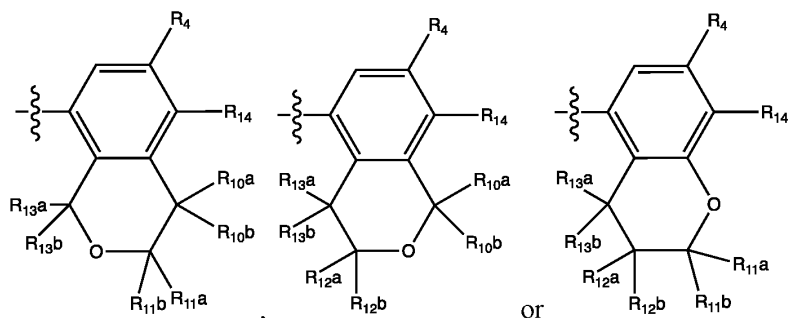
X₄ is CR_{8a}R_{8b} and

R_{8a} and R_{8b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen, or

R_{8a} and R_{8b} together form a 4- to 7-member heterocycloalkyl ring or a C₃₋₇ cycloalkyl ring, wherein the 4- to 7-member heterocycloalkyl or the C₃₋₇ cycloalkyl is optionally substituted with halogen, C₁₋₄ alkyl optionally substituted with one or more

halogen, a 4- to 7-member spirocyclic heterocycloalkyl, or a C₃₋₇ spirocyclic cycloalkyl, optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen.

Embodiment 9: The compound of Embodiment 6, wherein



wherein

R_{10a} and R_{10b} are each independently H, halogen, or a C₁₋₄ alkyl optionally substituted with one or more halogen; or R_{10a} and R_{10b} together form a spirocyclic C₃₋₆ cycloalkyl or a spirocyclic 6-member heterocycloalkyl;

R_{11a} and R_{11b} are each independently H, halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{12a} and R_{12b} are each independently H, halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{13a} is methyl, ethyl, or cyclopropyl;

R_{13b} is H;

R₁₄ is H, halogen, or a C₁₋₄ alkyl optionally substituted with one or more halogen.

Embodiment 10: The compound of Embodiment 9, wherein

R_{10a} and R_{10b} are each independently H or methyl;

R_{11a} and R_{11b} are each independently H, methyl, or ethyl;

R_{12a} and R_{12b} are each independently H or methyl;

R_{13a} is methyl, ethyl, or cyclopropyl;

R_{13b} is H;

R₁₄ is H, fluoro, or methyl.

Embodiment 11: The compound of Embodiment 10, wherein

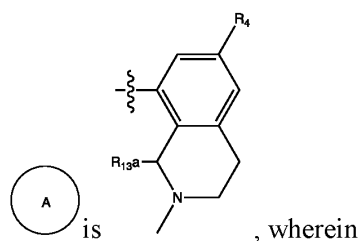
R_4 is H or fluoro;

R_{13a} is methyl, ethyl, or cyclopropyl; and

R_{14} is H.

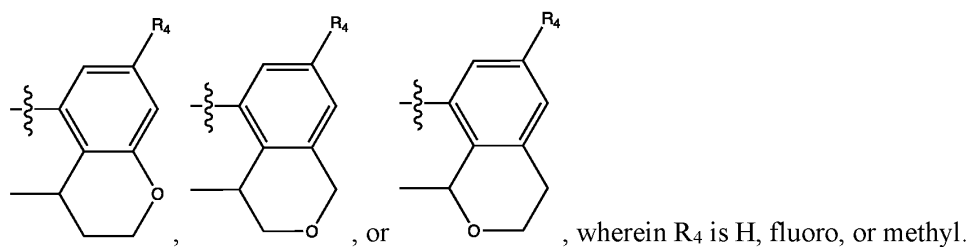
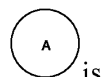
Embodiment 12: The compound of Embodiment 6, wherein X_2 is NR_{6c} and R_{6c} is C_{1-4} alkyl.

Embodiment 13: The compound of Embodiment 6, wherein



R_{13a} is H or methyl, and R_4 is H, F, or methyl.

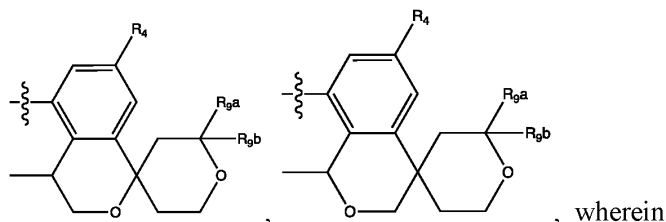
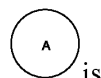
Embodiment 14: The compound of Embodiment 6, wherein



Embodiment 15: The compound of Embodiment 14, wherein R_{10a} , R_{10b} , and R_{11a} are each H or methyl.

Embodiment 16: The compound of Embodiment 14, wherein R_{11b} is H, methyl, or ethyl.

Embodiment 17: The compound of Embodiment 6, wherein



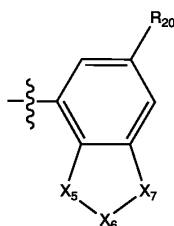
R_4 is H, halogen, or methyl optionally substituted with one or more halogen;

and

R_{9a} and R_{9b} are each independently H, halogen, or methyl optionally substituted with one or more halogen.

Embodiment 18: The compound of Embodiment 17, wherein R_4 is H, fluoro, or methyl; and R_{9a} and R_{9b} are each independently H, fluoro, chloro, or methyl optionally substituted with one or more fluoro.

