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(54) Title: CHROMAN DERIVATIVES AS ESTROGEN RECEPTOR DEGRADERS

(57) Abstract: Described herein are compounds of Formula (I) and pharmaceutically acceptable salts, solvates, or stereoisomers thereof, as well as their uses (e.g., as estrogen receptor degraders).

WO 2024/015409 A1

CHROMAN DERIVATIVES AS ESTROGEN RECEPTOR DEGRADERS

RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No. 63/388,297, filed July 12, 2022; and U.S. Provisional Application No. 63/408,601, filed September 21, 2022; the contents of each of which are incorporated herein by reference in their entireties.

BACKGROUND

[0002] Estrogen receptors (ERs) belong to the steroid/nuclear receptor superfamily involved in the regulation of eukaryotic gene expression, cellular proliferation, and differentiation in target tissues. ERs are in two forms: the estrogen receptor alpha (ER α) and the estrogen receptor beta (ER β) respectively encoded by the ESR1 and the ESR2 genes. ER α and ER β are ligand-activated transcription factors which are activated by the hormone estrogen (17 β -estradiol). In the absence of hormone, ERs are largely located in the cytosol of the cell. When the hormone estrogen binds to ERs, ERs migrate from the cytosol to the nucleus of the cell, form dimers and then bind to specific genomic sequences called Estrogen Response Elements (ERE). The DNA/ER complex interacts with co-regulators to modulate the transcription of target genes. ER α is mainly expressed in reproductive tissues such as uterus, ovary, breast, bone, and white adipose tissue. It is well known that deregulation of ER signaling, specifically through ER α , results in uncontrolled cellular proliferation which eventually results into cancer. ER+ breast cancer accounts for approximately 75% of all breast cancers diagnosed, as well as some ovarian and endometrial cancers.

[0003] Current therapy for ER+ breast cancer including agents that inhibit the ER activity through direct binding to the ligand binding domain of the receptor (e.g., tamoxifen); blocking the synthesis of estrogen (e.g., aromatase inhibitor such as anastrozole and letrozole); or inducing the degradation of ER. Selective estrogen receptor degraders (SERD) are small molecules that target ER α for proteasome-dependent degradation. Fulvestrant is the only SERD that has been approved for the treatment of postmenopausal women with advanced ER+ breast cancer with standard endocrine therapies. Because it has poor solubility and is not orally bioavailable, fulvestrant is administered clinically by a monthly intramuscular injection. To address the shortcomings of fulvestrant, oral bioavailable SERDs are being developed. However, the SERDs are only able to achieve partial degradation of the ER protein despite they are typically potent and effective in inducing degradation of ER protein in ER+ breast cancer cells.

[0004] It is believed that ER α degradation may occur when both ER α and a ubiquitin ligase (e.g., cereblon E3 ligase (CRBN)) are bound and brought into close proximity for ubiquitination and subsequent degradation by proteasomes. A new approach would be to utilize the naturally occurring cellular ubiquitin-mediated degradation to develop a completely new class of therapeutics for the treatment of ER+ metastatic breast cancer with nearly complete degradation of ER protein.

SUMMARY

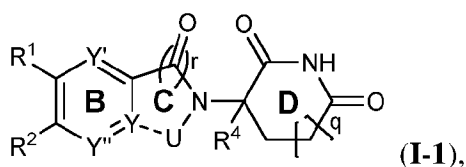
[0005] In certain aspects, the present disclosure provides compounds of Formula **I**:

T-L-C (I),

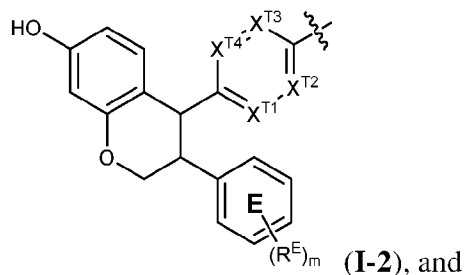
and pharmaceutically acceptable salts, solvates, or stereoisomers thereof,

wherein:

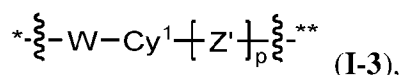
C is of Formula **I-1**



T is of Formula **I-2**:



L is of Formula **I-3**:



wherein each of the variables in Formulae **I**, **I-1**, **I-2**, and **I-3**, is described, embodied, and exemplified herein.

[0006] In certain aspects, the present disclosure provides pharmaceutical compositions comprising a compound disclosed herein, and a pharmaceutically acceptable excipient.

[0007] In certain aspects, the present disclosure provides methods of degrading an estrogen receptor in a subject, comprising administering to the subject a compound disclosed herein.

[0008] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for degrading an estrogen receptor in a subject.

[0009] In certain aspects, the present disclosure provides compounds disclosed herein for use in degrading an estrogen receptor in a subject.

[0010] In certain aspects, the present disclosure provides methods of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject a compound disclosed herein (e.g., in a therapeutically effective amount).

[0011] In certain aspects, the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a compound disclosed herein (e.g., in a therapeutically effective amount).

[0012] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder in a subject in need thereof.

[0013] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

[0014] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating or preventing a disease or disorder in a subject in need thereof.

[0015] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorder in a subject in need thereof.

DETAILED DESCRIPTION

[0016] The present disclosure relates to compounds and methods of degrading an estrogen receptor comprising contacting the estrogen receptor with a therapeutically effective amount of an estrogen receptor degrader disclosed herein. The invention also relates to methods of treating an estrogen receptor-mediated disease or condition in a subject in need thereof by administering a therapeutically effective amount of an estrogen receptor degrader disclosed herein. The present disclosure further relates to methods of treating an estrogen receptor-mediated disease or condition in a subject in need thereof, comprising administering a pharmaceutical composition comprising a therapeutically effective amount of an estrogen receptor degrader disclosed herein.

Compounds of the Application

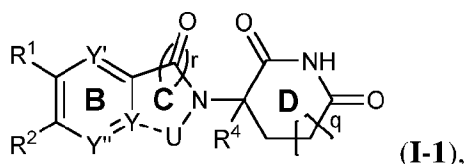
[0017] In certain aspects, the present disclosure provides compounds of Formula **I**:

T-L-C (I),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof,

wherein:

C is of Formula **I-1**



wherein:

R^1 is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R^2 is *-Cy²-, wherein * denotes attachment to **L**;

Cy² is 3- to 12-membered heterocyclylene, wherein the heterocyclylene is optionally substituted with one or more R^u; or

R^1 and R^2 , together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted C₃₋₁₂ carbocycle or 5- to 16-membered heterocycle;

Y'' is N or CR³;

R^3 is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl,

alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; or

R^2 and R^3 , together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted 5- to 16-membered heterocycle;

provided that R^1 and R^2 , and R^2 and R^3 , do not both form Ring A attached to **L**;

Y' is N or $CR^{Y'}$;

$R^{Y'}$ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

--- denotes an optional covalent bond between Y and U;

when the bond between Y and U is absent:

r is 0 or 1;

Y is N or CR^Y ;

R^Y is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

U is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u ;

when the bond between Y and U is present:

r is 1;

Y is C;

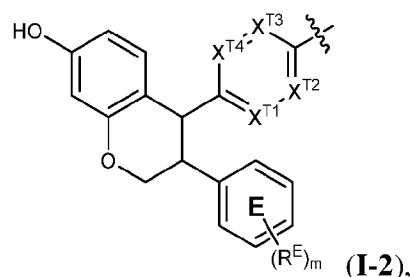
U is -CH₂-, -C(=O)-, -(C=O)-N(R^U)-*, or -N=C(R^U)-*;

R^U is H or C₁₋₆ alkyl optionally substituted with one or more R^u , and * denotes attachment to Ring B;

R^4 is hydrogen, deuterium, C₁₋₆ haloalkyl, or C₁₋₆ alkyl; and

q is an integer from 0 to 2,

T is of Formula **I-2**:



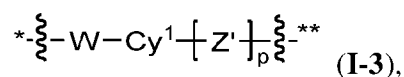
wherein:

each of $\mathbf{X}^{\text{T1}}$, $\mathbf{X}^{\text{T2}}$, $\mathbf{X}^{\text{T3}}$, and $\mathbf{X}^{\text{T4}}$ is independently $\mathbf{N}$ or $\mathbf{CR}^{\text{T}}$;

each R^E is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

m is an integer selected from 0 to 5,

L is of Formula I-3:



wherein:

* denotes attachment to **T** and ** denotes attachment to **C**;

W is absent; or

W is C₁₋₃ alkylene, -O-, -NR^W-, or -(C=O)-, wherein the alkylene is optionally substituted by one or more R^u;

Cy¹ is absent; or

Cy¹ is 6-membered heteroarylene, C₆ arylene, C₃₋₁₂ membered carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the arylene, heteroarylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

Z' is absent; or

each Z' is independently C₁₋₃ alkylene, -O-, -NR^W-, -(C=O)-, C₃₋₁₂ membered carbocyclene, or 3- to 12-membered heterocyclene, wherein the alkylene, carbocyclene, or heterocyclene is optionally substituted by one or more R^u;
 R^W is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u; and
 p is an integer selected from 0 to 8,

wherein:

each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl; or
 two R^u, together with the one or more intervening atoms, form C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl;
 each R^a is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;
 each R^b is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; and
 each R^c and R^d is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; or
 R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl,
 wherein each of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and
 each R^z is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

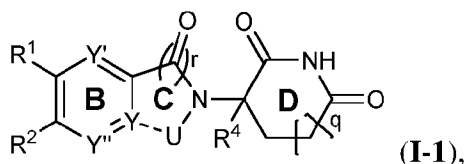
[0018] In certain aspects, the present disclosure provides compounds of Formula I:

T-L-C (I),

and pharmaceutically acceptable salts, solvates, or stereoisomers thereof,

wherein:

C is of Formula I-1



wherein:

--- denotes an optional covalent bond between Y and U;

R¹ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₄ aryl, 5- to 14-membered heteroaryl, C₃₋₁₀ carbocyclyl, 3- to 10-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R² is *-Cy²-, wherein * denotes attachment to L;

Cy² is 3- to 12-membered heterocyclylene, wherein the heterocyclylene is optionally substituted with one or more R^u; or

R¹ and R², together with the intervening carbon atoms, form Ring A attached to L, wherein Ring A is C₃₋₁₀ carbocycle or 5- to 16-membered heterocycle optionally substituted with one or more Rⁱ;

Y'' is N or CR³;

R³ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₄ aryl, 5- to 14-membered heteroaryl, C₃₋₁₀ carbocyclyl, 3- to 10-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl,

alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; or

R² and R³, together with the intervening carbon atoms, form Ring A attached to L, wherein Ring A is 5- to 16-membered heterocycle optionally substituted with one or more Rⁱ;

provided that R¹ and R², and R² and R³, do not both form Ring A attached to L; each Rⁱ is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₄ aryl, 5- to 14-membered heteroaryl, C₃₋₁₀ carbocyclyl, 3- to 10-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

Y' is N or CR^{Y'};

R^{Y'} is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

Y is N or CR^Y when the bond between Y and U is absent; or Y is C when the bond between Y and U is present;

R^Y is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u;

r is 0 or 1;

U is hydrogen or C₁₋₆ alkyl when the bond between Y and U is absent; or

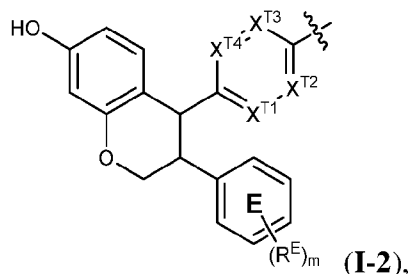
U is -CH₂-, -C(=O)-, -(C=O)-N(R^U)-*, -N=C(R^U)-* when the bond between Y and U is present;

R^U is H or C₁₋₆ alkyl, and * denotes attachment to Ring B;

R⁴ is hydrogen, deuterium, C₁₋₆ haloalkyl, or C₁₋₆ alkyl; and

q is an integer from 0 to 2;

T is of Formula **I-2**:



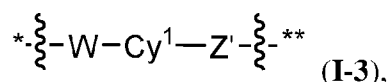
wherein:

each of X^{T1} , X^{T2} , X^{T3} , and X^{T4} is independently N or CR^T ;

each R^E is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₄ aryl, 5- to 14-membered heteroaryl, C₃₋₁₀ carbocyclyl, 3- to 10-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

m is an integer selected from 0 to 5,

L is of Formula I-3:



wherein:

W is absent; or

W is -CH₂-, -O-, -NR^W-, or -(C=O)-;

R^W is hydrogen or C₁₋₆ alkyl;

* denotes attachment to T and ** denotes attachment to C;

Cy¹ is 6-membered heteroarylene, C₆ arylene, C₃₋₁₂ membered carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the arylene, heteroarylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

Z' is absent; or

Z' is $-(C(=O))_p-(O)_{p'}-(C_{1-6} \text{ alkylene})_u-(3\text{- to } 6\text{-membered heterocyclylene})_v-(C(=O))_p-(C_{1-6} \text{ alkylene})_u-(3\text{- to } 6\text{-membered heterocyclylene})_v-(C(=O))_p$, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u;

each occurrence of p, p', and u is independently 0 or 1; and

each v is an integer independently selected from 0 to 3,

wherein:

each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₀ carbocyclyl, 3- to 10-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl; or

two R^u, together with the one or more intervening atoms, form C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₀ carbocyclyl or 3- to 10-membered heterocyclyl;

each R^a is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3- to 10-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;

each R^b is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3- to 10-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; and

each R^c and R^d is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₀ carbocyclyl, 3- to 10-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; or

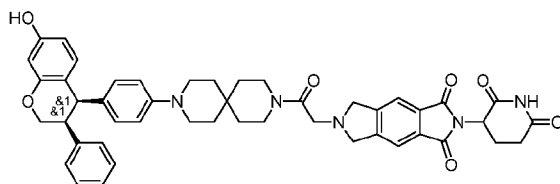
R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 10-membered heterocyclyl,

wherein each of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and

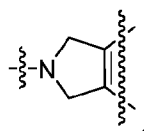
each R^z is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

[0019] In certain embodiments, when the bond between Y and U is present, U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$, and r is 1, then either R^1 and R^2 , or R^2 and R^3 , together with the intervening carbon atoms, form Ring A attached to L.

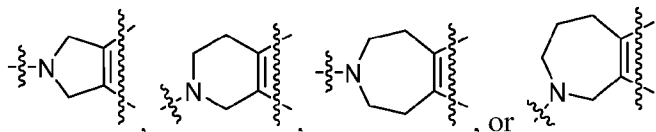
[0020] In certain embodiments, the compound is not



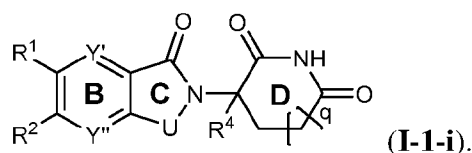
[0021] In certain embodiments, when the bond between Y and U is present, U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$, and r is 1, then Ring A is not



[0022] In certain embodiments, when the bond between Y and U is present, U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$, and r is 1, then Ring A is not

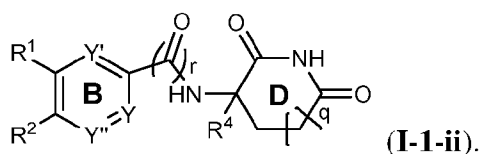


[0023] In certain embodiments, C is of Formula **I-1-i**



[0024] In certain embodiments, U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$. In certain embodiments, U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$ when the bond between Y and U is present. In certain embodiments, U is $-(\text{C}=\text{O})-\text{N}(\text{R}^U)-$ or $-\text{N}=\text{C}(\text{R}^U)-$ when the bond between Y and U is present.

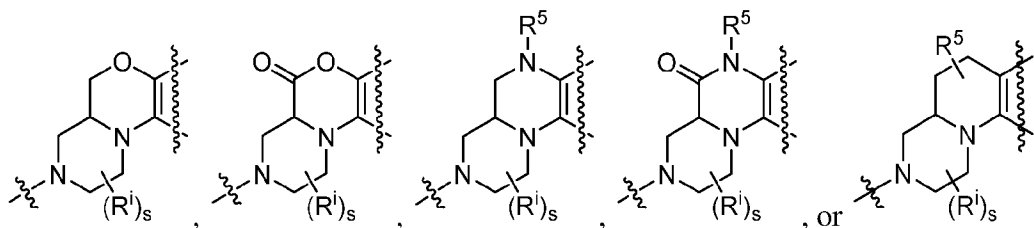
[0025] In certain embodiments, C is of Formula **I-1-ii**



[0026] In certain embodiments, R^1 and R^2 , together with the intervening carbon atoms, form Ring A attached to L, wherein the Ring A is optionally substituted 5- to 16-membered heterocycle.

[0027] In certain embodiments, Ring A is optionally substituted 7- to 16-membered fused heterocycle.

[0028] In certain embodiments, Ring A is



wherein:

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

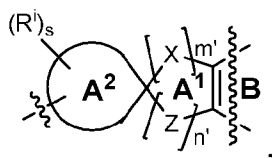
each R^i is independently oxo, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and

s is an integer selected from 0 to 8, as valency permits.

[0029] In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is C_{1-6} alkyl.

[0030] In certain embodiments, Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

[0031] In certain embodiments, Ring A is:



wherein:

Ring A^2 is C_{3-8} carbocycle or 3- to 8-membered heterocycle;

each X is independently $-C(R^{X1})_2-$, $-NR^{X2}-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

each Z is independently $-C(R^{Z1})_2-$, $-NR^{Z2}-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

two geminal R^{X1} or two geminal R^{Z1} together form oxo; or

two R^{X1} or two R^{Z1} , together with the intervening carbon atom(s), form C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u;

each occurrence of R^{X2} and R^{Z2} is independently hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u;

m' and n' are independently an integer selected from 0-3, wherein m' and n' are not both 0;

each Rⁱ is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

[0032] In certain embodiments, when none of m' and n' is 0, then Ring A¹ is 4- to 9-membered heterocycle.

[0033] In certain embodiments, Ring A² is C₃₋₈ carbocycle. In certain embodiments, Ring A² is 3- to 8-membered heterocycle.

[0034] In certain embodiments, each X is independently -C(R^{X1})₂-, -NR^{X2}-, or -O-.

[0035] In certain embodiments, each Z is independently -C(R^{Z1})₂-, -NR^{Z2}-, or -O-.

[0036] In certain embodiments, m' and n' are independently an integer selected from 0-2, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0-2, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0 and 1, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0 and 1, wherein m' and n' are not both 0.

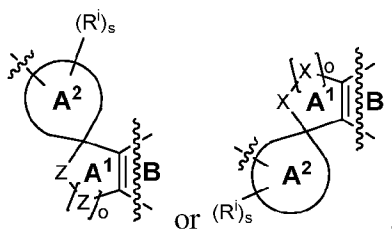
[0037] In certain embodiments, each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

[0038] In certain embodiments, two geminal R^{X1} or two geminal R^{Z1} together form oxo.

[0039] In certain embodiments, two R^{X1} or two R^{Z1} , together with the intervening carbon atom(s), form C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

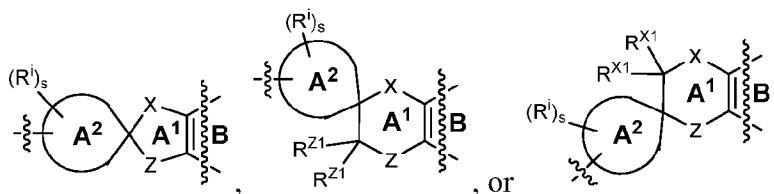
[0040] In certain embodiments, Ring A is:

1)



wherein o is 0 or 1; or

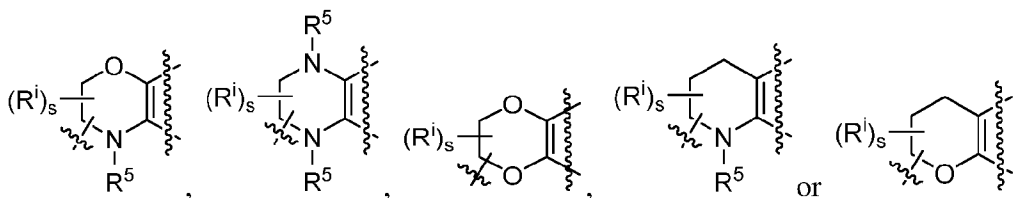
2)



[0041] In certain embodiments, o is 0. In certain embodiments, o is 1.

[0042] In certain embodiments, Ring A is optionally substituted 5- to 6-membered heterocycle.

[0043] In certain embodiments, Ring A is



wherein:

R⁵ is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u;

each Rⁱ is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

[0044] In certain embodiments, R⁵ is hydrogen. In certain embodiments, R⁵ is C₁₋₆ alkyl.

[0045] In certain embodiments, Y'' is N.

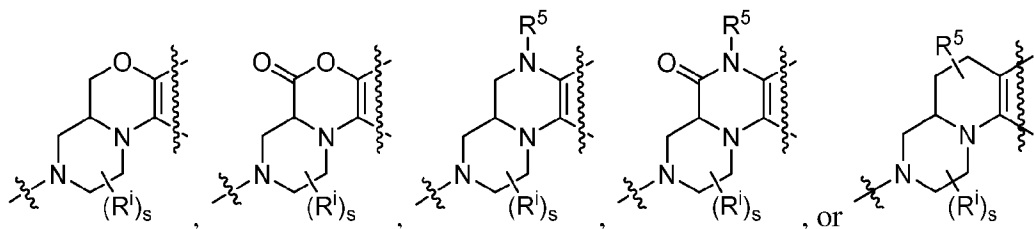
[0046] In certain embodiments, Y'' is CR³, and R³ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0047] In certain embodiments, R³ is hydrogen, halogen, or C₁₋₆ alkoxy, wherein the alkoxy is optionally substituted with one or more R^u.

[0048] In certain embodiments, R² and R³, together with the intervening carbon atoms, form Ring A attached to L, wherein the Ring A is optionally substituted 5- to 16-membered heterocycle.

[0049] In certain embodiments, Ring A is optionally substituted 7- to 16-membered fused heterocycle.

[0050] In certain embodiments, Ring A is



wherein:

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

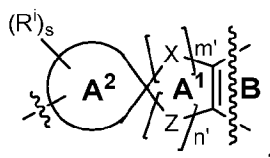
each R^i is independently oxo, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and

s is an integer selected from 0 to 8, as valency permits.

[0051] In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is C_{1-6} alkyl.

[0052] In certain embodiments, Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

[0053] In certain embodiments, Ring A is:



wherein:

Ring A^2 is C_{3-8} carbocycle or 3- to 8-membered heterocycle;

each X is independently $-C(R^{X1})_2$ -, $-NR^{X2}$ -, $-O$ -, $-S$ -, $-S(=O)$ -, or $-S(=O)_2$ -;

each Z is independently $-C(R^{Z1})_2$ -, $-NR^{Z2}$ -, $-O$ -, $-S$ -, $-S(=O)$ -, or $-S(=O)_2$ -;

each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-$

$\text{NR}^c\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{R}^a$, $-\text{OS}(=\text{O})_2\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$, $-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

two geminal R^{X1} or two geminal R^{Z1} together form oxo; or

two R^{X1} or two R^{Z1} , together with the intervening carbon atom(s), form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

each occurrence of R^{X2} and R^{Z2} is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

m' and n' are independently an integer selected from 0-3, wherein m' and n' are not both 0;

each R^i is independently oxo, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-\text{SR}^b$, $-\text{S}(=\text{O})\text{R}^a$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^b$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^c\text{S}(=\text{O})_2\text{R}^a$, $-\text{NR}^c\text{S}(=\text{O})\text{R}^a$, $-\text{NR}^c\text{S}(=\text{O})_2\text{OR}^b$, $-\text{NR}^c\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{R}^a$, $-\text{OS}(=\text{O})_2\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$, $-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and

s is an integer selected from 0 to 8, as valency permits.

[0054] In certain embodiments, when none of m' and n' is 0, then Ring A^1 is 4- to 9-membered heterocycle.

[0055] In certain embodiments, Ring A^2 is C_{3-8} carbocycle. In certain embodiments, Ring A^2 is 3- to 8-membered heterocycle.

[0056] In certain embodiments, each X is independently $-\text{C}(\text{R}^{\text{X1}})_2-$, $-\text{NR}^{\text{X2}}-$, or $-\text{O}-$.

[0057] In certain embodiments, each Z is independently $-\text{C}(\text{R}^{\text{Z1}})_2-$, $-\text{NR}^{\text{Z2}}-$, or $-\text{O}-$.

[0058] In certain embodiments, m' and n' are independently an integer selected from 0-2, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0-2, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0 and 1, wherein m' and n' are not both 0. In certain embodiments, m' and n' are independently an integer selected from 0 and 1, wherein m' and n' are not both 0.

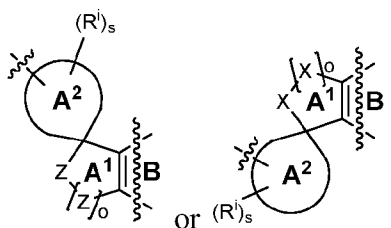
[0059] In certain embodiments, each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₆ carbocyclyl, 3- to 6-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

[0060] In certain embodiments, two geminal R^{X1} or two geminal R^{Z1} together form oxo.

[0061] In certain embodiments, two R^{X1} or two R^{Z1} , together with the intervening carbon atom(s), form C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u.

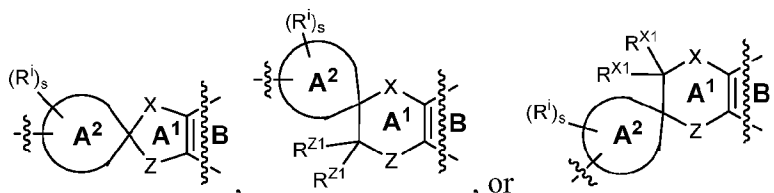
[0062] In certain embodiments, Ring A is:

1)



wherein o is 0 or 1; or

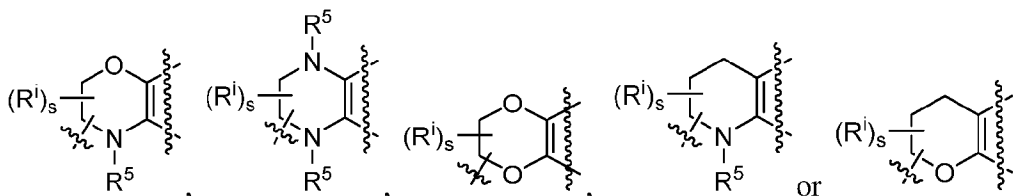
2)



[0063] In certain embodiments, o is 0. In certain embodiments, o is 1.

[0064] In certain embodiments, Ring A is optionally substituted 5- to 6-membered heterocycle.

[0065] In certain embodiments, Ring A is



wherein:

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

each R^i is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and

s is an integer selected from 0 to 8, as valency permits.

[0066] In certain embodiments, R^5 is hydrogen. In certain embodiments, R^5 is C_{1-6} alkyl.

[0067] In certain embodiments, R^i is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0068] In certain embodiments, wherein R^i is hydrogen, halogen, or C_{1-6} alkoxy, wherein the alkoxy is optionally substituted with one or more R^u .

[0069] In certain embodiments, each R^i is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

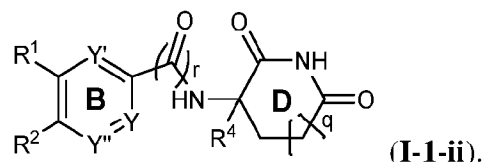
[0070] In certain embodiments, s is 0. In certain embodiments, s is 1. In certain embodiments, s is 2. In certain embodiments, s is 3. In certain embodiments, s is 4. In certain embodiments, s is 5. In certain embodiments, s is 6. In certain embodiments, s is 7. In certain embodiments, s is 8.

[0071] In certain embodiments, Ring A is optionally substituted with one or more R^u .

[0072] In certain embodiments, R^u is R^5 . In certain embodiments, R^u is R^i . In certain embodiments, R^u is R^{X1} . In certain embodiments, R^u is R^{X2} . In certain embodiments, R^u is R^{Z1} . In certain embodiments, R^u is R^{Z2} .

[0073] In certain embodiments, Ring A is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl.

[0074] In certain embodiments, C is of Formula I-1-ii



[0075] In certain embodiments, R² is *-Cy²-, wherein * denotes attachment to L.

[0076] In certain embodiments, *-Cy²- is 3-membered heterocyclylene. In certain embodiments, *-Cy²- is 4-membered heterocyclylene. In certain embodiments, *-Cy²- is 5-membered heterocyclylene. In certain embodiments, *-Cy²- is 6-membered heterocyclylene. In certain embodiments, *-Cy²- is 7-membered heterocyclylene. In certain embodiments, *-Cy²- is 8-membered heterocyclylene. In certain embodiments, *-Cy²- is 9-membered heterocyclylene. In certain embodiments, *-Cy²- is 10-membered heterocyclylene. In certain embodiments, *-Cy²- is 11-membered heterocyclylene. In certain embodiments, *-Cy²- is 12-membered heterocyclylene. In certain embodiments, the above *-Cy²- is optionally substituted with one or more R^u.

[0077] In certain embodiments, *-Cy²- is 3- to 12-membered heterocyclylene. In certain embodiments, *-Cy²- is 3- to 11-membered heterocyclylene. In certain embodiments, *-Cy²- is 3- to 10-membered heterocyclylene. In certain embodiments, *-Cy²- is 3- to 9-membered heterocyclylene. In certain embodiments, *-Cy²- is 3- to 8-membered heterocyclylene. In certain embodiments, *-Cy²- is 3- to 7-membered heterocyclylene. In certain embodiments, *-Cy²- is 3- to 6-membered heterocyclylene. In certain embodiments, *-Cy²- is 3- to 5-membered heterocyclylene. In certain embodiments, *-Cy²- is 3- to 4-membered heterocyclylene. In certain embodiments, *-Cy²- is 4- to 12-membered heterocyclylene. In certain embodiments, *-Cy²- is 4-

to 11-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 4- to 10-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 4- to 9-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 4- to 8-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 4- to 7-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 4- to 6-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 4- to 5-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 5- to 12-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 5- to 11-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 5- to 10-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 5- to 9-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 5- to 8-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 5- to 7-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 5- to 6-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 6- to 12-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 6- to 11-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 6- to 10-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 6- to 9-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 6- to 8-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 6- to 7-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 8- to 12-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 8- to 11-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 8- to 10-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 8- to 9-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 9- to 12-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 9- to 11-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 9- to 10-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 10- to 12-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 10- to 11-membered heterocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 11- to 12-membered heterocyclylene. In certain embodiments, the above $^{*}\text{-Cy}^2\text{-}$ is optionally substituted with one or more R^u .

[0078] In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 1 heteroatom selected from nitrogen, oxygen, and sulfur. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 4 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the above $^{*}\text{-Cy}^2\text{-}$ is optionally substituted with one or more R^u .

[0079] In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 1 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 1 to 2 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 2 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 2 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is heterocyclylene comprising 3 to 4 heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the above $^{*}\text{-Cy}^2\text{-}$ is optionally substituted with one or more R^u .

[0080] In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_3 carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_4 carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_5 carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_6 carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_7 carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_8 carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_9 carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{10} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{12} carbocyclylene. In certain embodiments, the above $^{*}\text{-Cy}^2\text{-}$ is optionally substituted with one or more R^u .

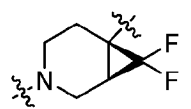
[0081] In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-12} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-10} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-9} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-8} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-7} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-6} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-5} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{3-4} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{4-12} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{4-11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{4-10} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{4-9} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{4-8} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{4-7} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{4-6} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{4-5} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{5-12} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{5-11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{5-10} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{5-9} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{5-8} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{5-7} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{5-6} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{6-12}

carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{6-11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{6-10} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{6-9} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{6-8} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{6-7} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{7-12} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{7-11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{7-10} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{7-9} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{7-8} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{8-12} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{8-11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{8-10} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{8-9} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{9-12} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{9-11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{9-10} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{10-12} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{10-11} carbocyclylene. In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{11-12} carbocyclylene. In certain embodiments, the above $^{*}\text{-Cy}^2\text{-}$ is optionally substituted with one or more R^u .

[0082] In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is C_{5-12} fused carbocyclylene or 5- to 12-membered fused heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more Ru .

[0083] In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is 5- to 12-membered fused heterocyclylene comprising 1 or 2 nitrogen atoms, wherein the heterocyclylene is optionally substituted with one or more Ru .

[0084] In certain embodiments, $^{*}\text{-Cy}^2\text{-}$ is



[0085] In certain embodiments, R^1 is hydrogen, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0086] In certain embodiments, R^1 is hydrogen, halogen, or C_{1-6} alkoxy, wherein the alkoxy is optionally substituted with one or more R^u .

[0087] In certain embodiments, Y'' is N .

[0088] In certain embodiments, Y'' is CR^3 .

[0089] In certain embodiments, R^3 is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0090] In certain embodiments, R^3 is hydrogen, halogen, or C₁₋₆ alkoxy, wherein the alkoxy is optionally substituted with one or more R^u .

[0091] In certain embodiments, Y is N.

[0092] In certain embodiments, Y is CR^Y .

[0093] In certain embodiments, R^Y is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

[0094] In certain embodiments, R^Y is hydrogen, halogen, or C₁₋₆ alkoxy, wherein the alkoxy is optionally substituted with one or more R^u . In certain embodiments, r is 0. In certain embodiments, r is 1.

[0095] In certain embodiments, R^4 is hydrogen. In certain embodiments, R^4 is deuterium. In certain embodiments, R^4 is C₁₋₆ haloalkyl. In certain embodiments, R^4 is C₁₋₆ alkyl.

[0096] In certain embodiments, q is 0. In certain embodiments, q is 1. In certain embodiments, q is 2.

[0097] In certain embodiments, each of X^{T1} , X^{T2} , X^{T3} , and X^{T4} is CR^T .

[0098] In certain embodiments, each of X^{T1} , X^{T2} , X^{T3} , and X^{T4} is CH. In certain embodiments, each of X^{T1} and X^{T4} is CH, one of X^{T2} and X^{T3} is CH, and the other one of X^{T2} and X^{T3} is CF. In certain embodiments, one of X^{T1} and X^{T4} is C(OCH₃), the other one of X^{T1} and X^{T4} is CH, and each X^{T2} and X^{T3} is CH. In certain embodiments, X^{T1} is C(OCH₃), X^{T3} is CF, and each of X^{T2} and X^{T4} is CH. In certain embodiments, X^{T2} is CF, X^{T4} is C(OCH₃), and each of X^{T1} and X^{T3} is CH.

[0099] In certain embodiments, one of X^{T1} , X^{T2} , X^{T3} , and X^{T4} is N.

[0100] In certain embodiments, one of X^{T1} and X^{T4} is N, the other one of X^{T1} and X^{T4} is CH, and each of X^{T2} and X^{T3} is CH. In certain embodiments, one of X^{T2} and X^{T3} is N, the other one of X^{T2} and X^{T3} is CH, and each of X^{T1} and X^{T4} is CH.

[0101] In certain embodiments, two of X^{T1} , X^{T2} , X^{T3} , and X^{T4} are N.

[0102] In certain embodiments, each of X^{T1} and X^{T4} is CH, and each of X^{T2} and X^{T3} is N.

[0103] In certain embodiments, each R^T is independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0104] In certain embodiments, each R^T is independently hydrogen, C₁₋₆ alkoxy, or halogen.

[0105] In certain embodiments, each R^E is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

[0106] In certain embodiments, R^E is C₁₋₆ alkoxy, wherein the alkoxy is optionally substituted with one or more R^u.

[0107] In certain embodiments, m is 0. In certain embodiments, m is 1. In certain embodiments, m is 2. In certain embodiments, m is 3. In certain embodiments, m is 4. In certain embodiments, m is 5.

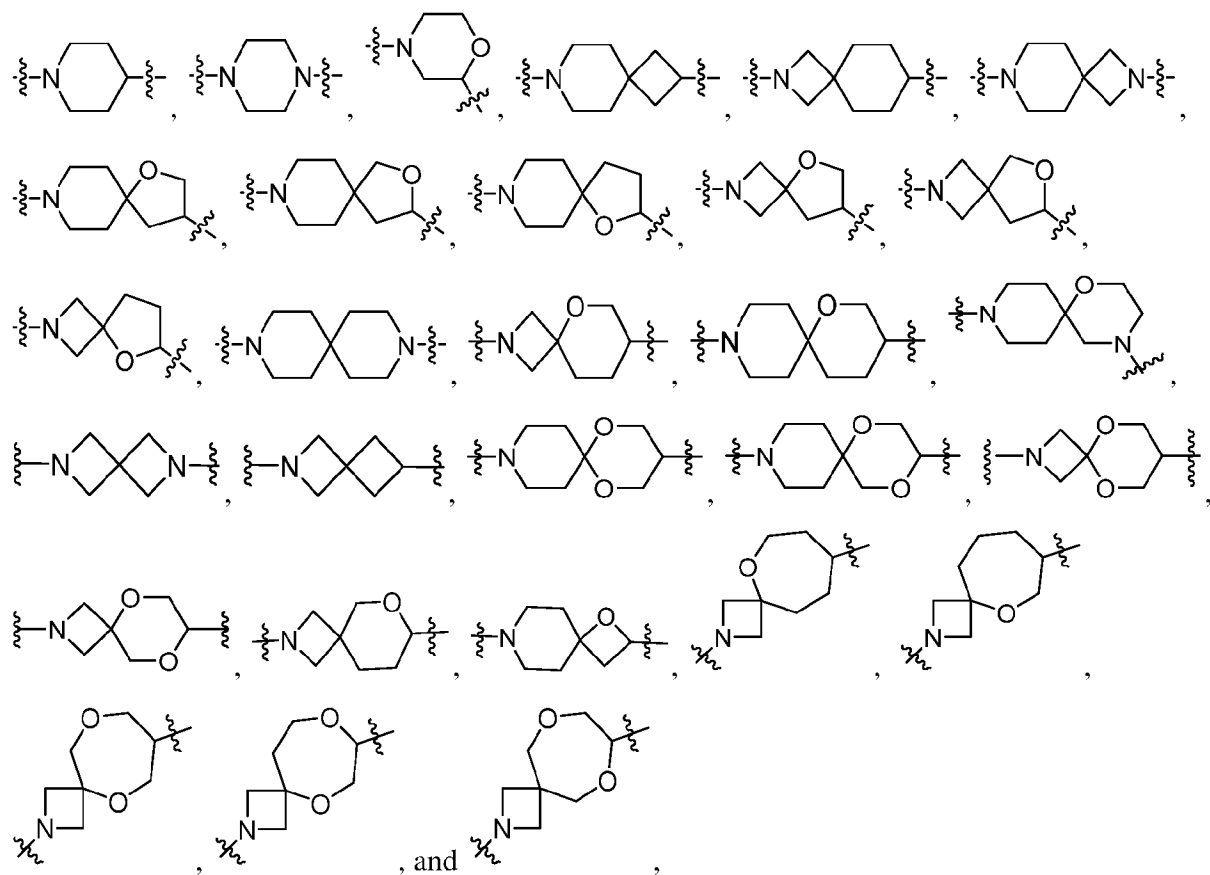
[0108] In certain embodiments, Cy¹ is C₃₋₁₀ carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted by one or more R^u. In certain embodiments, Cy¹ is 6-membered heteroarylene or C₆ arylen, wherein the heterocyclylene is optionally substituted by one or more R^u.

[0109] In certain embodiments, Cy¹ is 3- to 12-membered heterocyclylene, wherein the heterocyclylene is optionally substituted by one or more R^u.

[0110] In certain embodiments, Cy¹ is 3- to 12-membered heterocyclylene selected from morpholinylene, piperidinylene, piperazinylene, 7-azaspiro[3.5]nonanylene, 2,7-diazaspiro[3.5]nonanylene, 2-azaspiro[3.5]nonanylene, 2,7-diazaspiro[3.5]nonanylene, 1-oxa-8-azaspiro[4.5]decenylen, 2-oxa-8-azaspiro[4.5]decenylen, 5-oxa-2-azaspiro[3.4]octanylen, 6-

oxa-2-azaspiro[3.4]octanylene, 3,9-diazaspiro[5.5]undecanylene, 5-oxa-2-azaspiro[3.5]nonanylene, 1-oxa-9-azaspiro[5.5]undecanylene, 1-oxa-4,9-diazaspiro[5.5]undecanylene, 2,6-diazaspiro[3.3]heptanylene, 2-azaspiro[3.3]heptanylene, 1,5-dioxo-9-azaspiro[5.5]undecanylene, 1,4-dioxo-9-azaspiro[5.5]undecanylene, 5,9-dioxo-2-azaspiro[3.5]nonanylene, 5,8-dioxo-2-azaspiro[3.5]nonanylene, 6-oxo-2-azaspiro[3.5]nonanylene, 1-oxo-7-azaspiro[3.5]nonanylene, 5-oxo-2-azaspiro[3.6]decenylen, 5-oxo-2-azaspiro[3.6]decenylen, 5,9-dioxo-2-azaspiro[3.6]decenylen, 5,8-dioxo-2-azaspiro[3.6]decenylen, and 6,9-dioxo-2-azaspiro[3.6]decenylen, wherein the heterocyclylene is optionally substituted by one or more R^u.

[0111] In certain embodiments, Cy¹ is 3- to 12-membered heterocyclylene selected from:



wherein the heterocyclylene is optionally substituted by one or more R^u.

[0112] In certain embodiments, W is absent.

[0113] In certain embodiments, Z' is absent.

[0114] In certain embodiments, Z' is -C(=O)-, C₁₋₆ alkylene, *-O-(C₁₋₆ alkylene)-, *-(C₁₋₆ alkylene)-O-, *-C(=O)-(C₁₋₆ alkylene)-, *-(C₁₋₆ alkylene)-C(=O)-, 3- to 12-membered

heterocyclylene, *-C(=O)-(3- to 12-membered heterocyclylene)-, *-(3- to 12-membered heterocyclylene)-C(=O)-, *-(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-, *-(C₁₋₆ alkylene)-(3- to 12-membered heterocyclylene)-, *-(C₁₋₆ alkylene)-(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-, *-(C₁₋₆ alkylene)-(3- to 12-membered heterocyclylene)-(C(=O))-, *-(C(=O))-(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-, *-(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-(C(=O))-, *-(C(=O))-(C₁₋₆ alkylene)-(3- to 12-membered heterocyclylene)-, *-(C₁₋₆ alkylene)-(C(=O))-(3- to 12-membered heterocyclylene)-, or *-(3- to 12-membered heterocyclylene)-(C(=O))-(C₁₋₆ alkylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u, and *denotes attachment to C.

[0115] In certain embodiments, Z' is C₁₋₆ alkylene, *-C(=O)-(C₁₋₆ alkylene)-, *-(C₁₋₆ alkylene)-C(=O)-, *-C(=O)-(3- to 12-membered heterocyclylene)-, or *-(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u, and *denotes attachment to C.

[0116] In certain embodiments, the compound is selected from the compounds in Tables 1-3, or a pharmaceutically acceptable salt thereof.

[0117] In certain embodiments, the compound is selected from the compounds in Tables 1-3.

[0118] In certain embodiments, the compound is selected from the compounds in Table 1, or a pharmaceutically acceptable salt thereof.

[0119] In certain embodiments, the compound is selected from the compounds in Table 1.

[0120] In certain embodiments, the compound is selected from the compounds in Table 2, or a pharmaceutically acceptable salt thereof.

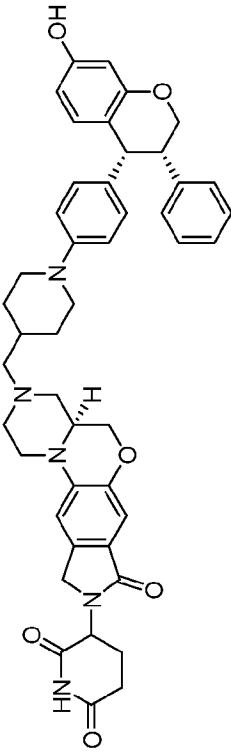
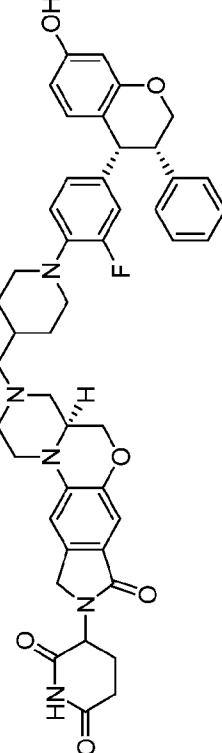
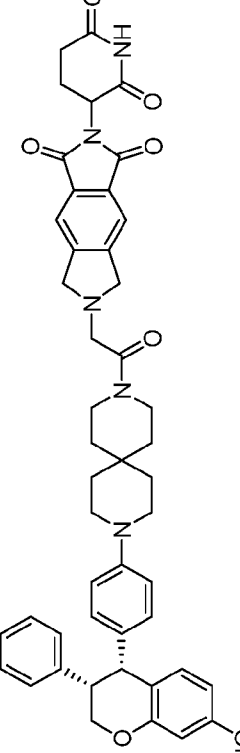
[0121] In certain embodiments, the compound is selected from the compounds in Table 2.