Embodiment 19: The compound of Embodiment 4, wherein  is



R_{20} is H, halogen, a C_{1-4} alkyl or a C_{1-4} alkoxy, wherein the C_{1-4} alkyl and the C_{1-4} alkoxy are each optionally substituted with one or more halogen;

X_5 is $CR_{25a}R_{25b}$ or NR_{25c}

R_{25a} and R_{25b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or alkoxy; or

R_{25a} and R_{25b} together form a C_{3-6} cycloalkyl ring or a 4- to 6-member heterocyclyl ring, each optionally substituted with halogen, C_{1-4} alkyl, a spirocyclic C_{3-6} cycloalkyl, or a spirocyclic 4- to 6-member heterocyclyl ring, wherein the C_{1-4} alkyl, the spirocyclic C_{3-6} cycloalkyl or the spirocyclic 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen or C_{1-4} alkyl;

R_{25c} is C_{1-4} alkyl, a 5-6 member heteroaryl, or a C_6 aryl, wherein the C_{1-4} alkyl, the 5-6 member heteroaryl, or the C_6 aryl is optionally substituted with one or more halogen or C_{1-4} alkoxy;

X_6 is $CR_{26a}R_{26b}$ or $C=O$;

R_{26a} and R_{26b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkyl;

X_7 is $CR_{27a}R_{27b}$ or NR_{27c} ;

R_{27a} and R_{27b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen or alkoxy;

R_{27a} and R_{27b} together form a C₃₋₆ cycloalkyl ring or a 4- to 6-member heterocyclyl ring, wherein the C₃₋₆ cycloalkyl ring or the 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen, one or more C₁₋₄ alkyl, a spirocyclic C₃₋₆ cycloalkyl or a spirocyclic 4 to 6 member heterocyclyl ring, wherein the C₁₋₄ alkyl, the spirocyclic C₃₋₆ cycloalkyl, or the spirocyclic 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen or C₁₋₄ alkyl; and

R_{27c} is H, a C₁₋₄ alkyl, a C₃₋₆ cycloalkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, a 5-6 member heteroaryl, or a C₆ aryl, wherein the C₁₋₄ alkyl, the C₃₋₆ cycloalkyl, the 4- to 6-member heterocycloalkyl, the 5- to 11-member spirocyclic heterocycloalkyl, the 5-6 member heteroaryl, or the C₆ aryl is optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

provided that only one of X₅ and X₇ comprise a N heteroatom.

Embodiment 20: The compound of Embodiment 19, wherein

R₂₀ is H, halogen, a C₁₋₄ alkyl, or a C₁₋₄ alkoxy, wherein the C₁₋₄ alkyl and the C₁₋₄ alkoxy is optionally substituted with one or more halogen;

X₅ is CR_{25a}R_{25b}

R_{25a} and R_{25b} are each independently methyl; or

R_{25a} and R_{25b} together form a cyclopropyl;

X₆ is C=O;

R_{26a} and R_{26b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen or C₁₋₄ alkyl;

X₇ is NR_{27c}; and

R_{27c} is a C₁₋₄ alkyl, a C₃₋₆ cycloalkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, a 5-6 member heteroaryl, or a C₆ aryl, wherein the C₁₋₄ alkyl, the C₃₋₆ cycloalkyl, the 4- to 6-member heterocycloalkyl, the 5- to 11-member spirocyclic heterocycloalkyl, the 5-6 member heteroaryl, or the C₆ aryl is

optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

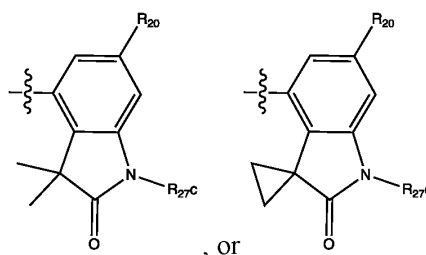
Embodiment 21: The compound of Embodiment 20, wherein R_{27c} is a C₁₋₄ alkyl.

Embodiment 22: The compound of Embodiment 20, wherein R_{27c} is a 5-member heteroaryl.

Embodiment 23: The compound of Embodiment 20, wherein R_{27c} is a C₃₋₆ cycloalkyl optionally substituted with one or more halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen.

Embodiment 24: The compound of Embodiment 20, wherein R_{27c} is a C₁₋₄ alkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, wherein the C₁₋₄ alkyl, the 4- to 7-member heterocycloalkyl, and the 5- to 11-member spirocyclic heterocycloalkyl is optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen.

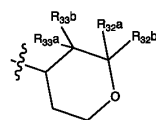
Embodiment 25: The compound of Embodiment 24, wherein  is



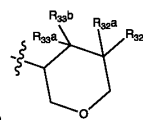
wherein R₂₀ is H, fluoro, methyl, ethyl, methoxy, -CH₂-O-CH₃, or -CF₃.

Embodiment 26: The compound of Embodiment 25, wherein R_{27c} is a tetrahydropyran optionally substituted by one or more methyl or fluoro.

Embodiment 27: The compound of Embodiment 25, wherein R_{27c} is



, wherein

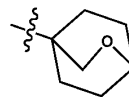


or

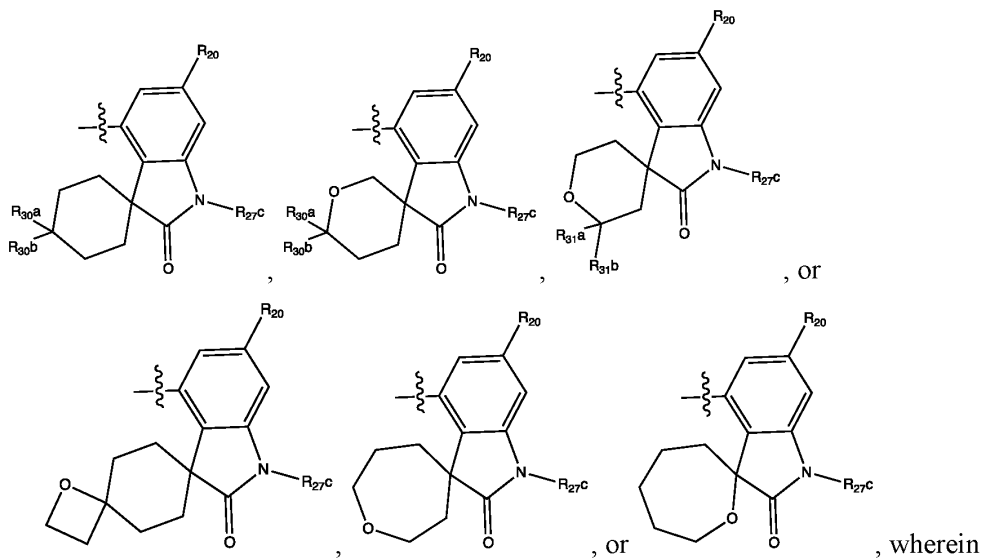
R_{32a}, R_{32b}, R_{33a} and R_{33b} are each independently H, methyl, or fluoro; or

one of R_{32a} and R_{32b} or R_{33a} and R_{33b} together form a spirocyclic C₃₋₆ cycloalkyl or a spirocyclic 3- to 6-member heterocyclic ring.

Embodiment 28: The compound of Embodiment 25, wherein R_{27c} is



Embodiment 29: The compound of Embodiment 19, wherein  is



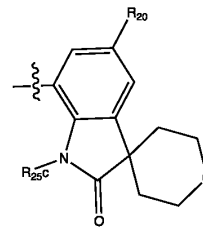
R_{30a}, R_{30b}, R_{31a}, and R_{31b} are each independently H, fluoro, or methyl;

R₂₀ is H, fluoro, methyl, ethyl, methoxy, -CH₂-O-CH₃, or -CF₃; and

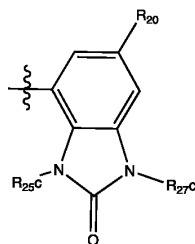
R_{27c} is methyl.

Embodiment 30: The compound of Embodiment 25, wherein R_{27c} is a C₁₋₄ alkyl.

Embodiment 31: The compound of Embodiment 19, wherein  is



Embodiment 32: The compound of Embodiment 4, wherein  is



wherein

R_{20} is H, halogen, a C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy, a C_{1-4} alkyl optionally substituted with a 4- to 6-member heterocyclyl or one or more halogen.

Embodiment 33: The compound of Embodiment 32, wherein

R_{25C} is a C_{1-4} alkyl; and

R_{27C} is a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkoxy, a C_{3-6} cycloalkyl or a 4- to 6-member heterocycloalkyl, wherein the C_{3-6} cycloalkyl or the 4- to 6-member heterocycloalkyl is optionally substituted with a C_{1-4} alkyl optionally substituted with one or more halogen.

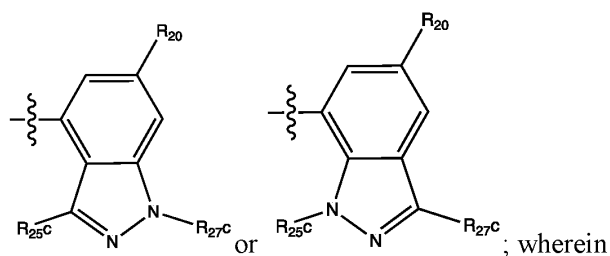
Embodiment 34: The compound of Embodiment 32, wherein

R_{27C} is a C_{1-4} alkyl; and

R_{25C} is a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkoxy, a C_{3-6} cycloalkyl or a 4- to 6-member heterocycloalkyl, wherein the C_{3-6} cycloalkyl or the 4- to 6-member heterocycloalkyl is optionally substituted with a C_{1-4} alkyl optionally substituted with one or more halogen.

Embodiment 35: The compound of any one of Embodiments 32-34, wherein R_{20} is H or methyl.

Embodiment 36: The compound of Embodiment 19, wherein  is

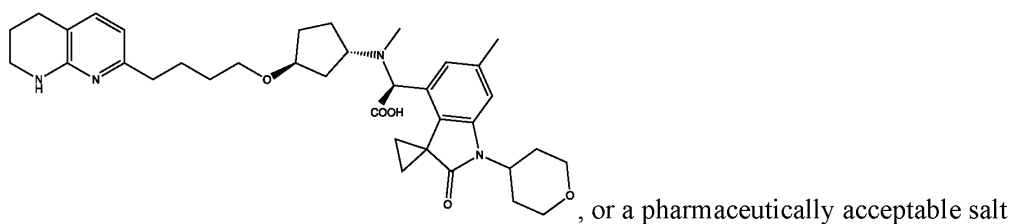


R₂₀ is H, halogen, a C₁₋₄ alkoxy optionally substituted with C₁₋₄ alkoxy, C₁₋₄ alkyl optionally substituted with a 4- to 6-member heterocyclyl or one or more halogen;

R_{25c} is a C₁₋₄ alkyl; and

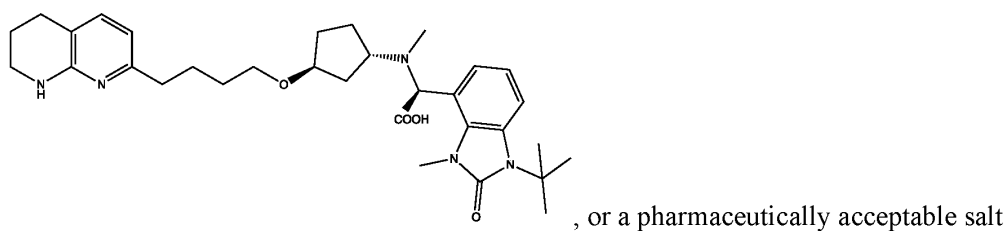
R_{27c} is a 4- to 6-member heterocyclyl or a C₃₋₆ cycloalkyl, wherein the 4- to 6-member heterocyclyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl.

Embodiment 37: A compound of the chemical formula



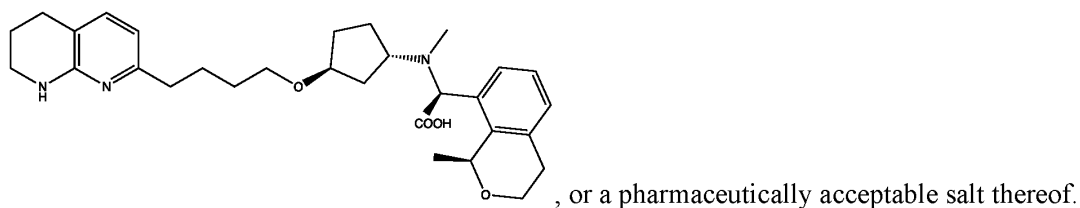
thereof.

Embodiment 38: A compound of the chemical formula

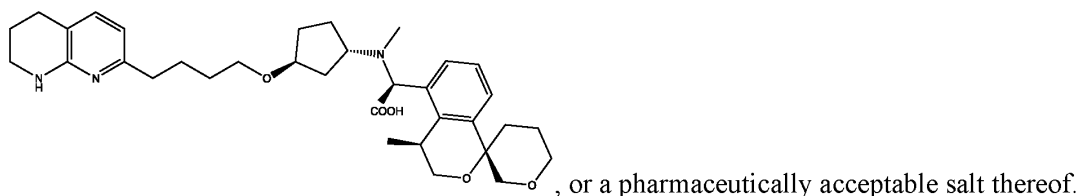


thereof.