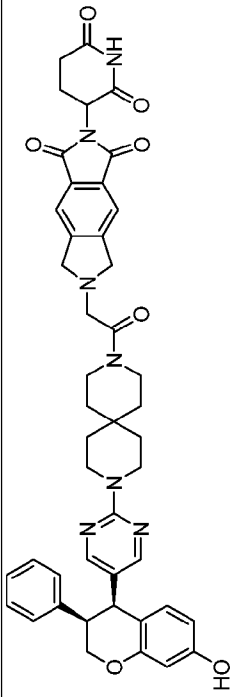
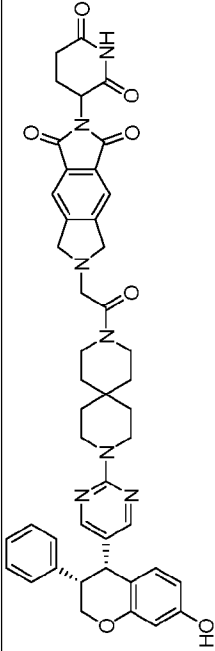
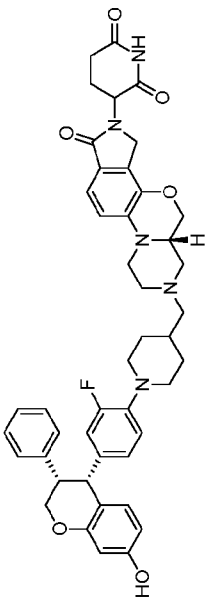
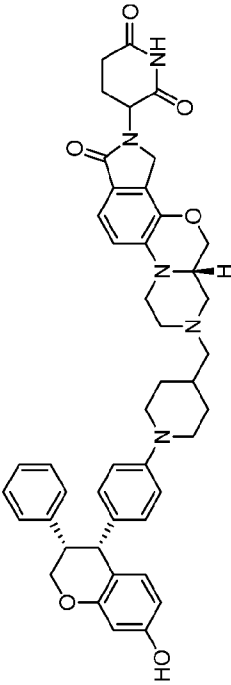
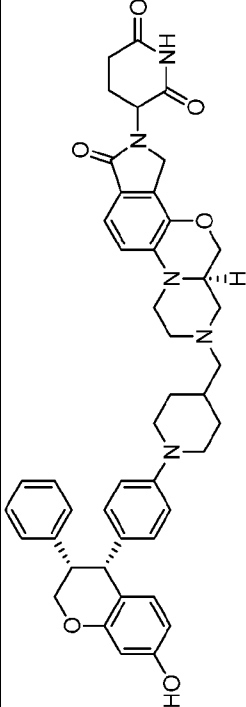
[0122] In certain embodiments, the compound is selected from the compounds in Table 3, or a pharmaceutically acceptable salt thereof.

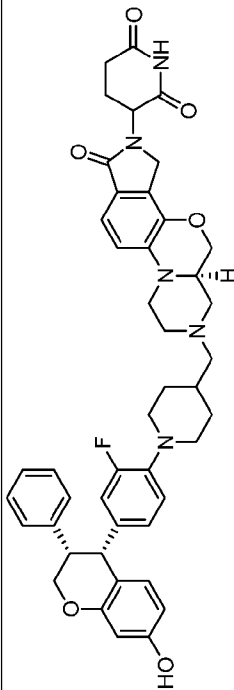
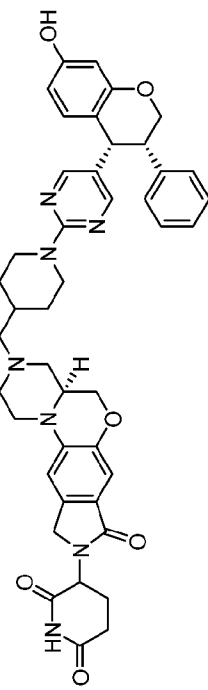
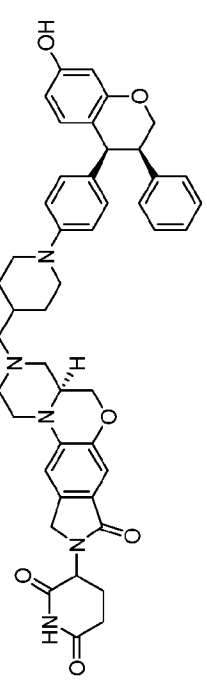
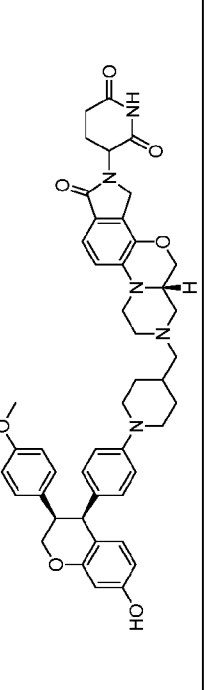
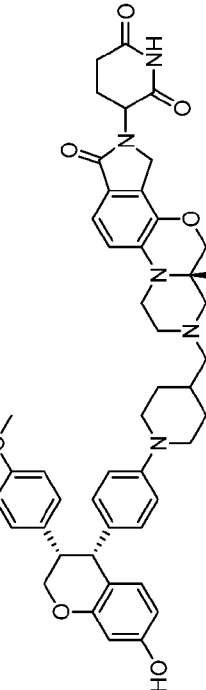
[0123] In certain embodiments, the compound is selected from the compounds in Table 3.

Table 1.

*designates that is enantiomerically pure with respect to the warhead (chroman part) but the absolute configuration is not determined; and the relative configuration of the two stereogenic centers is *cis*.

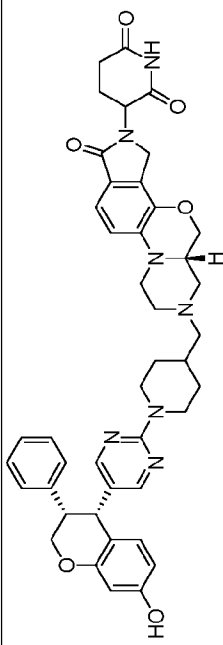
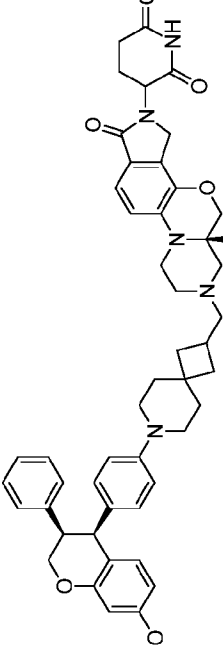
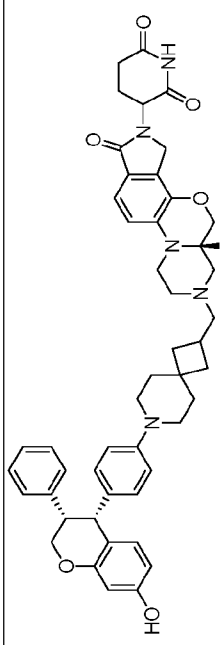
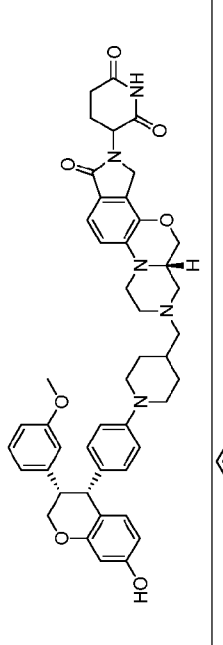
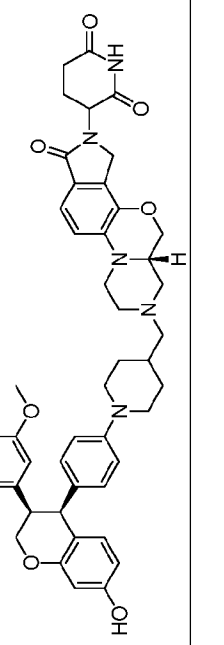
Compound No.	Structure	Compound Name
A1*		3-(S)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)methyl)-2,6-dione
A2*		3-(S)-3-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)methyl)-2,6-dione
A3*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

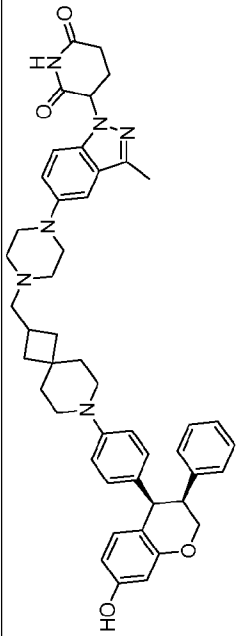
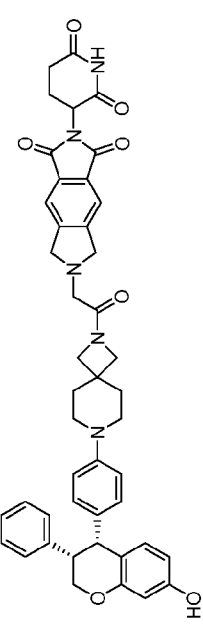
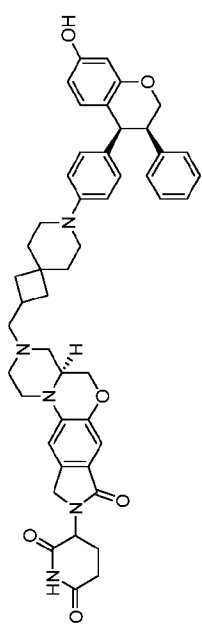
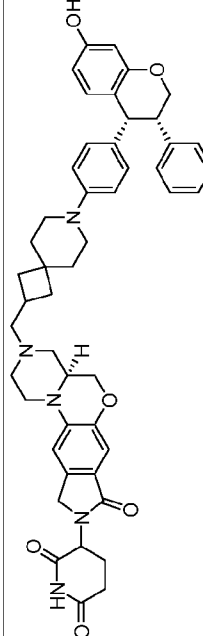
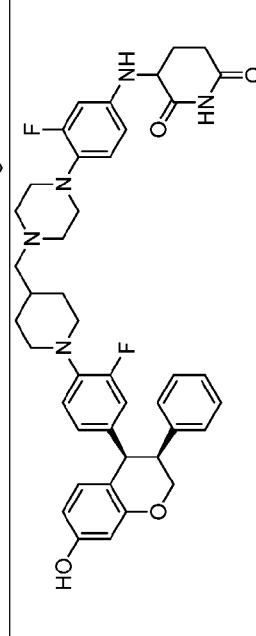
A4*		2-((2,6-dioxopiperidin-3-yl)-6-(2-(9-(5-yl)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A5*		2-((2,6-dioxopiperidin-3-yl)-6-(2-(9-(5-yl)pyrimidin-2-yl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A6*		3-((S)-7-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A7*		3-((S)-7-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A8*		3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

A9*		3-((R)-7-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1,2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A10*		3-((S)-3-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1,2':4,5][1,4]oxazino[2,3-e]isoindol-9-yl)piperidine-2,6-dione
A11*		3-((S)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1,2':4,5][1,4]oxazino[2,3-e]isoindol-9-yl)piperidine-2,6-dione
A12*		3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1,2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A13*		3-((S)-7-((1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1,2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

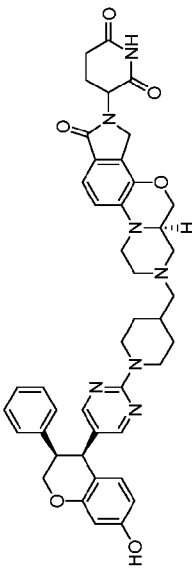
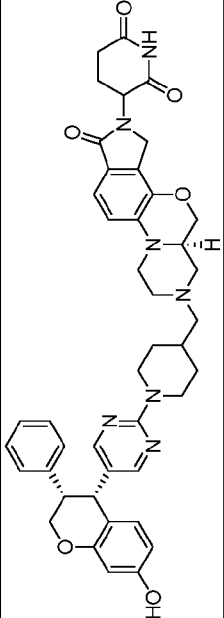
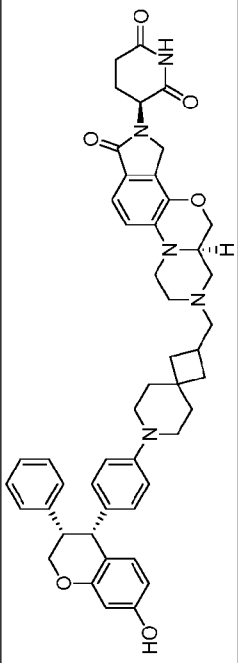
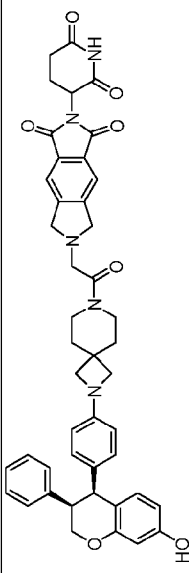
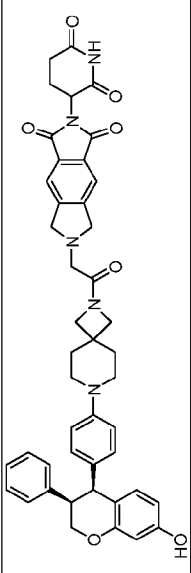
A14*	The structure of A14* features a central chromane core. At the 2-position, there is a 4-fluorophenyl group. At the 3-position, there is a 4-(4-(2-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-1H-indazol-1-yl)piperidine-2,6-dione substituent.	3-(5-(4-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-3-methyl-1H-indazol-1-yl)piperidine-2,6-dione
A15*	The structure of A15* features a central chromane core. At the 2-position, there is a 4-methoxyphenyl group. At the 3-position, there is a 4-(4-(2-(2-(4-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione substituent.	3-(((R))-7-((1-(4-((3R,4S)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A16*	The structure of A16* features a central chromane core. At the 2-position, there is a 4-methoxyphenyl group. At the 3-position, there is a 4-(4-(2-(2-(4-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione substituent.	3-(((R))-7-((1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

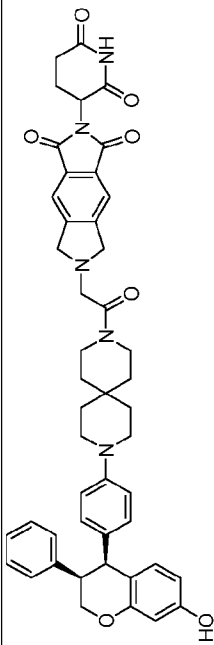
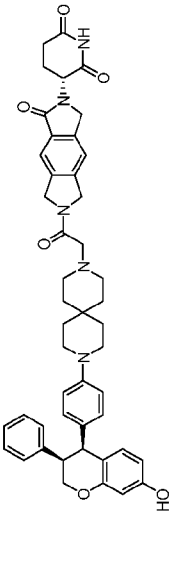
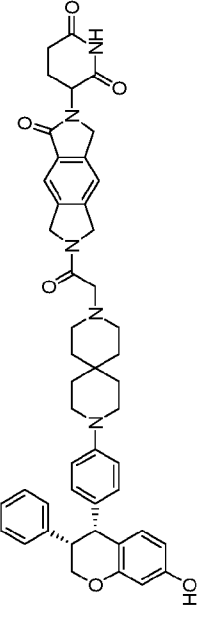
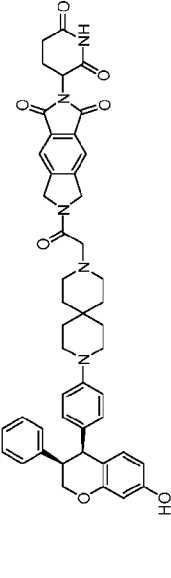
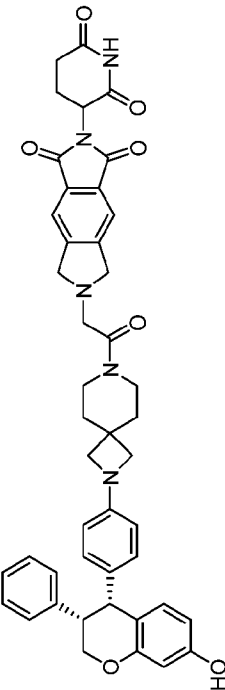
A17*	The chemical structure of A17* features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a cyclobutane ring. The other nitrogen is connected via a methylene group to a 4-phenylpiperazine moiety. This phenylpiperazine is further substituted with a 3-methyl-1H-indazol-1-yl group and a 3-oxo-3,4,5,6-tetrahydro-2H-pyridine-2,6-dione group.	3-(5-(4-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl))-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-3-methyl-1H-indazol-1-yl)piperidine-2,6-dione
A18*	The chemical structure of A18* is a complex molecule. It includes a central piperazine ring. One nitrogen is connected to a 4-phenylpiperazine moiety, which is further substituted with a 3-oxo-3,4,5,6-tetrahydro-2H-pyridine-2,6-dione group. The other nitrogen of the piperazine is connected to a 4-phenylpiperazine moiety, which is further substituted with a 3-oxo-3,4,5,6-tetrahydro-2H-pyridine-2,6-dione group. The structure also includes a 3-oxo-3,4,5,6-tetrahydro-2H-pyridine-2,6-dione group and a 3-oxo-3,4,5,6-tetrahydro-2H-pyridine-2,6-dione group.	3-((S)-3-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A19*	The chemical structure of A19* features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a cyclobutane ring. The other nitrogen is connected via a methylene group to a 4-phenylpiperazine moiety. This phenylpiperazine is further substituted with a 3-methyl-1H-indazol-1-yl group and a 3-oxo-3,4,5,6-tetrahydro-2H-pyridine-2,6-dione group.	3-((S)-7-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

A20*		3-((S)-7-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A21*		3-((S)-7-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A22*		3-((S)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A23*		3-((S)-7-((1-(4-((3S,4R)-7-hydroxy-3-(3-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A24*		3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-(3-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

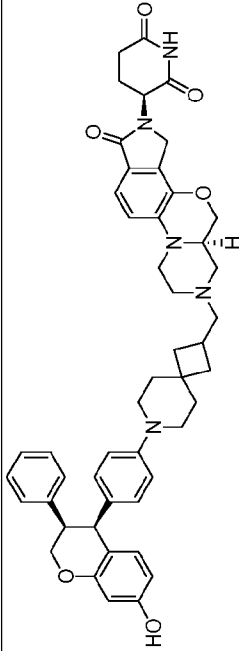
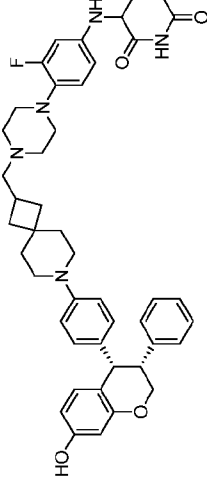
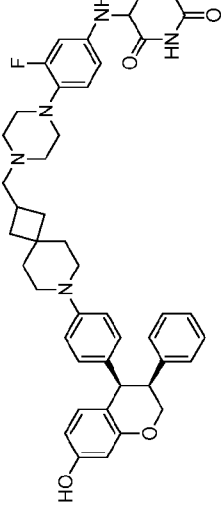
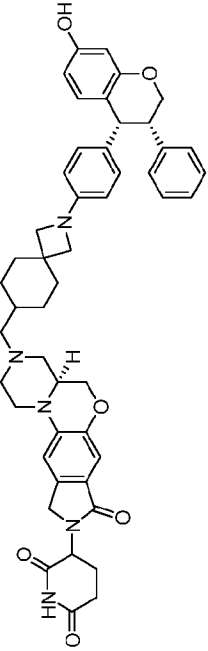
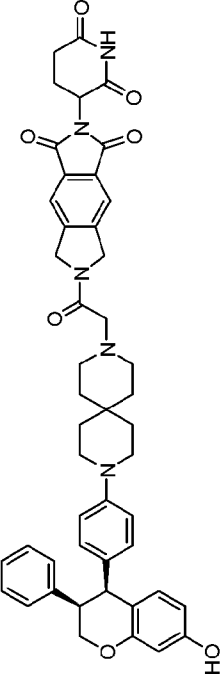
A25*		3-(5-(4-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-3-methyl-1H-indazol-1-yl)piperidine-2,6-dione
A26*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A27*		3-(S)-3-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A28*		3-(S)-3-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A29*		3-((3-fluoro-4-(4-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione

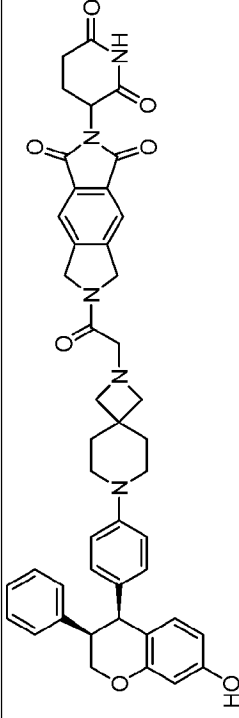
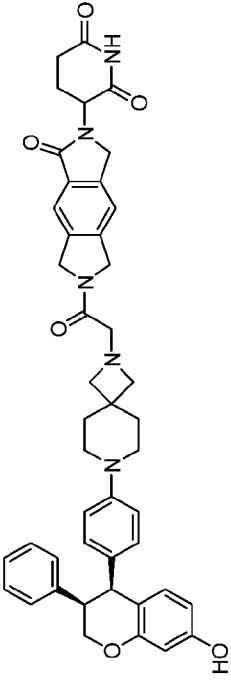
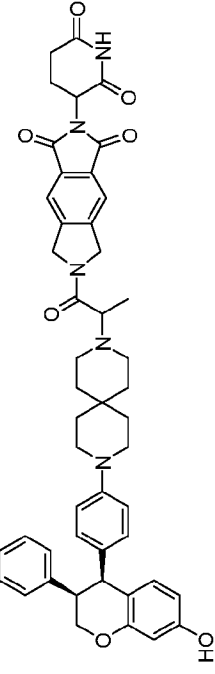
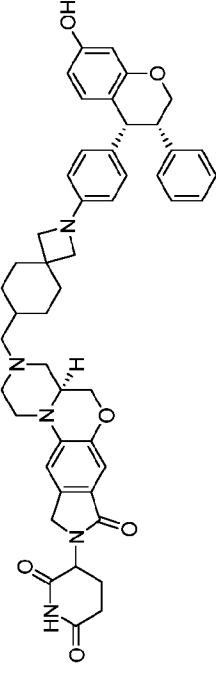
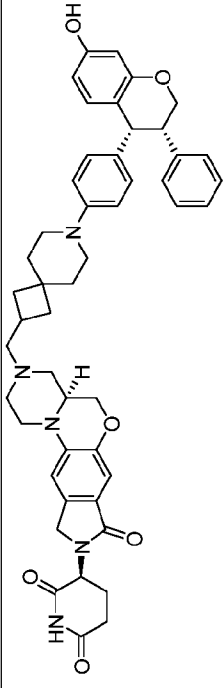
A30*	The chemical structure of A30* features a 3-fluoro-4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)phenylamino)piperidine-2,6-dione moiety. This is connected via a methylene bridge to a piperazine ring, which is further linked to a biphenyl system. The biphenyl system includes a 4-hydroxyphenyl group and a 3-phenylchroman-4-yl group.
A31*	The chemical structure of A31* consists of a 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione moiety. This is connected via a methylene bridge to a piperazine ring, which is further linked to a biphenyl system. The biphenyl system includes a 4-hydroxyphenyl group and a 3-phenylchroman-4-yl group.
A32*	The chemical structure of A32* features a 2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione moiety. This is connected via a methylene bridge to a piperazine ring, which is further linked to a biphenyl system. The biphenyl system includes a 4-hydroxyphenyl group and a 3-phenylchroman-4-yl group.
A33*	The chemical structure of A33* consists of a 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-(3-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione moiety. This is connected via a methylene bridge to a piperazine ring, which is further linked to a biphenyl system. The biphenyl system includes a 4-hydroxyphenyl group and a 3-phenylchroman-4-yl group.
A34*	The chemical structure of A34* features a 3-((R)-7-((1-(4-((3R,4S)-7-hydroxy-3-(3-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione moiety. This is connected via a methylene bridge to a piperazine ring, which is further linked to a biphenyl system. The biphenyl system includes a 4-hydroxyphenyl group and a 3-phenylchroman-4-yl group.

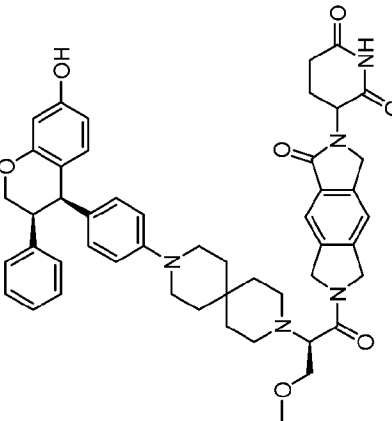
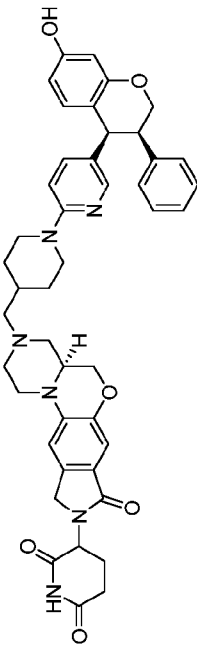
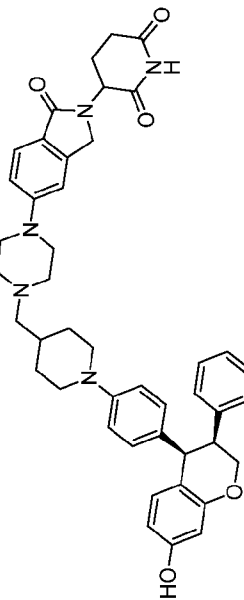
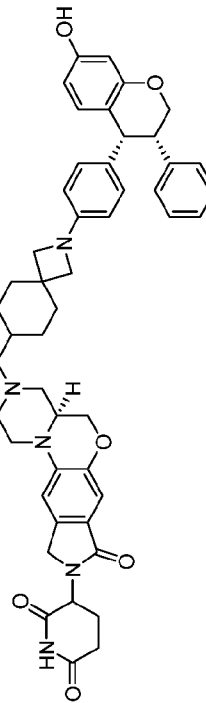
A35*		3-((R)-7-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A36*		3-((R)-7-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyrimidin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A37*		(S)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A38*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A39*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

A40*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A41*		(R)-3-(6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
A42*		3-(6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
A43*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A44*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

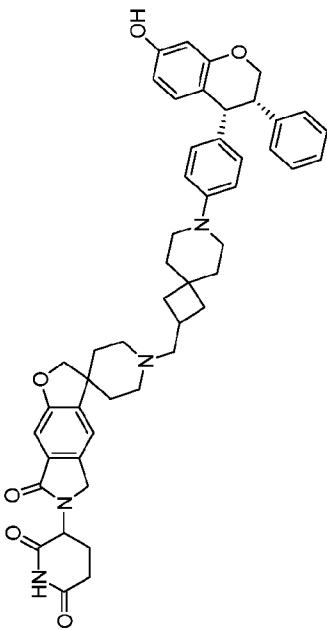
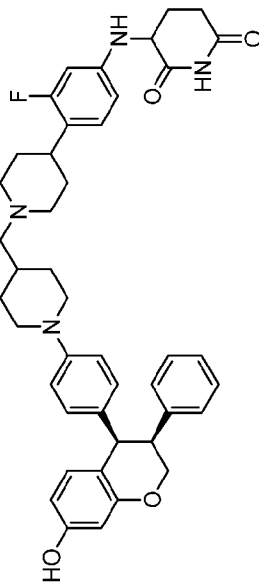
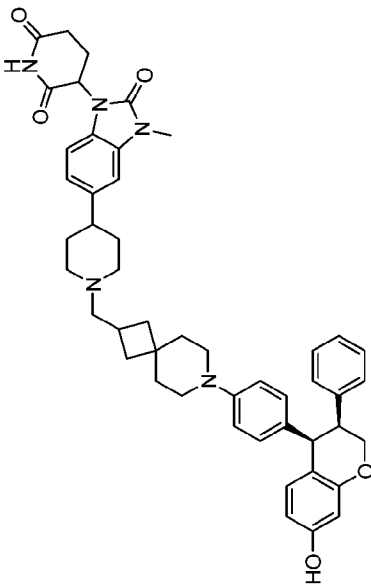
A45*		3-(6-(2-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
A46*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A47*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A48*		3-(6-(2-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
A49*		3-(6-(2-(2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-7-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione

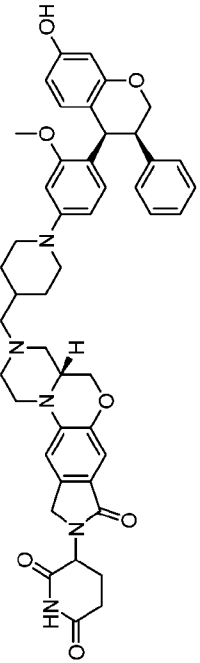
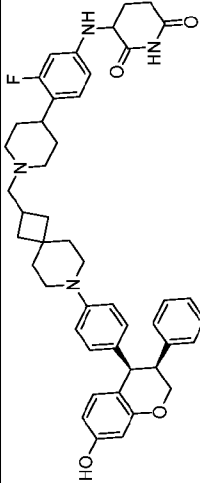
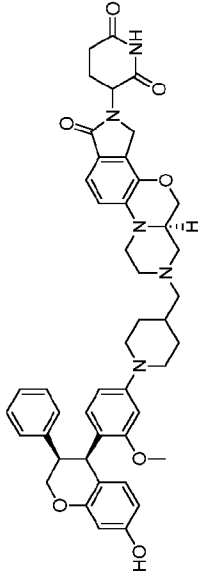
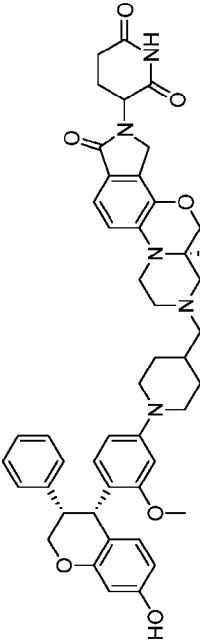
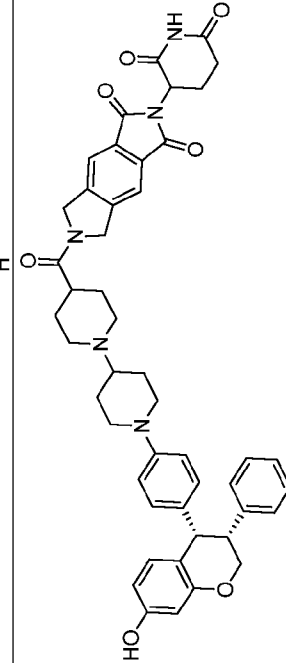
A50*		(S)-3-((R)-7-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A51*		3-((3-fluoro-4-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione
A52*		3-((3-fluoro-4-(4-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)phenyl)amino)piperidine-2,6-dione
A53*		3-((S)-3-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A54*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione formate

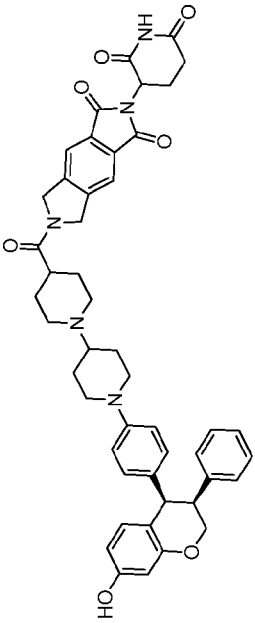
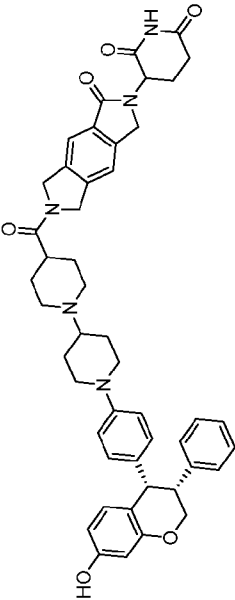
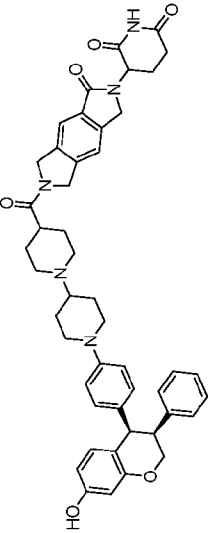
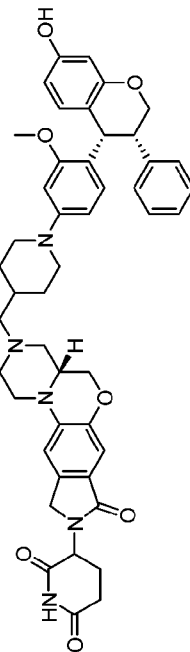
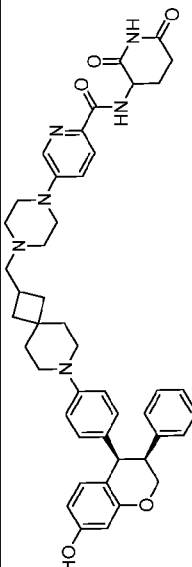
A55*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazapiro[3.5]nonan-2-yl)acetyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione formate
A56*		3-(6-(2-(7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazapiro[3.5]nonan-2-yl)acetyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione formate
A57*		2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazapiro[5.5]undecan-3-yl)propanoyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A58*		3-(S)-3-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azapiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A59*		(S)-3-((S)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azapiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

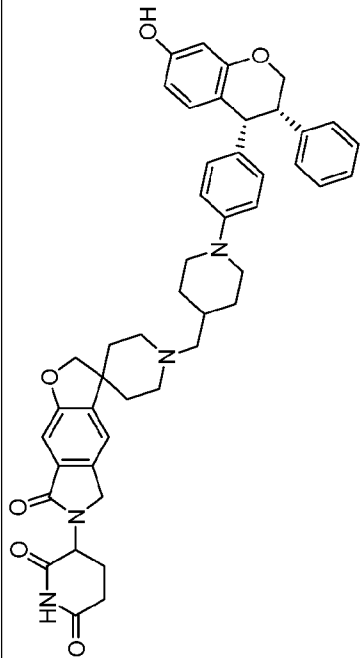
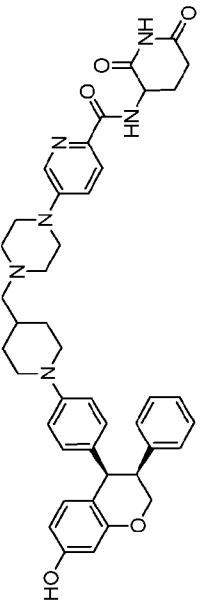
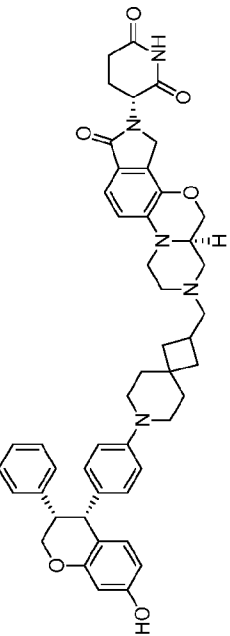
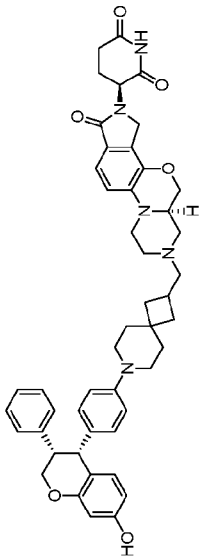
A60*		3-(6-((R)-2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-3-methoxypropanoyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
A61*		3-(5-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoin-dolin-2-yl)piperidine-2,6-dione
A62*		3-(5-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoin-dolin-2-yl)piperidine-2,6-dione
A63*		3-(5-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-1-oxoisoin-dolin-2-yl)piperidine-2,6-dione

A64*		3-((R)-7-((1-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A65*		3-((R)-7-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A66*		3-((R)-7-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A69*		3-((R)-7-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A70*		3-((S)-3-((1-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-

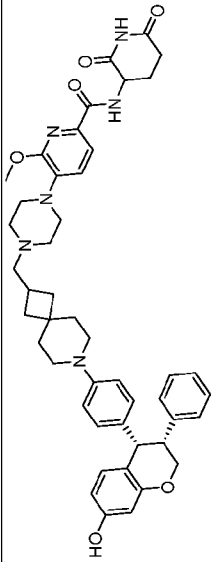
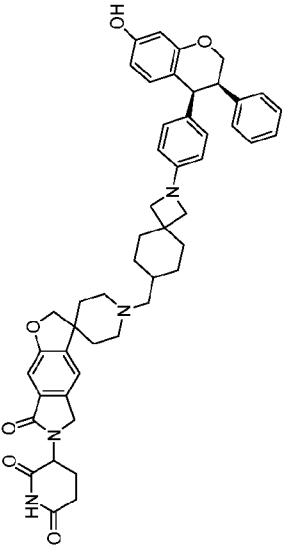
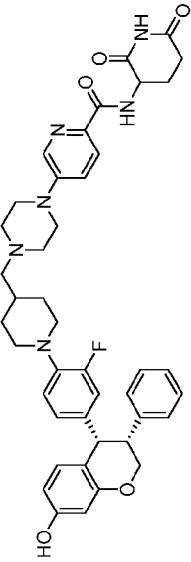
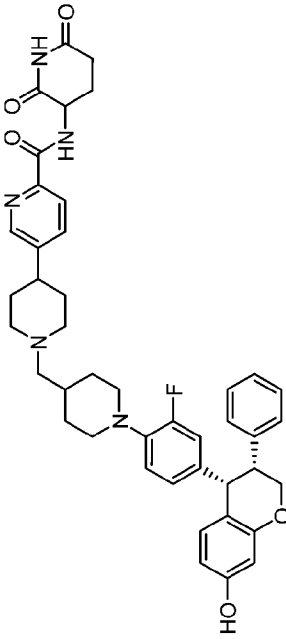
		pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A71*		3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl))-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A72*		3-(3-fluoro-4-(1-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A73*		3-(5-(1-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl))-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzodimidazol-1-yl)piperidine-2,6-dione

A74*		3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A75*		3-((3-fluoro-4-(1-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A76*		3-((R)-7-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-81pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A77*		3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A78*		2-(2,6-dioxopiperidin-3-yl)-6-(1'-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione

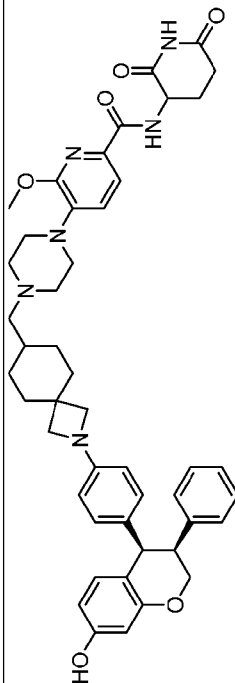
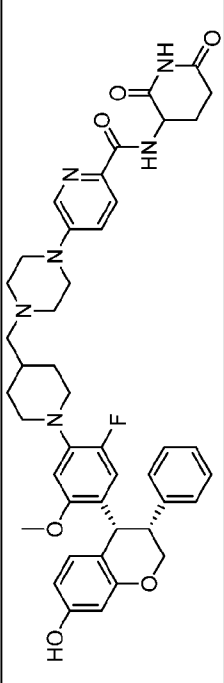
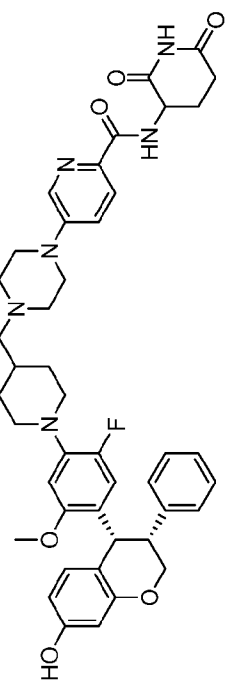
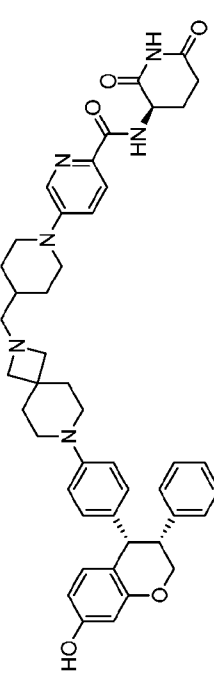
A79*		2-(2,6-dioxopiperidin-3-yl)-6-(1'-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1,4'-bipiperidine]-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
A80*		3-(6-(1'-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
A81*		3-(6-(1'-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
A84*		3-((R)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A85*		N-(2,6-dioxopiperidin-3-yl)-5-(4-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)picolinamide

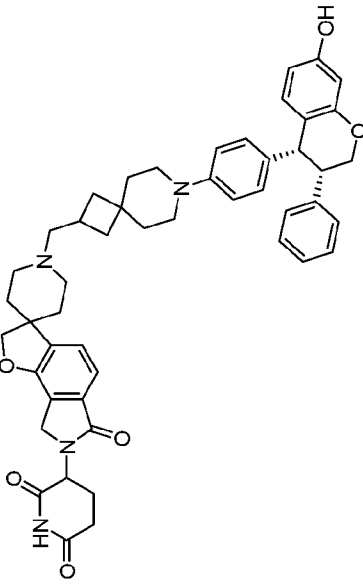
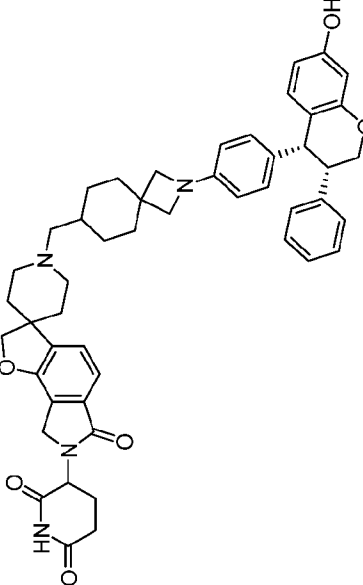
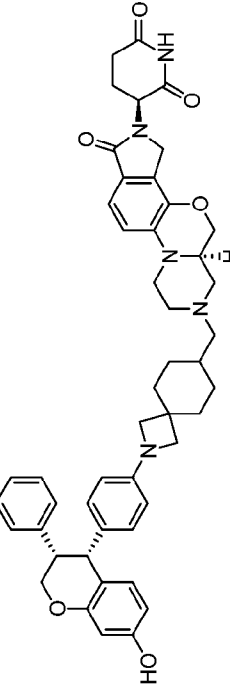
A86*		3-(1'-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A88*		N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide
A89*		(R)-3-((R)-7-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl))-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A90*		(S)-3-((R)-7-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl))-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

A91*	The chemical structure of A91* features a central benzodioxane core. It is substituted with a 2,6-dioxopiperidin-3-yl group, a 3-phenylpiperidin-4-yl group, a 1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl group, and a 2,6-dione hydrochloride group.	3-(((R)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)amino)piperidine-2,6-dione hydrochloride
A93*	The chemical structure of A93* is similar to A91* but lacks the 2,6-dione hydrochloride group, instead featuring a 2,6-dioxopiperidin-3-yl group.	(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A94*	The chemical structure of A94* is similar to A91* but lacks the 2,6-dione hydrochloride group, instead featuring a 2,6-dioxopiperidin-3-yl group.	3-(((R)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazin-8-yl)amino)piperidine-2,6-dione
A95*	The chemical structure of A95* is similar to A91* but lacks the 2,6-dione hydrochloride group, instead featuring a 2,6-dioxopiperidin-3-yl group.	(R)-3-(((R)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A96*	The chemical structure of A96* is similar to A91* but lacks the 2,6-dione hydrochloride group, instead featuring a 2,6-dioxopiperidin-3-yl group.	(R)-3-(((S)-3-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

A97*		N-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-6-methoxy)picolinamide
A99*		3-(1'-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A100*		N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide
A101*		N-(2,6-dioxopiperidin-3-yl)-5-(1-(1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperidin-4-yl)picolinamide

A102*	The chemical structure of A102* features a central benzene ring substituted with a hydroxyl group, a 2,3-dihydro-4H-benzofuran ring, and a 2-fluoro-4-(2-methoxyphenyl)phenyl group. This central moiety is connected via a piperazine ring to a 2-methoxyphenyl group, which is further linked to a 2,6-dioxopiperidin-3-yl group.	N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)-6-methoxypicolinamide
A103*	The chemical structure of A103* features a central benzene ring substituted with a hydroxyl group, a 2,3-dihydro-4H-benzofuran ring, and a 2-fluoro-4-(2-methoxyphenyl)phenyl group. This central moiety is connected via a piperazine ring to a 2-methoxyphenyl group, which is further linked to a 2,6-dioxopiperidin-3-yl group.	(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A104*	The chemical structure of A104* features a central benzene ring substituted with a hydroxyl group, a 2,3-dihydro-4H-benzofuran ring, and a 2-fluoro-4-(2-methoxyphenyl)phenyl group. This central moiety is connected via a piperazine ring to a 2-methoxyphenyl group, which is further linked to a 2,6-dioxopiperidin-3-yl group.	(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A105*	The chemical structure of A105* features a central benzene ring substituted with a hydroxyl group, a 2,3-dihydro-4H-benzofuran ring, and a 2-fluoro-4-(2-methoxyphenyl)phenyl group. This central moiety is connected via a piperazine ring to a 2-methoxyphenyl group, which is further linked to a 2,6-dioxopiperidin-3-yl group.	(R)-3-((S)-7-((1-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,7-dione
A106*	The chemical structure of A106* features a central benzene ring substituted with a hydroxyl group, a 2,3-dihydro-4H-benzofuran ring, and a 2-fluoro-4-(2-methoxyphenyl)phenyl group. This central moiety is connected via a piperazine ring to a 2-methoxyphenyl group, which is further linked to a 2,6-dioxopiperidin-3-yl group.	(R)-3-((S)-7-((1-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

A108*		N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-6-methoxypicolinamide
A109*		N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide
A110*		N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide
A111*		N-((R)-2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)methyl)piperidin-1-yl)picolinamide

A113*		3-(1'-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A114*		3-(1'-(2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A115*		(S)-3-((R)-7-(2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

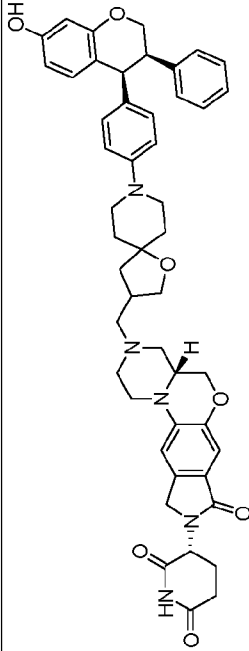
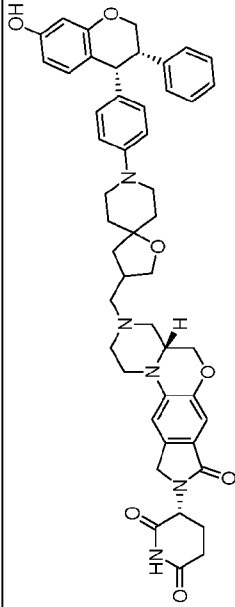
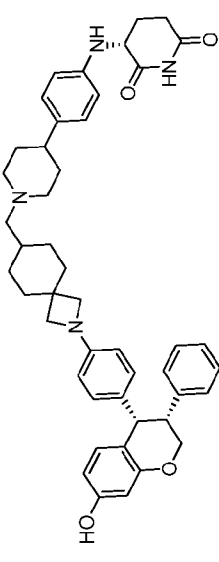
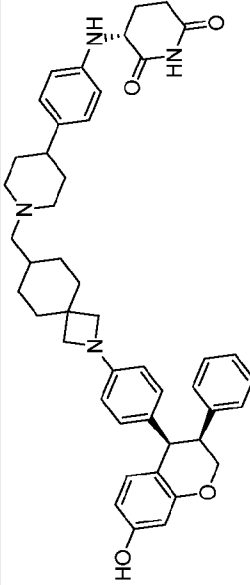
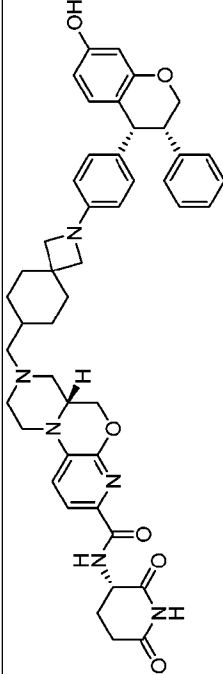
A116*	The chemical structure of A116* features a central benzene ring substituted with a 4-methoxyphenyl group, a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group, and a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group.
A117*	The chemical structure of A117* features a central benzene ring substituted with a 4-methoxyphenyl group, a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group, and a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group.
A118*	The chemical structure of A118* features a central benzene ring substituted with a 4-methoxyphenyl group, a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group, and a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group.
A119*	The chemical structure of A119* features a central benzene ring substituted with a 4-methoxyphenyl group, a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group, and a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group.
A120*	The chemical structure of A120* features a central benzene ring substituted with a 4-methoxyphenyl group, a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group, and a 4-(2,6-dioxopiperidin-3-yl)-5-(4-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide group.

A121*	A complex molecule featuring a central benzene ring substituted with a hydroxyl group, a methoxy group, and a side chain containing a piperidine ring, a chiral center, and a pyrazine ring.	(R)-3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A122*	A complex molecule featuring a central benzene ring substituted with a hydroxyl group, a methoxy group, and a side chain containing a piperidine ring, a chiral center, and a pyrazine ring.	(R)-3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A123*	A complex molecule featuring a central benzene ring substituted with a hydroxyl group, a methoxy group, and a side chain containing a piperidine ring, a chiral center, and a pyrazine ring.	3-(1'-(7-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl))-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A124*	A complex molecule featuring a central benzene ring substituted with a hydroxyl group, a methoxy group, and a side chain containing a piperidine ring, a chiral center, and a pyrazine ring.	N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide
A125*	A complex molecule featuring a central benzene ring substituted with a hydroxyl group, a methoxy group, and a side chain containing a piperidine ring, a chiral center, and a pyrazine ring.	(R)-3-((S)-7-(7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

A126*	The chemical structure of A126* features a central benzodioxane system. A 4-hydroxyphenyl group is attached to the dioxane ring. The other side of the dioxane ring is connected to a 1-phenyl-4-(2-oxo-2,3,4,5-tetrahydro-1H-pyridine-2-yl)pyrrolidine moiety. This pyrrolidine is further substituted with a 2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl group.	(R)-3-((S)-7-(7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A127*	The chemical structure of A127* is similar to A126* but lacks the 2-fluoro substituent on the phenyl ring of the pyrrolidine moiety. It features a 1-phenyl-4-(2-oxo-2,3,4,5-tetrahydro-1H-pyridine-2-yl)pyrrolidine core with a 2-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl substituent.	N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide
A128*	The chemical structure of A128* is similar to A127* but lacks the 3-methoxy substituent on the phenyl ring of the pyrrolidine moiety. It features a 1-phenyl-4-(2-oxo-2,3,4,5-tetrahydro-1H-pyridine-2-yl)pyrrolidine core with a 2-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl substituent.	N-(2,6-dioxopiperidin-3-yl)-5-(4-((4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)picolinamide
A129*	The chemical structure of A129* is similar to A128* but lacks the 4-hydroxy substituent on the phenyl ring of the pyrrolidine moiety. It features a 1-phenyl-4-(2-oxo-2,3,4,5-tetrahydro-1H-pyridine-2-yl)pyrrolidine core with a 2-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl substituent.	N-(2,6-dioxopiperidin-3-yl)-5-(4-((4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-1-yl)methyl)piperidin-1-yl)picolinamide

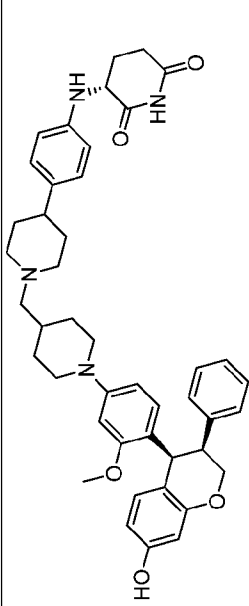
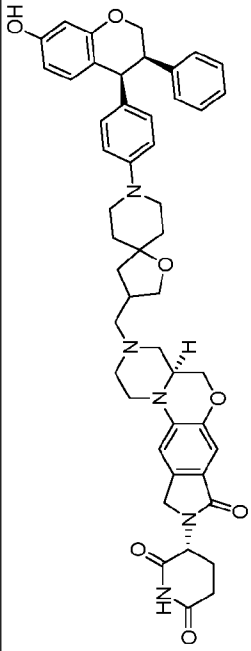
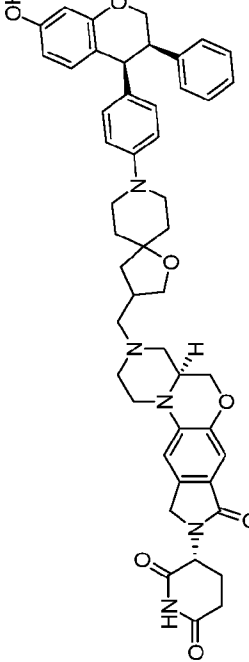
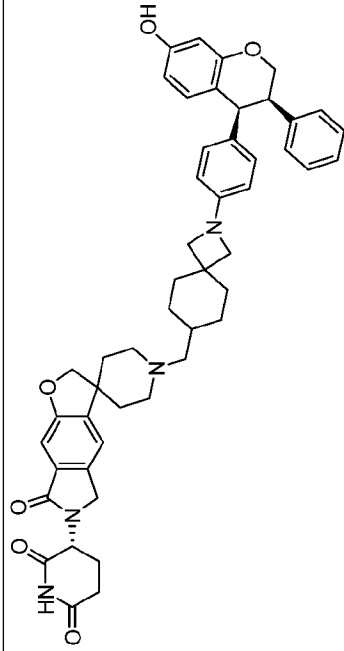
A130*	A complex molecule featuring a central benzene ring substituted with a 3-phenylchroman-4-yl group, a 7-hydroxy-3-methoxyphenyl group, and a 7-azaspiro[3.5]nonan-2-ylmethyl group. The 7-azaspiro[3.5]nonan-2-ylmethyl group is further substituted with a 6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl group.	3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A131*	A complex molecule featuring a central benzene ring substituted with a 3-phenylchroman-4-yl group, a 7-hydroxy-3-methoxyphenyl group, and a 7-azaspiro[3.5]nonan-2-ylmethyl group. The 7-azaspiro[3.5]nonan-2-ylmethyl group is further substituted with a 6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl group.	3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A132*	A complex molecule featuring a central benzene ring substituted with a 3-phenylchroman-4-yl group, a 7-hydroxy-3-methoxyphenyl group, and a 7-azaspiro[3.5]nonan-2-ylmethyl group. The 7-azaspiro[3.5]nonan-2-ylmethyl group is further substituted with a 6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl group.	(R)-3-((S)-7-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A133*	A complex molecule featuring a central benzene ring substituted with a 3-phenylchroman-4-yl group, a 7-hydroxy-3-methoxyphenyl group, and a 7-azaspiro[3.5]nonan-2-ylmethyl group. The 7-azaspiro[3.5]nonan-2-ylmethyl group is further substituted with a 6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl group.	(R)-3-((S)-7-(((S)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

A134*	The chemical structure of A134* features a central piperidine ring substituted with a 2,6-dioxopiperidin-3-yl group and a 3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide group.	(4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide
A135*	The chemical structure of A135* features a central piperidine ring substituted with a 3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group.	3-((1'-(1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A136*	The chemical structure of A136* features a central piperidine ring substituted with a 3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione group.	3-((1'-(1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione
A137*	The chemical structure of A137* features a central piperidine ring substituted with a 3-((1-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group.	3-((1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

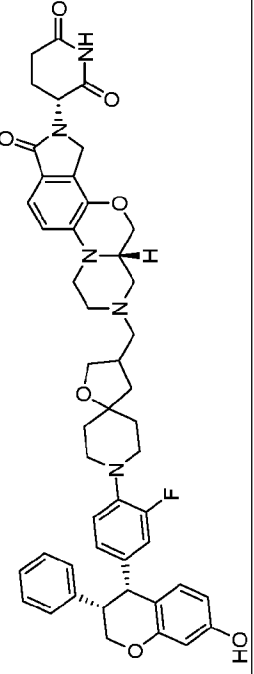
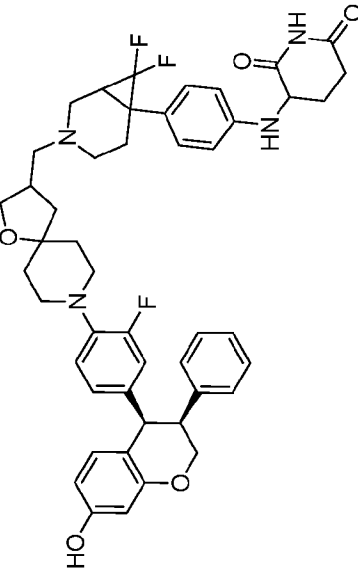
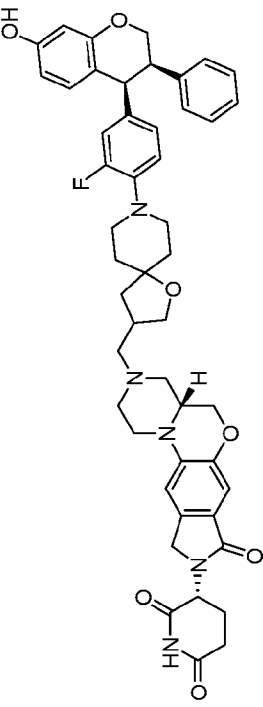
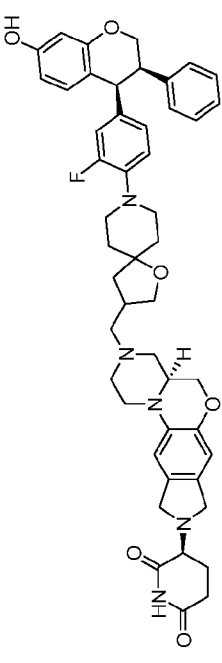
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A139*		(3R)-3-((4aR)-3-((8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A140*		(R)-3-((4-(1-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A141*		(R)-3-((4-(1-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A142*		(R)-N-(S)-2,6-dioxopiperidin-3-yl)-3-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide

A143*	The chemical structure of A143* is a complex molecule. It features a central benzene ring substituted with a 2,6-dioxopiperidin-3-yl group, a 7-hydroxy-3-phenylchroman-4-yl group, and a 7-azaspiro[3.5]nonan-2-ylmethyl group. The 7-azaspiro[3.5]nonan-2-ylmethyl group is further substituted with a 6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl group and a 2,6-dione group.	(R)-3-(1'-((7-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl))-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
A144*	The chemical structure of A144* is a complex molecule. It features a central benzene ring substituted with a 2,6-dioxopiperidin-3-yl group, a 7-hydroxy-3-phenylchroman-4-yl group, and a 7-azaspiro[3.5]nonan-2-ylmethyl group. The 7-azaspiro[3.5]nonan-2-ylmethyl group is further substituted with a 6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl group and a 2,6-dione group.	N-((R)-2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl))-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide
A145*	The chemical structure of A145* is a complex molecule. It features a central benzene ring substituted with a 2,6-dioxopiperidin-3-yl group, a 7-hydroxy-3-phenylchroman-4-yl group, and a 7-azaspiro[3.5]nonan-2-ylmethyl group. The 7-azaspiro[3.5]nonan-2-ylmethyl group is further substituted with a 6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl group and a 2,6-dione group.	N-((R)-2,6-dioxopiperidin-3-yl)-5-(4-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl))-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperazin-1-yl)picolinamide

A146*	The chemical structure of A146* is a complex molecule featuring a central benzene ring substituted with a 3-(1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group and a 3-(1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group.
A147*	The chemical structure of A147* is a complex molecule featuring a central benzene ring substituted with a 3-(1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group and a 3-(1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group.
A148*	The chemical structure of A148* is a complex molecule featuring a central benzene ring substituted with a 3-(1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group and a 3-(1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group.
A149*	The chemical structure of A149* is a complex molecule featuring a central benzene ring substituted with a 3-(1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group and a 3-(1'-(8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione group.

A150*		(R)-3-((4-(1-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A151*		(R)-3-((S)-3-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A152*		(R)-3-((S)-3-(((S)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A153*		(R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

A154*		(R)-3-(1'-(2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-ylpiperidine-2,6-dione
A155*		(R)-3-((S)-7-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazinol[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A156*		3-((4-(7,7-difluoro-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione
A157*		(S)-3-((R)-7-(((R)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazinol[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

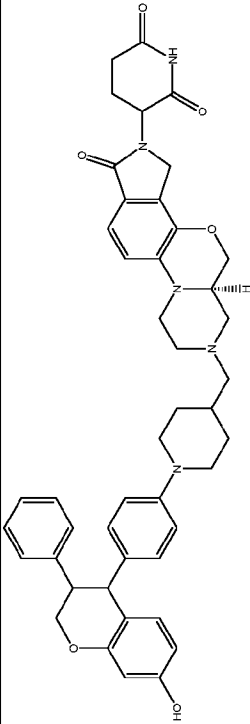
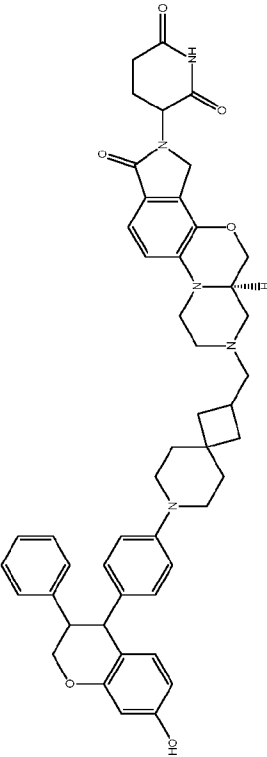
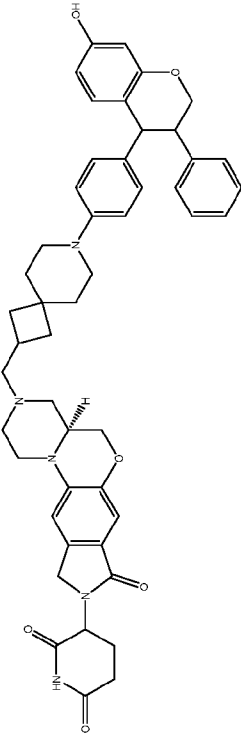
A158*		(3R)-3-((5aS)-7-((8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
A159*		3-((4-(7,7-difluoro-3-(((R)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione
A160*		(R)-3-((R)-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
A161*		(S)-3-((S)-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

A162*	The chemical structure of A162* features a central 2,3-diphenyl-3,4-dihydro-2H-benzoo[1,2-b]oxole core. The 2-position is substituted with a 4-hydroxyphenyl group, and the 3-position is substituted with a 4-phenyl group. The 4-phenyl group is further substituted with a 4-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-1-yl group. The 4-phenyl group is also substituted with a 4-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-1-yl group.	(R)-3-((3-fluoro-4-(1-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A163*	The chemical structure of A163* is identical to A162*, except for the stereochemistry of the 1-oxa-8-azaspiro[4.5]decan-3-yl group, which is specified as (S) instead of (R).	(R)-3-((3-fluoro-4-(1-(((S)-8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione
A164*	The chemical structure of A164* is identical to A162*, except for the stereochemistry of the 1-oxa-8-azaspiro[4.5]decan-3-yl group, which is specified as (S) instead of (R).	(R)-3-((3-fluoro-4-(1-(((S)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione

A165*	The chemical structure of A165* is a complex molecule. It features a central chiral center (a carbon atom) bonded to four different groups: a 4-hydroxyphenyl group, a 4-phenylpiperidine-2,6-dione group, a 4-(3-fluoro-4-((1-((R)-8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione group, and a 4-phenylpiperidine-2,6-dione group. The structure is drawn with stereochemistry indicating the (R) configuration at the chiral center.	(R)-3-((3-fluoro-4-(1-((R)-8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)piperidine-2,6-dione
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Table 2. Compounds B1-B5

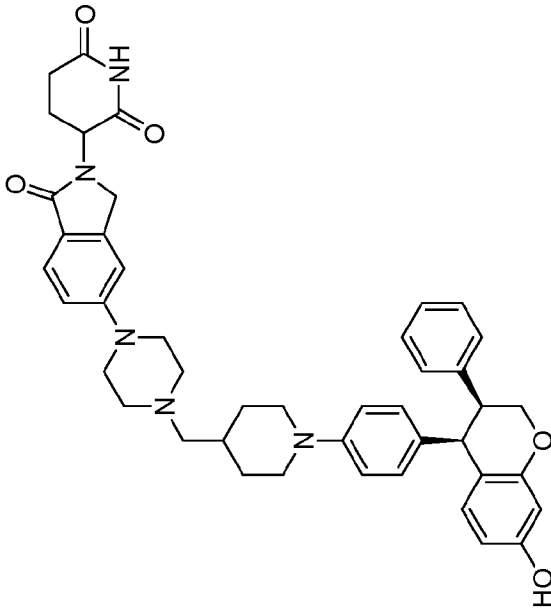
*designates that it is racemic with respect to the two stereogenic centers at the warhead (chroman); the relative configuration of the two stereogenic center is *cis*.

Compound No	Chemical Name	Chemical Name
B1*		3-((5aR)-7-((1-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B2*		3-((5aR)-7-((7-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
B3*		3-((4aS)-3-((7-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

B4*	The chemical structure of B4* is a complex molecule. It features a central benzene ring substituted with a 6-hydroxy-3,4-dihydro-2H-chromene group at the 1-position and a 3-((7-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)furo[2,3-e]isoindole-3,4'-piperidin-2,6-dione group at the 4-position. The chromene group consists of a benzene ring fused to a six-membered ring containing a hydroxyl group and an oxygen atom. The piperidine ring is part of a spiro system with a five-membered ring containing two carbonyl groups and a nitrogen atom.
B5*	The chemical structure of B5* is a complex molecule. It features a central benzene ring substituted with a 6-methoxy-3,4-dihydro-2H-chromene group at the 1-position and a 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione group at the 4-position. The chromene group consists of a benzene ring fused to a six-membered ring containing a methoxy group and an oxygen atom. The piperidine ring is part of a spiro system with a five-membered ring containing two carbonyl groups and a nitrogen atom.

Table 3. Selected Compounds from A1-A165

designates that it is enantiomerically pure with respect to the warhead (chroman) but the absolute configuration is not specified; the relative configuration of the two stereogenic centers is **cis.*

Compound No	Chemical Name	Chemical Name
A62*		3-(5-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)piperazin-1-yl)-1-yl)methyl)piperidine-2-yl)piperidine-2,6-dione

A67*	The chemical structure of A67* features a central spirocyclic system consisting of a cyclobutane ring fused to a piperidine ring. This spiro system is connected via a methylene bridge to a piperazine ring. The piperazine ring is further connected to a benzimidazole moiety, which is substituted with a 3-oxo-3,4-dihydro-1H-pyridin-2-yl group. The benzimidazole moiety is also substituted with a 3-oxo-3,4-dihydro-1H-pyridin-2-yl group. The piperidine ring is substituted with a 3-oxo-3,4-dihydro-1H-pyridin-2-yl group.	3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
A68*	The chemical structure of A68* is identical to A67*, but the piperidine ring is substituted with a 3-oxo-3,4-dihydro-1H-pyridin-2-yl group instead of a 3-oxo-3,4-dihydro-1H-pyridin-2-yl group.	3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione

A82*	The chemical structure of A82* features a 4-hydroxy-2-phenylchroman-3-yl group connected via a chiral center to a 4-phenylpiperazine ring. This piperazine ring is further connected via its nitrogen to a 4-phenylpiperidine ring, which is also connected via its nitrogen to a 2,4-dihydropyrimidin-1-yl group. The pyrimidine ring has a carbonyl group at position 2 and a hydroxyl group at position 4.	1-(4-(4-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-4-yl)methyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione
A83*	The chemical structure of A83* is similar to A82*, but the piperazine ring is substituted with a 3,5-dihydro-1H-benzodioxol-2-yl group instead of a phenyl group. The rest of the molecule, including the 4-phenylpiperidine and 2,4-dihydropyrimidin-1-yl groups, remains the same.	1-(4-(4-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

A87*	The chemical structure of A87* features a 3,4-dihydro-2H-chromene core. At the 2-position, there is a phenyl group. At the 3-position, there is a 4-hydroxyphenyl group. The 4-position is substituted with a 1-(4-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)methyl)piperidin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione moiety.	1-(4-(4-(7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2,7-diazaspiro[3.5]nonan-2-yl)methyl)piperidin-1-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione
A92*	The chemical structure of A92* features a 3,4-dihydro-2H-chromene core. At the 2-position, there is a pyridin-2-yl group. At the 3-position, there is a 4-hydroxyphenyl group. The 4-position is substituted with a 1-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione moiety.	(R)-3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione

A98*	The chemical structure of A98* features a central piperidine ring. One nitrogen of the piperidine is connected via a methylene group to a cyclobutane ring. The other nitrogen of the piperidine is connected to a pyridine ring. The pyridine ring is further connected to a biphenyl system, which includes a hydroxyl group. A side chain on the biphenyl system includes a morpholine ring and a phenyl group.	(R)-3-(5-(4-((7-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
A107*	The chemical structure of A107* features a central piperazine ring. One nitrogen of the piperazine is connected via a methylene group to a cyclobutane ring. The other nitrogen of the piperazine is connected to a phenyl ring. The phenyl ring is further connected to a biphenyl system, which includes a hydroxyl group. A side chain on the biphenyl system includes a morpholine ring and a phenyl group.	1-(4-(2-((4-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-1-yl)methyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)dihydropyrimidine-2,4(1H,3H)-dione

A112*		1-(4-(2-((4-(4-((3<i>S</i>,4<i>R</i>)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperazin-1-yl)methyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)dihydropyrimidine-2,4(1<i>H</i>,3<i>H</i>)-dione
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[0124] The compounds of the present disclosure may possess advantageous characteristics, as compared to known compounds, such as known estrogen receptor degraders. For example, the compounds of the present disclosure may display more potent estrogen receptor activity, more favorable pharmacokinetic properties (*e.g.*, as measured by $C_{\max}$, $T_{\max}$, and/or AUC), and/or less interaction with other cellular targets (*e.g.*, hepatic cellular transporter such as OATP1B1) and accordingly improved safety (*e.g.*, drug-drug interaction). These beneficial properties of the compounds of the present disclosure can be measured according to methods commonly available in the art, such as methods exemplified herein.

[0125] Due to the existence of double bonds, the compounds of the present disclosure may be in *cis* or *trans*, or Z or E, configuration. It is understood that although one configuration may be depicted in the structure of the compounds or formulae of the present disclosure, the present disclosure also encompasses the other configuration. For example, the compounds or formulae of the present disclosure may be depicted in *cis* or *trans*, or Z or E, configuration.

[0126] In some embodiments, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a pharmaceutically acceptable salt. In some embodiments, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a solvate. In some embodiments, a compound of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein) is a hydrate.

[0127] The details of the disclosure are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, illustrative methods and materials are now described. Other features, objects, and advantages of the disclosure will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Forms of Compounds Disclosed Herein

Pharmaceutically acceptable salts

[0128] In some embodiments, the compounds disclosed herein exist as their pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts. In some embodiments, the methods disclosed herein include methods of treating diseases by administering such pharmaceutically acceptable salts as pharmaceutical compositions.

[0129] In some embodiments, the compounds described herein possess acidic or basic groups and therefor react with any of a number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. In some embodiments, these salts are prepared *in situ* during the final isolation and purification of the compounds disclosed herein, or by separately reacting a purified compound in its free form with a suitable acid or base, and isolating the salt thus formed.

[0130] Examples of pharmaceutically acceptable salts include those salts prepared by reaction of the compounds described herein with a mineral, organic acid, or inorganic base, such salts including acetate, acrylate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, bisulfite, bromide, butyrate, butyn-1,4-dioate, camphorate, camphorsulfonate, caproate, caprylate, chlorobenzoate, chloride, citrate, cyclopentanepropionate, decanoate, digluconate, dihydrogenphosphate, dinitrobenzoate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptanoate, glycerophosphate, glycolate, hemisulfate, heptanoate, hexanoate, hexyne-1,6-dioate, hydroxybenzoate, γ -hydroxybutyrate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, iodide, isobutyrate, lactate, maleate, malonate, methanesulfonate, mandelate metaphosphate, methanesulfonate, methoxybenzoate, methylbenzoate, monohydrogenphosphate, 1-naphthalenesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, palmoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, pyrosulfate, pyrophosphate, propiolate, phthalate, phenylacetate, phenylbutyrate, propanesulfonate, salicylate, succinate, sulfate, sulfite, succinate, suberate, sebacate, sulfonate, tartrate, thiocyanate, tosylate, undecanoate, and xylenesulfonate.

[0131] Further, the compounds described herein can be prepared as pharmaceutically acceptable salts formed by reacting the free base form of the compound with a pharmaceutically acceptable

inorganic or organic acid, including, but not limited to, inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid metaphosphoric acid, and the like; and organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, p-toluenesulfonic acid, tartaric acid, trifluoroacetic acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, arylsulfonic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 2-naphthalenesulfonic acid, 4-methylbicyclo-[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis-(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, and muconic acid.

[0132] In some embodiments, those compounds described herein which comprise a free acid group react with a suitable base, such as the hydroxide, carbonate, bicarbonate, or sulfate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, tertiary, or quaternary amine. Representative salts include the alkali or alkaline earth salts, like lithium, sodium, potassium, calcium, and magnesium, and aluminum salts and the like. Illustrative examples of bases include sodium hydroxide, potassium hydroxide, choline hydroxide, sodium carbonate, $N^+(C_{1-4} \text{ alkyl})_4$, and the like.

[0133] Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like. It should be understood that the compounds described herein also include the quaternization of any basic nitrogen-containing groups they contain. In some embodiments, water or oil-soluble or dispersible products are obtained by such quaternization.

Solvates

[0134] Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as “solvates”. For example, a complex with water is known as a “hydrate”. Solvates are within the scope of the present disclosure.

[0135] It will also be appreciated by those skilled in organic chemistry that many organic compounds can exist in more than one crystalline form. For example, crystalline form may vary

from solvate to solvate. Thus, all crystalline forms or the pharmaceutically acceptable solvates thereof are contemplated and are within the scope of the present disclosure.

[0136] In some embodiments, the compounds described herein exist as solvates. The present disclosure provides for methods of treating diseases by administering such solvates. The present disclosure further provides for methods of treating diseases by administering such solvates as pharmaceutical compositions.

[0137] Solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of the compounds described herein can be conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein can exist in unsolvated as well as solvated forms. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the compounds and methods provided herein.

Isomers/Stereoisomers

[0138] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed “isomers.” Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.”

[0139] In some embodiments, the compounds described herein exist as geometric isomers. In some embodiments, the compounds described herein possess one or more double bonds. The compounds disclosed herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (E), and *zusammen* (Z) isomers as well as the corresponding mixtures thereof. All geometric forms of the compounds disclosed herein are contemplated and are within the scope of the present disclosure.

[0140] In some embodiments, the compounds disclosed herein possess one or more chiral centers and each center exists in the R configuration or S configuration. The compounds disclosed herein include all diastereomeric, enantiomeric, and epimeric forms as well as the corresponding mixtures thereof. All diastereomeric, enantiomeric, and epimeric forms of the compounds disclosed herein are contemplated and are within the scope of the present disclosure.

[0141] In additional embodiments of the compounds and methods provided herein, mixtures of enantiomers and/or diastereoisomers, resulting from a single preparative step, combination, or

interconversion are useful for the applications described herein. In some embodiments, the compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers, and recovering the optically pure enantiomers. In some embodiments, dissociable complexes are preferred. In some embodiments, the diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and are separated by taking advantage of these dissimilarities. In some embodiments, the diastereomers are separated by chiral chromatography, or preferably, by separation/resolution techniques based upon differences in solubility. In some embodiments, the optically pure enantiomer is then recovered, along with the resolving agent.

Tautomers

[0142] In some embodiments, compounds described herein exist as tautomers. The compounds described herein include all possible tautomers within the formulas described herein.

[0143] Tautomers are compounds that are interconvertible by migration of a hydrogen atom, accompanied by a switch of a single bond and an adjacent double bond. In bonding arrangements where tautomerization is possible, a chemical equilibrium of the tautomers will exist. All tautomeric forms of the compounds disclosed herein are contemplated and are within the scope of the present disclosure. The exact ratio of the tautomers depends on several factors, including temperature, solvent, and pH.

Pharmaceutical Compositions

[0144] In certain embodiments, the compound described herein is administered as a pure chemical. In some embodiments, the compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard

pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[0145] Accordingly, the present disclosure provides pharmaceutical compositions comprising a compound described herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable excipient.

[0146] In certain embodiments, the compound provided herein is substantially pure, in that it contains less than about 5%, less than about 1%, or less than about 0.1% of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[0147] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit (*e.g.*, an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity). Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[0148] In some embodiments, the pharmaceutical composition is formulated for oral, topical (including buccal and sublingual), rectal, vaginal, transdermal, parenteral, intrapulmonary, intradermal, intrathecal and epidural and intranasal administration. Parenteral administration includes intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. In some embodiments, the pharmaceutical composition is formulated for intravenous injection, oral administration, inhalation, nasal administration, topical administration, or ophthalmic administration. In some embodiments, the pharmaceutical composition is formulated for oral administration. In some embodiments, the pharmaceutical composition is formulated for intravenous injection. In some embodiments, the pharmaceutical composition is formulated as a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a suspension, a gel, a colloid, a dispersion, a suspension, a solution, an emulsion, an ointment, a lotion, an eye

drop, or an ear drop. In some embodiments, the pharmaceutical composition is formulated as a tablet.

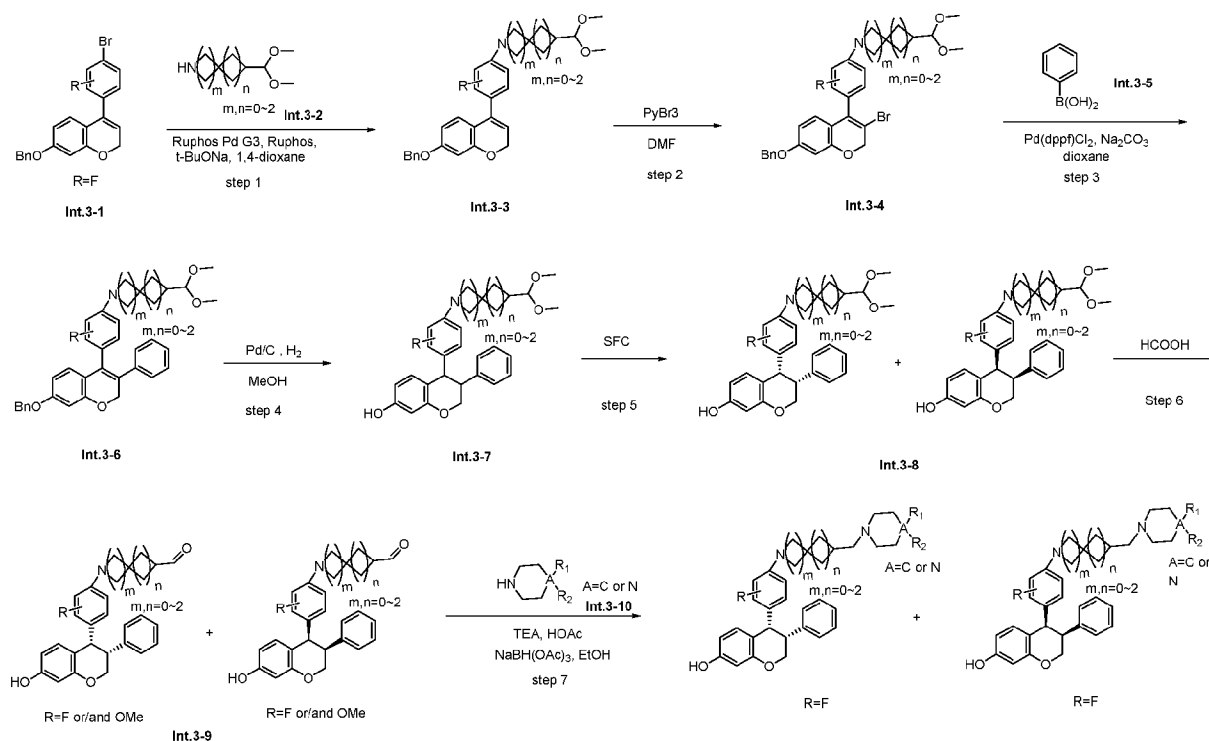
Preparation of the Compounds

[0149] The compounds of the present disclosure can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, the compounds of the present disclosure can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. The compounds of the present disclosure (*i.e.*, a compound of the present application (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein)) can be synthesized by following the general synthetic scheme below as well as the steps outlined in the examples, schemes, procedures, and/or synthesis described herein (*e.g.*, Examples).

General Synthetic Method

[0150] The compounds of the present disclosure can generally be prepared by first preparing pools of intermediates, including a pool of cereblon ligands, a pool of linkers, and a pool of inhibitors, as detailed in the Example section, then followed by subsequent reactions to connect a linker to an inhibitor and a cereblon ligand via metal-catalyzed coupling reactions and reductive amination. Large pool of compounds can be prepared by selecting different combinations of cereblon ligands, linkers, and inhibitors from each pool. General synthetic routes for preparing inhibitor-linker conjugate via metal-catalyzed coupling reactions, which is further coupled to cereblon ligand via reductive amination, are summarized below.

Scheme 1



[0151] Those skilled in the art will recognize if a stereocenter exists in the compounds of the present disclosure (*e.g.*, a compound of any of the formulae or any individual compounds disclosed herein). Accordingly, the present disclosure includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compound but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. *See*, for example, "Stereochemistry of Organic Compounds" by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

[0152] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH, Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chem Service Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co.

(Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[0153] Suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatises that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R.V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X,

in 8 volumes; “Organic Reactions” (1942-2000) John Wiley & Sons, in over 55 volumes; and “Chemistry of Functional Groups” John Wiley & Sons, in 73 volumes.

[0154] Specific and analogous reactants are optionally identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line. Chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference for the preparation and selection of pharmaceutical salts of the compounds described herein is P. H. Stahl & C. G. Wermuth “Handbook of Pharmaceutical Salts”, Verlag Helvetica Chimica Acta, Zurich, 2002.

Analytical Methods, Materials, and Instrumentation

[0155] Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either Bruker or Varian spectrometers at 400 MHz. Spectra are given in ppm (δ) and coupling constants, J, are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard. Liquid chromatography-mass spectrometry (LC/MS) were collected using a SHIMADZU LCMS-2020EV or Agilent 1260-6125B LCMS. Purity and low resolution mass spectral data were measured using Agilent 1260-6125B LCMS system (with Diode Array Detector, and Agilent G6125BA Mass spectrometer) or using Waters Acquity UPLC system (with Diode Array Detector, and Waters 3100 Mass Detector). The purity was characterized by UV wavelength 214 nm, 220 nm, 254 nm and ESI. Column: poroshell 120 EC-C18 2.7 μ m 4.6 X 100 mm; Flow rate 0.8 mL/min; Solvent A (100/0.1 water/formic acid), Solvent B (100 acetonitrile); gradient: hold 5% B to 0.3 min, 5-95% B from 0.3 to 2 min, hold 95% B to 4.8 min, 95-5% B from 4.8 to 5.4 min, then hold 5% B to 6.5 min. Or, column: Acquity UPLC BEH C18 1.7 μ m 2.1 X 50 mm; Flow rate 0.5 mL/min; Solvent A (0.1%formic acid water), Solvent B (acetonitrile); gradient: hold 5%B for 0.2 min, 5-95% B from 0.2 to 2.0 min, hold 95% B to 3.1 min, then 5% B at 3.5 min.

Biological Assays

[0156] The biological activities of the compounds of the present application can be assessed with methods and assays known in the art.

[0157] The CRBN-DDB1 binding potency of the present disclosure is determined using HTRF assay technology (Perkin Elmer). Compounds are serially diluted and are transferred multi-well plate. The reaction is conducted with addition of His tagged (e.g., CRBN+DDB-DLS7+CXU4) followed by addition of 60 nM fluorescent probe (e.g., Cy5-labeled Thalidomide), and MAb Anti-6HIS Tb cryptate Gold in the assay buffer. After one hour incubation at room temperature, the HTRF signals are read on Envision reader (Perkin Elemer).

[0158] ERa degradative activity of compounds can be assessed in MCF-7 and T47D Cells. MCF-7 and T47D cell are seeded and are subsequently treated with the compounds at certain concentrations (e.g., 0.02 to 300 nM). DMSO can be used as vehicle control. Cells are fixed and are blocked with Intercept (PBS) Blocking Buffer (e.g., Li-COR, Odyssey Blocking Buffer), and are stained with ER (e.g., 1:500, Cell signaling) primary antibody for overnight at cold room. Secondary Antibody (e.g., IRDye 800CW Goat anti-Rabbit IgG) and CellTag 700 Stain are added in Intercept (PBS) Blocking Buffer. Finally, cell plate is placed in incubator to dry. Image and signal are captured on Odyssey® DLx Imaging System.

[0159] In vitro assay can be accomplished by MCF-7 and T47D Cell Titer Glo (CTG) assay. MCF-7 and T47D cell (From HDB) are cultured in multi-well white plate with phenol red-free RPMI1640 + 10% CS-FBS + 1% P/S medium (e.g., at 1,000cells/well). On day 0: Cells are treated with compound at certain concentrations (e.g., 0.5 to 10000 nM) (DMSO and Staurosporine as control). On day 0 and day 6: add Cell Titer Glo reagent and read on EnVision after 30min incubation for data generation.

[0160] In-cell western blot analysis. Cells are seeded in multi-well plates (e.g., at 40,000 or 10,000 cells/well). Diluted compounds at certain concentration are added (final 0.5% DMSO) and cells are incubated for a certain period of time (e.g., 16 hours). Formaldehyde (e.g., PBS:FA=9:1) is added and followed by washing with PBS. The cells are blocked with Licor blocking buffer (Li-Cor). The relative ER percentage in treated cells were obtained by comparing the values of treated wells to those in untreated and DMSO-treated wells as 100%.

[0161] Western Blot Analysis. The cells that are treated with the compounds are lysed in Radioimmunoprecipitation Assay Protein Lysis and Extraction Buffer (e.g., 25 mmol/L Tris.HCl, pH 7.6, 150 mmol/L NaCl, 1% Nonidet P-40, 1% sodium deoxycholate, and 0.1% sodium dodecyl sulfate) containing proteinase inhibitor cocktail. Equal amounts of total protein are electrophoresed through 10% SDS-polyacrylamide gels after determination of protein concentration by BCA assay.

The separated protein bands are transferred onto PVDF membranes and blotted against different antibodies. The blots are scanned, and the band intensities are quantified (e.g., by using GelQuant.NET software provided by biochemlabsolutions.com). The relative mean intensity of target proteins is expressed after normalization to the intensity of glyceraldehyde-3-phosphate dehydrogenase bands.