Embodiment 39: A compound of the chemical formula



Embodiment 40: A compound of the chemical formula



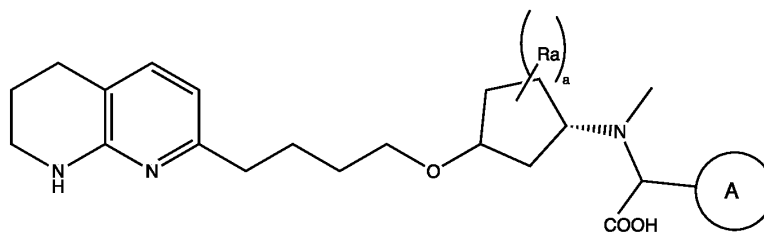
Embodiment 41: A compound selected from the group consisting of the compounds in Figure 1, or a pharmaceutically acceptable salt thereof.

Equivalents and Scope

[000538] 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:



(I),

wherein:

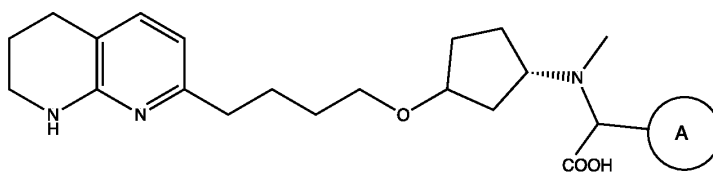
 is a 6- to 12-member aryl ring structure or a 3- to 19-member heterocyclyl ring structure,

wherein  is optionally substituted with halogen, C₁₋₆ alkyl, C₁₋₆alkyloxy, a 3-8 member heterocyclyl ring structure, an aryl, or a 5- to 6-member heteroaryl, wherein the C₁₋₆ alkyl, the C₁₋₆alkyloxy, the 3-8 member heterocyclyl ring structure, the aryl, or the 5- to 6-member heteroaryl are optionally substituted with one or more halogen, C₁₋₄alkyloxy, or C₁₋₆ alkyl optionally substituted with one or more halogen;

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

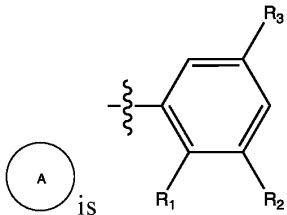
R_a is C₁₋₆ alkyl.

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



(IA).

3. The compound of any one of claims 1-2, wherein  is phenyl or a 6-member heteroaryl.

4. The compound of any one of claims 1-3, wherein  is

R_1 is C_{1-4} alkoxy; and R_2 is C_{1-4} alkyl optionally substituted with one or more halogen; or

 is a 9- to 19-member heterocyclyl when R_1 and R_2 are taken together to form a fused 5- to 8-member heterocycloalkyl ring, a fused 5- to 6-member heteroaryl ring, a fused 7- to 15-member spirocyclic heterocycloalkyl ring system, wherein the fused ring is optionally substituted with halogen, C_{1-4} alkyl, C_{3-6} cycloalkyl, or a 4- to 8-member heterocycloalkyl ring, wherein the C_{1-4} alkyl, the C_{3-6} cycloalkyl, or the 4- to 8-member heterocycloalkyl ring is optionally substituted with one or more halogen or C_{1-4} alkyl optionally substituted with one or more halogen; and

R_3 is C_{1-4} alkyl optionally substituted with one or more halogen.

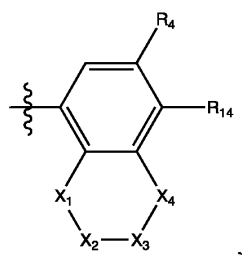
5. The compound of claim 4, wherein

R_1 is methoxy;

R_2 is fluoro; and

R_3 is C_{1-4} alkyl optionally substituted with one or more fluoro.

6. The compound of any one of claims 1-3, wherein  is



wherein

R_4 and R_{14} are each independently H, halogen or C_{1-4} alkyl optionally substituted with one or more halogen;

X₁ is CR_{5a}R_{5b} or NR_{5c}

R_{5a} is H or a C₁₋₄ alkyl optionally substituted with one or more halogen, and R_{5b} is a C₁₋₄ alkyl or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen; or

R_{5a} and R_{5b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a spirocyclic C₃₋₆ cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 6-member spirocyclic heterocycloalkyl or a C₃₋₆ spirocyclic cycloalkyl optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{5c} is a C₁₋₄ alkyl or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen;

X₂ is CR_{6a}R_{6b}, -CH₂CR_{6a}R_{6b}, C=O, O or NR_{6c};

R_{6a} and R_{6b} are each independently H, a C₁₋₄ alkyl, a 5- to 6-member heteroaryl, a 6-member aryl, a C₃₋₇ cycloalkyl, or a 4- to 7-member heterocycloalkyl, wherein the C₁₋₄ alkyl, the 5- to 6-member heteroaryl, the 6-member aryl, the C₃₋₈ cycloalkyl, or the 4- to 7-member heterocycloalkyl is each optionally substituted with one or more halogen or C₁₋₄ alkyl;

R_{6c} is C₁₋₄ alkyl optionally substituted with one or more halogen

X₃ is a direct bond, CR_{7a}R_{7b}, O or NR_{7c};

R_{7a} and R_{7b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{7c} is a C₁₋₄ alkyl optionally substituted with one or more halogen;

X₄ is CR_{8a}R_{8b} or NR_{8c}

R_{8a} is H and R_{8b} is halogen or a C₁₋₄ alkyl optionally substituted with one or more halogen;

R_{8a} and R_{8b} together form a spirocyclic 3- to 8-member heterocycloalkyl or a C₃₋₆ cycloalkyl, wherein the 3- to 8-member heterocycloalkyl or the C₃₋₆ cycloalkyl is optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen, a

4- to 8-member spirocyclic heterocycloalkyl or a C₃₋₇ spirocyclic cycloalkyl optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen; and

R_{8c} is H, C₁₋₄ alkyl, a 4- to 8-member heterocycloalkyl, or a C₃₋₆ cycloalkyl, wherein the C₁₋₄ alkyl, the 4- to 8-member heterocycloalkyl, or the C₃₋₆ cycloalkyl is optionally substituted with one or more halogen;

provided that no two of both X₂ and X₃ comprise O or N heteroatoms and no two of X₃ and X₄ comprise O or N heteroatoms.