[0162] Cell Growth Assay. The cells are seeded at certain concentration (e.g., at 1500/well) in multi-well plates overnight. Cells are subsequently treated with the compounds. A certain period of time (e.g., 4 days) after the compound treatment, 10% WST-8 reagent is added to the culture medium and incubate under certain condition (e.g., in a CO₂ incubator at 37°C for 2.5 hours). The absorbance is measured on each sample using a microplate reader at certain wavelength (e.g., 450 nm). The relative absorbance is calculated against the vehicle control from three individually repeats.

[0163] In vivo pharmacodynamic and efficacy studies. To develop breast cancer cell line xenografts, mice are given 17β-Estradiol in drinking water for a certain period of time. Certain number (e.g., five million) of cells in 50% Matrigel are injected subcutaneously into SCID mice to induce tumor formation. When tumors reach certain size (e.g., 100-400 mm³), mice are treated with vehicle control (e.g., 5% DMSO, 10% solutol, 85% Water) or the compound, and sacrificed at indicated time points. Tumor tissue is harvested for analysis. Tumor sizes and animal weights are measured 2-3 times per week. Tumor volume (mm³) = (length×width²)/2. Tumor growth inhibition is calculated using TGI (%) = (Vc-Vt)/(Vc-Vo) × 100, where Vc, Vt are the median of control and treated groups at the end of the study and Vo at the start.

Methods of Use

[0164] In certain aspects, the present disclosure provides methods of degrading an estrogen receptor in a subject, comprising administering to the subject a compound disclosed herein.

[0165] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for degrading an estrogen receptor in a subject.

[0166] In certain aspects, the present disclosure provides compounds disclosed herein for use in degrading an estrogen receptor in a subject.

[0167] In certain aspects, the present disclosure provides methods of treating or preventing a disease or disorder in a subject in need thereof, comprising administering to the subject a compound disclosed herein (e.g., in a therapeutically effective amount).

[0168] In certain aspects, the present disclosure provides methods of treating a disease or disorder in a subject in need thereof, comprising administering to the subject a compound disclosed herein (e.g., in a therapeutically effective amount).

[0169] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating or preventing a disease or disorder in a subject in need thereof.

[0170] In certain aspects, the present disclosure provides uses of a compound disclosed herein in the manufacture of a medicament for treating a disease or disorder in a subject in need thereof.

[0171] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating or preventing a disease or disorder in a subject in need thereof.

[0172] In certain aspects, the present disclosure provides compounds disclosed herein for use in treating a disease or disorder in a subject in need thereof.

[0173] In certain embodiments, the disease or disorder is an estrogen receptor-mediated disease or disorder.

[0174] In certain embodiments, the disease or disorder is cancer.

[0175] In certain embodiments, the disease or disorder is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

[0176] In certain embodiments, the cancer includes, but are not limited to, one or more of the cancers of **Table A**.

Table A.

adrenal cancer	acinic cell carcinoma	acoustic neuroma	acral lentiginous melanoma
acrosiroma	acute eosinophilic leukemia	acute erythroid leukemia	acute lymphoblastic leukemia
acute megakaryoblastic leukemia	acute monocytic leukemia	acute promyelocytic leukemia	adenocarcinoma
adenoid cystic carcinoma	adenoma	adenomatoid odontogenic tumor	adenosquamous carcinoma
adipose tissue neoplasm	adrenocortical carcinoma	adult T-cell leukemia/lymphoma	aggressive NK-cell leukemia

AIDS-related lymphoma	alveolar rhabdomyosarcoma	alveolar soft part sarcoma	ameloblastic fibroma
anaplastic large cell lymphoma	anaplastic thyroid cancer	angioimmunoblastic T-cell lymphoma	angiomyolipoma
angiosarcoma	astrocytoma	atypical teratoid rhabdoid tumor	B-cell chronic lymphocytic leukemia
B-cell prolymphocytic leukemia	B-cell lymphoma	basal cell carcinoma	biliary tract cancer
bladder cancer	blastoma	bone cancer	Brenner tumor
Brown tumor	Burkitt's lymphoma	breast cancer	brain cancer
carcinoma	carcinoma in situ	carcinosarcoma	cartilage tumor
cementoma	myeloid sarcoma	chondroma	chordoma
choriocarcinoma	choroid plexus papilloma	clear-cell sarcoma of the kidney	craniopharyngioma
cutaneous T-cell lymphoma	cervical cancer	colorectal cancer	Degos disease
desmoplastic small round cell tumor	diffuse large B-cell lymphoma	dysembryoplastic neuroepithelial tumor	dysgerminoma
embryonal carcinoma	endocrine gland neoplasm	endodermal sinus tumor	enteropathy-associated T-cell lymphoma
esophageal cancer	fetus in fetu	fibroma	fibrosarcoma
follicular lymphoma	follicular thyroid cancer	ganglioneuroma	gastrointestinal cancer
germ cell tumor	gestational choriocarcinoma	giant cell fibroblastoma	giant cell tumor of the bone
glial tumor	glioblastoma multiforme	glioma	gliomatosis cerebri
glucagonoma	gonadoblastoma	granulosa cell tumor	gynandroblastoma
gallbladder cancer	gastric cancer	hairy cell leukemia	hemangioblastoma
head and neck cancer	hemangiopericytoma	hematological cancer	hepatoblastoma
hepatosplenic T-cell lymphoma	Hodgkin's lymphoma	non-Hodgkin's lymphoma	invasive lobular carcinoma

intestinal cancer	kidney cancer	laryngeal cancer	lentigo maligna
lethal midline carcinoma	leukemia	leydig cell tumor	liposarcoma
lung cancer	lymphangioma	lymphangiosarcoma	lymphoepithelioma
lymphoma	acute lymphocytic leukemia	acute myelogenous leukemia	chronic lymphocytic leukemia
liver cancer	small cell lung cancer	non-small cell lung cancer	MALT lymphoma
malignant fibrous histiocytoma	malignant peripheral nerve sheath tumor	malignant triton tumor	mantle cell lymphoma
marginal zone B-cell lymphoma	mast cell leukemia	mediastinal germ cell tumor	medullary carcinoma of the breast
medullary thyroid cancer	medulloblastoma	melanoma	meningioma
merkel cell cancer	mesothelioma	metastatic urothelial carcinoma	mixed Mullerian tumor
mucinous tumor	multiple myeloma	muscle tissue neoplasm	mycosis fungoides
myxoid liposarcoma	myxoma	myxosarcoma	nasopharyngeal carcinoma
neurinoma	neuroblastoma	neurofibroma	neuroma
nodular melanoma	ocular cancer	oligoastrocytoma	oligodendroglioma
oncocytoma	optic nerve sheath meningioma	optic nerve tumor	oral cancer
osteosarcoma	ovarian cancer	Pancoast tumor	papillary thyroid cancer
paraganglioma	pinealoblastoma	pineocytoma	pituicytoma
pituitary adenoma	pituitary tumor	plasmacytoma	polyembryoma
precursor T-lymphoblastic lymphoma	primary central nervous system lymphoma	primary effusion lymphoma	preprimary peritoneal cancer
prostate cancer	pancreatic cancer	pharyngeal cancer	pseudomyxoma peritonei
renal cell carcinoma	renal medullary carcinoma	retinoblastoma	rhabdomyoma
rhabdomyosarcoma	Richter's transformation	rectal cancer	sarcoma

Schwannomatosis	seminoma	Sertoli cell tumor	sex cord-gonadal stromal tumor
signet ring cell carcinoma	skin cancer	small blue round cell tumors	small cell carcinoma
soft tissue sarcoma	somatostatinoma	soot wart	spinal tumor
splenic marginal zone lymphoma	squamous cell carcinoma	synovial sarcoma	Sezary's disease
small intestine cancer	squamous carcinoma	stomach cancer	T-cell lymphoma
testicular cancer	thecoma	thyroid cancer	transitional cell carcinoma
throat cancer	urachal cancer	urogenital cancer	urothelial carcinoma
uveal melanoma	uterine cancer	verrucous carcinoma	visual pathway glioma
vulvar cancer	vaginal cancer	Waldenstrom's macroglobulinemia	Warthin's tumor
Wilms' tumor			

[0177] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the cancer is a hematological cancer. Exemplary hematological cancers include, but are not limited to, the cancers listed in **Table B**. In certain embodiments, the hematological cancer is acute lymphocytic leukemia, chronic lymphocytic leukemia (including B-cell chronic lymphocytic leukemia), or acute myeloid leukemia.

Table B.

acute lymphocytic leukemia (ALL)	acute eosinophilic leukemia
acute myeloid leukemia (AML)	acute erythroid leukemia
chronic lymphocytic leukemia (CLL)	acute lymphoblastic leukemia
small lymphocytic lymphoma (SLL)	acute megakaryoblastic leukemia
multiple myeloma (MM)	acute monocytic leukemia
Hodgkins lymphoma (HL)	acute promyelocytic leukemia
non-Hodgkin's lymphoma (NHL)	acute myelogenous leukemia
mantle cell lymphoma (MCL)	B-cell prolymphocytic leukemia
marginal zone B-cell lymphoma	B-cell lymphoma

splenic marginal zone lymphoma	MALT lymphoma
follicular lymphoma (FL)	precursor T-lymphoblastic lymphoma
Waldenstrom's macroglobulinemia (WM)	T-cell lymphoma
diffuse large B-cell lymphoma (DLBCL)	mast cell leukemia
marginal zone lymphoma (MZL)	adult T cell leukemia/lymphoma
hairy cell leukemia (HCL)	aggressive NK-cell leukemia
Burkitt's lymphoma (BL)	angioimmunoblastic T-cell lymphoma
Richter's transformation	

[0178] In certain embodiments, the subject is a mammal.

[0179] In certain embodiments, the subject is a human.

[0180] In certain embodiments, the subject is a biological sample (e.g., a cell population).

Definitions

[0181] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

Chemical Definitions

[0182] Definitions of specific functional groups and chemical terms are described in more detail below. The chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed., inside cover, and specific functional groups are generally defined as described therein. Additionally, general principles of organic chemistry, as well as specific functional moieties and reactivity, are described in Thomas Sorrell, Organic Chemistry, University Science Books, Sausalito, 1999; Smith and March, March's Advanced Organic Chemistry, 5th Edition, John Wiley & Sons, Inc., New York, 2001; Larock, Comprehensive Organic Transformations, VCH Publishers, Inc., New York, 1989; and Carruthers, Some Modern Methods of Organic Synthesis, 3rd Edition, Cambridge University Press, Cambridge, 1987.

[0183] Compounds described herein can comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer or

geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high pressure liquid chromatography (HPFC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. See, for example, Jacques et al., *Enantiomers, Racemates and Resolutions* (Wiley Interscience, New York, 1981); Wilen et al., *Tetrahedron* 33:2725 (1977); Eliel, *Stereochemistry of Carbon Compounds* (McGraw-Hill, NY, 1962); and Wilen, *Tables of Resolving Agents and Optical Resolutions* p. 268 (E.F. Eliel, Ed., Univ. of Notre Dame Press, Notre Dame, IN 1972).

[0184] The present disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0185] When a range of values is listed, it is intended to encompass each value and sub-range within the range. For example, “C₁₋₆ alkyl” is intended to encompass, C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₁₋₅, C₁₋₄, C₁₋₃, C₁₋₂, C₂₋₆, C₂₋₅, C₂₋₄, C₂₋₃, C₃₋₆, C₃₋₅, C₃₋₄, C₄₋₆, C₄₋₅, and C₅₋₆ alkyl.

[0186] The following terms are intended to have the meanings presented therewith below and are useful in understanding the description and intended scope of the present disclosure. When describing the invention, which may include compounds, pharmaceutical compositions containing such compounds and methods of using such compounds and compositions, the following terms, if present, have the following meanings unless otherwise indicated. It should also be understood that when described herein any of the moieties defined forth below may be substituted with a variety of substituents, and that the respective definitions are intended to include such substituted moieties within their scope as set out below. Unless otherwise stated, the term “substituted” is to be defined as set out below. It should be further understood that the terms “groups” and “radicals” can be considered interchangeable when used herein. The articles “a” and “an” may be used herein to refer to one or to more than one (i.e., at least one) of the grammatical objects of the article. By way of example “an analogue” means one analogue or more than one analogue.

[0187] “Alkyl” as used herein, refers to a radical of a straight-chain or branched saturated hydrocarbon group having from 1 to 20 carbon atoms (“C₁₋₂₀ alkyl”). In certain embodiments, an alkyl group has 1 to 12 carbon atoms (“C₁₋₁₂ alkyl”). In certain embodiments, an alkyl group has 1 to 10 carbon atoms (“C₁₋₁₀ alkyl”). In certain embodiments, an alkyl group has 1 to 9 carbon atoms (“C₁₋₉ alkyl”). In certain embodiments, an alkyl group has 1 to 8 carbon atoms (“C₁₋₈ alkyl”). In

certain embodiments, an alkyl group has 1 to 7 carbon atoms (“C₁₋₇ alkyl”). In certain embodiments, an alkyl group has 1 to 6 carbon atoms (“C₁₋₆ alkyl”, which is also referred to herein as “lower alkyl”). In certain embodiments, an alkyl group has 1 to 5 carbon atoms (“C₁₋₅ alkyl”). In certain embodiments, an alkyl group has 1 to 4 carbon atoms (“C₁₋₄ alkyl”). In certain embodiments, an alkyl group has 1 to 3 carbon atoms (“C₁₋₃ alkyl”). In certain embodiments, an alkyl group has 1 to 2 carbon atoms (“C₁₋₂ alkyl”). In certain embodiments, an alkyl group has 1 carbon atom (“C₁ alkyl”). Examples of C₁₋₆ alkyl groups include methyl (C₁), ethyl (C₂), *n*-propyl (C₃), isopropyl (C₃), *n*-butyl (C₄), *tert*-butyl (C₄), *sec*-butyl (C₄), isobutyl (C₄), *n*-pentyl (C₅), 3-pentanyl (C₅), amyl (C₅), neopentyl (C₅), 3-methyl-2-butanyl (C₅), tertiary amyl (C₅), and *n*-hexyl (C₆). Additional examples of alkyl groups include *n*-heptyl (C₇), *n*-octyl (C₈) and the like. Unless otherwise specified, each instance of an alkyl group is independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents; e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkyl group is unsubstituted C₁₋₁₀ alkyl (e.g., -CH₃). In certain embodiments, the alkyl group is substituted C₁₋₁₀ alkyl. Common alkyl abbreviations include Me (-CH₃), Et (-CH₂CH₃), *i*-Pr (-CH(CH₃)₂), *n*-Pr (-CH₂CH₂CH₃), *n*-Bu (-CH₂CH₂CH₂CH₃), or *i*-Bu (-CH₂CH(CH₃)₂).

[0188] “Alkylene” as used herein, refers to an alkyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular “alkylene” group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An “alkylene” group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary unsubstituted divalent alkylene groups include, but are not limited to, methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-), butylene (-CH₂CH₂CH₂CH₂-), pentylene (-CH₂CH₂CH₂CH₂CH₂-), hexylene (-CH₂CH₂CH₂CH₂CH₂CH₂-), and the like. Exemplary substituted divalent alkylene groups, e.g., substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted methylene (-CH(CH₃)-, (-C(CH₃)₂-), substituted ethylene (-CH(CH₃)CH₂-, -CH₂CH(CH₃)-, -C(CH₃)₂CH₂-, -CH₂C(CH₃)₂-), substituted propylene (-CH(CH₃)CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -CH₂CH₂CH(CH₃)-, -C(CH₃)₂CH₂CH₂-, -CH₂C(CH₃)₂CH₂-, -CH₂CH₂C(CH₃)₂-), and the like.

[0189] “Alkenyl” as used herein, refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon double bonds (e.g., 1, 2, 3,

or 4 carbon-carbon double bonds), and optionally one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon triple bonds) (“C₂₋₂₀ alkenyl”). In certain embodiments, alkenyl does not contain any triple bonds. In certain embodiments, an alkenyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkenyl”). In certain embodiments, an alkenyl group has 2 to 9 carbon atoms (“C₂₋₉ alkenyl”). In certain embodiments, an alkenyl group has 2 to 8 carbon atoms (“C₂₋₈ alkenyl”). In certain embodiments, an alkenyl group has 2 to 7 carbon atoms (“C₂₋₇ alkenyl”). In certain embodiments, an alkenyl group has 2 to 6 carbon atoms (“C₂₋₆ alkenyl”). In certain embodiments, an alkenyl group has 2 to 5 carbon atoms (“C₂₋₅ alkenyl”). In certain embodiments, an alkenyl group has 2 to 4 carbon atoms (“C₂₋₄ alkenyl”). In certain embodiments, an alkenyl group has 2 to 3 carbon atoms (“C₂₋₃ alkenyl”). In certain embodiments, an alkenyl group has 2 carbon atoms (“C₂ alkenyl”). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of C₂₋₄ alkenyl groups include ethenyl (C₂), 1-propenyl (C₃), 2-propenyl (C₃), 1-butenyl (C₄), 2-butenyl (C₄), butadienyl (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkenyl groups as well as pentenyl (C₅), pentadienyl (C₅), hexenyl (C₆), and the like. Additional examples of alkenyl include heptenyl (C₇), octenyl (C₈), octatrienyl (C₈), and the like. Unless otherwise specified, each instance of an alkenyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkenyl group is unsubstituted C₂₋₁₀ alkenyl. In certain embodiments, the alkenyl group is substituted C₂₋₁₀ alkenyl.

[0190] “Alkenylene” as used herein, refers to an alkenyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular “alkenylene” group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An “alkenylene” group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary unsubstituted divalent alkenylene groups include, but are not limited to, ethenylene (-CH=CH-) and propenylene (*e.g.*, -CH=CHCH₂-, -CH₂-CH=CH-). Exemplary substituted divalent alkenylene groups, *e.g.*, substituted with one or more alkyl (methyl) groups, include but are not limited to, substituted ethylene (-C(CH₃)=CH-, -CH=C(CH₃)-), substituted propylene (*e.g.*, -C(CH₃)=CHCH₂-, -CH=CHCH₂-, -CH=CHCH(CH₃)-, -CH=CHC(CH₃)₂-, -CH(CH₃)-CH=CH-, -C(CH₃)₂-CH=CH-, -CH₂-C(CH₃)=CH-, -CH₂-CH=C(CH₃)-), and the like.

[0191] “Alkynyl” as used herein, refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 20 carbon atoms, one or more carbon-carbon triple bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon triple bonds), and optionally one or more carbon-carbon double bonds (*e.g.*, 1, 2, 3, or 4 carbon-carbon double bonds) (“C₂₋₂₀ alkynyl”). In certain embodiments, alkynyl does not contain any double bonds. In certain embodiments, an alkynyl group has 2 to 10 carbon atoms (“C₂₋₁₀ alkynyl”). In certain embodiments, an alkynyl group has 2 to 9 carbon atoms (“C₂₋₉ alkynyl”). In certain embodiments, an alkynyl group has 2 to 8 carbon atoms (“C₂₋₈ alkynyl”). In certain embodiments, an alkynyl group has 2 to 7 carbon atoms (“C₂₋₇ alkynyl”). In certain embodiments, an alkynyl group has 2 to 6 carbon atoms (“C₂₋₆ alkynyl”). In certain embodiments, an alkynyl group has 2 to 5 carbon atoms (“C₂₋₅ alkynyl”). In certain embodiments, an alkynyl group has 2 to 4 carbon atoms (“C₂₋₄ alkynyl”). In certain embodiments, an alkynyl group has 2 to 3 carbon atoms (“C₂₋₃ alkynyl”). In certain embodiments, an alkynyl group has 2 carbon atoms (“C₂ alkynyl”). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of C₂₋₄ alkynyl groups include, without limitation, ethynyl (C₂), 1-propynyl (C₃), 2-propynyl (C₃), 1-butyne (C₄), 2-butyne (C₄), and the like. Examples of C₂₋₆ alkenyl groups include the aforementioned C₂₋₄ alkynyl groups as well as pentynyl (C₅), hexynyl (C₆), and the like. Additional examples of alkynyl include heptynyl (C₇), octynyl (C₈), and the like. Unless otherwise specified, each instance of an alkynyl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents; *e.g.*, for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent. In certain embodiments, the alkynyl group is unsubstituted C₂₋₁₀ alkynyl. In certain embodiments, the alkynyl group is substituted C₂₋₁₀ alkynyl.

[0192] “Alkynylene” as used herein, refers to a linear alkynyl group wherein two hydrogens are removed to provide a divalent radical. When a range or number of carbons is provided for a particular “alkynylene” group, it is understood that the range or number refers to the range or number of carbons in the linear carbon divalent chain. An “alkynylene” group may be substituted or unsubstituted with one or more substituents as described herein. Exemplary divalent alkynylene groups include, but are not limited to, substituted or unsubstituted ethynylene, substituted or unsubstituted propynylene, and the like.

[0193] The term “heteroalkyl,” as used herein, refers to an alkyl group, as defined herein, which further comprises 1 or more (*e.g.*, 1, 2, 3, or 4) heteroatoms (*e.g.*, oxygen, sulfur, nitrogen, boron,

silicon, phosphorus) within the parent chain, wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, i.e., between the point of attachment. In certain embodiments, a heteroalkyl group refers to a saturated group having from 1 to 10 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC₁₋₁₀ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 9 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC₁₋₉ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 8 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC₁₋₈ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 7 carbon atoms and 1, 2, 3, or 4 heteroatoms (“heteroC₁₋₇ alkyl”). In certain embodiments, a heteroalkyl group is a group having 1 to 6 carbon atoms and 1, 2, or 3 heteroatoms (“heteroC₁₋₆ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 5 carbon atoms and 1 or 2 heteroatoms (“heteroC₁₋₅ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 4 carbon atoms and/or 2 heteroatoms (“heteroC₁₋₄ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 3 carbon atoms and 1 heteroatom (“heteroC₁₋₃ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 to 2 carbon atoms and 1 heteroatom (“heteroC₁₋₂ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 1 carbon atom and 1 heteroatom (“heteroC₁ alkyl”). In certain embodiments, a heteroalkyl group is a saturated group having 2 to 6 carbon atoms and 1 or 2 heteroatoms (“heteroC₂₋₆ alkyl”). Unless otherwise specified, each instance of a heteroalkyl group is independently unsubstituted (an “unsubstituted heteroalkyl”) or substituted (a “substituted heteroalkyl”) with one or more substituents. In certain embodiments, the heteroalkyl group is an unsubstituted heteroC₁₋₁₀ alkyl. In certain embodiments, the heteroalkyl group is a substituted heteroC₁₋₁₀ alkyl.

[0194] The term “heteroalkenyl,” as used herein, refers to an alkenyl group, as defined herein, which further comprises one or more (*e.g.*, 1, 2, 3, or 4) heteroatoms (*e.g.*, oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, i.e., between the point of attachment. In certain embodiments, a heteroalkenyl group refers to a group having from 2 to 10 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms (“heteroC₂₋₁₀ alkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 9 carbon atoms at least one double bond, and 1, 2, 3, or 4 heteroatoms

(“heteroC₂₋₉ alkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 8 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms (“heteroC₂₋₈ alkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 7 carbon atoms, at least one double bond, and 1, 2, 3, or 4 heteroatoms (“heteroC₂₋₇ alkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1, 2, or 3 heteroatoms (“heteroC₂₋₆ alkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 5 carbon atoms, at least one double bond, and 1 or 2 heteroatoms (“heteroC₂₋₅ alkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 4 carbon atoms, at least one double bond, and 1 or 2 heteroatoms (“heteroC₂₋₄ alkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 3 carbon atoms, at least one double bond, and 1 heteroatom (“heteroC₂₋₃ alkenyl”). In certain embodiments, a heteroalkenyl group has 2 to 6 carbon atoms, at least one double bond, and 1 or 2 heteroatoms (“heteroC₂₋₆ alkenyl”). Unless otherwise specified, each instance of a heteroalkenyl group is independently unsubstituted (an “unsubstituted heteroalkenyl”) or substituted (a “substituted heteroalkenyl”) with one or more substituents. In certain embodiments, the heteroalkenyl group is an unsubstituted heteroC₂₋₁₀ alkenyl. In certain embodiments, the heteroalkenyl group is a substituted heteroC₂₋₁₀ alkenyl.

[0195] The term “heteroalkynyl,” as used herein, refers to an alkynyl group, as defined herein, which further comprises one or more (*e.g.*, 1, 2, 3, or 4) heteroatoms (*e.g.*, oxygen, sulfur, nitrogen, boron, silicon, phosphorus) wherein the one or more heteroatoms is inserted between adjacent carbon atoms within the parent carbon chain and/or one or more heteroatoms is inserted between a carbon atom and the parent molecule, *i.e.*, between the point of attachment. In certain embodiments, a heteroalkynyl group refers to a group having from 2 to 10 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms (“heteroC₂₋₁₀ alkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 9 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms (“heteroC₂₋₉ alkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 8 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms (“heteroC₂₋₈ alkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 7 carbon atoms, at least one triple bond, and 1, 2, 3, or 4 heteroatoms (“heteroC₂₋₇ alkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1, 2, or 3 heteroatoms (“heteroC₂₋₆ alkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 5 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms (“heteroC₂₋₅ alkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 4 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms (“heteroC₂₋₄ alkynyl”). In certain embodiments, a

heteroalkynyl group has 2 to 3 carbon atoms, at least one triple bond, and 1 heteroatom (“heteroC₂₋₃ alkynyl”). In certain embodiments, a heteroalkynyl group has 2 to 6 carbon atoms, at least one triple bond, and 1 or 2 heteroatoms (“heteroC₂₋₆ alkynyl”). Unless otherwise specified, each instance of a heteroalkynyl group is independently unsubstituted (an “unsubstituted heteroalkynyl”) or substituted (a “substituted heteroalkynyl”) with one or more substituents. In certain embodiments, the heteroalkynyl group is an unsubstituted heteroC₂₋₁₀ alkynyl. In certain embodiments, the heteroalkynyl group is a substituted heteroC₂₋₁₀ alkynyl.

[0196] Analogous to “alkylene,” “alkenylene,” and “alkynylene” as defined above, “heteroalkylene,” “heteroalkenylene,” and “heteroalkynylene,” as used herein, refer to a divalent radical of heteroalkyl, heteroalkenyl, and heteroalkynyl group respectively. When a range or number of carbons is provided for a particular “heteroalkylene,” “heteroalkenylene,” or “heteroalkynylene,” group, it is understood that the range or number refers to the range or number of carbons in the linear divalent chain. “Heteroalkylene,” “heteroalkenylene,” and “heteroalkynylene” groups may be substituted or unsubstituted with one or more substituents as described herein.

[0197] “Aryl” refers to a radical of a monocyclic or polycyclic (e.g., bicyclic or tricyclic) $4n+2$ aromatic ring system (e.g., having 6, 10, or 14 π electrons shared in a cyclic array) having 6-14 ring carbon atoms and zero heteroatoms provided in the aromatic ring system (“C₆₋₁₄ aryl”). In some embodiments, an aryl group has six ring carbon atoms (“C₆ aryl”; e.g., phenyl). In some embodiments, an aryl group has ten ring carbon atoms (“C₁₀ aryl”; e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In some embodiments, an aryl group has fourteen ring carbon atoms (“C₁₄ aryl”; e.g., anthracyl).

[0198] Typical aryl groups include, but are not limited to, groups derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, coronene, fluoranthene, fluorene, hexacene, hexaphene, hexalene, as-indacene, s-indacene, indane, indene, naphthalene, octacene, octaphene, octalene, ovalene, penta-2,4-diene, pentacene, pentalene, pentaphene, perylene, phenalene, phenanthrene, picene, pleiadene, pyrene, pyranthrene, rubicene, triphenylene, and trinaphthalene. Particular aryl groups include phenyl, naphthyl, indenyl, and tetrahydronaphthyl. Unless otherwise specified, each instance of an aryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted

aryl”) with one or more substituents. In certain embodiments, the aryl group is unsubstituted C₆₋₁₄ aryl. In certain embodiments, the aryl group is substituted C₆₋₁₄ aryl.

[0199] “Aralkyl” is a subset of alkyl and aryl, as defined herein, and refers to an optionally substituted alkyl group substituted by an optionally substituted aryl group.

[0200] “Heteroaryl” refers to a radical of a 5- to 14-membered monocyclic or polycyclic 4n+2 aromatic ring system (*e.g.*, having 6, 10, or 14 π electrons shared in a cyclic array) having ring carbon atoms and 1-8 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen and sulfur (“5- to 14-membered heteroaryl”). In heteroaryl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Heteroaryl bicyclic ring systems can include one or more heteroatoms in one or both rings.

[0201] “Heteroaryl” also includes ring systems wherein the heteroaryl group, as defined above, is fused with one or more aryl groups wherein the point of attachment is either on the heteroaryl or the one or more aryl groups, and in such instances, the number of ring members designates the total number of ring members in the fused (aryl/heteroaryl) ring system. When substitution is indicated in such instances, unless otherwise specified, substitution can occur on either the heteroaryl or the one or more aryl groups. Bicyclic heteroaryl groups wherein one ring does not contain a heteroatom (*e.g.*, indolyl, quinolinyl, carbazolyl, and the like) the point of attachment can be on either ring, *i.e.*, either the ring bearing a heteroatom (*e.g.*, 2-indolyl) or the ring that does not contain a heteroatom (*e.g.*, 5-indolyl).

[0202] In certain embodiments, a heteroaryl is a 5- to 10-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 10-membered heteroaryl”). In certain embodiments, a heteroaryl is a 5- to 9-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 9-membered heteroaryl”). In certain embodiments, a heteroaryl is a 5- to 8-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 8-membered heteroaryl”). In certain embodiments, a heteroaryl group is a 5- to 6-membered aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms provided in the aromatic ring system,

wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 6-membered heteroaryl”). In certain embodiments, the 5- to 6-membered heteroaryl has 1-3 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heteroaryl has 1-2 ring heteroatoms independently selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heteroaryl has 1 ring heteroatom selected from nitrogen, oxygen, and sulfur. Unless otherwise specified, each instance of a heteroaryl group is independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted heteroaryl”) or substituted (a “substituted heteroaryl”) with one or more substituents. In certain embodiments, the heteroaryl group is unsubstituted 5- to 14-membered heteroaryl. In certain embodiments, the heteroaryl group is substituted 5- to 14-membered heteroaryl.

[0203] Exemplary 5-membered heteroaryl containing one heteroatom include, without limitation, pyrrolyl, furanyl and thiophenyl. Exemplary 5-membered heteroaryl containing two heteroatoms include, without limitation, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, and isothiazolyl. Exemplary 5-membered heteroaryl containing three heteroatoms include, without limitation, triazolyl, oxadiazolyl, and thiadiazolyl. Exemplary 5-membered heteroaryl containing four heteroatoms include, without limitation, tetrazolyl. Exemplary 6-membered heteroaryl containing one heteroatom include, without limitation, pyridinyl. Exemplary 6-membered heteroaryl containing two heteroatoms include, without limitation, pyridazinyl, pyrimidinyl, and pyrazinyl. Exemplary 6-membered heteroaryl containing three or four heteroatoms include, without limitation, triazinyl and tetrazinyl, respectively. Exemplary 7-membered heteroaryl containing one heteroatom include, without limitation, azepinyl, oxepinyl, and thiepinyl. Exemplary 5,6-bicyclic heteroaryl include, without limitation, indolyl, isoindolyl, indazolyl, benzotriazolyl, benzothiophenyl, isobenzothiophenyl, benzofuranyl, benzoisofuranyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzoxadiazolyl, benzthiazolyl, benzisothiazolyl, benzthiadiazolyl, indolizinyl, and purinyl. Exemplary 6,6-bicyclic heteroaryl include, without limitation, naphthyridinyl, pteridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, and quinazolinyl.

[0204] “Heteroaralkyl” is a subset of alkyl and heteroaryl, as defined herein, and refers to an optionally substituted alkyl group substituted by an optionally substituted heteroaryl group.

[0205] “Carbocyclyl” refers to a radical of a non-aromatic cyclic hydrocarbon group having from 3 to 12 ring carbon atoms (“C₃₋₁₂ carbocyclyl”) and zero heteroatoms in the nonaromatic ring

system. In certain embodiments, a carbocyclyl group has 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”). In certain embodiments, a carbocyclyl group has 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In certain embodiments, a carbocyclyl group has 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In certain embodiments, a carbocyclyl group has 5 to 12 ring carbon atoms (“C₅₋₁₂ carbocyclyl”). In certain embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). In certain embodiments, a carbocyclyl group has 5 to 8 ring carbon atoms (“C₅₋₈ carbocyclyl”). In certain embodiments, a carbocyclyl group has 5 or 6 ring carbon atoms (“C₅₋₆ carbocyclyl”). Exemplary C₃₋₆ carbocyclyl include, without limitation, cyclopropyl (C₃), cyclopropenyl (C₃), cyclobutyl (C₄), cyclobutenyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆), and the like. Exemplary C₃₋₈ carbocyclyl include, without limitation, the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptenyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), cyclooctenyl (C₈), bicyclo[2.2.1]heptanyl (C₇), bicyclo[2.2.2]octanyl (C₈), and the like. Exemplary C₃₋₁₀ carbocyclyl include, without limitation, the aforementioned C₃₋₈ carbocyclyl groups as well as cyclononyl (C₉), cyclononenyl (C₉), cyclodecyl (C₁₀), cyclodecenyl (C₁₀), octahydro-1*H*-indenyl (C₉), decahydronaphthalenyl (C₁₀), spiro[4.5]decanyl (C₁₀), and the like.

[0206] In certain embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 12 ring carbon atoms (“C₃₋₁₂ carbocyclyl”). In certain embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 10 ring carbon atoms (“C₃₋₁₀ carbocyclyl”). In certain embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 8 ring carbon atoms (“C₃₋₈ carbocyclyl”). In certain embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 3 to 6 ring carbon atoms (“C₃₋₆ carbocyclyl”). In certain embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having from 5 to 12 ring carbon atoms (“C₅₋₁₂ carbocyclyl”). In certain embodiments, a carbocyclyl group has 5 to 10 ring carbon atoms (“C₅₋₁₀ carbocyclyl”). In certain embodiments, a carbocyclyl group has 5 to 8 ring carbon atoms (“C₅₋₈ carbocyclyl”). In certain embodiments, “carbocyclyl” is a monocyclic, saturated carbocyclyl group having 5 or 6 ring carbon atoms (“C₅₋₆ carbocyclyl”). Examples of C₅₋₆ carbocyclyl include cyclopentyl (C₅) and cyclohexyl (C₅). Examples of C₃₋₆ carbocyclyl include the aforementioned C₅₋₆ carbocyclyl groups as well as cyclopropyl (C₃) and cyclobutyl (C₄). Examples of C₃₋₈ carbocyclyl include the aforementioned C₃₋₆ carbocyclyl groups as well as cycloheptyl (C₇) and cyclooctyl (C₈). Unless otherwise specified, each instance of a

carbocyclyl group is independently unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C₃₋₁₂ carbocyclyl. In certain embodiments, the carbocyclyl group is substituted C₃₋₁₂ carbocyclyl.

[0207] As the foregoing examples illustrate, in certain embodiments, the carbocyclyl group is either monocyclic (“monocyclic carbocyclyl”) or polycyclic (“polycyclic carbocyclyl”) that contains a fused, bridged or spiro ring system and can be saturated or can be partially unsaturated. Unless otherwise specified, each instance of a carbocyclyl group is independently optionally substituted, i.e., unsubstituted (an “unsubstituted carbocyclyl”) or substituted (a “substituted carbocyclyl”) with one or more substituents. In certain embodiments, the carbocyclyl group is unsubstituted C₃₋₁₂ carbocyclyl. In certain embodiments, the carbocyclyl group is a substituted C₃₋₁₂ carbocyclyl.

[0208] “Fused carbocyclyl” or “fused carbocycle” refers to ring systems wherein the carbocyclyl group, as defined above, is fused with, i.e., share one common bond with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on any of the fused rings. In such instances, the number of carbons designates the total number of carbons in the fused ring system. When substitution is indicated, unless otherwise specified, substitution can occur on any of the fused rings.

[0209] “Spiro carbocyclyl” or “spiro carbocycle” refers to ring systems wherein the carbocyclyl group, as defined above, form spiro structure with, i.e., share one common atom with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on the carbocyclyl rings in which the spiro structure is embedded. In such instances, the number of carbons designates the total number of carbons of the carbocyclyl rings in which the spiro structure is embedded. When substitution is indicated, unless otherwise specified, substitution can occur on the carbocyclyl rings in which the spiro structure is embedded.

[0210] “Bridged carbocyclyl” or “bridged carbocycle” refers to ring systems wherein the carbocyclyl group, as defined above, form bridged structure with, i.e., share more than one atoms (as such, share more than one bonds) with, one or more carbocyclyl groups, as defined above, wherein the point of attachment is on any of the carbocyclyl rings in which the bridged structure is embedded. In such instances, the number of carbons designates the total number of carbons of

the bridged rings. When substitution is indicated, unless otherwise specified, substitution can occur on any of the carbocyclyl rings in which the bridged structure is embedded.

[0211] “Heterocyclyl” refers to a radical of a 3- to 12-membered non-aromatic ring system having ring carbon atoms and 1 to 4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“3- to 12-membered heterocyclyl”). In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. Exemplary 3-membered heterocyclyl groups containing one heteroatom include, without limitation, azirdinyl, oxiranyl, thiorenlyl. Exemplary 4-membered heterocyclyl groups containing one heteroatom include, without limitation, azetidiny, oxetanyl and thietanyl. Exemplary 5-membered heterocyclyl groups containing one heteroatom include, without limitation, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothiophenyl, dihydrothiophenyl, pyrrolidinyl, dihydropyrrolyl and pyrrolyl-2,5-dione. Exemplary 5-membered heterocyclyl groups containing two heteroatoms include, without limitation, dioxolanyl, oxasulfuranyl, disulfuranyl, and oxazolidin-2-one. Exemplary 5-membered heterocyclyl groups containing three heteroatoms include, without limitation, triazoliny, oxadiazoliny, and thiadiazoliny. Exemplary 6-membered heterocyclyl groups containing one heteroatom include, without limitation, piperidinyl, tetrahydropyranyl, dihydropyridiny, and thianyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, piperazinyl, morpholinyl, dithianyl, dioxanyl. Exemplary 6-membered heterocyclyl groups containing two heteroatoms include, without limitation, triazinanyl. Exemplary 7-membered heterocyclyl groups containing one heteroatom include, without limitation, azepanyl, oxepanyl and thiepanyl. Exemplary 8-membered heterocyclyl groups containing one heteroatom include, without limitation, azocanyl, oxecanyl and thiocanyl. Exemplary 5-membered heterocyclyl groups fused to a C₆ aryl ring (also referred to herein as a 5,6-bicyclic heterocyclic ring) include, without limitation, indoliny, isoindoliny, dihydrobenzofuranyl, dihydrobenzothienyl, benzoxazolinonyl, and the like. Exemplary 6-membered heterocyclyl groups fused to an aryl ring (also referred to herein as a 6,6-bicyclic heterocyclic ring) include, without limitation, tetrahydroquinoliny, tetrahydroisoquinoliny, and the like.

[0212] In certain embodiments, a heterocyclyl group is a 5- to 12-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“5- to 12-

membered heterocyclyl”). In certain embodiments, a heterocyclyl group is a 5- to 10-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, sulfur, boron, phosphorus, and silicon (“5- to 10-membered heterocyclyl”). In certain embodiments, a heterocyclyl group is a 5- to 8-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 8-membered heterocyclyl”). In certain embodiments, a heterocyclyl group is a 5- to 6-membered non-aromatic ring system having ring carbon atoms and 1-4 ring heteroatoms, wherein each heteroatom is independently selected from nitrogen, oxygen, and sulfur (“5- to 6-membered heterocyclyl”). In certain embodiments, the 5- to 6-membered heterocyclyl has 1-3 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heterocyclyl has 1-2 ring heteroatoms selected from nitrogen, oxygen, and sulfur. In certain embodiments, the 5- to 6-membered heterocyclyl has one ring heteroatom selected from nitrogen, oxygen, and sulfur.

[0213] As the foregoing examples illustrate, in certain embodiments, a heterocyclyl group can either be monocyclic (“monocyclic heterocyclyl”) or polycyclic (“polycyclic heterocyclyl”) that contains a fused, bridged or spiro ring system, and can be saturated or can be partially unsaturated. Heterocyclyl polycyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl group, as defined above, is fused with one or more carbocyclyl groups wherein the point of attachment is either on the carbocyclyl or heterocyclyl ring, and in such instances, the number of ring members designates the total number of ring members in the entire ring system. When substitution is indicated in such instances, unless otherwise specified, substitution can occur on either the heterocyclyl or the one or more carbocyclyl groups. Unless otherwise specified, each instance of heterocyclyl is independently optionally substituted, i.e., unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. In certain embodiments, the heterocyclyl group is unsubstituted 3- to 12-membered heterocyclyl. In certain embodiments, the heterocyclyl group is substituted 3- to 12-membered heterocyclyl.

[0214] “Fused heterocyclyl” or “fused heterocycle” refers to ring systems wherein the heterocyclyl group, as defined above, is fused with, i.e., share one common bond with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on any of the fused rings. In such instances, the number of carbons designates the total number of ring members in the

fused ring system. When substitution is indicated, unless otherwise specified, substitution can occur on any of the fused rings.

[0215] “Spiro heterocyclyl” or “spiro heterocycle” refers to ring systems wherein the heterocyclyl group, as defined above, form spiro structure with, i.e., share one common atom with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on the heterocyclyl or carbocyclyl rings in which the spiro structure is embedded. In such instances, the number of ring members designates the total number of ring members of the heterocyclyl or carbocyclyl rings in which the spiro structure is embedded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the heterocyclyl or carbocyclyl rings in which the spiro structure is embedded.

[0216] “Bridged heterocyclyl” or “bridged heterocycle” refers to ring systems wherein the heterocyclyl group, as defined above, form bridged structure with, i.e., share more than one atoms (as such, share more than one bonds) with, one or more heterocyclyl or carbocyclyl groups, as defined above, wherein the point of attachment is on the heterocyclyl or carbocyclyl rings in which the bridged structure is embedded. In such instances, the number of ring members designates the total number of ring members of the heterocyclyl or carbocyclyl rings in which the bridged structure is embedded. When substitution is indicated, unless otherwise specified, substitution can occur on any of the bridged rings.

[0217] “Hetero” when used to describe a compound or a group present on a compound means that one or more carbon atoms in the compound or group have been replaced by a nitrogen, oxygen, sulfur, boron, phosphorus, and silicon heteroatom, as valency permits. Hetero may be applied to any of the hydrocarbyl groups described above having from 1 to 5, and particularly from 1 to 3 heteroatoms.

[0218] “Acyl” as used herein, refers to a radical $-C(O)R$, wherein R is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, as defined herein. Representative acyl groups include, but are not limited to, formyl ($-CHO$), acetyl ($-C(=O)CH_3$), cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl ($-C(=O)Ph$), and benzylcarbonyl ($-C(=O)CH_2Ph$).

[0219] “Acylamino” as used herein, refers to a radical $-NRC(=O)R$, wherein each instance of R is independently hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl,

substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, as defined herein. Exemplary “acylamino” groups include, but are not limited to, formylamino, acetylamino, cyclohexylcarbonylamino, cyclohexylmethyl-carbonylamino, benzoylamino and benzylcarbonylamino.

[0220] “Acyloxy” as used herein, refers to a radical -OC(=O)R , wherein R is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted carbocyclyl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl, as defined herein. Representative examples include, but are not limited to, formyl, acetyl, cyclohexylcarbonyl, cyclohexylmethylcarbonyl, benzoyl and benzylcarbonyl.

[0221] “Alkoxy” as used herein, refers to the group -OR , wherein R is alkyl as defined herein. C_{1-6} alkoxy refers to the group -OR , wherein each R is C_{1-6} alkyl, as defined herein. Exemplary C_{1-6} alkyl is set forth above.

[0222] “Alkylamino” as used herein, refers to the group -NHR or -NR_2 , wherein each R is independently alkyl, as defined herein. C_{1-6} alkylamino refers to the group -NHR or -NR_2 , wherein each R is independently C_{1-6} alkyl, as defined herein. Exemplary C_{1-6} alkyl is set forth above.

[0223]

[0224] “Oxo” refers to =O . When a group other than aryl and heteroaryl or an atom is substituted with an oxo, it is meant to indicate that two geminal radicals on that group or atom form a double bond with an oxygen radical. When a heteroaryl is substituted with an oxo, it is meant to indicate that a resonance structure/tautomer involving a heteroatom provides a carbon atom that is able to form two geminal radicals, which form a double bond with an oxygen radical.

[0225] “Azido” refers to the radical -N_3 .

[0226] “Amino” refers to the radical -NH_2 .

[0227] “Hydroxy” refers to the radical -OH .

[0228] “Thioketo” refers to the group =S .

[0229] “Carboxy” refers to the radical -C(=O)OH .

[0230] “Cyano” refers to the radical -CN .

[0231] “Halo” or “halogen” refers to fluoro (F), chloro (Cl), bromo (Br), and iodo (I). In certain embodiments, the halo group is either fluoro or chloro.

[0232] “Nitro” refers to the radical -NO₂.

[0233] “Protecting group” as used herein is art-recognized and refers to a chemical moiety introduced into a molecule by chemical modification of a functional group (e.g., hydroxyl, amino, thio, and carboxylic acid) to obtain chemoselectivity in a subsequent chemical reaction, during which the unmodified functional group may not survive or may interfere with the chemical reaction. Common functional groups that need to be protected include but not limited to hydroxyl, amino, thiol, and carboxylic acid. Accordingly, the protecting groups are termed hydroxyl-protecting groups, amino-protecting groups, thiol-protecting groups, and carboxylic acid-protecting groups, respectively.

[0234] Common types of hydroxyl-protecting groups include but not limited to ethers (e.g., methoxymethyl (MOM), β -Methoxyethoxymethyl (MEM), tetrahydropyranyl (THP), *p*-methoxyphenyl (PMP), *t*-butyl, triphenylmethyl (Trityl), allyl, and benzyl ether (Bn)), silyl ethers (e.g., *t*-butyldiphenylsilyl (TBDPS), trimethylsilyl (TMS), triisopropylsilyl (TIPS), tri-*iso*-propylsilyloxymethyl (TOM), and *t*-butyldimethylsilyl (TBDMS)), and esters (e.g., pivalic acid ester (Piv) and benzoic acid ester (benzoate; Bz)).

[0235] Common types of amino-protecting groups include but not limited to carbamates (e.g., *t*-butyloxycarbonyl (Boc), 9-fluorenylmethyloxycarbonyl (Fmoc), *p*-methoxybenzyl carbonyl (Moz or MeOZ), 2,2,2-trichloroethoxycarbonyl (Troc), and benzyl carbamate (Cbz)), esters (e.g., acetyl (Ac); benzoyl (Bz), trifluoroacetyl, and phthalimide), amines (e.g., benzyl (Bn), *p*-methoxybenzyl (PMB), *p*-methoxyphenyl (PMP), and triphenylmethyl (trityl)), and sulfonamides (e.g., tosyl (Ts), *N*-alkyl nitrobenzenesulfonamides (Nosyl), and 2-nitrophenylsulfenyl (Nps)).

[0236] Common types of thiol-protecting groups include but not limited to sulfide (e.g., *p*-methylbenzyl (Meb), *t*-butyl, acetamidomethyl (Acm), and triphenylmethyl (Trityl)).

[0237] Common types of carboxylic acid-protecting groups include but not limited to esters (e.g., methyl ester, triphenylmethyl (Trityl), *t*-butyl ester, benzyl ester (Bn), *S*-*t*-butyl ester, silyl esters, and orthoesters) and oxazoline.

[0238] These and other exemplary substituents are described in more detail in the Detailed Description, Examples, and claims. The invention is not intended to be limited in any manner by the above exemplary listing of substituents.

Other Definitions

[0239] As used herein, “pharmaceutically acceptable” means approved or approvable by a regulatory agency of the Federal or a state government or the corresponding agency in countries other than the United States, or that is listed in the U.S. Pharmacopoeia or other generally recognized pharmacopoeia for use in animals, and more particularly, in humans.

[0240] As used herein, “pharmaceutically acceptable salt” refers to a salt of a compound of the present disclosure that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. In particular, such salts are non-toxic may be inorganic or organic acid addition salts and base addition salts. Specifically, such salts include: (1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo [2.2.2]-oct-2-ene-1-carboxylic acid, glucoheptonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or (2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine and the like. Salts further include, by way of example only, sodium potassium, calcium, magnesium, ammonium, tetraalkylammonium, and the like; and when the compound contains a basic functionality, salts of nontoxic organic or inorganic acids, such as hydrochloride, hydrobromide, tartrate, mesylate, acetate, maleate, oxalate and the like.

[0241] As used herein, the term “pharmaceutically acceptable cation” refers to an acceptable cationic counterion of an acidic functional group. Such cations are exemplified by sodium, potassium, calcium, magnesium, ammonium, tetraalkylammonium cations, and the like (see, *e.g.*, Berge, et al., J. Pharm. Sci. 66 (1):1-79 (January 77)).

[0242] As used herein, “Pharmaceutically acceptable vehicle” refers to a diluent, adjuvant, excipient or carrier with which a compound of the present disclosure is administered.

[0243] As used herein, “pharmaceutically acceptable metabolically cleavable group” refers to a group which is cleaved *in vivo* to yield the parent molecule of the structural formula indicated herein. Examples of metabolically cleavable groups include -COR, -COOR, -CONR₂ and -CH₂OR radicals, where R is selected independently at each occurrence from alkyl, trialkylsilyl, carbocyclic aryl or carbocyclic aryl substituted with one or more of alkyl, halogen, hydroxy or alkoxy. Specific examples of representative metabolically cleavable groups include acetyl, methoxycarbonyl, benzoyl, methoxymethyl and trimethylsilyl groups.

[0244] As used herein, “solvate” refers to forms of the compound that are associated with a solvent or water (also referred to as “hydrate”), usually by a solvolysis reaction. This physical association includes hydrogen bonding. Conventional solvents include water, ethanol, acetic acid and the like. The compounds of the present disclosure may be prepared *e.g.*, in crystalline form and may be solvated or hydrated. Suitable solvates include pharmaceutically acceptable solvates, such as hydrates, and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates. Representative solvates include hydrates, ethanolates and methanolates.

[0245] As used herein, a “subject” to which administration is contemplated includes, but is not limited to, humans (*i.e.*, a male or female of any age group, *e.g.*, a pediatric subject (*e.g.* infant, child, adolescent) or an adult subject (*e.g.*, young adult, middle aged adult or senior adult) and/or a non-human animal, *e.g.*, a mammal such as primates (*e.g.*, cynomolgus monkeys, rhesus monkeys), cattle, pigs, horses, sheep, goats, rodents, cats, and/or dogs. In certain embodiments, the subject is a human. In certain embodiments, the subject is a non-human animal.

[0246] As used herein, an “effective amount” means the amount of a compound that, when administered to a subject for treating or preventing a disease, is sufficient to effect such treatment or prevention. The “effective amount” can vary depending on the compound, the disease and its severity, and the age, weight, etc., of the subject to be treated. A “therapeutically effective amount” refers to the effective amount for therapeutic treatment. A “prophylactically effective amount” refers to the effective amount for prophylactic treatment.

[0247] As used herein, “subject in need thereof” refers to a subject having a disease or having an increased risk of developing the disease. A subject in need thereof can be one who has previously

been diagnosed or identified as having a disease or disorder disclosed herein. A subject in need thereof can also be one who is suffering from a disease or disorder disclosed herein. Alternatively, a subject in need thereof can be one who has an increased risk of developing such disease or disorder relative to the population at large (i.e., a subject who is predisposed to developing such disorder relative to the population at large). A subject in need thereof can have a refractory or resistant disease or disorder disclosed herein (i.e., a disease or disorder disclosed herein that does not respond or has not yet responded to treatment). The subject may be resistant at start of treatment or may become resistant during treatment. In some embodiments, the subject in need thereof received and failed all known effective therapies for a disease or disorder disclosed herein. In some embodiments, the subject in need thereof received at least one prior therapy.

[0248] As used herein, “preventing”, “prevention” or “prophylactic treatment” refers to a reduction in risk of acquiring or developing a disease or disorder (*i.e.*, causing at least one of the clinical symptoms of the disease not to develop in a subject not yet exposed to a disease-causing agent, or in a subject who is predisposed to the disease in advance of disease onset).

[0249] As used herein, the term “prophylaxis” is related to “prevention,” and refers to a measure or procedure the purpose of which is to prevent, rather than to treat or cure a disease. Non limiting examples of prophylactic measures may include the administration of vaccines; the administration of low molecular weight heparin to hospital patients at risk for thrombosis due, for example, to immobilization, and the administration of an anti-malarial agent such as chloroquine, in advance of a visit to a geographical region where malaria is endemic or the risk of contracting malaria is high.

[0250] As used herein, “treating” or “treatment” or “therapeutic treatment” of any disease or disorder refers, in some embodiments, to ameliorating the disease or disorder (*i.e.*, arresting the disease or reducing the manifestation, extent or severity of at least one of the clinical symptoms thereof). In some embodiments, “treating” or “treatment” refers to ameliorating at least one physical parameter, which may not be discernible by the subject. In some embodiments, “treating” or “treatment” refers to modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. In a further embodiment, “treating” or “treatment” relates to slowing the progression of the disease.

[0251] It is also to be understood that compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are

termed “isomers.” Isomers that only differ in the arrangement of their atoms in space are termed “stereoisomers.”

[0252] Stereoisomers that are not mirror images of one another are termed “diastereomers” and those that are non-superimposable mirror images of each other are termed “enantiomers.” When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the R - and S - sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+)- or (-)- isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is termed a “racemic mixture”.

[0253] As used herein “tautomers” refer to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of it electrons and an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro-forms of phenylnitromethane, that are likewise formed by treatment with acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

[0254] As used herein a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (*i.e.*, in enantiomeric excess). In other words, an “S” form of the compound is substantially free from the “R” form of the compound and is, thus, in enantiomeric excess of the “R” form. The term “enantiomerically pure” or “pure enantiomer” denotes that the compound comprises more than 95% by weight, more than 96% by weight, more than 97% by weight, more than 98% by weight, more than 98.5% by weight, more than 99% by weight, more than 99.2% by weight, more than 99.5% by weight, more than 99.6% by weight, more than 99.7% by weight, more than 99.8% by weight or more than 99.9% by weight, of the enantiomer. In certain embodiments, the weights are based upon total weight of all enantiomers or stereoisomers of the compound.

[0255] As used herein and unless otherwise indicated, the term “enantiomerically pure (R)-compound” refers to at least about 95% by weight (R)-compound and at most about 5% by weight

(S)-compound, at least about 99% by weight (R)-compound and at most about 1% by weight (S)-compound, or at least about 99.9 % by weight (R)-compound and at most about 0.1% by weight (S)-compound. In certain embodiments, the weights are based upon total weight of compound.

[0256] As used herein and unless otherwise indicated, the term “enantiomerically pure (S)-compound” refers to at least about 95% by weight (S)-compound and at most about 5% by weight (R)-compound, at least about 99% by weight (S)-compound and at most about 1% by weight (R)-compound or at least about 99.9% by weight (S)-compound and at most about 0.1% by weight (R)-compound. In certain embodiments, the weights are based upon total weight of compound.

[0257] In the compositions provided herein, an enantiomerically pure compound or a pharmaceutically acceptable salt, solvate, hydrate or prodrug thereof can be present with other active or inactive ingredients. For example, a pharmaceutical composition comprising enantiomerically pure (R)-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure (R)-compound. In certain embodiments, the enantiomerically pure (R)-compound in such compositions can, for example, comprise, at least about 95% by weight (R)-compound and at most about 5% by weight (S)-compound, by total weight of the compound. For example, a pharmaceutical composition comprising enantiomerically pure (S)-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure (S)-compound. In certain embodiments, the enantiomerically pure (S)-compound in such compositions can, for example, comprise, at least about 95% by weight (S)-compound and at most about 5% by weight (R)-compound, by total weight of the compound. In certain embodiments, the active ingredient can be formulated with little or no excipient or carrier.

[0258] Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art.

[0259] As used herein, the term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability or within statistical experimental error, and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. In certain embodiments, the number or numerical range vary by 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, or 15% of the stated number or numerical range.

[0260] As used herein, the term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, “consist of” or “consist essentially of” the described features.

[0261] As used herein, 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” may refer, in some embodiments, to A only (optionally including elements other than B); in some embodiments, to B only (optionally including elements other than A); in some embodiments, to both A and B (optionally including other elements); etc.

[0262] 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.

[0263] 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”) may refer, in some embodiments, to at least one, optionally including more than one, A, with no B present (and optionally including elements other than B); in some embodiments, to at least one, optionally including more than one, B, with no A present (and optionally including elements other than A); in some embodiments, 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.

[0264] While the present teachings have been described in conjunction with various embodiments and examples, it is not intended that the present teachings be limited to such embodiments or examples. On the contrary, the present teachings encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

[0265] While various inventive embodiments have been described and illustrated herein, those of ordinary skill in the art will readily envision a variety of other means and/or structures for performing the function and/or obtaining the results and/or one or more of the advantages described herein, and each of such variations and/or modifications is deemed to be within the scope of the inventive embodiments described herein. More generally, those skilled in the art will readily appreciate that all parameters, dimensions, materials, and configurations described herein are meant to be exemplary and that the actual parameters, dimensions, materials, and/or configurations will depend upon the specific application or applications for which the inventive teachings is/are used. Those skilled in the art will recognize many equivalents to the specific inventive embodiments described herein. It is, therefore, to be understood that the foregoing embodiments are presented by way of example only and that, within the scope of the appended claims and equivalents thereto, inventive embodiments may be practiced otherwise than as specifically described and claimed. Inventive embodiments of the present disclosure are directed to each individual feature, system, article, material, kit, and/or method described herein. In addition, any combination of two or more such features, systems, articles, materials, kits, and/or methods, if such features, systems, articles, materials, kits, and/or methods are not mutually inconsistent, is included within the inventive scope of the present disclosure.

[0266] The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made by one of ordinary skill in the art without departing from the spirit and scope of the appended claims. All embodiments that come within the spirit and scope of the following claims and equivalents thereto are claimed.

EXAMPLES

[0267] In order that the invention described herein may be more fully understood, the following examples are set forth. The examples described in this application are offered to illustrate the compounds, pharmaceutical compositions, and methods provided herein and are not to be construed in any way as limiting their scope.

[0268] It is understood that the values presented in the examples are approximate values, and they are subject to instrumental and/or experimental variations.

I. SYNTHESIS AND CHARACTERIZATION OF INTERMEDIATES AND COMPOUNDS A1-A165

[0269] The chemical reagents were purchased from commercial sources (such as Alfa, Acros, Sigma Aldrich, TCI, and Shanghai Chemical Reagent Company), and used without further purification.

[0270] In obtaining the compounds described in the examples below and the corresponding analytical data, the following experimental and analytical protocols were followed unless otherwise indicated.

[0271] A summary of LC-MS methods is shown below:

Method A:

Waters SunFire C18 50*4.6 mm 5µm 2.000 ml/min 2.6 min Column Temperature: 40 °C

Gradient: 5% B hold for 0.2 min, increase to 95 % B within 1.40 min, hold at 95 % B for 0.9 min, then back to 5% B within 0.01 min

Pump A: 0.1% formic acid (FA) and 10% acetonitrile (ACN) in H₂O

Pump B: 0.1%FA and 10% H₂O in ACN.

Method B:

Waters SunFire C18 50*4.6 mm 5µm 2.000 ml/min 2.6 min Column Temperature: 40 °C

Gradient: 5% B hold for 0.2 min, increase to 95 % B within 1.40 min, hold at 95 % B for 0.9 min, then back to 5% B within 0.01 min

Pump A: 0.03% trifluoroacetic acid (TFA) in H₂O

Pump B: 0.03% TFA in ACN

Method C:

Column: Sunfire C18 150*4.6 mm 5um 1.00 ml/min Column Temperature: 40 °C

Gradient: 10% B hold for 1.8 min, increase to 95 % B within 10.2 min, hold at 95 % B for 3.0 min, then back to 10% B within 0.01 min

Pump A: 0.03% TFA in H₂O

Pump B: 0.03% TFA in ACN

Method D:

Column: Luna C18 30*2.0 mm 3um 1.200 ml/min 1.5 min Column Temp.: 50 °C 5% B increase to 95 % B within 0.7 min, hold at 95 % B for 0.4 min, back to 5% B within 0.01 min

Pump A: 0.03% TFA in H₂O

Pump B: 0.03% TFA in ACN

Method E:

SunFire C18 50*4.6 mm 5um 2.6 min 2.0 ml/min

Temperature: 40 °C

Gradient: 10% B increase to 30% B for 0.40 min, increase to 95 % B within 1.60 min, 95% B hold for 0.90 min, back to 10% B within 0.01 min, A70B30

Method F:

SunFire C18 50*4.6 mm 5um 2.6 min 2.0 ml/min

Temperature: 40 °C

Gradient: 10% B increase to 30% B for 0.40 min, increase to 95 % B within 1.60 min, 95% B hold for 0.90 min, back to 10% B within 0.01 min, A50B50.

[0272] Unless otherwise stated, reaction mixtures were magnetically stirred at room temperature (rt) under a nitrogen atmosphere. Where solutions were “dried,” they were generally dried over a drying agent such as Na₂SO₄ or MgSO₄. Where mixtures, solutions, and extracts were “concentrated”, they were typically concentrated on a rotary evaporator under reduced pressure.

[0273] Compound purification was carried out as needed using a variety of traditional methods including, but not limited to, preparative chromatography under acidic, neutral, or basic conditions using either normal phase or reverse phase HPLC or flash columns or Prep-TLC plates.

[0274] Flash chromatography was performed on a Biotage Isolera One via column with silica gel particles of 200-300 mesh. Analytical and preparative thin-layer chromatography was performed using silica gel 60 GF254 plates. Normal-phase silica gel chromatography (FCC) was also performed on silica gel (SiO₂) using prepacked cartridges.

[0275] Preparative reverse-phase high performance liquid chromatography (RP HPLC) was performed on either:

METHOD 1.

[0276] Prep-HPLC with Waters-Sunfire C18 21.2x250mmx10um, and mobile phase of 10-20% ACN in water (0.1% HCOOH) over 15 min and then hold at 100% ACN for 5 min, at a flow rate of 20 mL/min. or

METHOD 2.

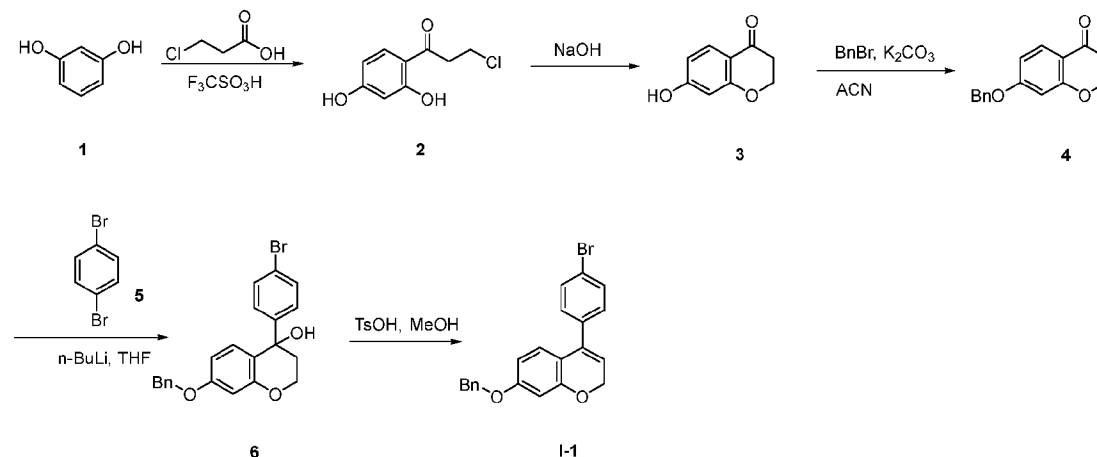
[0277] Preparative supercritical fluid high performance liquid chromatography (SFC) was performed either on a Waters 150 Prep-SFC system from Waters. The ABPR was set to 100 bar to keep the CO₂ in SF conditions, and the flow rate may verify according to the compound characteristics, with a flow rate ranging from 70g/min to 140 g/min. The column temperature was ambient temperature

[0278] Nuclear magnetic resonance (NMR) spectra were recorded using Bruker AVANCE NEO 400 MHz at around 20 - 30°C unless otherwise specified. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublet; dt, doublet of triplets; bs, broad signal. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. It will be understood that for compounds comprising an exchangeable proton, said proton may or may not be visible on an NMR spectrum depending on the choice of solvent used for running the NMR spectrum and the concentration of the compound in the solution.

[0279] Mass spectra (MS) were obtained on a SHIMADZU LC-MS-2020 MSD using electrospray ionization (ESI) in positive mode unless otherwise indicated. Calculated (calcd.) mass corresponds to the exact mass.

[0280] Chemical names were generated using ChemDraw Ultra 12.0, ChemDraw Ultra 14.0 (CambridgeSoft Corp., Cambridge, MA) or ACD/Name Version 10.01 (Advanced Chemistry).

[0281] Compounds designated as R* or S* are enantiopure compounds where the absolute configuration was not determined.

Intermediate 1: 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene*Step 1: 3-chloro-1-(2,4-dihydroxyphenyl)propan-1-one*

[0283] To a solution of resorcinol (110 g, 1.0 mol, 1.0 eq) and 3-chloropropanoic acid (120 g, 1.1 mol, 1.1 eq) at 40°C was added $\text{CF}_3\text{SO}_3\text{H}$ (500 g, 3.6 mol, 320 mL, 3.50 eq). The mixture was stirred at 80°C for 1 hour, cool to rt, and poured into ice-water (3 L). The precipitate was collected by filtration to afford 3-chloro-1-(2,4-dihydroxyphenyl)propan-1-one (200 g, 100% crude yield).

Step 2: crude 7-hydroxychroman-4-one

[0284] The crude 3-chloro-1-(2,4-dihydroxyphenyl)propan-1-one (200 g, 1.0 mol, 1.0 eq) was mixed with NaOH (160 g, 4.0 mol, 4.0 eq) in H_2O (1.0 L), then the mixture was stirred at 0° C for 1 hour. The reaction mixture was first adjusted to pH = 5 with 6 N HCl, then extracted with EtOAc (2 x 500 mL). The organic layers were combined, dried over Na_2SO_4 , filtrated, and concentrated under reduced pressure to afford crude 7-hydroxychroman-4-one (164 g, 100% crude yield) as brown gum.

Step 3: 7-(benzyloxy)chroman-4-one

[0285] To a solution of 7-hydroxychroman-4-one (164 g, 1.0 mol, 1.0 eq) in ACN (1.50 L) was added K_2CO_3 (276 g, 2.0 mol, 2.0 eq) and benzylbromide (190 g, 1.1 mol, 1.1 eq) slowly. The mixture was stirred at 25° C for 12 hours, then poured into H_2O (3 L), and extracted with EtOAc (2 x 1 L). The combined organic layer was washed with brine (2 L), dried over Na_2SO_4 , filtered and concentrated in vacuum. The residue was purified by column chromatography on silica gel using 0-15% EtOAc/hexane to afford 7-(benzyloxy)chroman-4-one (185 g, 73% yield) as a yellow solid.

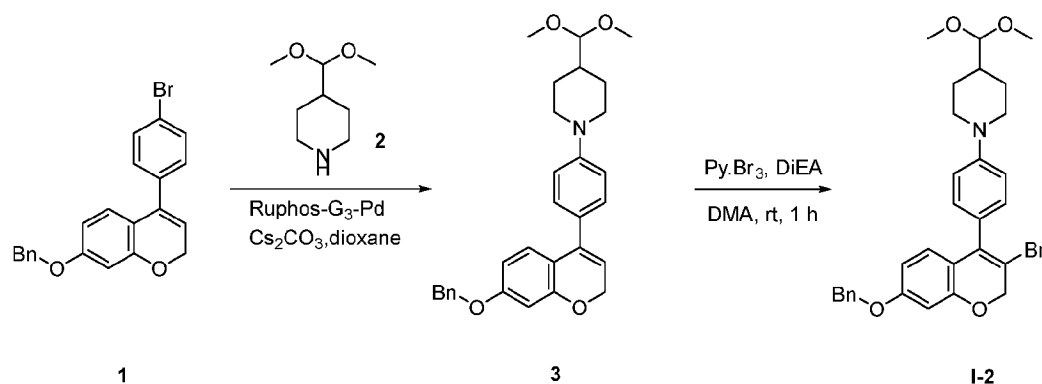
Step 4: 7-(benzyloxy)-4-(4-bromophenyl) chroman-4-ol

[0286] To a mixture of 1,4-dibromobenzene (5.1 g, 21.7 mmol, 1.1 eq) in dry THF (15 mL) was added n-BuLi (1.6 M, 25.6 mL, 1.30 eq) dropwise and the mixture was stirred at -78°C for 1 h. Then a solution of 7-(benzyloxy)chroman-4-one (5 g, 19.7 mmol, 1.0 eq) in THF (15 mL) was added and the mixture was stirred at -78°C for 1 h. The reaction was quenched with NH₄Cl solution (30 mL), extracted with EtOAc (2 x 20 mL). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-bromophenyl) chroman-4-ol (4.2 g, 52% yield) as a white solid.

Step 5: 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene

[0287] To a solution of 7-(benzyloxy)-4-(4-bromophenyl)chroman-4-ol (4.2 g, 10.2 mmol, 1.0 eq) in MeOH (20 mL) was added TsOH (39 mg, 0.2 mmol, 0.02 eq) and the mixture was stirred at 70 °C for 30 min and the mixture was concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (3.7 g, 92% yield) as a yellow gum. LC-MS purity: 96.9% (UV at 254 nm), 392.9 [M+H]⁺.

Intermediate 2: 1-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine

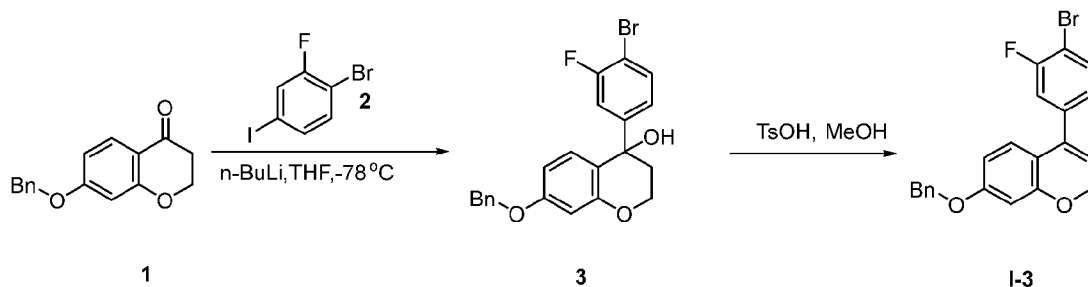
*Step 1: 1-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine*

[0288] To a mixture of 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (5.3 g, 13.5 mmol, 1 eq.), 4-(dimethoxymethyl)piperidine (2.36 g, 14.8 mmol, 1.05 eq.), RuphosPdG₃ (1.13 g, 1.35 mmol, 0.1 eq.), CS₂CO₃ (8.79 g, 27 mmol, 2 eq.) in dioxane (50 mL). The mixture was purged with N₂ and heated to 100 °C for 16 h. LCMS showed reaction was complete. The mixture was poured into

H₂O (30 mL), extracted with EtOAc (20 mLx2), and the organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel using 0-30% EtOAc/hexane to afford 1-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine (4.7 g, 73.9% yield) as a yellow solid. LC-MS purity: 98% (UV at 254 nm), 472.0 [M+H]⁺

Step 2: 1-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine
[0289] To a solution of 1-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine (850 mg, 1.8 mmol, 1.00 eq.) and DIEA (465 mg, 3.6 mmol, 2.00 eq.) in DMA (5 mL), was added pyridinium tribromide (634 mg, 1.98 mmol, 1.1 eq.) at 0°C, and the mixture was stirred at 25° C for 1 h. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into H₂O (30 mL), extracted with EtOAc (20 mLx2), and the organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by column chromatography on silica gel using 0-20% EtOAc/hexane to afford 1-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-4-(dimethoxymethyl)piperidine (560 mg, 56.6% yield) as a yellow solid. LC-MS purity: 47% (UV at 254 nm), 551.9 [M+H]⁺

Intermediate 3: 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)-2H-chromene



Step 1: 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)chroman-4-ol

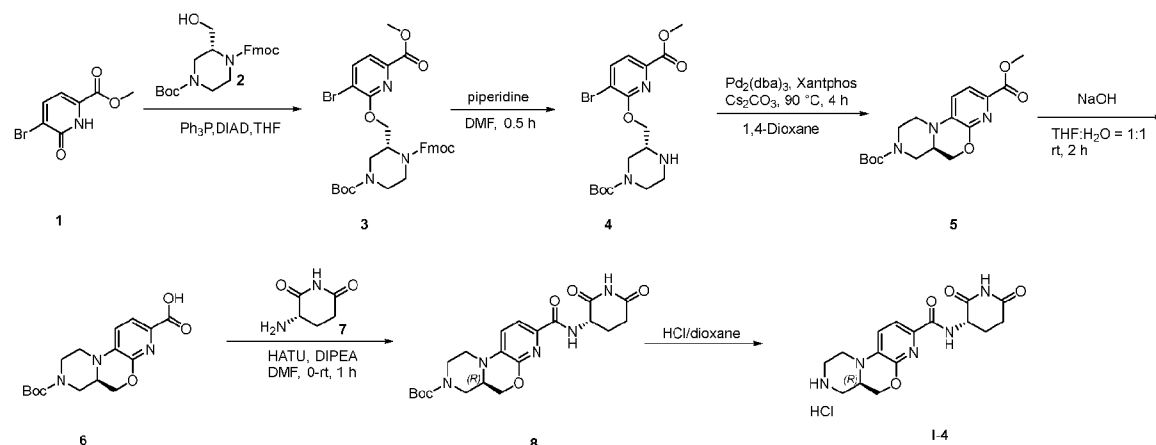
[0290] To a mixture of 1-bromo-2-fluoro-4-iodobenzene (6.6 g, 22.0 mmol, 1.1 eq) in dry THF (15 mL) was added n-BuLi (1.6 M, 25.6 mL, 1.30 eq) dropwise and the mixture was stirred at -78°C for 1 h. Then a solution of 7-(benzyloxy)chroman-4-one (5 g, 19.7 mmol, 1.0 eq) in THF (15 mL) was added and the mixture was stirred at -78°C for 1 h. The reaction was quenched with NH₄Cl solution (30 mL), extracted with EtOAc (2 x 20 mL), and the combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude

product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)chroman-4-ol (4.3 g, 50% yield) as a white solid.

Step 2: 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)-2H-chromene

[0291] To a solution of 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)chroman-4-ol (4.3 g, 10.0 mmol, 1.0 eq) in MeOH (20 mL) was added TsOH (39 mg, 0.2 mmol, 0.02 eq) and the mixture was stirred at 70 °C for 30 min and the mixture was concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-bromo-3-fluorophenyl)-2H-chromene (3.6 g, 90% yield) as a yellow gum. LC-MS purity: 47% (UV at 254 nm), 392.9 [M+H]⁺.

Intermediate 4: (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride salt



Step 1: (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate

[0292] A mixture of methyl 5-bromo-6-oxo-1,6-dihydropyridine-2-carboxylate (2.5 g, 10.7 mmol, 1 eq.) in THF (50 mL) was added (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(hydroxymethyl)piperazine-1,4-dicarboxylate (5.7 g, 12.9 mmol, 1.2 eq.) and PPh₃ (8.4 g, 32.1 mmol, 3 eq.) was warmed to 60 °C under Ar. To the mixture was added DIAD (6.5 g, 32.1 mmol, 3 eq.) dropwise and the mixture was stirred at 60 °C for 2 hours. The mixture was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-

(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate (5.0 g, 70 % yield) as a yellow solid.

Step 2: (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate

[0293] To a mixture of (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate (5 g, 7.6 mmol 1 eq.) in DMF (50 mL) was added piperidine (1.1 g, 15.2 mmol, 2 eq.). The mixture was stirred at room temperature for 0.5 hour, diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine, dried over Na₂SO₄ and filtered. The filtrate was evaporated in *vacuo*. The residue was purified by column chromatography on silica gel eluted with 0-5% DCM in methanol to afford (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate (2.4 g, 75 % yield). LC-MS purity: 100% (UV at 254 nm), 430.2 [M+H]⁺.

Step 3: (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate

[0294] To a mixture of (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate (2.4 g, 5.6 mmol, 1 eq.), XantPhos (486 mg, 0.84 mmol, 0.15 eq.), and Cs₂CO₃ (5.4 g, 16.8 mmol, 3 eq.) in dioxane (50 mL) was added Pd₂(dba)₃ (511 mg, 0.56 mmol, 0.1 eq.) and the mixture was stirred at 90 °C for 4 hours under Ar. The mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine, dried over Na₂SO₄, and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate (1.3 g, 68 % yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 350.4 [M+H]⁺.

Step 4: (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid

[0295] To a mixture of (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate (1.3 g, 3.7 mmol, 1 eq.) in THF (10 mL) and water (10 mL) was added sodium hydroxide (590 mg, 14.8 mmol, 4 eq) and the mixture was stirred at room temperature for 2 hours. The mixture was adjusted to pH=5-6 with aq. HCl (1 M) and extracted

with ethyl acetate (20 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was evaporated to afford (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (1.3 g, crude) as a white solid. LC-MS purity: 100% (UV at 254 nm), 336.3[M+H]⁺.

Step 5: tert-butyl (R)-8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate

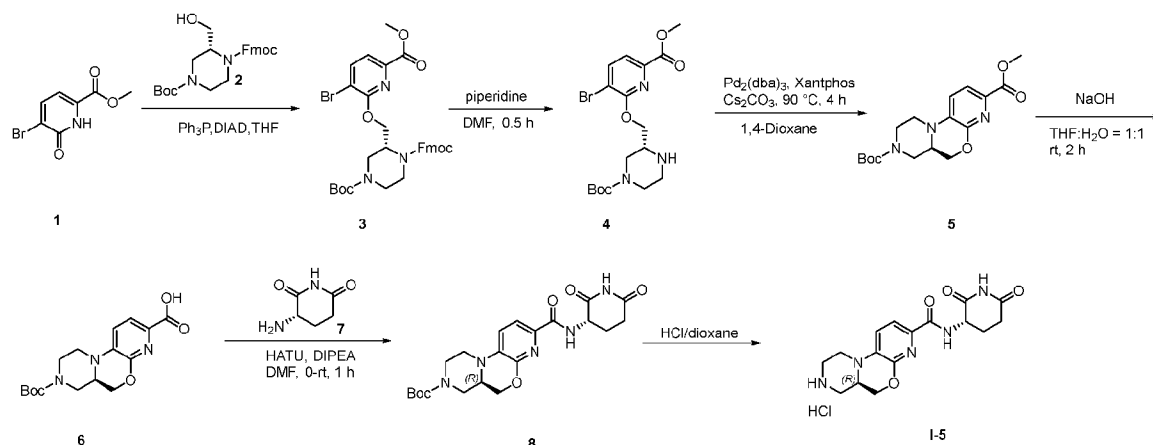
[0296] To a mixture of (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (1.3 g, 3.8 mmol, 1 eq.) and (S)-3-aminopiperidine-2,6-dione (580 mg, 4.6 mmol, 1.2 eq.) in DMF (10 mL) was added HATU (1.7 g, 4.6 mmol, 1.2 eq.) and DIPEA (980 mg, 7.6 mmol, 2 eq.) and the mixture was stirred at room temperature for 1 h. The mixture was purified directly by reverse phase column chromatography (0-90% acetonitrile/0.05% formic acid) to afford (R)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (1.3 g, 76 % yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 446.2[M+H]⁺.

Step 6: (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride

[0297] A mixture of (R)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (1.3 g, 2.9 mmol, 1 eq.) in HCl/dioxane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated to afford (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride (1.0 g, 91% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 346.2[M+H]⁺.

[0298] ¹H NMR (400 MHz, DMSO): δ 10.84 (s, 1H), 9.63-9.33 (m, 2H), 8.56 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 4.77-4.70 (m, 1H), 4.51-4.49 (m, 2H), 4.20-4.05 (m, 2H), 3.66-3.55 (m, 1H), 3.47-3.39 (m, 2H), 3.22-2.98 (m, 2H), 2.89-2.67 (m, 2H), 2.26-2.11 (m, 1H), 2.02-1.90 (m, 1H).

Intermediate 5: (S)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride salt



Step 1: (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate

[0299] A mixture of methyl 5-bromo-6-oxo-1,6-dihydropyridine-2-carboxylate (2.5 g, 10.7 mmol, 1 eq.) in THF (50 mL) was added (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-((hydroxymethyl)piperazine-1,4-dicarboxylate (5.7 g, 12.9 mmol, 1.2 eq.) and PPh₃ (8.4 g, 32.1 mmol, 3 eq.) was warmed to 60 °C under Ar. To the mixture was added DIAD (6.5 g, 32.1 mmol, 3 eq.) dropwise and the mixture was stirred at 60 °C for 2 hours. The mixture was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate (5.0 g, 70 % yield) as a yellow solid.

Step 2: (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate

[0300] To a mixture of (R)-1-((9H-fluoren-9-yl)methyl) 4-tert-butyl 2-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1,4-dicarboxylate (5 g, 7.6 mmol 1 eq.) in DMF (50 mL) was added piperidine (1.1 g, 15.2 mmol, 2 eq.). The mixture was stirred at room temperature for 0.5 hour, diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine, dried over Na₂SO₄ and filtered. The filtrate was evaporated in *vacuo*. The residue was purified by column chromatography on silica gel eluted with 0-5% DCM in methanol to afford (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate (2.4 g, 75 % yield). LC-MS purity: 100% (UV at 254 nm), 430.2 [M+H]⁺.

Step 3: (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate

[0301] To a mixture of (R)-tert-butyl 3-(((3-bromo-6-(methoxycarbonyl)pyridin-2-yl)oxy)methyl)piperazine-1-carboxylate (2.4 g, 5.6 mmol, 1 eq.), XantPhos (486 mg, 0.84 mmol, 0.15 eq.), and Cs₂CO₃ (5.4 g, 16.8 mmol, 3 eq.) in dioxane (50 mL) was added Pd₂(dba)₃ (511 mg, 0.56 mmol, 0.1 eq.) and the mixture was stirred at 90 °C for 4 hours under Ar. The mixture was diluted with ethyl acetate (100 mL) and washed with water (50 mL). The organic phase was washed with brine, dried over Na₂SO₄, and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate (1.3 g, 68 % yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 350.4 [M+H]⁺.

Step 4: (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid

[0302] To a mixture of (R)-3-tert-butyl 8-methyl 1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3,8(4H)-dicarboxylate (1.3 g, 3.7 mmol, 1 eq.) in THF (10 mL) and water (10 mL) was added sodium hydroxide (590 mg, 14.8 mmol, 4 eq) and the mixture was stirred at room temperature for 2 hours. The mixture was adjusted to pH=5-6 with aq. HCl (1 M) and extracted with ethyl acetate (20 mL). The organic layer was washed with brine, dried over sodium sulfate, and filtered. The filtrate was evaporated to afford (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (1.3 g, crude) as a white solid. LC-MS purity: 100% (UV at 254 nm), 336.3[M+H]⁺.

Step 5: tert-butyl (R)-8-(((S)-2,6-dioxopiperidin-3-yl)carbonyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate

[0303] To a mixture of (R)-3-(tert-butoxycarbonyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxylic acid (1.3 g, 3.8 mmol, 1 eq.) and (S)-3-aminopiperidine-2,6-dione (580 mg, 4.6 mmol, 1.2 eq) in DMF (10 mL) was added HATU (1.7 g, 4.6 mmol, 1.2 eq.) and DIPEA (980 mg, 7.6 mmol, 2 eq.) and the mixture was stirred at room temperature for 1 h. The mixture was purified directly by reverse phase column chromatography (0-90% Acetonitrile/ 0.05% Formic acid) to afford (R)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-

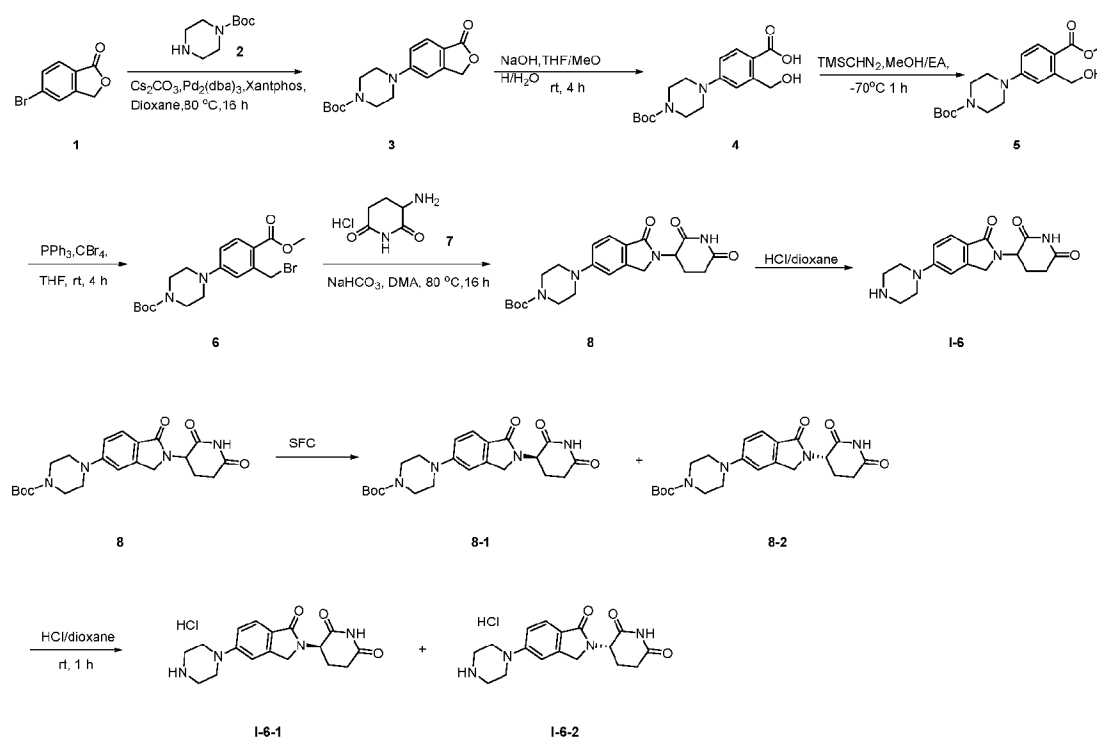
yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (1.3 g, 76 % yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 446.2[M+H]⁺.

Step 6: (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride

[0304] A mixture of (R)-tert-butyl 8-(((S)-2,6-dioxopiperidin-3-yl)carbamoyl)-1,2,4a,5-tetrahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-3(4H)-carboxylate (1.3 g, 2.9 mmol, 1 eq.) in HCl/dioxane (10 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated to afford (R)-N-((S)-2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide hydrochloride (1.0 g, 91% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 346.2[M+H]⁺.

[0305] ¹H NMR (400 MHz, DMSO): δ 10.84 (s, 1H), 9.63-9.33 (m, 2H), 8.56 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 4.77-4.70 (m, 1H), 4.51-4.49 (m, 2H), 4.20-4.05 (m, 2H), 3.66-3.55 (m, 1H), 3.47-3.39 (m, 2H), 3.22-2.98 (m, 2H), 2.89-2.67 (m, 2H), 2.26-2.11 (m, 1H), 2.02-1.90 (m, 1H).

Intermediate 6: 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt



Step 1: tert-butyl 4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate

[0306] To a mixture of 5-bromoisobenzofuran-1(3H)-one (10.0 g, 46.95 mmol, 1.0 eq) and tert-butyl piperazine-1-carboxylate in 1,4-dioxane (100 mL) was added Cs₂CO₃ (30.6 g, 93.90 mmol, 2.0 eq) and Xantphos (2.8 g, 4.70 mmol, 0.1 eq) followed by the addition of Pd₂(dba)₃ (2.2 g, 2.347 mmol, 0.05 eq.). The mixture was stirred at 80 °C for 12 hours under N₂ protection. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by column chromatography on silica gel (0-20% of EtOAc in PE) to afford tert-butyl 4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate (6.50 g, 63.3%) as a yellow solid. LC-MS purity: 100 % (UV at 254 nm), 319.2 [M+H]⁺.