7. The compound of claim 6, wherein

R₁₄ is H; and

X₁ is CR_{5a}R_{5b} and R_{5a} is H, and R_{5b} is methyl or cyclopropyl.

8. The compound of any one of claims 6-7, wherein

R₄ is H, fluoro, or methyl;

X₁ is CR_{5a}R_{5b} and R_{5a} is H, and R_{5b} is methyl;

X₂ is O and X₃ is CR_{7a}R_{7b} and R_{7a} and R_{7b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen; or

X₃ is O and X₂ is CR_{6a}R_{7b} and R_{6a} and R_{6b} are each independently H; and

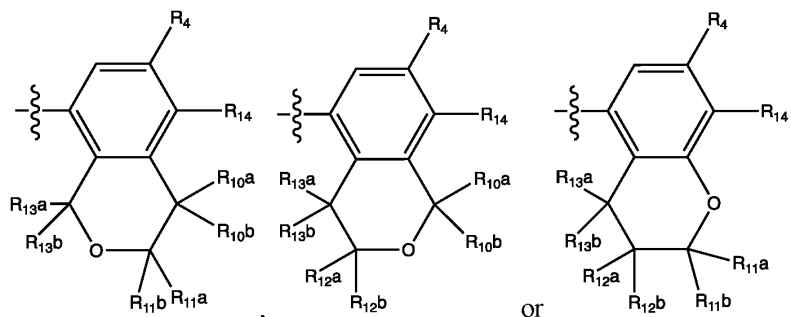
X₄ is CR_{8a}R_{8b} and

R_{8a} and R_{8b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen, or

R_{8a} and R_{8b} together form a 4- to 7-member heterocycloalkyl ring or a C₃₋₇ cycloalkyl ring, wherein the 4- to 7-member heterocycloalkyl or the C₃₋₇ cycloalkyl is optionally substituted with halogen, C₁₋₄ alkyl optionally substituted with one or more halogen, a 4- to 7-member spirocyclic heterocycloalkyl, or a C₃₋₇ spirocyclic cycloalkyl, optionally substituted with C₁₋₄ alkyl optionally substituted with one or more halogen.

9. The compound of claim 6, or a pharmaceutically acceptable salt thereof, wherein





wherein

R_{10a} and R_{10b} are each independently H, halogen, or a C_{1-4} alkyl optionally substituted with one or more halogen; or R_{10a} and R_{10b} together form a spirocyclic C_{3-6} cycloalkyl or a spirocyclic 6-member heterocycloalkyl;

R_{11a} and R_{11b} are each independently H, halogen or a C_{1-4} alkyl optionally substituted with one or more halogen;

R_{12a} and R_{12b} are each independently H, halogen or a C_{1-4} alkyl optionally substituted with one or more halogen;

R_{13a} is methyl, ethyl, or cyclopropyl;

R_{13b} is H;

R_{14} is H, halogen, or a C_{1-4} alkyl optionally substituted with one or more halogen.

10. The compound of claim 9, wherein

R_{10a} and R_{10b} are each independently H or methyl;

R_{11a} and R_{11b} are each independently H, methyl, or ethyl;

R_{12a} and R_{12b} are each independently H or methyl;

R_{13a} is methyl, ethyl, or cyclopropyl;

R_{13b} is H;

R_{14} is H, fluoro, or methyl.

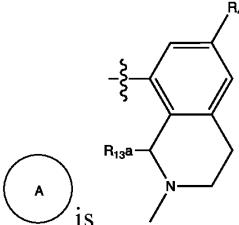
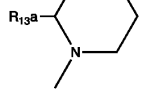
11. The compound of claim 10, wherein

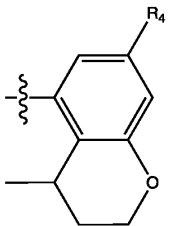
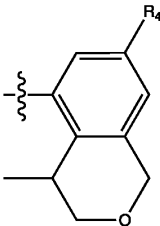
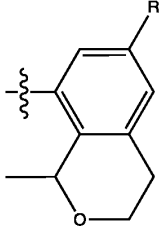
R_4 is H or fluoro;

R_{13a} is methyl, ethyl, or cyclopropyl; and

R_{14} is H.

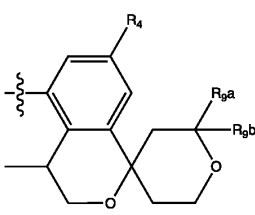
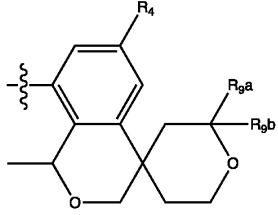
12. The compound of claim 6, wherein X_2 is NR_{6c} and R_{6c} is C_{1-4} alkyl.

13. The compound of claim 6, wherein  is , wherein R_{13a} is H or methyl, and R_4 is H, F, or methyl.

14. The compound of claim 6, wherein  is , , or , wherein R_4 is H, fluoro, or methyl.

15. The compound of claim 14, wherein R_{10a} , R_{10b} , and R_{11a} are each H or methyl.

16. The compound of claim 14, wherein R_{11b} is H, methyl, or ethyl.

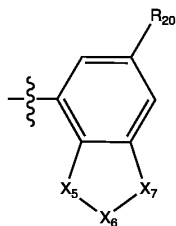
17. The compound of claim 6, wherein  is , , wherein

R_4 is H, halogen, or methyl optionally substituted with one or more halogen;
and

R_{9a} and R_{9b} are each independently H, halogen, or methyl optionally substituted with one or more halogen.

18. The compound of claim 17, wherein R_4 is H, fluoro, or methyl; and R_{9a} and R_{9b} are each independently H, fluoro, chloro, or methyl optionally substituted with one or more fluoro.