Step 2: 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(hydroxymethyl)benzoic acid

[0307] To a mixture of tert-butyl 4-(1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate (6.5 g, 20.38 mmol, 1.0 eq) in MeOH (15 mL)/THF (15 mL)/H₂O (15 mL) was added NaOH (3.7 g, 81.51 mmol, 4.0 eq). stirred at room temperature for 4 hours. The resulting mixture was dilute with water, adjusted to pH 5~6 with 1N HCl filtered. The solid was dried to afford 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(hydroxymethyl)benzoic acid (7.10 g, crude) as a white solid. LC-MS purity: 100 % (UV at 254 nm), 337.1 [M+H]⁺.

Step 3: tert-butyl 4-(3-(hydroxymethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate

[0308] To a mixture of 4-(4-(tert-butoxycarbonyl)piperazin-1-yl)-2-(hydroxymethyl)benzoic acid (7.1 g, 21.131 mmol, 1.0 eq) in EtOAc (35 mL)/MeOH (35 mL) was dropwise TMSCHN₂ (2 M in n-Hexane, 27 mL) at -70°C and the mixture stirred for 1 hour under N₂ protection. The resulting mixture was concentrated under vacuum. The residue was purified by column chromatography on silica gel (0-20% of EtOAc in PE) to afford tert-butyl 4-(3-(hydroxymethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (7.8 g, crude) as yellow oil. LC-MS purity: 100 % (UV at 254 nm), 351.3 [M+H]⁺.

Step 4: tert-butyl 4-(3-(bromomethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate

[0309] To a mixture of tert-butyl 4-(3-(hydroxymethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (7.8 g, 22.222 mmol, 1.0 eq) in THF (70 mL) was added PPh₃ (8.8 g, 33.333 mmol, 1.5 eq), CBr₄ (11.1 g, 33.333 mmol, 1.5 eq). The resulting was stirred at room temperature for 4 hours, concentrated. The residue was purified by silica gel chromatography column chromatography on silica gel (0-20% of EtOAc in PE) to afford tert-butyl 4-(3-(bromomethyl)-4-

(methoxycarbonyl)phenyl)piperazine-1-carboxylate (6.8 g, 73.9% yield) as a yellow solid. LC-MS purity: 100 % (UV at 254 nm), 414.9 [M+H]⁺.

Step 5: tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate

[0310] To a mixture of tert-butyl 4-(3-(bromomethyl)-4-(methoxycarbonyl)phenyl)piperazine-1-carboxylate (3.4 g, 8.226 mmol, 1.0 eq.), 3-aminopiperidine-2,6-dione hydrochloride (4.1 g, 24.679 mmol, 3.0 eq.) in DMA (20 mL) was added NaHCO₃ (2.1 g, 24.679 mmol, 3.0 eq.) and the mixture stirred at 80 °C for 16 hours. The resulting mixture was purified by reverse flash chromatography, with the following conditions: column, C18 silica gel; mobile phase, ACN in water, 0% to 100% gradient in 20 min; detector, UV 254 nm to afford tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate (1.5 g, 43.0% yield) as a blue solid. LC-MS purity: 100 % (UV at 254 nm), 429.0 [M+H]⁺.

[0311] ¹H NMR (400 MHz, DMSO): δ 10.93 (s, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.12 – 7.01 (m, 2H), 5.05 (dd, J = 13.2, 5.2 Hz, 1H), 4.27 (dd, J = 49.2, 16.8 Hz, 2H), 3.48 – 3.44 (m, 3H), 3.32 – 3.25 (m, 5H), 2.96 – 2.84 (m, 1H), 2.62 – 2.55 (m, 1H), 2.43 – 2.31 (m, 1H), 2.00 – 1.92 (m, 1H), 1.42 (s, 9H).

Step 6: 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt

[0312] A mixture of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate (100 mg) in HCl/dioxane (2 mL) was stirred at rt for 1 hour. Then the solution was concentrated to afford 3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt as light-blue solid (90 mg, crude, ca. 100% yield). LC-MS purity: 100 % (UV at 254 nm), 329.0 [M+H]⁺.

Step 7: SFC separation of tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate

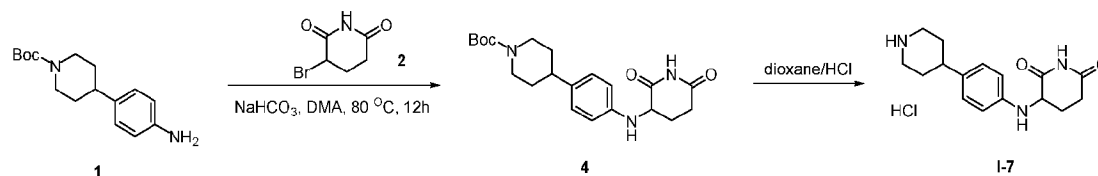
[0313] tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate (500 mg) was separated via SFC to afford (R)-tert-butyl-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate and (S)-tert-butyl-4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisindolin-5-yl)piperazine-1-carboxylate (isomer 1: 240 mg, isomer 2: 220 mg).

System:	Waters SFC 150
Column name:	DAICELCHIRALPAK®AD
Column size:	250*25 mm 10 μm
Mobile Phase A:	Supercritical CO ₂ ,
Mobile Phase B:	MEOH (+0.1% 7.0mol/l Ammonia in MEOH)
A:B:	75:25
Wavelength:	214 nm
Flow:	70ml/min
Column temp:	RT
Back Pressure:	100 bar
Injection:	1mL
Cycle time:	3.8min
Solvent:	MeOH: redistilled grade Supercritical CO ₂ : Food grade

Step 8: (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt or (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt

[0314] A mixture of (R)-tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate or (s)-tert-butyl 4-(2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)piperazine-1-carboxylate (100 mg) in HCl/dioxane (2 mL) was stirred at rt for 1 hour. Then the solution was concentrated to afford (R)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt or (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride salt (90 mg, 100% crude yield) as a light-blue solid. LC-MS purity: 100 % (UV at 254 nm), 329.0 [M+H]⁺.

Intermediate 7: 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt



Step 1: tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate

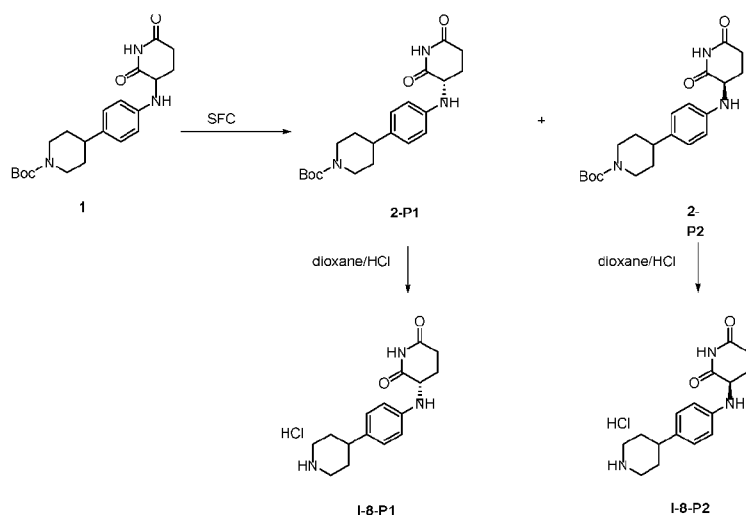
[0315] To a mixture of tert-butyl 4-(4-aminophenyl)piperidine-1-carboxylate (1.5 g, 5.4 mmol 1.0 eq.) in DMA (8 mL) was added 3-bromopiperidine-2,6-dione (1.0 g, 5.428 mmol 1.0 eq) and NaHCO₃ (456 mg, 5.4 mmol 1.0 eq.). The mixture was stirred at 80 °C for 12 hours and cooled to

room temperature. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (1.6 g, 76.0 % yield) as a light blue solid. LC-MS purity: 100% (UV at 254 nm), 388.0 [M+H]⁺:

Step 2: 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt

[0316] A mixture of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (1.6 g, 4.1 mmol, 1.0 eq.) in HCl/dioxane (10 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride (1.5 g, crude). LC-MS purity: 100% (UV at 254 nm), 288.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO): δ 10.83 (s, 1H), 9.11 – 8.76 (m, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 4.33 (dd, J = 11.6, 4.8 Hz, 1H), 3.35 – 3.25 (m, 2H), 3.00 – 2.84 (m, 2H), 2.79 – 2.56 (m, 3H), 2.15 – 2.01 (m, 1H), 1.92 – 1.73 (m, 5H).

Intermediate 8: Two single isomers of 3-((4-(piperidin-4-yl)phenyl)amino) piperidine-2,6-dione hydrochloride salt (structures were tentatively assigned)



Step 1: Two single isomers of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate

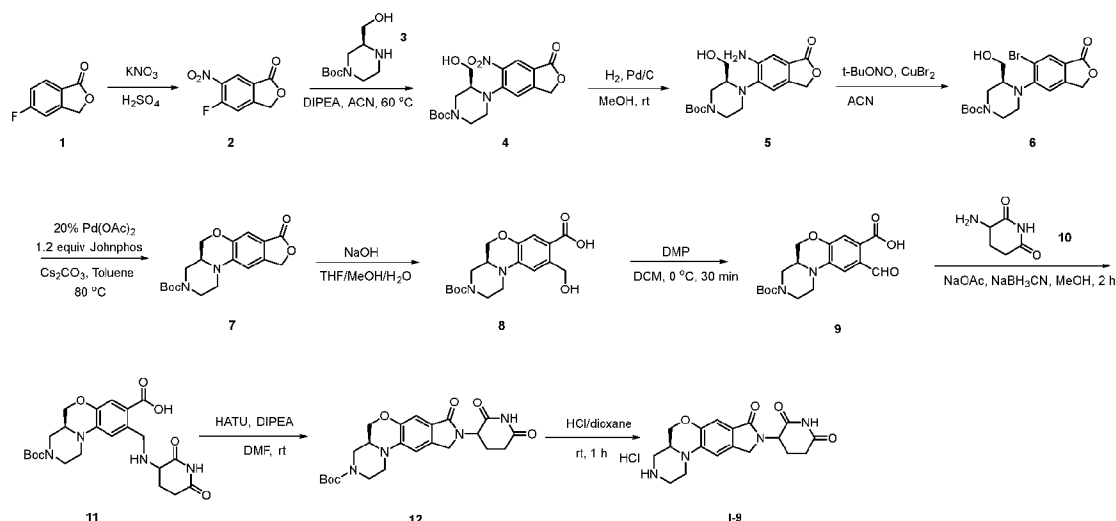
[0317] tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (1.9 g, 5 mmol) was purified via SFC as method below to afford two single isomers (P1:450 mg, P2: 480 mg), LC-MS purity: 100% (UV at 254 nm), 388.0 [M+H]⁺.

System:	Waters SFC 150
Column name:	DAICELCHIRALPAK®AS
Column size:	250*25 mm 10 μm
Mobile Phase A:	Supercritical CO ₂ ,
Mobile Phase B:	MEOH (+0.1% 7.0mol/l Ammonia in MEOH)
A:B:	75:25
Wavelength:	214 nm
Flow:	70ml/min
Column temp:	RT
Back Pressure:	100 bar
Injection:	1mL
Cycle time:	3.8min
Solvent:	MeOH: redistilled grade Supercritical CO ₂ : Food grade

Step 2: Two single isomers of 3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt

[0318] A mixture of (S)-tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate or (R)-tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)phenyl)piperidine-1-carboxylate (100 mg, 0.25 mmol, 1.0 eq) in HCl/dioxane (2 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford (R/S)-3-((4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt (90 mg, 100% crude yield). LC-MS purity: 100% (UV at 254 nm), 288.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.11 – 8.76 (m, 2H), 6.98 (d, J = 8.4 Hz, 2H), 6.72 (d, J = 8.4 Hz, 2H), 4.33 (dd, J = 11.6, 4.8 Hz, 1H), 3.35 – 3.25 (m, 2H), 3.00 – 2.84 (m, 2H), 2.79 – 2.56 (m, 3H), 2.15 – 2.01 (m, 1H), 1.92 – 1.73 (m, 5H).

Intermediate 9: 3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride salt



Step 1: 5-fluoro-6-nitroisobenzofuran-1(3H)-one

[0319] To a solution of 5-fluoroisobenzofuran-1(3H)-one (10 g, 65.8 mmol, 1.0 eq.) in H_2SO_4 (50 mL) was added KNO_3 (9.97 g, 98.7 mmol, 1.5 eq.) in portions. The reaction mixture was stirred at room temperature for 3 h, then slowly poured into ice water (100 mL) and extracted with EtOAc (100 mL x 3). The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford 5-fluoro-6-nitroisobenzofuran-1(3H)-one (10.4 g, 80% yield) as a white solid.

Step 2: tert-butyl (S)-3-(hydroxymethyl)-4-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate

[0320] To a solution of 5-fluoro-6-nitroisobenzofuran-1(3H)-one (1 g, 5.0 mmol, 1 eq.) and tert-butyl (S)-3-(hydroxymethyl)piperazine-1-carboxylate (1.7 g, 7.5 mmol, 1.5 eq.) in acetonitrile (10 mL) was added DIPEA (2.2 mL, 12.5 mmol, 2.5 eq.) and the mixture was stirred at 60 °C for 6 h. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-5% MeOH/DCM to afford tert-butyl (S)-3-(hydroxymethyl)-4-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate (1.3 g, 66% yield) as yellow foam. LC-MS purity: 77.1% (UV at 254 nm), 394.0 $[\text{M}+\text{H}]^+$.

Step 3: tert-butyl (S)-4-(6-amino-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate

[0321] To a solution of tert-butyl (S)-3-(hydroxymethyl)-4-(6-nitro-1-oxo-1,3-dihydroisobenzofuran-5-yl)piperazine-1-carboxylate (1.0 g, 2.8 mmol, 1 eq.) in MeOH (15 mL)

was added Pd/C (300 mg, 10% on Carbon, wetted with ca. 55% water). The mixture was degassed and purged with H₂ three times and stirred at room temperature for 4 h. The catalyst was removed by filtration and the filtrate was evaporated to afford tert-butyl (S)-4-(6-amino-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (860 mg, 93% yield) as light yellow foam. LC-MS purity: 95.7% (UV at 254 nm), 364.1 [M+H]⁺

Step 4: tert-butyl (S)-4-(6-bromo-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate

[0322] To a solution of tert-butyl (S)-4-(6-amino-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (468 mg, 1.3 mmol, 1 eq.) in acetonitrile (25 mL) was added *t*-BuONO (0.2 mL, 1.7 mmol, 1.3 eq.) under ice bath and the mixture was stirred for 30 min. Then a solution of CuBr₂ (300 mg, 1.3 mmol, 1 eq.) in acetonitrile (6 mL) was added to the solution dropwise and the mixture was stirred at room temperature for 3 h. Then the mixture was diluted with EA (120 mL) and water (120 mL). The organic phase was washed with brine, dried over Na₂SO₄, and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-5% MeOH/DCM to afford tert-butyl (S)-4-(6-bromo-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (415 mg, 75% yield) as brown oil. LC-MS purity: 46% (UV at 254 nm), 427.1, 429.1 [M+H]⁺.

Step 5: tert-butyl (S)-8-oxo-1,2,4a,5,8,10-hexahydroisobenzofuro[5,6-b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate

[0323] A mixture of tert-butyl (S)-4-(6-bromo-1-oxo-1,3-dihydroisobenzofuran-5-yl)-3-(hydroxymethyl)piperazine-1-carboxylate (140 mg, 0.3 mmol, 1 eq.), Pd(OAc)₂ (36.8 mg, 0.15 mmol, 0.5 eq.), JohnPhos (118 mg, 0.36 mmol, 1.2 eq.) and Cs₂CO₃ (214 mg, 0.7 mmol, 2 eq.) in toluene was degassed and purged with N₂ three times, and then the mixture was stirred at 80 °C for 3 h. The mixture was cooled to room temperature, filtered through Celite, and the filtrate was concentrated. The residue was triturated with MeOH, and the solid was collected by filtration to afford tert-butyl (S)-8-oxo-1,2,4a,5,8,10-hexahydroisobenzofuro[5,6-b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (90 mg, 80% yield) as a yellow solid. LC-MS purity: 45.5% (UV at 254 nm), 347.1 [M+H]⁺.

Step 6: (S)-3-(tert-butoxycarbonyl)-9-(hydroxymethyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid

[0324] To a solution of tert-butyl (S)-8-oxo-1,2,4a,5,8,10-hexahydroisobenzofuro[5,6-b]pyrazino[1,2-d][1,4]oxazine-3(4H)-carboxylate (87 mg, 0.25 mmol, 1 eq.) in THF (3 mL) was added a solution of NaOH (60 mg, 1.3 mmol, 6 eq.) in H₂O (1 mL) and the mixture was stirred at 40 °C for 6 h. Then the mixture was concentrated, and the residue was diluted with water (4 mL) and acidified to pH=3-4 with 2 N HCl. The mixture was extracted with DCM (10 mL) and the organic phase was washed with brine, dried over Na₂SO₄ and filtered. The filtrate was evaporated in *vacuo* to afford (S)-3-(tert-butoxycarbonyl)-9-(hydroxymethyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (76 mg, 83% yield) as a white solid. LC-MS purity: 68.9% (UV at 254 nm), ms: 347.0 [M+H-18]⁺.

Step 7: (S)-3-(tert-butoxycarbonyl)-9-formyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid

[0325] To a solution of (S)-3-(tert-butoxycarbonyl)-9-(hydroxymethyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (54 mg, 0.15 mmol, 1 eq.) in DCM (10 mL) cooled at 0 °C was added DMP (93.7 mg, 0.23 mmol, 1.5 eq.) in small portions and the mixture was stirred at 0 °C for 30 min. Then the mixture was diluted with DCM (20 mL) and washed with brine. The organic phase was dried over Na₂SO₄ and filtered. The filtrate was evaporated in *vacuo* to afford (S)-3-(tert-butoxycarbonyl)-9-formyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (50 mg, crude) as a yellow solid.

Step 8: (4aS)-3-(tert-butoxycarbonyl)-9-(((2,6-dioxopiperidin-3-yl)amino)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid

[0326] To a mixture of (S)-3-(tert-butoxycarbonyl)-9-formyl-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (70 mg, 0.2 mmol, 1 eq.), 3-aminopiperidine-2,6-dione (47.6 mg, 0.3 mmol, 1.5 eq.) and NaOAc (23.7 mg, 0.3 mmol, 1.5 eq.) in MeOH (6 mL) was added NaBH₃CN (36 mg, 0.6 mmol, 3 eq.) and the mixture was stirred at room temperature for 2 h. Then the reaction was quenched with water (5 mL) and the mixture was purified by reverse phase column chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford (4aS)-3-(tert-butoxycarbonyl)-9-(((2,6-dioxopiperidin-3-yl)amino)methyl)-1,2,3,4,4a,5-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (35 mg, 38% yield) as a white solid. LC-MS purity: 65.6% (UV at 254 nm), 475.2 [M+H]⁺.

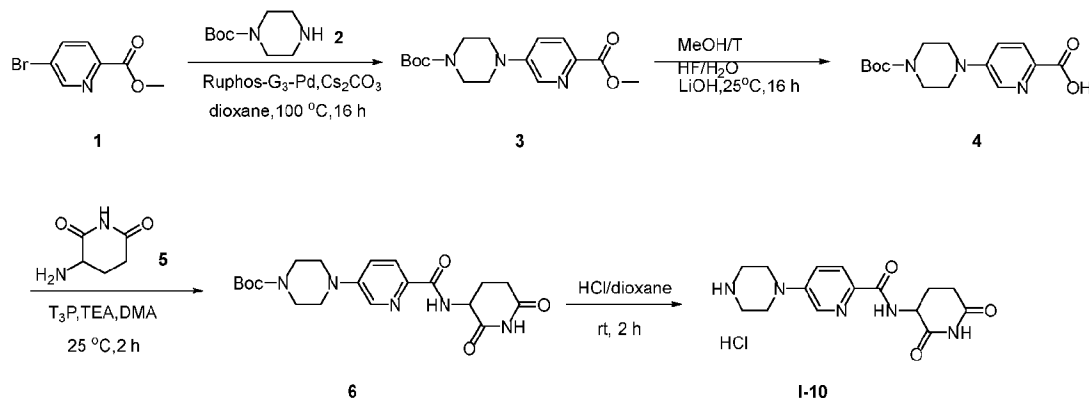
Step 9: tert-butyl (4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindole-3(4H)-carboxylate

[0327] To a solution of (4aS)-3-(tert-butoxycarbonyl)-9-(((2,6-dioxopiperidin-3-yl)amino)methyl)-1,2,3,4,4a,5,9,10-hexahydrobenzo[b]pyrazino[1,2-d][1,4]oxazine-8-carboxylic acid (47 mg, 0.1 mmol, 1 eq.) in DMF (2.5 mL) was added HATU (54 mg, 0.15 mmol, 1.5 eq.) followed by DIPEA (40 mg, 0.3 mmol, 3 eq.) and the mixture was stirred at room temperature for 1 h. Then the reaction was quenched with water (2.5 mL) and the mixture was purified by reverse phase column chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford tert-butyl (4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindole-3(4H)-carboxylate (30 mg, 66% yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 457.2 [M+H]⁺.

Step 10: 3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride salt

[0328] A mixture of tert-butyl (4aS)-9-(2,6-dioxopiperidin-3-yl)-8-oxo-1,2,4a,5,9,10-hexahydro-8H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindole-3(4H)-carboxylate (30 mg, 1.0 eq) and HCl/dioxane (2 mL) was stirred at room temperature for 1 h. The mixture was concentrated to afford 3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride salt (26 mg, crude) as a white solid. LC-MS purity: 100% (UV at 254 nm), 357.2 [M+H]⁺

Intermediate 10: N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride



Step 1: tert-butyl 4-(6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate

[0329] To a mixture of methyl 5-bromopicolinate (15 g, 69.4 mmol 1 eq.), tert-butyl piperazine-1-carboxylate (12.9 g, 69.4 mmol, 1 eq.) and Cs₂CO₃ (45 g, 139 mmol, 2 eq.) in dioxane (150 mL) was added Ruphos-G3-Pd (2.2 g, 3.5 mmol, 0.05 eq.). The mixture was stirred at 100 °C for 16 h under Ar and then cooled to room temperature, concentrated. The residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford tert-butyl 4-(6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (22 g, crude). LC-MS purity: 76.1% (UV at 254 nm), 322.4 [M+H]⁺.

Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)picolinic acid

[0330] To a mixture of tert-butyl 4-(6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (22 g, 68.5 mmol, 1 eq.) in MeOH (40 mL)/THF (100 mL)/H₂O (40 mL) was added LiOH (5.5 g, 137 mmol, 2 eq.) and the mixture was stirred at room temperature for 16 h. The mixture was concentrated to remove THF and then adjusted to pH=6 with 1N HCl. The precipitate was collected by filtration and dried in vacuo to afford 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)picolinic acid (16.3 g, 76.4% yield). LC-MS purity: 79.5% (UV at 254 nm), 308.1 [M+H]⁺.

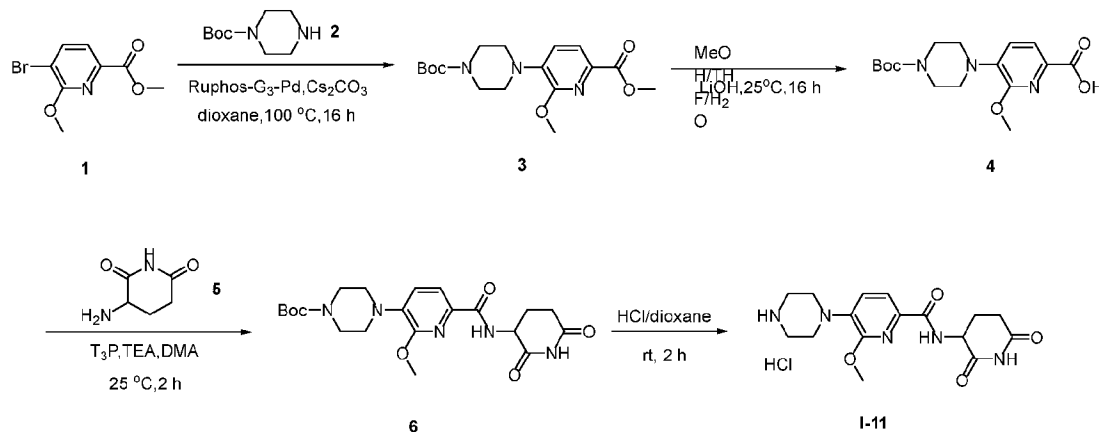
Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate

[0331] To a mixture of 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)picolinic acid (1 g, 3.2 mmol, 1 eq.), 3-aminopiperidine-2,6-dione (537 mg, 3.2 mmol, 1 eq.) in DMA (5 mL) was added TEA (0.8 mL, 6.4 mmol, 2 eq.) and T₃P (3 mL, 4.8 mmol, 1.5 eq.). The reaction mixture was stirred at room temperature for 2 h, poured into water (50 mL) and extracted with EtOAc (20 mL). The organic phase was dried over Na₂SO₄ and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate (1.0 g, 78%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 418.4 [M+H]⁺.

Step 4: N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride salt

[0332] A mixture of tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate (1 g, 2.5 mmol, 1.0 eq) in HCl/dioxane (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride salt (950 mg, crude) as a white solid. LC-MS purity: 100% (UV at 254 nm), 318.1 [M+H]⁺

Intermediate 11: N-(2,6-dioxopiperidin-3-yl)-6-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride



Step 1: tert-butyl 4-(2-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate

[0333] To a mixture of methyl 5-bromo-6-methoxypicolinate (900 mg, 3.7 mmol, 1 eq.), tert-butyl piperazine-1-carboxylate (818 mg, 4.4 mmol, 1.2 eq.) and Cs_2CO_3 (1.4 g, 4.4 mmol, 1.2 eq.) in dioxane (15 mL) was added Ruphos-G3-Pd (153 mg, 0.18 mmol, 0.05 eq.). The mixture was stirred at 100 °C for 16 h under Ar and then cooled to room temperature. The residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford tert-butyl 4-(2-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (770 mg, 50%). LC-MS purity: 39% (UV at 254 nm), 352.2 $[\text{M}+\text{H}]^+$

Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-methoxypicolinic acid

[0334] To a mixture of tert-butyl 4-(2-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (70 mg, 0.2 mmol, 1 eq.) in MeOH (1 mL)/THF (1 mL)/ H_2O (1 mL) was added LiOH (14 mg, 0.6 mmol, 3 eq.) and the mixture was stirred at room temperature for 16 h. The mixture was concentrated to remove MeOH and THF and the residue was adjusted to pH=6 with 1N HCl. The precipitate was collected by filtration and dried in vacuo to afford 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-methoxypicolinic acid (65 mg, crude). LC-MS purity: 100% (UV at 254 nm), 338.1 $[\text{M}+\text{H}]^+$

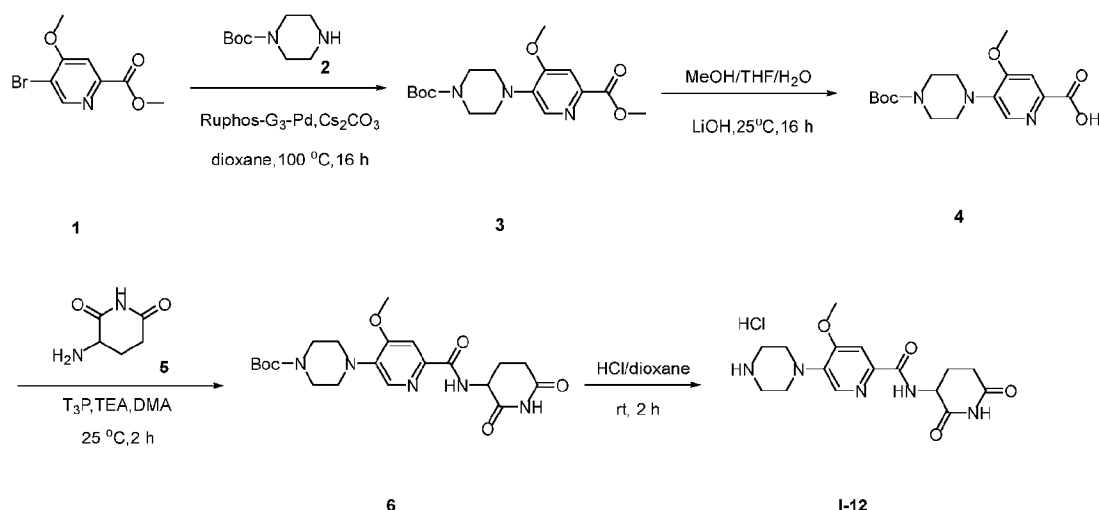
Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methoxypyridin-3-yl)piperazine-1-carboxylate

[0335] To a mixture of 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-6-methoxypicolinic acid (80 mg, 0.24 mmol, 1 eq.), 3-aminopiperidine-2,6-dione (46 mg, 0.28 mmol, 1.2 eq.) in DMA (3 mL) was added TEA (48 mg, 0.48 mmol, 2 eq.) and T3P (152 mg, 0.48 mmol, 2 eq.). The reaction

mixture was stirred at room temperature for 2 h, then poured into water (30 mL) and extracted with EtOAc (10 mL). The organic phase was dried over Na₂SO₄ and filtered. The filtrate was evaporated in *vacuo* and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methoxypyridin-3-yl)piperazine-1-carboxylate (101 mg, 97%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 448.1 [M+H]⁺.

Step 4: N-(2,6-dioxopiperidin-3-yl)-6-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt [0336] A mixture of tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-2-methoxypyridin-3-yl)piperazine-1-carboxylate (450 mg, 1 mmol, 1.0 eq.) in HCl/dioxane (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford N-(2,6-dioxopiperidin-3-yl)-6-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt as white solid (950 mg, crude). 100% (UV at 254 nm), 348.1 [M+H]⁺.

Intermediate 12: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)pyridin-3-yl)piperazine-1-carboxylate.



Step 1: tert-butyl 4-(4-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate

[0337] To a mixture of methyl methyl 5-bromo-4-methoxypicolinate (1 g, 4.0 mmol, 1 eq.), tert-butyl piperazine-1-carboxylate (818 mg, 4.4 mmol, 1.2 eq.) and Cs₂CO₃ (1.4 g, 4.4 mmol, 1.2 eq.) in dioxane (15 mL) was added Ruphos-G₃-Pd (153 mg, 0.18 mmol, 0.05 eq.) under Ar flow. The mixture was stirred at 100 °C for 16 h and cooled to room temperature. The residue was purified by column chromatography on silica gel eluted with 0-50% EtOAc/hexane to afford tert-butyl 4-

(4-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (370 mg, 23% yield). LC-MS purity: 25.3% (UV at 254 nm), 352.2 [M+H]⁺.

Step 2: 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxypicolinic acid

[0338] To a mixture of tert-butyl 4-(2-methoxy-6-(methoxycarbonyl)pyridin-3-yl)piperazine-1-carboxylate (70 mg, 0.2 mmol, 1 eq.) in MeOH (1 mL)/THF (1 mL)/H₂O (1 mL) was added LiOH (14 mg, 0.6 mmol, 3 eq.) and the mixture was stirred at room temperature for 16 h. The mixture was concentrated, and the residue was adjusted to pH=6 with 1N HCl. The precipitate was collected by filtration and dried in vacuo to afford 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxypicolinic acid (65 mg, crude). LC-MS purity: 100% (UV at 254 nm), 338.1 [M+H]⁺

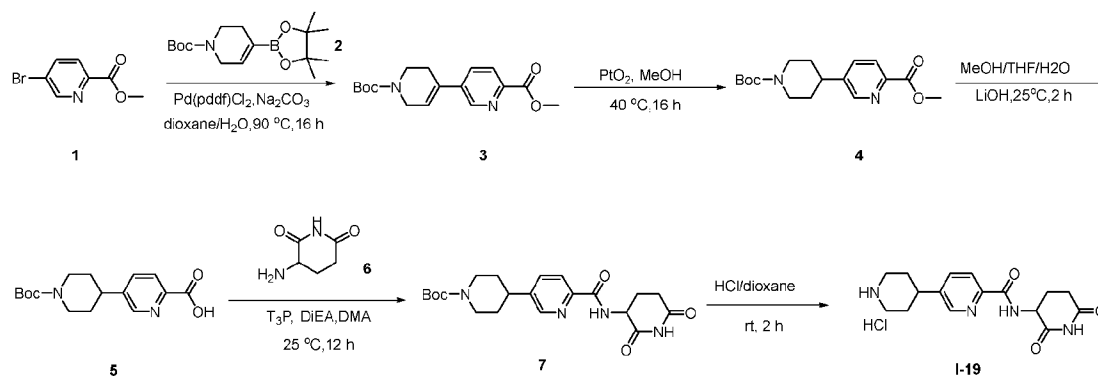
Step 3: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-4-methoxypyridin-3-yl)piperazine-1-carboxylate

[0339] To a mixture of 5-(4-(tert-butoxycarbonyl)piperazin-1-yl)-4-methoxypicolinic acid (160 mg, 0.48 mmol, 1 eq.), 3-aminopiperidine-2,6-dione (92 mg, 0.56 mmol, 1.2 eq.) in DMA (3 mL) was added TEA (97 mg, 0.97 mmol, 2 eq.) and T₃P (152 mg, 0.48 mmol, 1 eq.). The reaction mixture was stirred at room temperature for 2 h, poured into water (30 mL) and extracted with EtOAc (10 mL). The organic phase was dried over Na₂SO₄ and filtered. The filtrate was evaporated in vacuo and the residue was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-4-methoxypyridin-3-yl)piperazine-1-carboxylate (97 mg, 95%) as a white solid. LC-MS purity: 100% (UV at 254 nm), 448.1 [M+H]⁺.

Step 4: N-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt

[0340] A mixture of tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl)carbamoyl)-4-methoxypyridin-3-yl)piperazine-1-carboxylate (100 mg, 0.22 mmol, 1.0 eq.) in HCl/dioxane (5 mL) was stirred at room temperature for 2 h. The mixture was concentrated to afford N-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-(piperazin-1-yl)picolinamide hydrochloride salt as white solid (90 mg, crude). LC-MS purity: 100% (UV at 254 nm), 348.1 [M+H]⁺.

Intermediate 13: N-(2,6-dioxopiperidin-3-yl)-5-(piperazin-1-yl)picolinamide hydrochloride salt



Step 1: 1'-(tert-butyl) 6-methyl 3',6'-dihydro-[3,4'-bipyridine]-1',6(2'H)-dicarboxylate

[0341] To a mixture of methyl 5-bromopicolinate (10 g, 46.2 mmol 1 eq.) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (15.7 g, 50.9 mmol, 1.1 eq.) in dioxane (100 mL)/H₂O (20 ml) was added Pd(pddf)Cl₂ (2.1 g, 2.31 mmol, 0.05 eq.) and Na₂CO₃ (9.7 g, 92.4 mmol, 2 eq.). The reaction mixture was stirred at 90 °C under N₂ for 16 hours, concentrated. The residue was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford 1'-(tert-butyl) 6-methyl 3',6'-dihydro-[3,4'-bipyridine]-1',6(2'H)-dicarboxylate (15.1 g, 95% yield) as yellow oil. LC-MS purity: 100% (UV at 254 nm), 319.2 [M+H]⁺.

Step 2: methyl 5-(1-(tert-butoxycarbonyl) piperidin-4-yl) picolinate

[0342] To a mixture of 1'-(tert-butyl) 6-methyl 3',6'-dihydro-[3,4'-bipyridine]-1',6(2'H)-dicarboxylate (15.1 g, 1 eq.) in MeOH (150ml) was added PtO₂ (680 mg). The reaction mixture was stirred at 40 °C for 16 h under H₂. The catalyst was removed by filtration and the filtrate was concentrated to afford methyl 5-(1-(tert-butoxycarbonyl) piperidin-4-yl) picolinate (15 g, crude). LC-MS purity: 100% (UV at 254 nm), ms: 321.2 [M+1]⁺.

Step 3: 5-(1-(tert-butoxycarbonyl) piperidin-4-yl) picolinic acid.

[0343] To a mixture of methyl 5-(1-(tert-butoxycarbonyl) piperidin-4-yl)picolinate (3.2 g, 10 mmol, 1 eq.) in MeOH (15 ml)/THF(15 ml)/H₂O(15 ml). The reaction mixture was stirred at room temperature for 2 hours. The mixture was concentrated, and the residue was adjusted to pH=6 with 1N HCl. The precipitate was collected by filtration and dried in vacuo to afford 5-(1-(tert-butoxycarbonyl) piperidin-4-yl) picolinic acid. LC-MS purity: 100% (UV at 254 nm), 307.0 [M+H]⁺

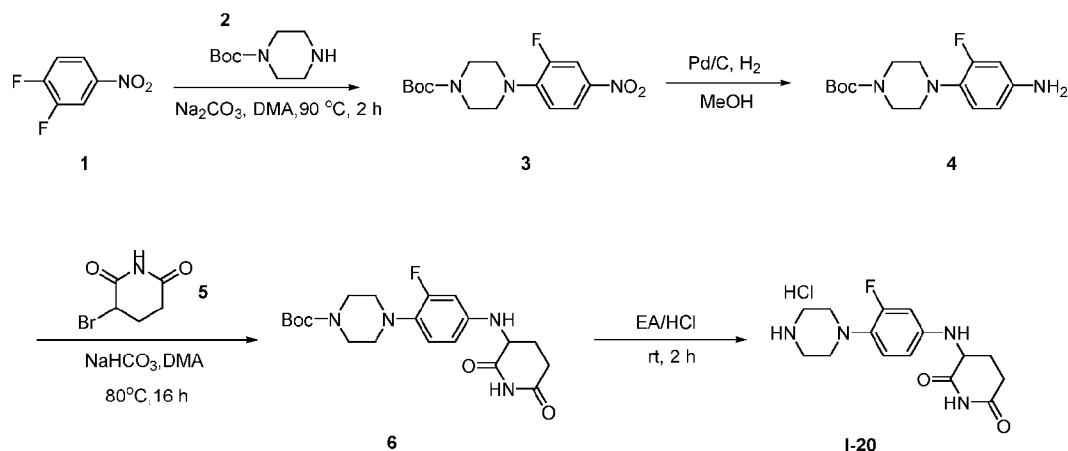
Step 4: tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl) carbamoyl)pyridin-3-yl)piperazine-1-carboxylate

[0344] To a mixture of 5-(1-(tert-butoxycarbonyl)piperidin-4-yl)picolinic acid (500 mg, 1.6 mmol, 1 eq.) and 3-aminopiperidine-2,6-dione (204 mg, 1.9 mmol, 1.2 eq.) in DMA (20 ml) was added TEA (660 mg, 6.4 mmol, 4 eq.) and TBTU (786 mg, 10 mmol, 1.5 eq.). The mixture was stirred at room temperature for 12 h under N₂. The mixture was purified by column chromatography on silica gel eluted with 0-100% EtOAc/hexane to afford tert-butyl 4-(6-((2,6-dioxopiperidin-3-yl) carbamoyl)pyridin-3-yl)piperazine-1-carboxylate (360 mg, 70% yield). LC-MS purity: 100% (UV at 254 nm), 417.2 [M+H]⁺.

Step 5: N-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)picolinamide hydrochloride salt

[0345] A mixture of 4-(6-((2,6-dioxopiperidin-3-yl) carbamoyl)pyridin-3-yl)piperazine-1-carboxylate (100 mg, 1.0 eq) in HCl/dioxane (2 mL) was stirred at 20 °C for 2 h. The after reaction was direct concentration as to give N-(2,6-dioxopiperidin-3-yl)-5-(piperidin-4-yl)picolinamide hydrochloride salt (90 mg, crude) as a white solid. LC-MS purity: 100% (UV at 254 nm), 317.2 [M+H]⁺.

Intermediate 14: 3-((4-(piperazin-1-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt



Step 1: tert-butyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate

[0346] To a mixture of 1,2-difluoro-4-nitrobenzene (10 g, 62.9 mmol 1 eq.) and KCO₃ (17.4 g, 125.7 mmol, 2 eq.) in DMA (50 mL) was added tert-butyl piperazine-1-carboxylate (14.1 g, 75.4 mmol, 1.2 eq.) and the reaction mixture was stirred at 90°C for 2 h. The mixture was poured into ice water (500 mL) and stirred for 30 min. The precipitate was collected by filtration and dried in

vacuo to afford tert-butyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate (20.4 g, crude) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 270.1 [M+H]⁺.

Step 2: tert-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate

[0347] To a solution of tert-butyl 4-(2-fluoro-4-nitrophenyl)piperazine-1-carboxylate (3.2 g, 10 mmol, 1 eq.) in MeOH (50 mL) was added Pd/C (640 mg, 10% on Carbon, wetted with ca. 55% water) and the reaction mixture was stirred at room temperature for 16 h. The catalyst was removed by filtration and the filtrate was concentrated to afford tert-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate (2.9 g, crude) as a purple solid. LC-MS purity: 99.1% (UV at 254 nm), 296.1 [M+H]⁺.

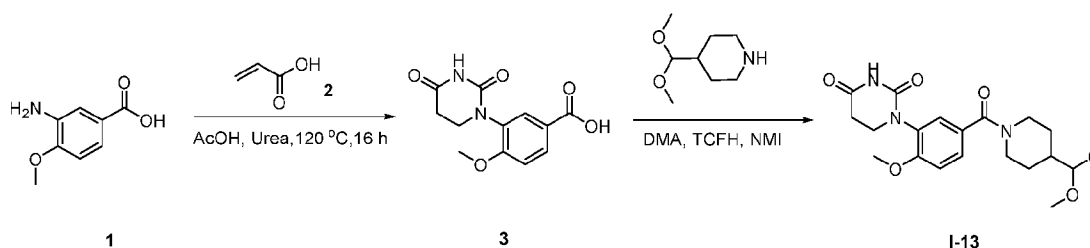
Step 3: tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenyl)piperazine-1-carboxylate

[0348] To a mixture of tert-butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate (1.0 g, 3.4 mmol 1 eq.) and 3-bromopiperidine-2,6-dione (650 mg, 3.4 mmol, 1 eq.) in DMA (20 mL) was added NaHCO₃ (290 mg, 3.4 mmol, 1 eq.). The reaction mixture was stirred at 80 °C for 16 h, cooled to room temperature and then poured into water (200 mL). The precipitate was collected by filtration and dried in vacuo to afford tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenyl)piperazine-1-carboxylate (860 mg, crude) as a green solid. LC-MS purity: 100% (UV at 254 nm), 407.2 [M+H]⁺.

Step 4: 3-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt

[0349] A mixture of tert-butyl 4-(4-((2,6-dioxopiperidin-3-yl)amino)-2-fluorophenyl)piperazine-1-carboxylate (860 mg, 2.8 mmol, 1 eq.) in EA/HCl (10 ml) was stirred at room temperature for 2 h. The mixture was concentrated to afford 3-((3-fluoro-4-(piperazin-1-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt (840 mg, crude) as a blue solid. LC-MS purity: 100% (UV at 254 nm), 307.1 [M+H]⁺.