19. The compound of any one of claims 1-4, wherein  is



R_{20} is H, halogen, a C_{1-4} alkyl or a C_{1-4} alkoxy, wherein the C_{1-4} alkyl and the C_{1-4} alkoxy are each optionally substituted with one or more halogen;

X_5 is $CR_{25a}R_{25b}$ or NR_{25c}

R_{25a} and R_{25b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or alkoxy; or

R_{25a} and R_{25b} together form a C_{3-6} cycloalkyl ring or a 4- to 6-member heterocyclyl ring, each optionally substituted with halogen, C_{1-4} alkyl, a spirocyclic C_{3-6} cycloalkyl, or a spirocyclic 4- to 6-member heterocyclyl ring, wherein the C_{1-4} alkyl, the spirocyclic C_{3-6} cycloalkyl or the spirocyclic 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen or C_{1-4} alkyl;

R_{25c} is C_{1-4} alkyl, a 5-6 member heteroaryl, or a C_6 aryl, wherein the C_{1-4} alkyl, the 5-6 member heteroaryl, or the C_6 aryl is optionally substituted with one or more halogen or C_{1-4} alkoxy;

X_6 is $CR_{26a}R_{26b}$ or $C=O$;

R_{26a} and R_{26b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkyl;

X_7 is $CR_{27a}R_{27b}$ or NR_{27c} ;

R_{27a} and R_{27b} are each independently H or a C_{1-4} alkyl optionally substituted with one or more halogen or alkoxy;

R_{27a} and R_{27b} together form a C₃₋₆ cycloalkyl ring or a 4- to 6-member heterocyclyl ring, wherein the C₃₋₆ cycloalkyl ring or the 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen, one or more C₁₋₄ alkyl, a spirocyclic C₃₋₆ cycloalkyl or a spirocyclic 4 to 6 member heterocyclyl ring, wherein the C₁₋₄ alkyl, the spirocyclic C₃₋₆ cycloalkyl, or the spirocyclic 4- to 6-member heterocyclyl ring is optionally substituted with one or more halogen or C₁₋₄ alkyl; and

R_{27c} is H, a C₁₋₄ alkyl, a C₃₋₆ cycloalkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, a 5-6 member heteroaryl, or a C₆ aryl, wherein the C₁₋₄ alkyl, the C₃₋₆ cycloalkyl, the 4- to 6-member heterocycloalkyl, the 5- to 11-member spirocyclic heterocycloalkyl, the 5-6 member heteroaryl, or the C₆ aryl is optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

provided that only one of X₅ and X₇ comprise a N heteroatom.

20. The compound of claim 19, wherein

R₂₀ is H, halogen, a C₁₋₄ alkyl, or a C₁₋₄ alkoxy, wherein the C₁₋₄ alkyl and the C₁₋₄ alkoxy is optionally substituted with one or more halogen;

X₅ is CR_{25a}R_{25b}

R_{25a} and R_{25b} are each independently methyl; or

R_{25a} and R_{25b} together form a cyclopropyl;

X₆ is C=O;

R_{26a} and R_{26b} are each independently H or a C₁₋₄ alkyl optionally substituted with one or more halogen or C₁₋₄ alkyl;

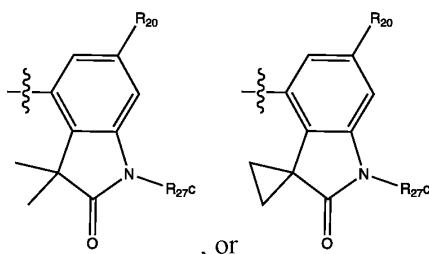
X₇ is NR_{27c}; and

R_{27c} is a C₁₋₄ alkyl, a C₃₋₆ cycloalkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, a 5-6 member heteroaryl, or a C₆ aryl, wherein the C₁₋₄ alkyl, the C₃₋₆ cycloalkyl, the 4- to 6-member heterocycloalkyl, the 5- to 11-member spirocyclic heterocycloalkyl, the 5-6 member heteroaryl, or the C₆ aryl is optionally substituted with one or more halogen or C₁₋₄ alkyl optionally substituted with one or more halogen;

21. The compound of claim 20, wherein R_{27c} is a C₁₋₄ alkyl.

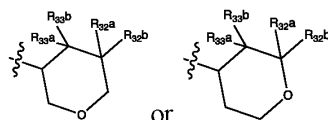
22. The compound of claim 20, wherein R_{27c} is a 5-member heteroaryl.
23. The compound of claim 20, wherein R_{27c} is a C_{3-6} cycloalkyl optionally substituted with one or more halogen or a C_{1-4} alkyl optionally substituted with one or more halogen.
24. The compound of claim 20, wherein R_{27c} is a C_{1-4} alkyl, a 4- to 7-member heterocycloalkyl, or a 5- to 11-member spirocyclic heterocycloalkyl, wherein the C_{1-4} alkyl, the 4- to 7-member heterocycloalkyl, and the 5- to 11-member spirocyclic heterocycloalkyl is optionally substituted with one or more halogen or C_{1-4} alkyl optionally substituted with one or more halogen.

25. The compound of claim 24, wherein  is



wherein R_{20} is H, fluoro, methyl, ethyl, methoxy, $-\text{CH}_2\text{-O-CH}_3$, or $-\text{CF}_3$.

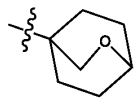
26. The compound of claim 25, wherein R_{27c} is a tetrahydropyan optionally substituted by one or more methyl or fluoro.



27. The compound of claim 25, wherein R_{27c} is  or , wherein

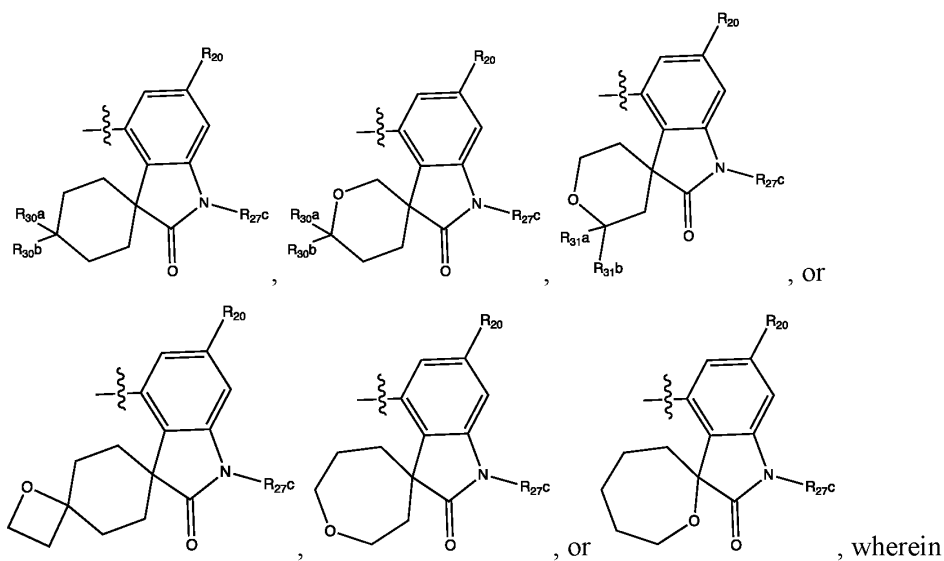
R_{32a} , R_{32b} , R_{33a} and R_{33b} are each independently H, methyl, or fluoro; or

one of R_{32a} and R_{32b} or R_{33a} and R_{33b} together form a spirocyclic C_{3-6} cycloalkyl or a spirocyclic 3- to 6-member heterocyclic ring.