Intermediate 15: 4-(5-(4-(dimethoxymethyl)piperidine-1-carbonyl)-2-methoxyphenyl)piperazine-2,6-dione



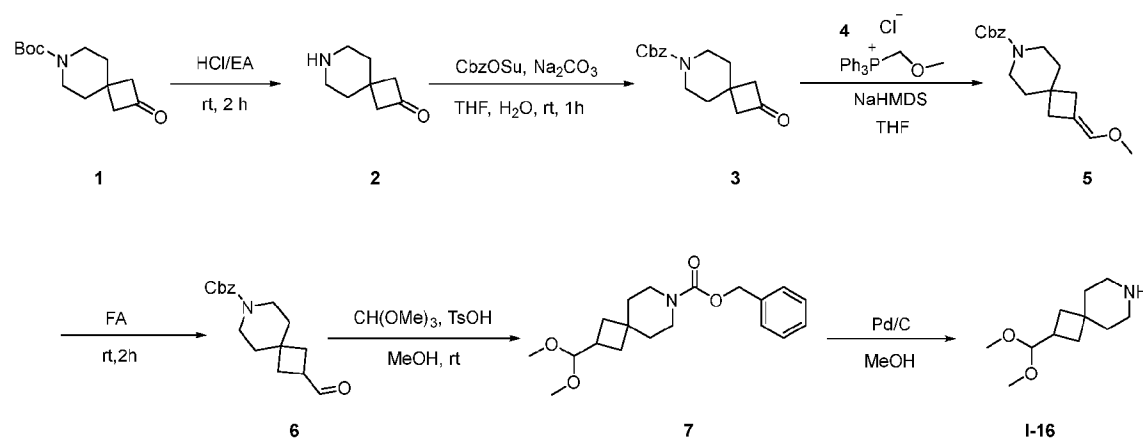
Step 1: 3-(3,5-dioxopiperazin-1-yl)-4-methoxybenzoic acid

[0350] To a mixture of methyl-3-amino-4-methoxybenzoic acid (3.0 g, 17.9 mmol, 1 eq.) and acrylic acid (4.8 ml, 72.1 mmol, 4 eq.) in AcOH (20 mL) was added urea (6.6 g). The reaction mixture was stirred at 120 °C for 16 hours and then cooled to room temperature. The mixture was poured into ice-water (100 mL). The precipitate was collected by filtration, dried in *vacuo* to afford 3-(3,5-dioxopiperazin-1-yl)-4-methoxybenzoic acid (3.8 g, crude) as a yellow solid. LC-MS purity: 59.4% (UV at 254 nm), 265.0 [M+H]⁺.

Step 2:

[0351] To a mixture of 3-(3,5-dioxopiperazin-1-yl)-4-methoxybenzoic acid (150 mg, 0.566 mmol, 1 eq.) in DMA (1.5 ml) was added NMI (0.45 ml, 5.660 mmol, 10 eq.) and TCFH (317 mg, 1.132 mmol, 2.0 eq.) and the mixture was stirred for 30min. Then to the mixture was added 4-(dimethoxymethyl) piperidine (108 mg, 0.679 mmol, 1.2 eq) and the resulting mixture was stirred at 25°C for 12 h. The mixture was purified by prep-HPLC to afford 4-(5-(4-(dimethoxymethyl)piperidine-1-carbonyl)-2-methoxyphenyl)piperazine-2,6-dione (180 mg) as a white solid. LC-MS: 265.0 [M+H]⁺.

Intermediate 16: 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane



Step 1: benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate

[0352] To a stirred solution of tert-butyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (24 g, 0.1 mol, 1 eq.) in EtOAc (50 mL) was added conc. HCl (45 mL, 0.5 mol, 5 eq.) slowly at room temperature and the reaction mixture was stirred at room temperature for 2 hours. Then the mixture was diluted with EtOAc (150 mL), poured into Na₂CO₃ suspension (106 g, 1 mol, 10 eq., in 500 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (25 g, 0.1

mmol, 1 eq.) and the mixture was stirred for 1 hour. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (27 g, 100% yield) as light yellow oil.

Step 2: benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate

[0353] To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (68 g, 0.2 mol, 2 eq.) in dried THF (300 mL) cooled at -78 °C was added NaHMDS (100 mL, 0.2 mol, 2 eq.) dropwise and the mixture was warmed to 0 °C slowly and stirred for 2 hours. Then the mixture was cooled at -78 °C and a solution of benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (27 g, 0.1 mol, 1eq.) in THF (50 mL) was added. The mixture was warmed to room temperature slowly and stirred for 2 hours. The mixture was quenched by NH₄Cl solution (500 mL) and diluted with EA (200 mL). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford compound benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate (20 g, 67% yield) as light yellow oil.

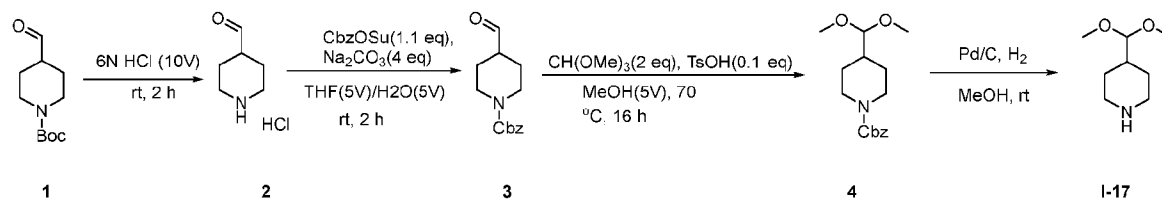
Step 3: benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate

[0354] A solution of benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate (24 g, 0.67 mol, 1 eq.) in HCOOH (50 mL) was stirred at room temperature for 2 hours. The mixture was concentrated, and the residue was dissolved in MeOH (120 mL). To the mixture was added CH(OMe)₃ (10.6 g, 0.1 mol, 1.5 eq.) followed by TsOH·H₂O (1.5 g, 0.07 mol, 0.1 eq.) and the mixture was stirred at 70 °C for 12 h. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (14.6 g, 67% yield) as light yellow oil.

Step 4: 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0355] To a solution of benzyl 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane-7-carboxylate (14.6 g, 440 mmol, 1 eq.) in MeOH (100 mL) was added Pd/C (4 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at room temperature for 12 h under H₂ (1 atm). The catalyst was removed by filtration and the filtrate was concentrated to afford 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (8.9 g, ca.100%) as a white solid.

[0356] ¹H NMR (400 MHz, DMSO-d₆) δ 4.57 (d, *J* = 6.8 Hz, 1H), 3.20 (m, 6H), 2.61 (s, 2H), 2.47-2.43 (m, 1H), 1.74 (t, 2H), 1.54-1.44 (m, 4H), 1.34 (t, 2H).

Intermediate 17: 4-(dimethoxymethyl)piperidine*Step 1: benzyl 4-formylpiperidine-1-carboxylate*

[0357] To a stirred solution of tert-butyl 4-formylpiperidine-1-carboxylate (500 g, 2.2 mol, 1 eq.) in EA (500 mL) at room temperature was added conc. HCl (600 mL, 6.6 mol, 3 eq.) slowly and the reaction mixture was stirred at room temperature for 2 hours. The mixture was diluted with EA (500 mL), poured into Na₂CO₃ suspension (1160 g, 11 mol, 5 eq., in 3000 mL of water) and stirred for 20 min. To the mixture was added CbzOSu (550 g, 2.2 mmol, 1 eq.) and the mixture was stirred for 2 hours. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 4-formylpiperidine-1-carboxylate (550 g, 95% yield) as light yellow oil.

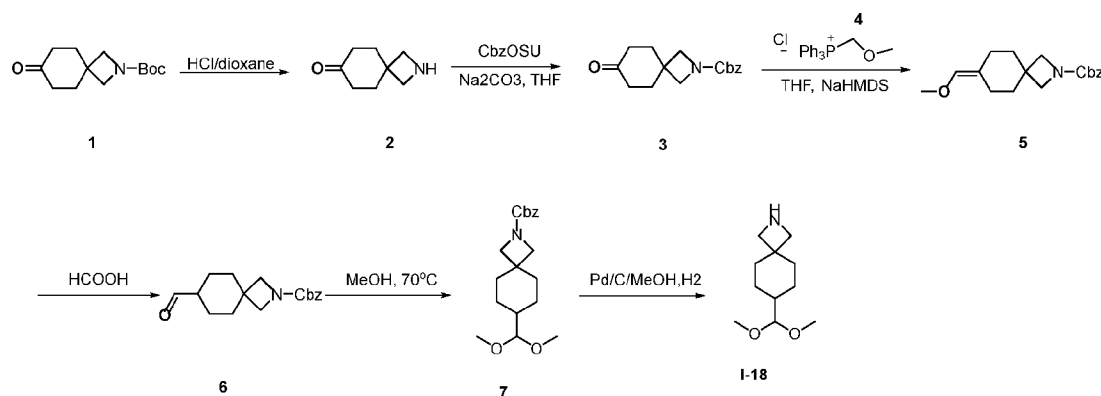
Step 2: benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate

[0358] To a solution of benzyl 4-formylpiperidine-1-carboxylate (150 g, 0.5 mol, 1 eq.) in MeOH (500 mL) was added CH(OMe)₃ (212 g, 1 mol, 2 eq.) followed by TsOH·H₂O (19 g, 0.1 mol, 0.1 eq.) and the mixture was stirred at 70 °C for 16 hours. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate (120 g, 82% yield) as light yellow oil.

Step 3: 4-(dimethoxymethyl)piperidine

[0359] To a solution of benzyl 4-(dimethoxymethyl)piperidine-1-carboxylate (120 g, 0.44 mol, 1 eq.) in MeOH (400 mL) was added Pd/C (20 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at room temperature for 12 h under H₂ (1 atm). The catalyst was removed by filtration and the filtrate was concentrated to afford 4-(dimethoxymethyl)piperidine (65 g, crude) as a white solid.

Intermediate 18: 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane



Step 1: benzyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate

[0360] To a stirred solution of tert-butyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (12 g, 50 mmol, 1 eq.) in EA (30 mL) at room temperature was added conc. HCl (20 mL, 0.25 mol, 5 eq.) slowly and the reaction mixture was stirred at room temperature for 1 h. Then the mixture was diluted with EtOAc (70 mL), poured into Na₂CO₃ suspension (53 g, 0.5 mol, 10 eq., in 500 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (12.5 g, 50 mmol, 1 eq.) and the mixture was stirred for 1 h. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (13 g, 96% yield) as light yellow oil.

Step 2: benzyl 2-(methoxymethylene)-7-azaspiro[3.5]nonane-7-carboxylate

[0361] To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (34 g, 0.1 mol, 2 eq.) in dried THF (300 mL) cooled at -70 °C was added NaHMDS (50 mL, 0.1 mol, 2 eq.) dropwise and the mixture was warmed to 0 °C slowly and stirred for 2 h. Then the mixture was cooled at -70 °C and a solution of benzyl 7-oxo-2-azaspiro[3.5]nonane-2-carboxylate (13 g, 50 mmol, 1eq.) in THF (50 mL) was added. The mixture was warmed to room temperature slowly and stirred for 2 h. The mixture was quenched by NH₄Cl solution (200 mL) and diluted with EtOAc (100 mL). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 7-(methoxymethylene)-2-azaspiro[3.5]nonane-2-carboxylate (9.1 g, mmol, 61% yield) as light yellow oil.

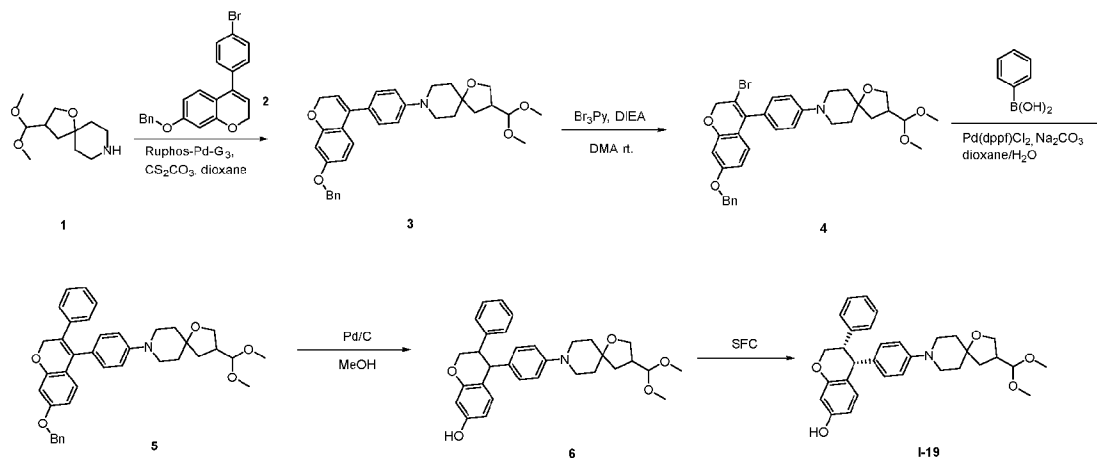
Step 3: benzyl 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate

[0362] A solution of benzyl 7-(methoxymethylene)-2-azaspiro[3.5]nonane-2-carboxylate (9.1 g, 61 mmol, 1 eq.) in Formic acid (20 mL) was stirred at room temperature for 4 h. The mixture was concentrated, and the residue was dissolved in MeOH (120 mL). To the mixture was added $\text{CH}(\text{OMe})_3$ (9.1 g, 90 mmol, 1.5 eq.) followed by $\text{TsOH} \cdot \text{H}_2\text{O}$ (1.1 g, 0.06 mol, 0.1 eq.) and the mixture was stirred at 70 °C for 12 h. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate (8 g, 40% yield) as light yellow oil.

Step 4: 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane

[0363] To a solution of benzyl 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane-2-carboxylate (8 g, 24 mmol, 1 eq.) in MeOH (50 mL) was added Pd/C (2 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at room temperature for 12 h under H_2 (balloon). The catalyst was removed by filtration and the filtrate was concentrated to afford 7-(dimethoxymethyl)-2-azaspiro[3.5]nonane (4.8 g, crude, ca. 100% yield) as a white solid.

Intermediate 19: (3S,4R)-4-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)phenyl)-3-phenylchroman-7-ol



Step 1: 8-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0364] To a solution of 3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (1.28 g, 5.95 mmol, 1.00 eq) in dioxane (15 mL) was added Ruphos-Pd-G3 (500 mg, 0.6 mmol, 0.1 eq), Cs_2CO_3 (3.88 g, 12 mmol, 2 eq), 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (2.33 g, 5.95 mmol, 1 eq) and the mixture was stirred at 100 °C for 12 hours. The mixture concentrated in vacuum. The crude

product was purified by column chromatography on silica gel using 0-20% EtOAc/hexane to afford 8-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.1 g, 70.5% yield) as yellow solid.

Step 2: 8-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

[0365] To a solution of 8-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.1 g, 3.98 mmol, 1 eq.) and DIEA (1.0 g, 7.97 mmol, 2.00 eq) in DMA (10 mL) was added pyridinium tribromide (1.5 g, 4.8 mmol, 1.2 eq.) at 0° C, and the mixture was stirred at room temperature for 1 hour. The mixture was poured into H₂O (30 mL), extracted with EtOAc (20 mL x 2). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by column chromatography on silica gel using 0-20% EtOAc/hexane to afford 8-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.2 g, 91.36% yield) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 606.3[M+H]⁺.

Steps 3: 8-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane

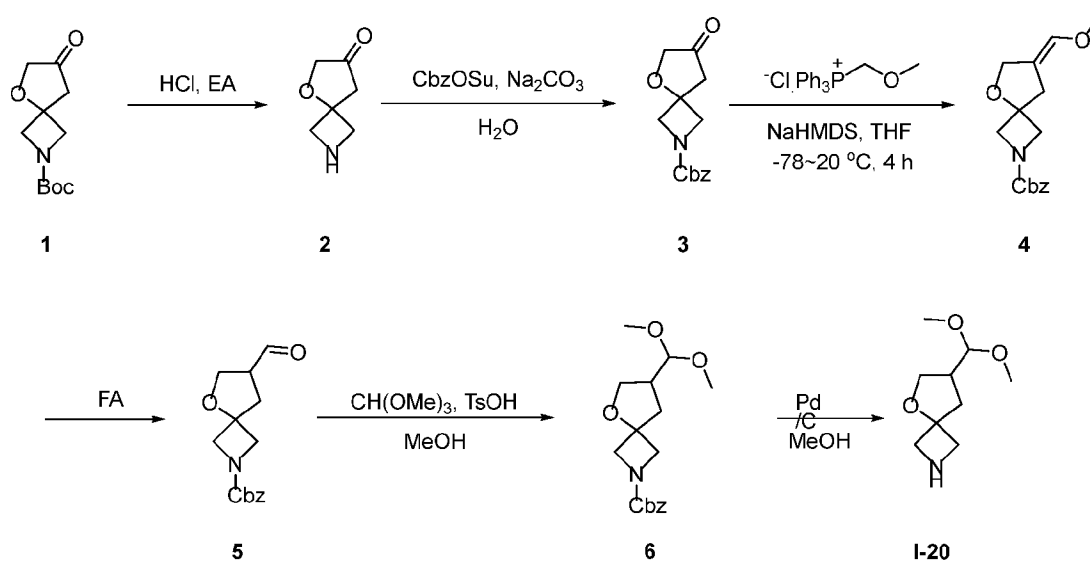
[0366] To a mixture of 8-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (2.2 g, 3.64 mmol, 1.00 eq) in dioxane (10 mL) and H₂O (2 mL) was added Na₂CO₃ (1.16 g, 10.92 mmol, 3.00 eq) and Pd(dppf)Cl₂ (330 mg, 0.36 mmol, 0.1 eq), phenylboronic acid (0.53 g, 4.36 mmol, 1.20 eq) and the mixture was stirred at 100°C for 12 hours under Ar. The mixture was poured into H₂O (50 mL), extracted with EtOAc (20 mL x 2). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by column chromatography on silica gel eluted with 0-30% EtOAc/hexane to afford 8-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (1.4 g, 63.8%) as yellow solid. LC-MS purity: 100% (UV at 254 nm), 604.5[M+H]⁺.

Steps 4: 4-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)phenyl)-3-phenylchroman-7-ol

[0367] To a solution of 8-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decane (1.4 g, 2.32 mmol, 1.00 eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on carbon, wetted with c.a.55% water) and the mixture stirred at

room temperature overnight under H_2 . The mixture was filtered, and the filtrate was concentrated in vacuum to afford 4-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)phenyl)-3-phenylchroman-7-ol (1.01 g, 84.53 % yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 516.4 $[M+H]^+$.

Intermediate 20: (3S,4R)-4-(4-(3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)phenyl)-3-phenylchroman-7-ol



Step 1: benzyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate

[0368] To a stirred solution of tert-butyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (10 g, 40 mmol, 1 eq.) in EtOAc (50 mL) at room temperature was added conc. HCl (20 mL, 0.2 mol, 5 eq.) slowly and the reaction mixture was stirred at room temperature for 1 h. Then the mixture was diluted with EA (150 mL), poured into Na_2CO_3 suspension (40 g, 0.4 mol, 10 eq. in 500 mL of water) and the mixture was stirred for 20 min. To the mixture was added CbzOSu (10 g, 40 mmol, 1 eq.) and the mixture was stirred for 1 hour. The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 7-oxo-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (10.8 g, 100% yield) as light yellow oil.

Step 2: benzyl (E)-7-(methoxymethylene)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate

[0369] To a stirred solution of (methoxymethyl)triphenylphosphonium chloride (28.3 g, 80 mmol, 2 eq.) in dried THF (300 mL) cooled at $-78^\circ C$ was added NaHMDS (40 mL, 160 mmol, 2 eq.)

dropwise and the mixture was warmed to 0 °C slowly and stirred for 2 hours. Then the mixture was cooled at -78 °C and a solution of benzyl 2-oxo-7-azaspiro[3.5]nonane-7-carboxylate (10.8 g, 40 mmol, 1 eq.) in THF (20 mL) was added. The mixture was warmed to room temperature slowly and stirred for 2 hours. The mixture was quenched by NH₄Cl solution (200 mL) and diluted with EtOAc (100 mL). The organic phase was separated, washed with brine, dried, concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl (E)-7-(methoxymethylene)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (4.5 g, 40% yield) as light yellow oil.

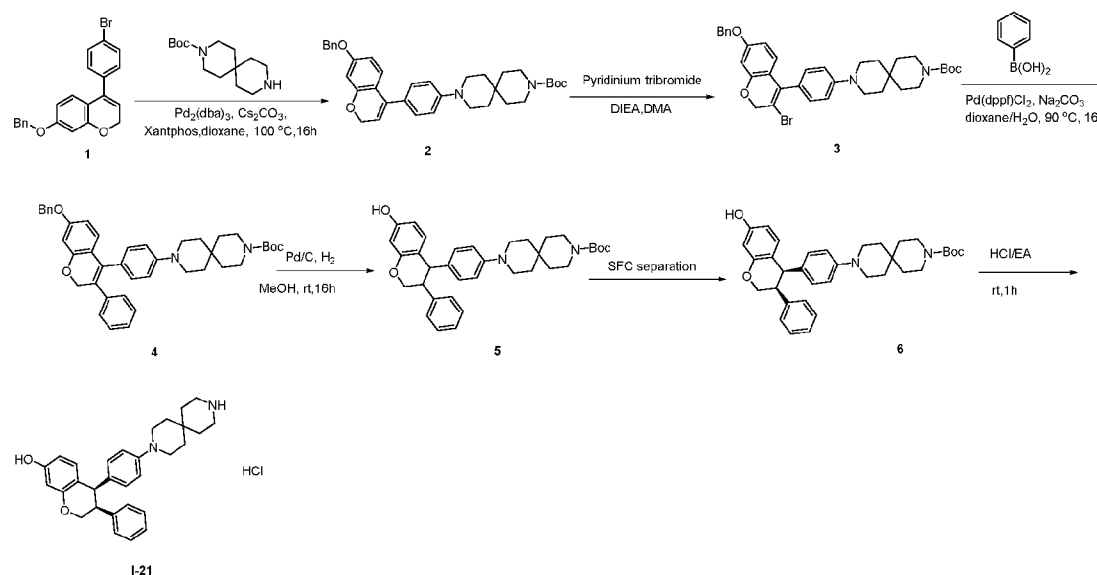
Step 3: benzyl 7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate

[0370] A solution of benzyl (E)-7-(methoxymethylene)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (4.5 g, 16 mmol, 1 eq.) in Formic acid (20 mL) was stirred at room temperature for 4 hours. The mixture was concentrated, and the residue was dissolved in MeOH (20 mL). To the mixture was added CH(OMe)₃ (2.5 g, 24 mmol, 1.5 eq.) followed by TsOH·H₂O (3.1 g, 1.6 mmol, 0.1 eq.) and the mixture was stirred at 70 °C for 12 hours. The mixture was concentrated and the residue was purified by column chromatography on silica gel eluted with 0-40% EtOAc/hexane to afford benzyl 7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (2.5 g, 49% yield) as light yellow oil.

Step 4: 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0371] To a solution of benzyl 7-(dimethoxymethyl)-5-oxa-2-azaspiro[3.4]octane-2-carboxylate (2.5 g, 7.8 mmol, 1 eq.) in MeOH (20 mL) was added Pd/C (1 g, 10% on Carbon, wetted with ca. 55% water) and the mixture was stirred at room temperature for 12 hours under H₂ (1 atm). The catalyst was removed by filtration and the filtrate was concentrated to afford 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.5 g, crude, ca. 100% yield) as a white solid.

Intermediate 21: (3S,4R)-4-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-3-phenylchroman-7-ol hydrochloride



Step 1: tert-butyl 9-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0372] To a mixture of 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (3.7 g, 9.4 mmol, 1 eq.), tert-butyl 3,9-diazaspiro[5.5]undecane-3-carboxylate (2.4 g, 9.4 mmol, 1 eq.), $\text{Pd}_2(\text{dba})_3$ (861 mg, 0.94 mmol, 0.1 eq.), Xantphos (545 mg, 0.94 mmol, 0.1 eq.), CS_2CO_3 (6.14 g, 18.8 mmol, 2 eq.) in dioxane (20 mL). The mixture was purged with N_2 and heated to 100 °C for 16 h. TLC showed reaction was complete. The mixture was diluted with ethyl acetate and washed with water. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to give tert-butyl 9-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate as a yellow solid. (0.77 g, 14 % yield), LC-MS purity: 100% (UV at 254 nm), 567.4 $[\text{M}+\text{H}]^+$.

Step 2: tert-butyl 9-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0373] To a solution of tert-butyl 9-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (0.77 g, 1.36 mmol, 1.00 eq) and DIEA (0.35 g, 2.7 mmol, 2.00 eq) in DMA (300 mL), was added pyridinium tribromide (521 mg, 1.63 mmol, 1.2 eq) at 0° C., and the mixture was stirred at 25° C for 1 h. TLC (PE:EA=3:1) showed the starting material was consumed completely. The mixture was poured into H₂O (30 mL), extracted with EtOAc (20 mLx2), and the organic layer was washed with brine (50 mL), dried over Na_2SO_4 , filtered, and concentrated in vacuum. The residue was purified by silica gel column chromatography using 0-

20% EtOAc/hexane to afford tert-butyl 9-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (535 mg, 61%) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 645.4 [M+H]⁺.

Steps 3: tert-butyl 9-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0374] To a mixture of tert-butyl 9-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (535 mg, 0.83 mmol, 1.00 eq) in dioxane (10 mL) and H₂O (2 mL), was added phenylboronic acid (121 mg, 1 mmol, 1.2 eq), Na₂CO₃ (176 g, 1.66 mmol, 2.00 eq) and Pd(dppf)Cl₂ (61 mg, 0.08 mmol, 0.1 eq), and the mixture was stirred at 90 °C for 12 hours. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into H₂O (50 mL), extracted with EtOAc (20 mLx2). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to afford tert-butyl 9-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (430 mg, 81% yield) as yellow solid. LC-MS purity: 100% (UV at 254 nm), 643.5 [M+H]⁺.

Steps 4: tert-butyl 9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate

[0375] To a solution of tert-butyl 9-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (430 mg, 0.67 mmol, 1.00 eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on carbon, wetted with c.a.55% water) stirred at rt overnight under H₂. The mixture was filtered, and the filtrate was concentrated in vacuum to afford tert-butyl 9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (380 mg, crude) as white solid. LC-MS purity: 100% (UV at 254 nm), 555.1 [M+H]⁺.

Steps 5: Two single isomers of tert-butyl 9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate tert-butyl 9-(4-(7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (380 mg) was purified via SFC as method below to afford two single isomers (P1:150 mg, P2: 150 mg), LC-MS purity: 100% (UV at 254 nm), 555.1 [M+H]⁺.

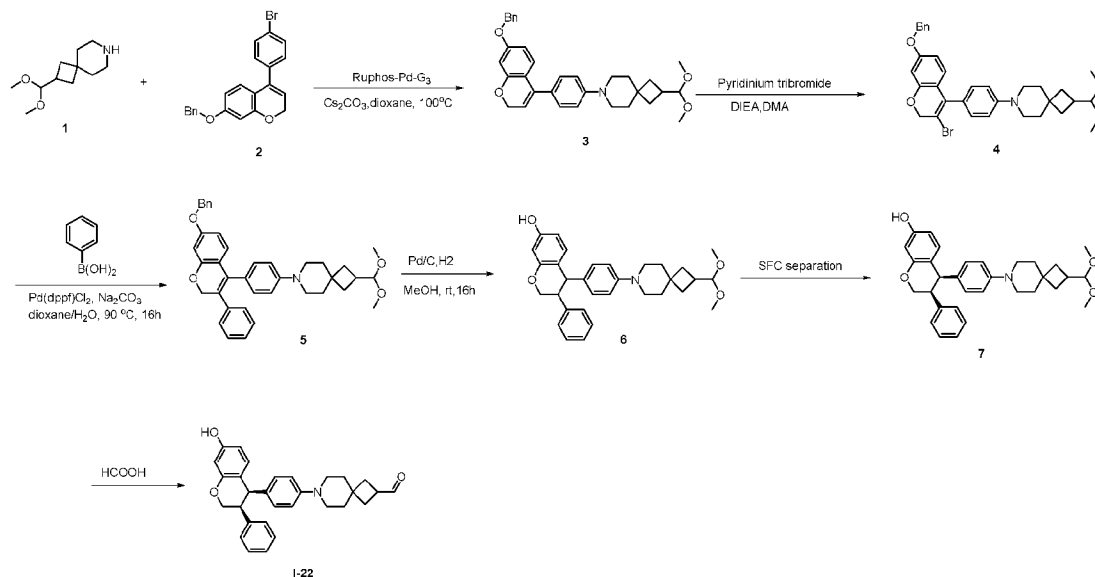
System:	Waters SFC 150
Column name:	DAICELCHIRALPAK®AS
Column size:	250*25 mm 10 μm

Mobile Phase A:	Supercritical CO ₂ ,
Mobile Phase B:	MEOH (+0.1% 7.0mol/l Ammonia in MEOH)
A:B:	75:25
Wavelength:	214 nm
Flow:	70ml/min
Column temp:	RT
Back Pressure:	100 bar
Injection:	1mL
Cycle time:	3.8min
Solvent:	MeOH: redistilled grade Supercritical CO ₂ : Food grade

Steps 6: (3S,4R)-4-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-3-phenylchroman-7-ol hydrochloride

[0376] To a mixture of tert-butyl 9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecane-3-carboxylate (160 mg, 0.29 mmol, 1 eq.) in HCl/EA (3 mL). The mixture was stirred at rt for 1 h. The after reaction was direct concentration as to give (3S,4R)-4-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-3-phenylchroman-7-ol hydrochloride as a white soild (140 mg, yield 100%). LC/MS (ESI) m/z: 455.4. Rt: 0.922 min.

Intermediate 22: 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde



Step 1: 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0377] To a mixture of 7-(benzyloxy)-4-(4-bromophenyl)-2H-chromene (11 g, 28 mmol, 1 eq), 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (5.6 g, 28 mmol, 1 eq), RuphosPdG₃ (1.17 g, 1.4 mmol, 0.05 eq), Cs₂CO₃ (18.2 g, 56 mmol, 2 eq.) in dioxane (50 mL). The mixture was purged with N₂ and heated to 100 °C for 16 h. TLC showed reaction was complete. The mixture was diluted with ethyl acetate and washed with water. The organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to give 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane as yellow solid. (9 g, 63% yield), LC-MS purity: 100% (UV at 254 nm), 512.4 [M+H]⁺.

Step 2: 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0378] To a solution of 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.6 g, 3.13 mmol, 1.00 eq) and DIEA (0.8 mg, 6.3 mmol, 2.00 eq) in DMA (10 mL), was added pyridinium tribromide (1.5 mg, 4.7 mmol, 1.5 eq) at 0 °C, and the mixture was stirred at 25 °C for 1 hour. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into H₂O (30 mL), extracted with EtOAc (20 mLx2), and the organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuum. The residue was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1 g, 54% yield) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 590.0 [M+H]⁺.

Steps 3: 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0379] To a mixture of 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (1.4 g, 2.4 mmol, 1.00 eq) in dioxane (10 mL) and H₂O (2 mL), was added phenylboronic acid (318 mg, 2.6 mmol, 1.1 eq), Na₂CO₃ (360 g, 3.4 mmol, 2.00 eq) and Pd(dppf)Cl₂ (223 mg, 0.24 mmol, 0.1 eq), and the mixture was stirred at 90 °C for 12 h. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into H₂O (50 mL), extracted with EtOAc (20 mL). The organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(4-(7-

(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (0.9 mg, 64% yield) as yellow solid. LC-MS purity: 100% (UV at 254 nm), 588.4 [M+H]⁺.

Steps 4: 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-ol [0380] To a solution of 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)phenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (0.9 mg, 1.5 mmol, 1.00 eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on carbon, wetted with c.a.55% water) stirred at room temperature overnight under H₂. The mixture was filtered, and the filtrate was concentrated in vacuum to afford 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-ol (500 mg, 67% yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 500.5 [M+H]⁺.

Step 5: Two single isomers of 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-ol-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-ol (500 mg) was purified via SFC as method below to afford two single isomers (isomer 1:240 mg, isomer 2: 220 mg), LC-MS purity: 100% (UV at 254 nm), 500.5 [M+H]⁺.

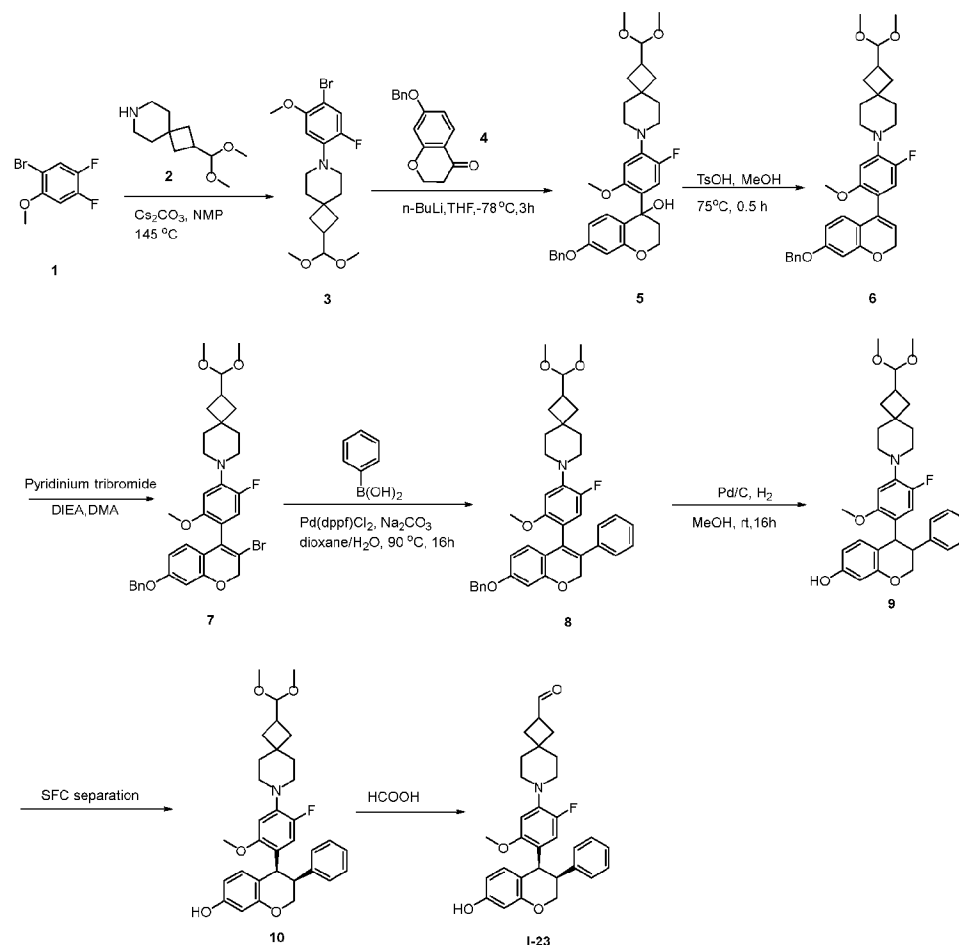
Sample Name:	
System:	Waters SFC 150
Column name:	DAICELCHIRALPAK®AD
Column size:	250*25mm 10 μm
Mobile Phase A:	Supercritical CO ₂ ,
Mobile Phase B:	MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
A:B:	45:55
Wavelength:	214 nm
Flow:	80ml/min
Column temp:	RT
Back Pressure:	100 bar
Injection:	4mL
Cycle time:	5.5min
Solvent:	MeOH: redistilled grade Supercritical CO ₂ : Food grade
Preparation of sample solution:	sample was dissolved in about 50 mL MeOH:DCM(1:1)

Step 6: 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyd

[0381] To a mixture of 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)phenyl)-3-phenylchroman-7-ol (300 mg, 0.6 mmol, 1.00 eq) in FA (3 mL), and the mixture was stirred at rt

for 1 hour. The mixture was concentrated in vacuum to afford 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (300 mg, crude) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 454.4 [M+H]⁺.

Intermediate 23: 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde



Step 1: 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0382] To a mixture of 1-bromo-4,5-difluoro-2-methoxybenzene (10 g, 44.8 mmol, 1 eq.) and 2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (4.46 g, 22.4 mmol, 0.5 eq.) in NMP (50 mL) was added Cs₂CO₃ (29.2 g, 89.7 mmol, 2 eq.), the mixture was stirred at 145°C overnight under N₂. The mixture was poured into H₂O (200 mL), extracted with EtOAc (50 mLx2), and the combined organic layer was washed with brine (50.0 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20%

EtOAc/hexane to afford 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (2.5 g, 28% yield) as a yellow oil. LC-MS purity: 100% (UV at 254 nm), 402.1 [M+H]⁺.

Step 2: 7-(benzyloxy)-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)chroman-4-ol

[0383] To a mixture of 7-(4-bromo-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (2.5 g, 6.2 mmol, 1 eq.) in dry THF (10 mL) was added n-BuLi (1.6 M, 5 mL, 1.30 eq.), the mixture was stirred at -78°C for 1 h, then 7-(benzyloxy)chroman-4-one (1.4 g, 5.6 mmol, 0.9 eq.) was added and the mixture was stirred at -78°C for 1 h. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into H₂O (30 mL), extracted with EtOAc (20 mL), and the combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(benzyloxy)-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)chroman-4-ol (460 mg, 14% yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 578.5 [M+H]⁺

Step 3: 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0384] To a solution of 7-(benzyloxy)-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)chroman-4-ol (460 mg, 0.8 mmol, 1.00 eq) in MeOH (8 mL), was added TsOH (3 mg, 0.02 mmol, 0.02 eq), and the mixture was stirred at 75°C for 30 min. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (390 mg, 87% yield) as a yellow solid.

Step 4: 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0385] To a solution of 7-(4-(7-(benzyloxy)-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (390 mg, 0.7 mmol, 1 eq.) and DIEA (180 mg, 1.39 mmol, 2 eq.) in DMA (10 mL), was added pyridinium tribromide (267 mg, 0.84 mmol, 1.2 eq.) at 0° C, and the mixture was stirred at room temperature for 1 hour. The mixture was poured into H₂O (30 mL), extracted with EtOAc (20 mL), and the organic layer was washed with brine (50

mL), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by silica gel column chromatography using 0-20% EtOAc/hexane to afford 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (380 mg, 85% yield) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 638.3 [M+H]⁺.

Steps 5: 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane

[0386] To a mixture of 7-(4-(7-(benzyloxy)-3-bromo-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (380 mg, 0.6 mmol, 1.00 eq) in dioxane (10 mL) and H₂O (2 mL), was added phenylboronic acid (87 mg, 0.71 mmol, 1.2 eq), Na₂CO₃ (126 g, 1.19 mmol, 2.00 eq) and Pd(dppf)Cl₂ (44 mg, 0.06 mmol, 0.1 eq), and the mixture was stirred at 90°C for 12 h. TLC (PE:EA=5:1) showed the starting material was consumed completely. The mixture was poured into H₂O (50 mL), extracted with EtOAc (20 mLx2). The combined organic layer was washed with brine (50 mL), dried over Na₂SO₄, filtered, and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-30% EtOAc/hexane to afford 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (320 mg, 84% yield) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 636.5 [M+H]⁺.

Steps 6: 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol

[0387] To a solution of 7-(4-(7-(benzyloxy)-3-phenyl-2H-chromen-4-yl)-2-fluoro-5-methoxyphenyl)-2-(dimethoxymethyl)-7-azaspiro[3.5]nonane (320 mg, 0.5 mmol, 1eq) in MeOH (10 mL) was added Pd/C (100 mg, 10% on carbon, wetted with c.a.55% water) stirred at rt overnight under H₂. The mixture was filtered, and the filtrate was concentrated in vacuum to afford 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol (180 mg, 66 % yield) as a white solid. LC-MS purity: 100% (UV at 254 nm), 548.4[M+H]⁺.

Step 7: Two single isomers of 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol

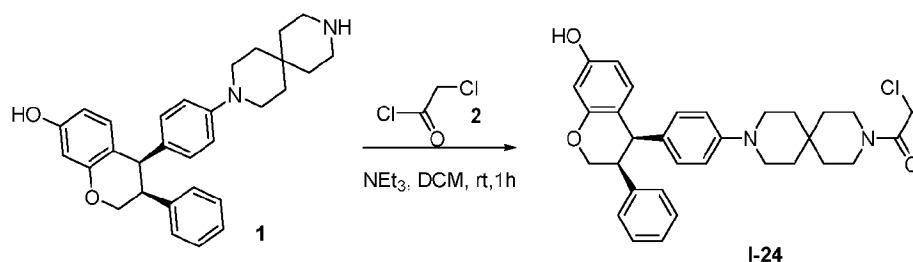
[0388] 4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol (180 mg) was purified via SFC as method below to afford two single isomers (P1:80 mg, P2: 80 mg), LC-MS purity: 100% (UV at 254 nm), 548.4[M+H]⁺.