28. The compound of claim 25, wherein R_{27c} is .

29. The compound of claim 19, wherein  is

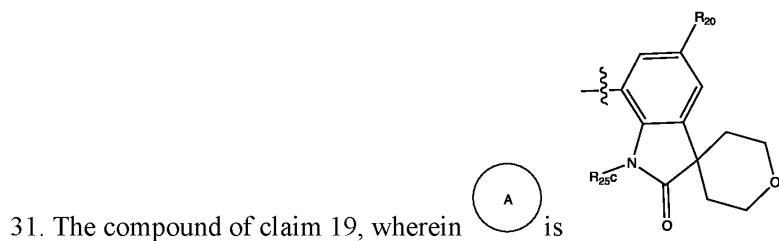


R_{30a} , R_{30b} , R_{31a} , and R_{31b} are each independently H, fluoro, or methyl;

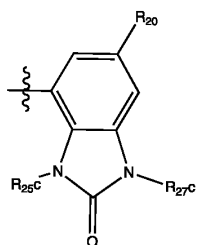
R_{20} is H, fluoro, methyl, ethyl, methoxy, $-\text{CH}_2\text{-O-CH}_3$, or $-\text{CF}_3$; and

R_{27c} is methyl.

30. The compound of claim 25, wherein R_{27c} is a C_{1-4} alkyl.



32. The compound of any one of claims 1-4, wherein  is



wherein

R_{20} is H, halogen, a C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy, a C_{1-4} alkyl optionally substituted with a 4- to 6-member heterocyclyl or one or more halogen.

33. The compound of claim 32, wherein

R_{25c} is a C_{1-4} alkyl; and

R_{27c} is a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkoxy, a C_{3-6} cycloalkyl or a 4- to 6-member heterocycloalkyl, wherein the C_{3-6} cycloalkyl or the 4- to 6-member heterocycloalkyl is optionally substituted with a C_{1-4} alkyl optionally substituted with one or more halogen.

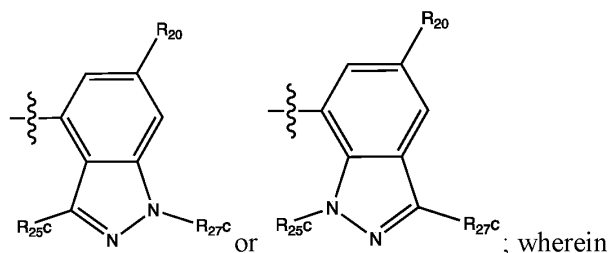
34. The compound of claim 32, wherein

R_{27c} is a C_{1-4} alkyl; and

R_{25c} is a C_{1-4} alkyl optionally substituted with one or more halogen or C_{1-4} alkoxy, a C_{3-6} cycloalkyl or a 4- to 6-member heterocycloalkyl, wherein the C_{3-6} cycloalkyl or the 4- to 6-member heterocycloalkyl is optionally substituted with a C_{1-4} alkyl optionally substituted with one or more halogen.

35. The compound of any one of claims 32-34, wherein R_{20} is H or methyl.

36. The compound of claim 19, wherein  is

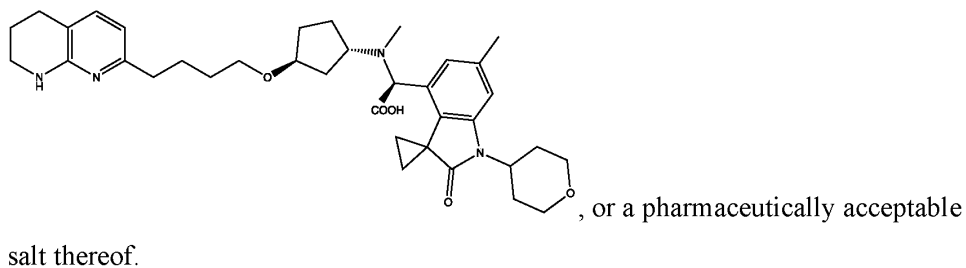


R_{20} is H, halogen, a C_{1-4} alkoxy optionally substituted with C_{1-4} alkoxy, C_{1-4} alkyl optionally substituted with a 4- to 6-member heterocyclyl or one or more halogen;

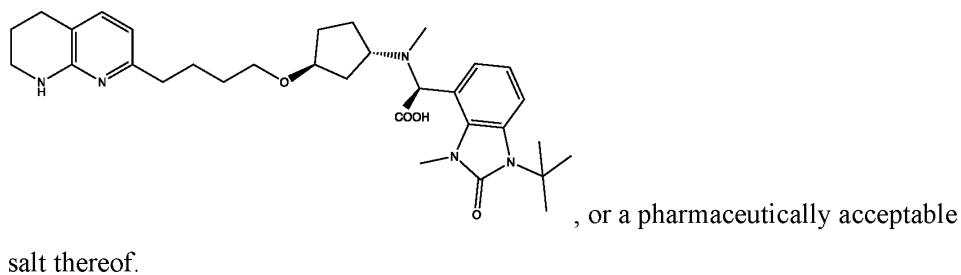
R_{25c} is a C_{1-4} alkyl; and

R_{27c} is a 4- to 6-member heterocyclyl or a C_{3-6} cycloalkyl, wherein the 4- to 6-member heterocyclyl or the C_{3-6} cycloalkyl is optionally substituted with C_{1-4} alkyl.

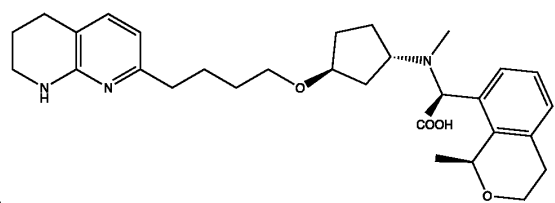
37. A compound of the chemical formula



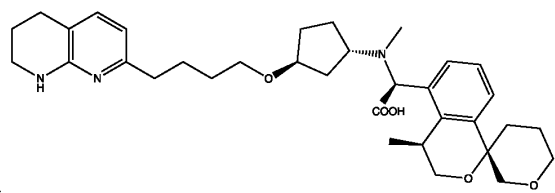
38. A compound of the chemical formula



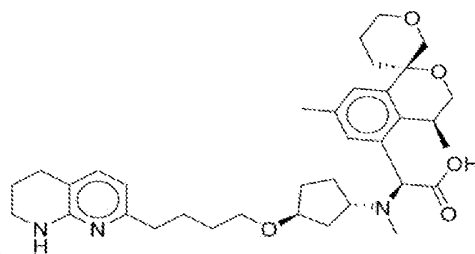
39. A compound of the chemical formula
or a pharmaceutically acceptable salt thereof.

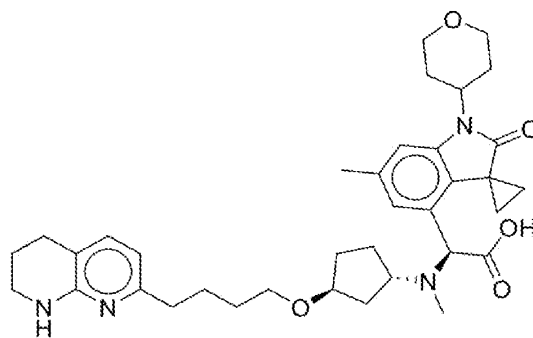


40. A compound of the chemical formula
or a pharmaceutically acceptable salt thereof.

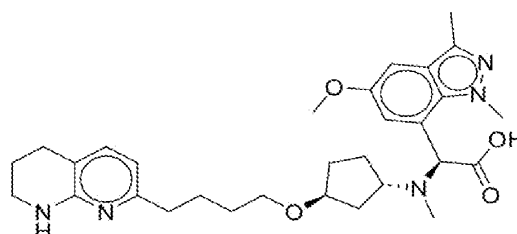


41. A compound of the chemical formula
pharmaceutically acceptable salt thereof.

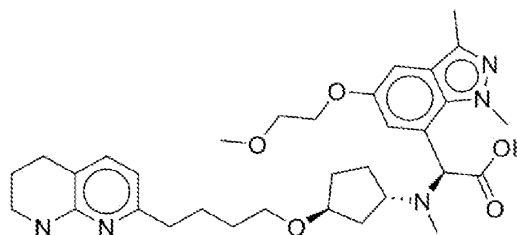




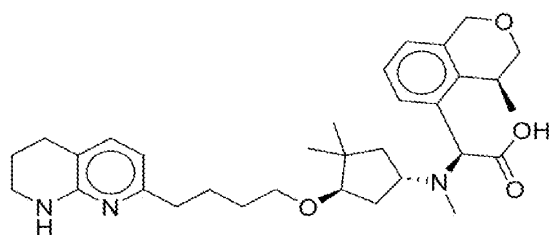
42. A compound of the chemical formula
or a pharmaceutically acceptable salt thereof.



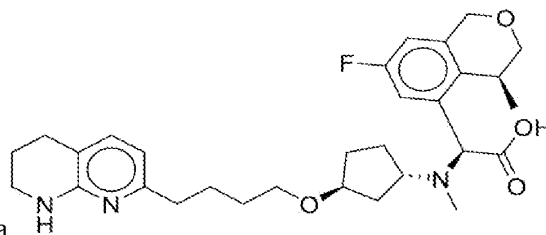
43. A compound of the chemical formula
a pharmaceutically acceptable salt thereof.



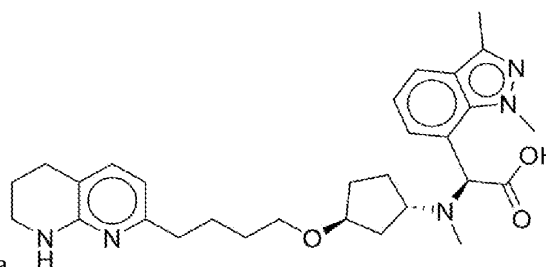
44. A compound of the chemical formula
a pharmaceutically acceptable salt thereof.



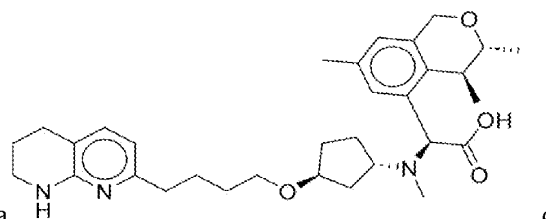
45. A compound of the chemical formula
or a pharmaceutically acceptable salt thereof.



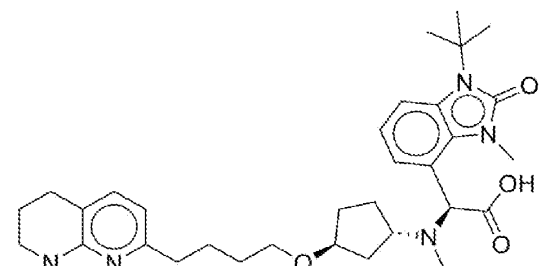
46. A compound of the chemical formula
or a pharmaceutically acceptable salt thereof.



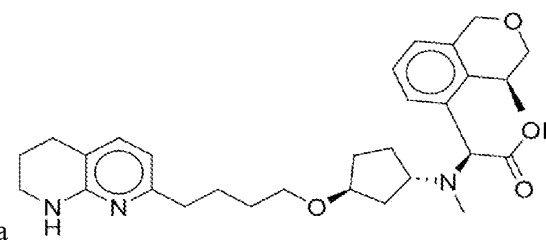
47. A compound of the chemical formula
or a pharmaceutically acceptable salt thereof.



48. A compound of the chemical formula
a pharmaceutically acceptable salt thereof.



49. A compound of the chemical formula
a pharmaceutically acceptable salt thereof.



50. A compound of the chemical formula
or a pharmaceutically acceptable salt thereof.

51. A compound selected from the group consisting of the compounds in Figure 1, or a pharmaceutically acceptable salt thereof.
52. A compound selected from the group consisting of the compounds in Table 3, or a pharmaceutically acceptable salt thereof.