Sample Name:	
System:	Waters SFC 150
Column name:	DAICELCHIRALPAK®IC
Column size:	250*25 mm 10 μm
Mobile Phase A:	Supercritical CO ₂
Mobile Phase B:	MeOH (+0.1% 7.0mol/l Ammonia in MeOH)
A:B:	45:55
Wavelength:	214 nm
Flow:	70ml/min
Column temp:	RT
Back Pressure:	100 bar
Injection:	2mL
Cycle time:	4.5min
Solvent:	MeOH : redistilled grade Supercritical CO ₂ : Food grade
Preparation of sample solution:	sample was dissolved in about 40Ml MeOH: DCM (1: 1)

Steps 8: 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde

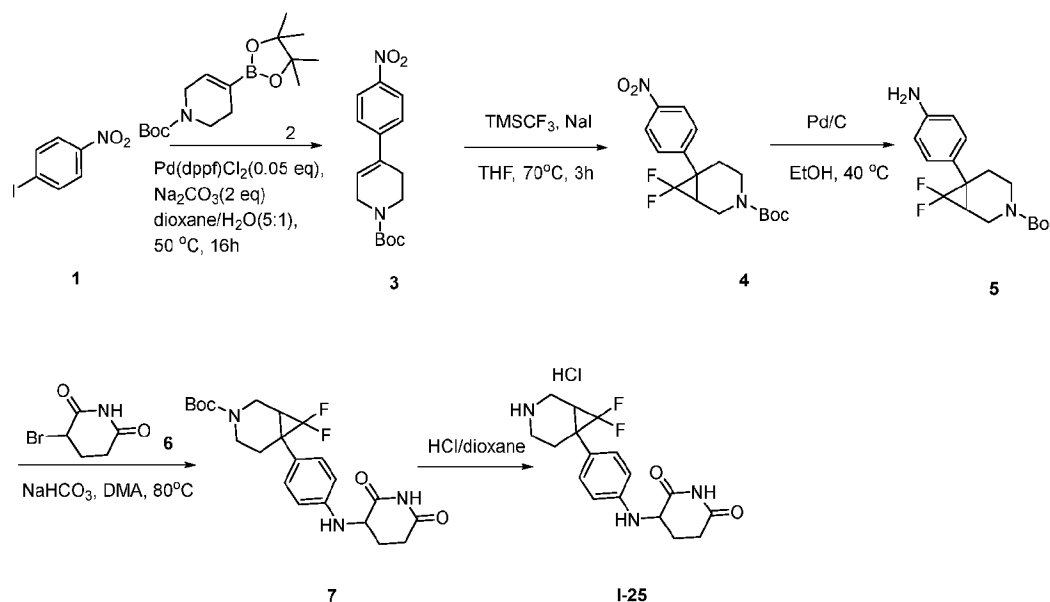
[0389] To a mixture of (3S,4S)-4-(4-(2-(dimethoxymethyl)-7-azaspiro[3.5]nonan-7-yl)-5-fluoro-2-methoxyphenyl)-3-phenylchroman-7-ol (87 mg, 0.16 mmol, 1.00 eq) in FA (2 mL), and the mixture was stirred at rt for 1 h. The mixture was concentrated in vacuum to afford 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (85 mg, crude) as a yellow solid. LC-MS purity: 100% (UV at 254 nm), 502.4 [M+H]⁺

Intermediate 24: 2-chloro-1-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethan-1-one



[0390] To a mixture of (3S,4R)-4-(4-(3,9-diazaspiro[5.5]undecan-3-yl)phenyl)-3-phenylchroman-7-ol hydrochloride (140 mg, 0.3 mmol, 1.00 eq) in DCM (6 mL) was added TEA (62 mg, 0.62 mmol, 2 eq) and 2-chloroacetyl chloride (36.5 mg, 0.32 mmol, 1.05 eq), and the mixture was stirred at rt for 1 h. The mixture was poured into H₂O (20 mL), extracted with DCM (10 mLx2). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated in vacuum. The crude product was purified by silica gel column chromatography using 0-40% EtOAc/hexane to afford 2-chloro-1-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethan-1-one (160 mg, crude) as a yellow oil. LC-MS purity: 100% (UV at 254 nm), 531.4 [M+H]⁺

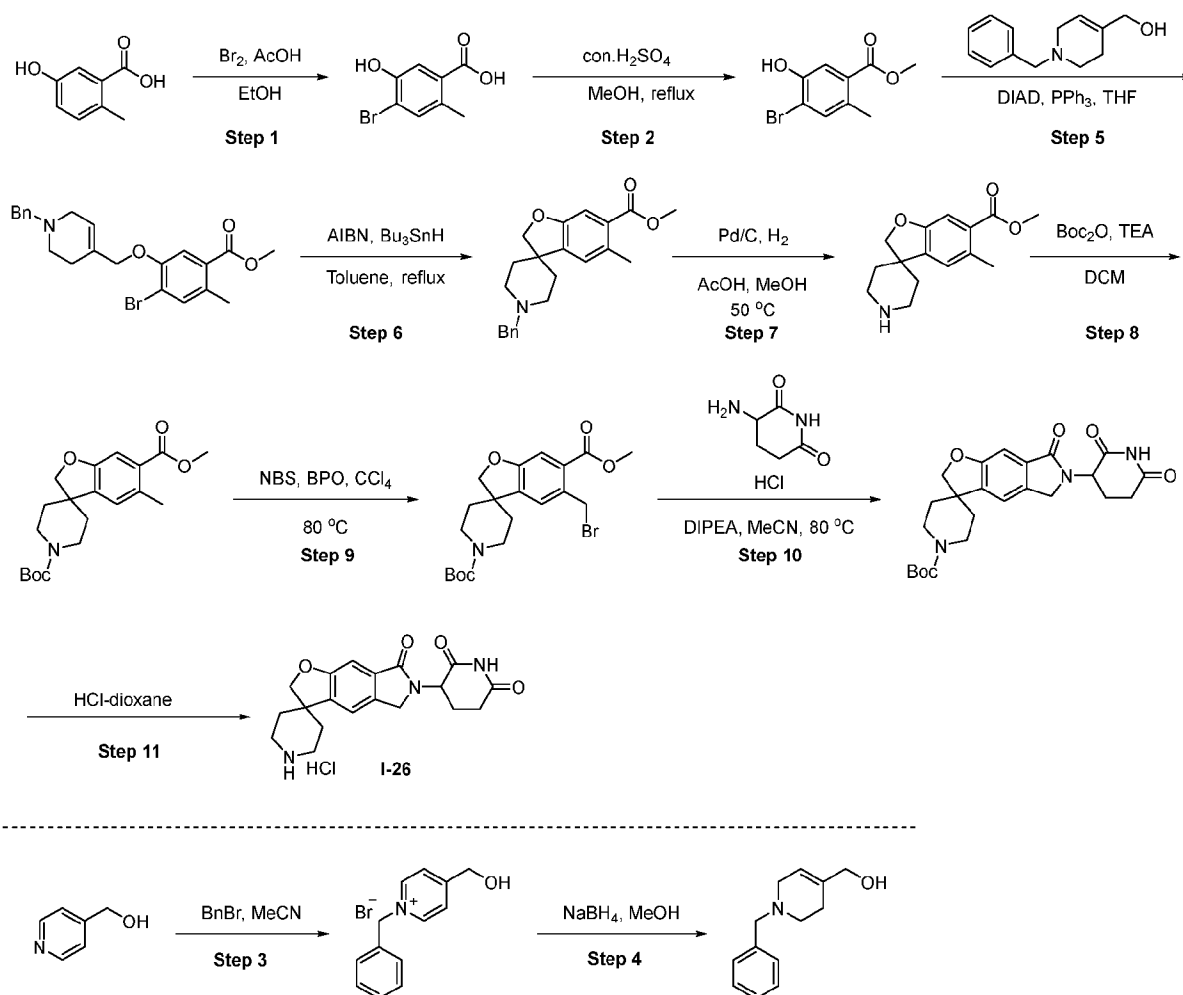
Intermediate 25. 3-((4-(7,7-difluoro-3-azabicyclo[4.1.0]heptan-6-yl)phenyl)amino)piperidine-2,6-dione hydrochloride salt



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

[0391] To a mixture of 1-iodo-4-nitrobenzene (10 g, 40.1 mmol 1 eq.) and tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2H)-carboxylate (14.9 g, 48.2 mmol, 1.2 eq.) in dioxane (100 mL)/H₂O (20 mL) was added Pd(pddf)Cl₂ (1.9 g, 2.0 mmol, 0.05 eq.) and Na₂CO₃ (12.8 g, 120.5 mmol, 3 eq.) under Ar. The reaction mixture was stirred at 50 °C under N₂ for 16 h. The mixture was concentrated and purified by column chromatography on silica gel eluted with 0-20% EtOAc/hexane to afford tert-butyl 4-(4-nitrophenyl)-3,6-dihydropyridine-1(2H)-carboxylate (6.7 g, 54% yield) as white solid.

Intermediate 26. 3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione hydrochloride



Step 1: 4-bromo-5-hydroxy-2-methylbenzoic acid.

[0392] To a solution of 5-hydroxy-2-methylbenzoic acid (5.0 g, 32.9 mmol, 1.0 eq) in a mixture of ethanol (20 mL) and acetic acid (10 mL) was added dropwise bromine (3.4 mL, 65.7 mmol, 2.0 eq.). The reaction mixture was stirred for 10 h at room temperature, quenched with aqueous sodium thiosulfate solution (50 mL), and concentrated. The aqueous layer was extracted with ethyl acetate (50 mL x 3). The organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to get crude 4-bromo-5-hydroxy-2-methylbenzoic acid (7.6 g, yield 100%) as a white solid. The crude product was directly used in next step without further purification. LC-MS (ESI): mass calcd. for $\text{C}_8\text{H}_7\text{BrO}_3$, 229.96; m/z found, 231.2 $[\text{M}+\text{H}]^+$.

Step 2: methyl 4-bromo-5-hydroxy-2-methylbenzoate

[0393] Con. H₂SO₄ (12 mL) was added to a suspension of 4-bromo-5-hydroxy-2-methylbenzoic acid (15 g, 65.72 mmol) in methanol (100 mL). The mixture was refluxed for 16 h. After evaporation, the residue was diluted with water (100 mL) and extracted with EA (100 mL x 3). The organic layer was washed with H₂O (100 mL x 2), saturated aqueous NaHCO₃ solution (100 mL x 2) and brine (100 mL). The organic layer was dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue purified by flash column chromatography on silica gel (PE/EA = 4/1) to afford methyl 4-bromo-5-hydroxy-2-methylbenzoate (7.5 g, yield 47%) as a colorless solid. LC-MS (ESI): mass calcd. for C₉H₉BrO₃, 243.97; m/z found, 245.2 [M+H]⁺.

[0394] ¹H NMR (400 MHz, CDCl₃) δ 7.56 (s, 1H), 7.36 (s, 1H), 5.52 (s, 1H), 3.88 (s, 3H), 2.50 (s, 3H).

Step 3: 1-benzyl-4-(hydroxymethyl)pyridin-1-ium bromide

[0395] To a solution of (pyridin-4-yl)methanol (8.9 g, 81.6 mmol, 1.0 eq) in CH₃CN (80 mL) was added a solution of (bromomethyl)benzene (11.705 mL, 97.9 mmol, 1.2 eq) in CH₃CN (40 mL). The reaction mixture was refluxed stirred at 90 °C for 3 h. After evaporation, the residue was washed with methyl tert-butyl ether, filtered, and dried to afford 1-benzyl-4-(hydroxymethyl)pyridin-1-ium bromide (16.33 g, yield 100%) as a yellow solid. LC-MS (ESI): mass calcd. for C₁₃H₁₄NO, 200.11; m/z found, 200.3 [M]⁺.

Step 4: (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methanol

[0396] To a solution of 1-benzyl-4-(hydroxymethyl)pyridin-1-ium bromide (16.3 g, 81.4 mmol, 1.0 eq) in CH₃OH (150 mL) was added NaBH₄ (9.3 g, 244.2 mmol, 3.0 eq) in portions at -20 °C. The mixture was stirred at -20 °C for 1 h. The reaction was quenched with brine (100 mL) and extracted with EtOAc (200 mL x 3). The organic layer was washed with brine (100 mL x 3), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (CH₃OH in DCM, from 0% to 10%) to afford (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methanol (15 g, yield 91%) as a red oil. LC-MS (ESI): mass calcd. for C₁₃H₁₇NO, 203.13; m/z found, 204.4 [M+H]⁺.

[0397] ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.24 - 7.18 (m, 4H), 7.16 - 7.12 (m, 1H), 5.43 (s, 1H), 4.61 (s, 1H), 3.71 (s, 2H), 3.42 (s, 2H), 2.76 (s, 2H), 2.39 (t, *J* = 5.6 Hz, 2H), 1.91 (s, 2H).

Step 5: methyl 5-[(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methoxy]-4-bromo-2-methylbenzoate

[0398] To a solution of methyl 4-bromo-5-hydroxy-2-methylbenzoate (200 mg, 0.82 mmol, 1.0 eq), (1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methanol (166 mg, 0.82 mmol, 1.0 eq), and PPh₃ (321 mg, 1.22 mmol, 1.5 eq) in dry THF (10 mL) was added dropwise DIAD (0.25 mL, 1.22 mmol, 1.5 eq) at 0 °C under the N₂ atmosphere. The solution was stirred for 2 h. After evaporation, the residue was purified by flash column chromatography on silica gel (PE/EA = 2/1 to 1/1) to afford methyl 5-[(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methoxy]-4-bromo-2-methylbenzoate (300 mg, yield 85%) as a white solid. LC-MS (ESI): mass calcd. for C₂₂H₂₄BrNO₃, 429.09; m/z found, 431.30 [M+H]⁺.

Step 6: methyl 1'-(cyclohexylmethyl)-5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate

[0399] Tributyl tin hydride (0.5 mL, 1.84 mmol, 4.0 equiv) was added to a solution of methyl 5-[(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)methoxy]-4-bromo-2-methylbenzoate (200 mg, 0.46 mmol, 1.0 eq) and AIBN (15 mg, 0.09 mmol, 0.2 eq) in toluene (10 mL). The solution was refluxed in a sealed tube for 6 h. After cooled down to room temperature, The solution was quenched with saturated potassium fluoride solution (40 mL) and stirred at room temperature for 0.5 h. The mixture was extracted with EA (40 mL x 3). The organic layer was washed brine (40 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by prep-TLC (EA/PE = 1/1) to afford methyl 1'-(cyclohexylmethyl)-5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate (20 mg, yield 43%) as a yellow solid. LC-MS (ESI): mass calcd. for C₂₂H₂₅NO₃, 351.18; m/z found, 352.30 [M+H]⁺.

[0400] ¹H NMR (400 MHz, CDCl₃) δ 7.37 - 7.27 (m, 6H), 6.99 (s, 1H), 4.37 (s, 2H), 3.85 (s, 3H), 3.54 (s, 2H), 2.89 (d, *J* = 10.2 Hz, 2H), 2.52 (s, 3H), 2.10 - 1.95 (m, 4H), 1.70 (d, *J* = 11.4 Hz, 2H).

Step 7: methyl 5-methyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylate

[0401] A mixture of methyl 1'-benzyl-5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate (1.0 g, 2.845 mmol, 1.0 eq), acetic acid (1 mL, 5.7 mmol, 6.1 eq), and 10% Pd/C (200 mg) in MeOH (20 mL) was stirred at 50 °C under H₂ (1 atm) for 3 h. After filtration, the filtrate was concentrated to get methyl 5-methyl-2H-spiro[benzofuran-3,4'-piperidine]-6-carboxylate (970 mg, yield 100%) as a colorless oil, which was directly used in the next step without further purification. LC-MS (ESI): mass calcd. for C₁₅H₁₉NO₃, 261.14; m/z found, 262.40 (M+H)⁺.

Step 8: 1'-(tert-butyl) 6-methyl 5-methyl-2H-spiro[benzofuran-3,4'-piperidine]-1',6-dicarboxylate

[0402] To a stirred solution of methyl 5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate (970 mg, 3.7 mmol, 1.0 eq) and TEA (1 mL, 7.4 mmol, 2.0 eq) in DCM (10 mL) was added dropwise Boc_2O (0.8 mL, 3.7 mmol, 2.0 eq) at 0 °C. The mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water (10 mL) and extracted with DCM (30 mL x 2). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford 1'-(tert-butyl) 6-methyl 5-methyl-2H-spiro[benzofuran-3,4'-piperidine]-1',6-dicarboxylate (1.28 g, yield 100%) as a white solid. LC-MS (ESI): mass calcd. for $\text{C}_{20}\text{H}_{27}\text{NO}_5$, 361.19; m/z found, 306.4 $[\text{M}+\text{H}-56]^+$.

Step 9: 1'-(tert-butyl) 6-methyl 5-(bromomethyl)-2H-spiro[benzofuran-3,4'-piperidine]-1',6-dicarboxylate

[0403] A mixture of methyl 1'-benzyl-5-methyl-2H-spiro[1-benzofuran-3,4'-piperidine]-6-carboxylate (220 mg, 0.609 mmol, 1 eq), NBS (130 mg, 0.73 mmol, 1.2 eq), and BPO (60 mg, 0.243 mmol, 0.4 eq) in CCl_4 (10 mL) was refluxed for 4 h. After cooled to room temperature, the mixture was filtered, then the filtration was concentrated and to give 1'-tert-butyl 6-methyl 5-(bromomethyl)-2H-spiro[1-benzofuran-3,4'-piperidine]-1',6-dicarboxylate (100 mg, yield 37%) as a light-yellow solid. LC-MS (ESI): mass calcd. for $\text{C}_{20}\text{H}_{26}\text{BrNO}_5$, 439.10; m/z found, 462.20, $[\text{M}+\text{Na}]^+$.

Step 10: tert-butyl 6-(2,6-dioxopiperidin-3-yl)-7-oxo-6,7-dihydro-2H,5H-spiro[furo[2,3-f]isoindole-3,4'-piperidine]-1'-carboxylate

[0404] DIPEA (0.12 mL, 0.681 mmol, 3.0 eq) was added to 1'-tert-butyl 6-methyl 5-(bromomethyl)-2H-spiro[1-benzofuran-3,4'-piperidine]-1',6-dicarboxylate (100 mg, 0.227 mmol, 1.0 eq) and 3-aminopiperidine-2,6-dione hydrochloride (56 mg, 0.341 mmol, 1.5 eq) in MeCN (5 mL) under nitrogen. The resulting suspension was stirred at 80 °C for 24 h. The reaction mixture was cooled to room temperature and filtered. The solid was washed with MeCN and purified by prep-TLC (100% EtOAc) to afford tert-butyl 6-(2,6-dioxopiperidin-3-yl)-7-oxo-6,7-dihydro-2H,5H-spiro[furo[2,3-f]isoindole-3,4'-piperidine]-1'-carboxylate (50 mg, yield 48%) as a white solid. LC-MS (ESI): mass calcd. for $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_6$, 455.51; m/z found, 456.50, $(\text{M}+\text{H})^+$.

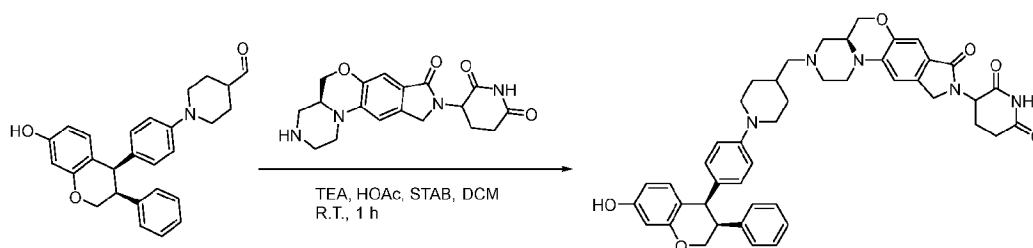
Step 11: 3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

[0405] To a solution of tert-butyl 6-(2,6-dioxopiperidin-3-yl)-7-oxo-2,5,6,7-tetrahydrospiro[furo[2,3-f]isoindole-3,4'-piperidine]-1'-carboxylate (50 mg, 0.11 mmol, 1.0 eq) in

DCM (1 mL) was added HCl-dioxane solution (4 M, 1 mL, 4 mmol, 36 eq) and the mixture was stirred for 30 min. After evaporation, the residue was purified by prep-HPLC with YMC-TA C18 (5 μ m, 20 x 250 mm), and mobile phase of 5-95% ACN in water over 10 min, and then hold at 100% ACN for 2 min, at a flow rate of 25 mL/min to get 3-{7-oxo-2,5,6,7-tetrahydrospiro[furo[2,3-f]isoindole-3,4'-piperidine]-6-yl}piperidine-2,6-dione hydrochloride (30 mg, yield 70%) as a white solid. LC-MS (ESI): mass calcd. for C₁₉H₂₁N₃O₄, 355.19; m/z found, 356.20 [M+H]⁺.

[0406] ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.98 (s, 1H), 8.78 (s, 2H), 7.36 (s, 1H), 7.06 (s, 1H), 5.11 - 5.06 (m, 1H), 4.58 (s, 2H), 4.38 (d, *J* = 17.0 Hz, 1H), 4.25 (d, *J* = 17.0 Hz, 1H), 3.30 - 3.27 (m, 2H), 3.04 - 2.92 (m, 2H), 2.93 - 2.84 (m, 1H), 2.62 - 2.56 (m, 1H), 2.44 - 2.29 (m, 1H), 2.09 - 1.97 (m, 3H), 1.90 - 1.79 (m, 2H).

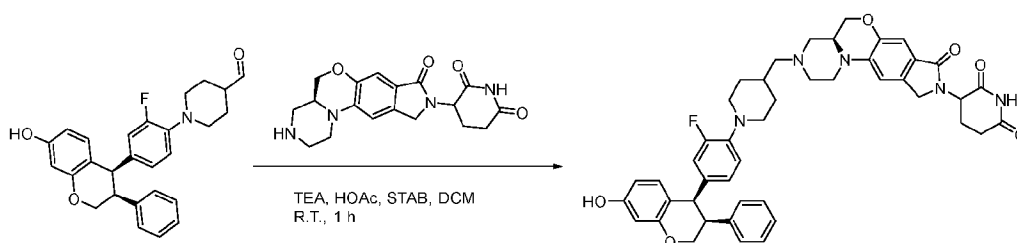
Compound A1 : 3-((S)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0407] To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidine-4-carbaldehyde (30 mg, 0.073 mmol, 1 eq.), 3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (34 mg, 0.087 mmol, 1.2 eq.), TEA (11 mg, 0.109 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.4 mg, 0.12 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (31 mg, 0.15 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford 3-((S)-3-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (27 mg, 49.1% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 794.2 [M+H]⁺

[0408] ^1H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.26 (s, 1H), 7.18 – 7.09 (m, 3H), 6.99 (d, J = 44.2 Hz, 2H), 6.81 – 6.72 (m, 2H), 6.64 (dd, J = 19.4, 8.4 Hz, 3H), 6.42 – 6.24 (m, 4H), 5.06 – 4.98 (m, 1H), 4.38 – 4.10 (m, 6H), 3.85 (d, J = 37.8 Hz, 2H), 3.60 – 3.47 (m, 3H), 3.17 (s, 1H), 3.01 – 2.82 (m, 3H), 2.41 – 2.03 (m, 7H), 1.81 – 1.62 (m, 4H), 1.24 (s, 4H).

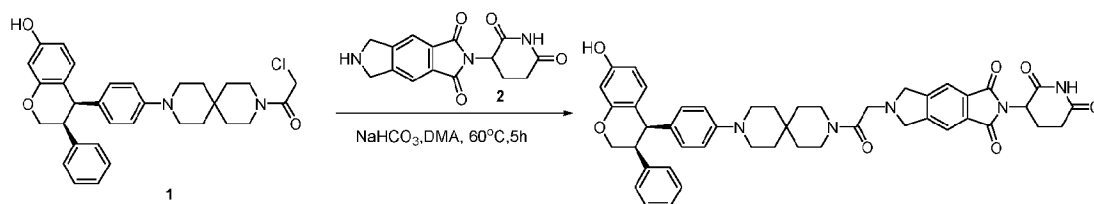
Compound A2 : 3-((S)-3-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0409] To a mixture of 1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidine-4-carbaldehyde (100 mg, 0.23 mmol, 1 eq.), 3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione hydrochloride (109 mg, 0.28 mmol, 1.2 eq.), TEA (35 mg, 0.35 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (24 mg, 0.39 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (98 mg, 0.46 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/0.05% Formic acid) to afford 3-((S)-3-((1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (39 mg, 22% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 772.0 $[\text{M}+\text{H}]^+$

[0410] ^1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.33 (s, 1H), 7.17 (t, J = 3.0 Hz, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.82 – 6.64 (m, 4H), 6.35 – 6.25 (m, 3H), 6.20 – 6.08 (m, 1H), 5.06 – 4.99 (m, 1H), 4.36 – 4.09 (m, 6H), 3.95 – 3.78 (m, 2H), 3.59 – 3.51 (m, 1H), 3.27 – 3.11 (m, 3H), 2.99 – 2.71 (m, 4H), 2.65 – 2.52 (m, 3H), 2.41 – 2.28 (m, 1H), 2.27 – 2.14 (m, 2H), 2.13 – 2.03 (m, 1H), 2.01 – 1.90 (m, 1H), 1.82 – 1.59 (m, 4H), 1.29 – 1.15 (m, 2H).

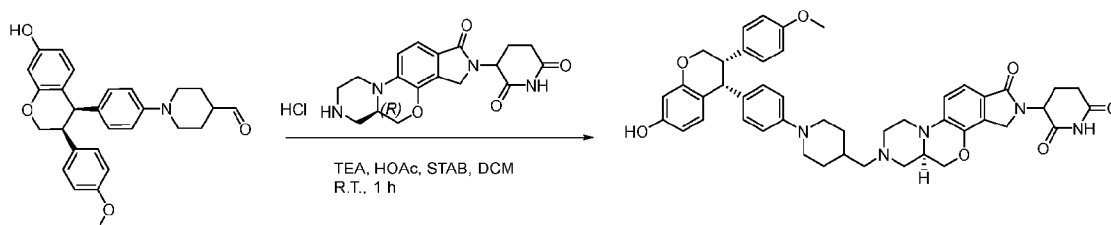
Compound A3: 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione



[0411] To a mixture of 2-chloro-1-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)ethan-1-one (160 mg, 0.3 mmol, 1.00 eq) in DMA (5 mL) was added NaHCO₃ (76 mg, 0.9 mmol, 3 eq), KI (25 mg, 0.35 mmol, 0.5 eq) and 2-(2,6-dioxopiperidin-3-yl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione (121 mg, 0.36 mmol, 1.2 eq), and the mixture was stirred at 60°C for 5 h. The mixture was added into HCl (1M) (20 mL), extracted with EA (10 mLx2). The combined organic layer was washed with brine (20 mL), dried over Na₂SO₄, filtered, and concentrated in vacuum. The crude product was purified by pre-HPLC to afford 2-(2,6-dioxopiperidin-3-yl)-6-(2-(9-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-3,9-diazaspiro[5.5]undecan-3-yl)-2-oxoethyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione (7.53 mg, 3%) as a yellow solid. LC/MS (ESI) m/z: 794.0. Rt: 0.747 min.

[0412] ¹H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 8.41 (s, 1H), 7.80 (s, 2H), 7.22 – 7.01 (m, 3H), 6.76 (s, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.4 Hz, 2H), 6.32 – 6.23 (m, 2H), 5.18 – 5.06 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.22 – 4.14 (m, 2H), 4.09 (s, 4H), 3.61 (s, 2H), 3.45 (s, 4H), 3.01 (s, 4H), 2.94 – 2.83 (m, 1H), 2.68 – 2.55 (m, 3H), 2.11 – 2.00 (m, 1H), 1.52 (s, 4H), 1.40 (d, J = 16.4 Hz, 4H).

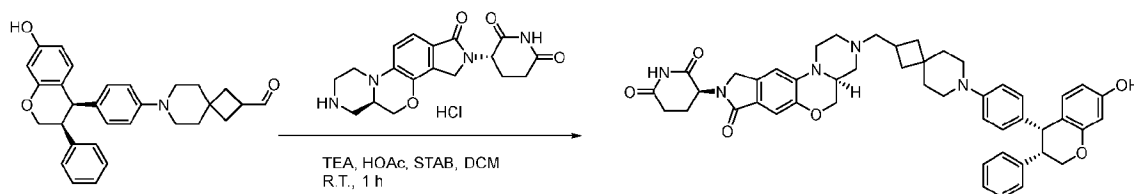
Compound A16 : 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0413] To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidine-4-carbaldehyde (30 mg, 0.068 mmol, 1 eq.), 3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (30 mg, 0.07 mmol, 1.2 eq.), TEA (10.3 mg, 0.102 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.9 mg, 0.115 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.135 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/0.05% formic acid) to afford 3-((R)-7-((1-(4-((3S,4R)-7-hydroxy-3-(4-methoxyphenyl)chroman-4-yl)phenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (5.34 mg, 10% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 784.5 [M+H]⁺

[0414] ¹H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.46 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.76 – 6.58 (m, 7H), 6.40 (d, J = 7.8 Hz, 2H), 6.33 – 6.22 (m, 2H), 5.08 – 4.96 (m, 1H), 4.37 – 4.23 (m, 2H), 4.18 – 4.05 (m, 3H), 4.03 – 3.91 (m, 1H), 3.88 – 3.78 (m, 1H), 3.68 (s, 3H), 3.62 – 3.52 (m, 2H), 2.99 – 2.82 (m, 3H), 2.81 – 2.69 (m, 1H), 2.43 – 2.29 (m, 2H), 2.27 – 2.05 (m, 3H), 2.04 – 1.89 (m, 2H), 1.83 – 1.59 (m, 4H), 1.33 – 1.11 (m, 6H).

Compound A59 : (S)-3-((S)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

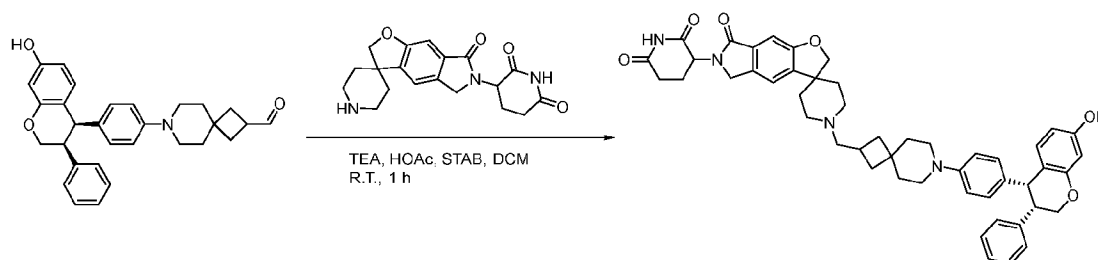


[0415] To a mixture of 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (S)-3-((R)-1-oxo-

1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (31 mg, 0.079 mmol, 1.2 eq.), TEA (10 mg, 0.099 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.7 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford (S)-3-((S)-3-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (23 mg, 44% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 794.5 [M+H]⁺

[0416] ¹H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 7.18 – 7.09 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.80 – 6.71 (m, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.06 – 4.98 (m, 1H), 4.36 – 4.11 (m, 6H), 3.94 – 3.74 (m, 2H), 3.53 – 3.49 (m, 1H), 3.17 – 3.11 (m, 1H), 3.01 – 2.83 (m, 7H), 2.79 – 2.69 (m, 1H), 2.63 – 2.53 (m, 2H), 2.44 – 2.33 (m, 3H), 2.16 – 2.03 (m, 1H), 2.01 – 1.87 (m, 3H), 1.75 – 1.59 (m, 3H), 1.54 – 1.36 (m, 4H).

Compound A71 : 3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione

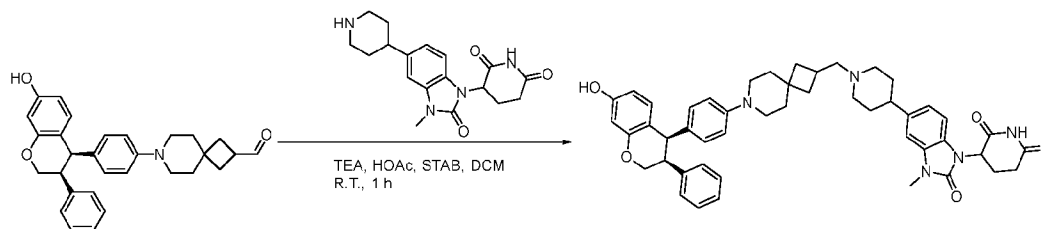


[0417] To a mixture of 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (S)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione hydrochloride (31 mg, 0.079 mmol, 1.2 eq.), TEA (10 mg, 0.099 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.7 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford 3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-

yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (9.84 mg, 19% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 793.5 [M+H]⁺

[0418] ¹H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 8.20 (s, 1H), 7.44 (s, 1H), 7.21 – 7.08 (m, 3H), 7.00 (s, 1H), 6.82 – 6.54 (m, 5H), 6.44 – 6.20 (m, 4H), 5.12 – 5.02 (m, 1H), 4.50 – 4.40 (m, 2H), 4.38 – 4.27 (m, 2H), 4.25 – 4.14 (m, 3H), 3.53 – 3.50 (m, 1H), 3.01 – 2.95 (m, 2H), 2.93 – 2.85 (m, 3H), 2.79 (d, J = 9.4 Hz, 2H), 2.64 – 2.54 (m, 1H), 2.45 – 2.30 (m, 4H), 2.02 – 1.84 (m, 7H), 1.71 – 1.57 (m, 4H), 1.55 – 1.46 (m, 2H), 1.41 (t, J = 9.8 Hz, 2H).

Compound A73 : 3-(5-(1-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione

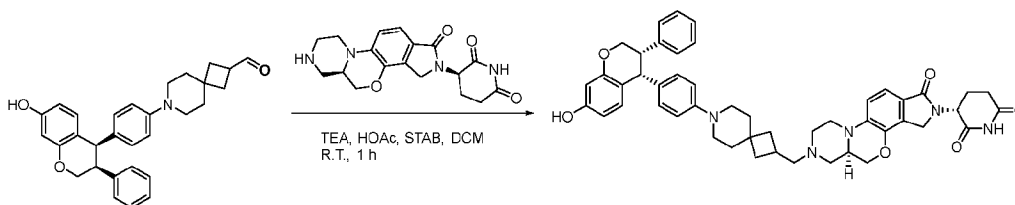


[0419] To a mixture of 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), 3-(3-methyl-2-oxo-5-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione hydrochloride (30 mg, 0.079 mmol, 1.2 eq.), TEA (10 mg, 0.099 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.7 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid)) to afford 3-(5-(1-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperidin-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-2,6-dione (5.55 mg, 11% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 780.5[M+H]⁺

[0420] ¹H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 8.30 (s, 1H), 7.17 – 7.07 (m, 4H), 7.01 – 6.87 (m, 2H), 6.79 – 6.73 (m, 2H), 6.67 – 6.58 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.37 – 5.29 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.17 (t, J = 6.8 Hz, 2H), 3.52 – 3.50 (m, 1H), 3.32

(s, 3H), 3.01 – 2.95 (m, 2H), 2.94 – 2.86 (m, 5H), 2.73 – 2.58 (m, 2H), 2.44 – 2.34 (m, 4H), 2.02 – 1.88 (m, 5H), 1.72 – 1.60 (m, 6H), 1.54 – 1.47 (m, 2H), 1.45 – 1.36 (m, 2H).

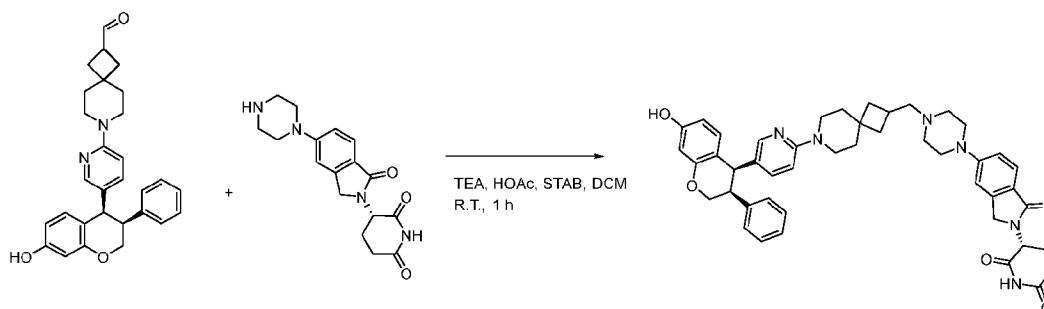
Compound A89: (R)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0421] To a mixture of 7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (120 mg, 0.26 mmol, 1 eq.), (R)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (125 mg, 0.32 mmol, 1.2 eq.), TEA (40 mg, 0.396 mmol, 1.5 eq.) in DCM (5.0 mL) was added acetic acid (27 mg, 0.45 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (112 mg, 0.529 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/ 0.05% formic acid) to afford (R)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (70 mg, 34% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 794.3 [M+H]⁺

[0422] ¹H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.23 (s, 1H), 7.24 – 7.08 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 8.6 Hz, 2H), 6.37 (d, J = 8.6 Hz, 2H), 6.33 – 6.23 (m, 2H), 5.09 – 4.90 (m, 1H), 4.36 – 4.08 (m, 6H), 4.01 – 3.90 (m, 1H), 3.80 (d, J = 11.4 Hz, 1H), 3.52 – 3.47 (m, 1H), 3.18 – 3.12 (m, 1H), 3.01 – 2.94 (m, 2H), 2.92 – 2.82 (m, 5H), 2.77 – 2.67 (m, 1H), 2.61 – 2.53 (m, 2H), 2.43 – 2.37 (m, 3H), 2.10 (t, J = 10.2 Hz, 1H), 2.00 – 1.88 (m, 3H), 1.73 (t, J = 10.6 Hz, 1H), 1.67 – 1.58 (m, 2H), 1.56 – 1.36 (m, 4H).

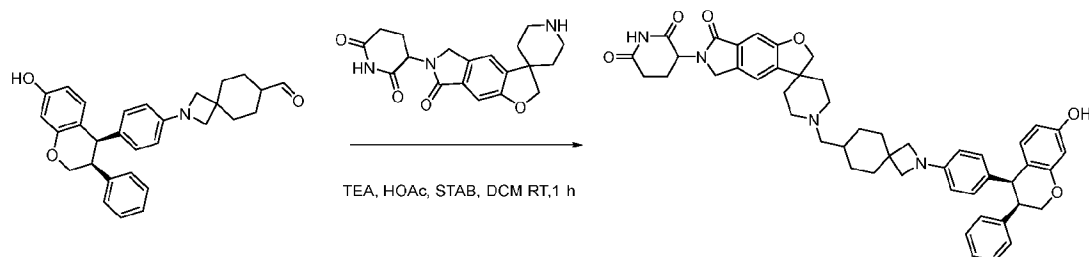
Compound A92 : (R)-3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione



[0423] To a mixture of 7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonane-2-carbaldehyde (100 mg, 0.22 mmol 1 eq), (S)-3-(1-oxo-5-(piperazin-1-yl)isoindolin-2-yl)piperidine-2,6-dione hydrochloride (120 mg, 0.33 mmol 1.5 eq), TEA (33.33 mg, 0.33 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (22.4 mg, 0.37 mmol, 1.7 eq) followed by sodium triacetoxyborohydride (93 mg, 0.44 mmol 2.0 eq). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/ 0.05% formic acid) to afford (R)-3-(5-(4-((7-(5-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione (47.49 mg, 28.2 % yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 767.5 [M+H]⁺

[0424] ¹H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 8.30 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.28 – 7.13 (m, 4H), 7.04 (d, J = 7.8 Hz, 2H), 6.90 – 6.78 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 8.8 Hz, 1H), 6.36 – 6.25 (m, 2H), 5.13 – 4.96 (m, 1H), 4.33 – 4.14 (m, 5H), 3.36 – 3.21 (m, 10H), 2.96 – 2.85 (m, 1H), 2.65 – 2.56 (m, 1H), 2.50 – 2.34 (m, 8H), 2.02 – 1.87 (m, 3H), 1.59 – 1.48 (m, 2H), 1.46 – 1.36 (m, 4H).

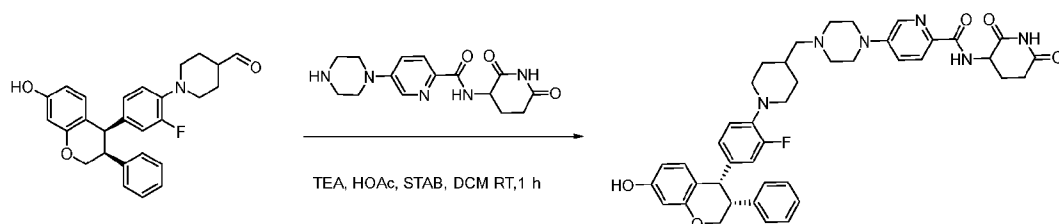
Compound A99 : 3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione



[0425] To a mixture of 2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), 3-(7-oxo-5,7-dihydro-2H,6H-1'H2-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (23 mg, 0.072 mmol, 1.2 eq.), TEA (6.7 mg, 0.066 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/ 0.05% formic acid)) to afford rac-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (8.5 mg, 16.3% yield) as white solid. LC-MS purity: 99.7% (UV at 254 nm), 793.4 [M+H]⁺

[0426] ¹H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 7.45 (s, 1H), 7.24 – 7.07 (m, 3H), 7.00 (s, 1H), 6.82 – 6.72 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.39 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.49 – 4.40 (m, 2H), 4.37 – 4.27 (m, 2H), 4.25 – 4.11 (m, 3H), 3.54 – 3.46 (m, 2H), 3.42 – 3.39 (m, 2H), 3.37 – 3.33 (m, 2H), 2.95 – 2.78 (m, 3H), 2.62 – 2.55 (m, 1H), 2.41 – 2.30 (m, 1H), 2.12 (d, J = 6.8 Hz, 2H), 2.02 – 1.79 (m, 7H), 1.73 – 1.60 (m, 4H), 1.55 – 1.37 (m, 3H), 0.98 – 0.83 (m, 2H).

Compound A100 : N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide

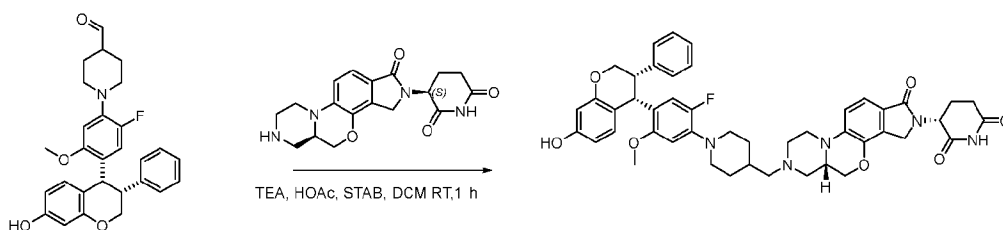


[0427] To a mixture of 1-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidine-4-carbaldehyde (30 mg, 0.070 mmol, 1 eq.), N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide

(piperazin-1-yl)picolinamide (22 mg, 0.084 mmol, 1.2 eq.), TEA (7.1 mg, 0.070 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (8.4 mg, 0.140 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (30 mg, 0.140 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/ 0.05% formic acid) to afford rac-N-(2,6-dioxopiperidin-3-yl)-5-(4-((1-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)piperidin-4-yl)methyl)piperazin-1-yl)picolinamide (12.82 mg, 25.1% yield) as white solid. LC-MS purity: 99.1% (UV at 254 nm), 793.4 [M+H]⁺.

[0428] ¹H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.38 – 8.22 (m, 1H), 7.92 – 7.76 (m, 1H), 7.47 – 7.28 (m, 1H), 7.21 – 7.10 (m, 3H), 6.85 – 6.58 (m, 4H), 6.35 – 6.23 (m, 3H), 6.15 (d, J = 13.2 Hz, 1H), 4.81 – 4.69 (m, 1H), 4.40 – 4.08 (m, 3H), 3.61 – 3.48 (m, 2H), 3.41 – 3.14 (m, 9H), 2.97 – 2.64 (m, 2H), 2.60 – 2.53 (m, 2H), 2.38 – 1.90 (m, 5H), 1.81 – 1.59 (m, 3H), 1.34 – 1.08 (m, 2H).

Compound A106: (R)-3-((S)-7-((1-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

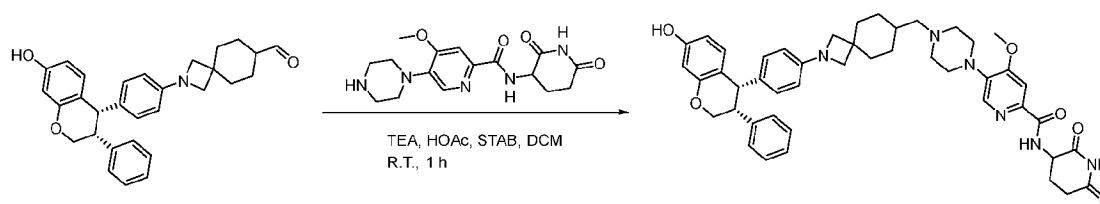


[0429] To a mixture of 1-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidine-4-carbaldehyde (30 mg, 0.065 mmol, 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (28 mg, 0.078 mmol, 1.2 eq.), TEA (6.5 mg, 0.065 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.8 mg, 0.130 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.130 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/ 0.05% formic acid) to afford (R)-3-((S)-7-((1-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-

pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (28.18 mg, 54.1% yield) as a yellow solid. LC-MS purity: 98.4% (UV at 254 nm), 802.4 [M+H]⁺.

[0430] ¹H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.32 (s, 1H), 7.22 – 6.96 (m, 5H), 6.77 – 6.55 (m, 3H), 6.36 – 6.20 (m, 4H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.38 – 4.20 (m, 3H), 4.14 – 4.04 (m, 2H), 4.03 – 3.91 (m, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.29 – 3.22 (m, 2H), 3.21 – 3.14 (m, 1H), 3.06 (s, 3H), 2.97 – 2.85 (m, 3H), 2.80 – 2.68 (m, 1H), 2.66 – 2.52 (m, 3H), 2.43 – 2.32 (m, 1H), 2.27 – 2.18 (m, 2H), 2.14 – 2.04 (m, 1H), 2.01 – 1.90 (m, 1H), 1.85 – 1.59 (m, 4H), 1.36 – 1.17 (m, 2H).

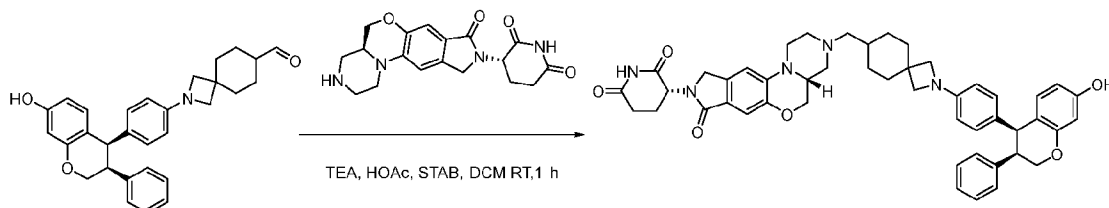
Compound A117 : N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide



[0431] To a mixture of 2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), N-(2,6-dioxopiperidin-3-yl)-4-methoxy-5-(piperazin-1-yl)picolinamide (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0–50% acetonitrile/0.05% formic acid) to afford N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.5% (UV at 254 nm), 785.1 [M+H]⁺.

[0432] ¹H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.26 (s, 1H), 8.86 (d, J = 8.2 Hz, 1H), 8.05 (s, 1H), 7.57 (s, 1H), 7.14 (s, 3H), 6.76 (s, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.40 – 6.22 (m, 4H), 6.09 (d, J = 8.3 Hz, 2H), 4.75 (t, J = 12.9 Hz, 1H), 4.36 – 4.21 (m, 1H), 4.20 – 4.08 (m, 2H), 3.93 (s, 3H), 3.49 (d, J = 11.2 Hz, 2H), 3.13 (s, 6H), 2.89 – 2.55 (m, 2H), 2.38 – 2.09 (m, 4H), 2.11 – 1.97 (m, 2H), 1.90 – 1.60 (m, 4H), 1.41 (s, 1H), 1.00 – 0.84 (m, 2H).

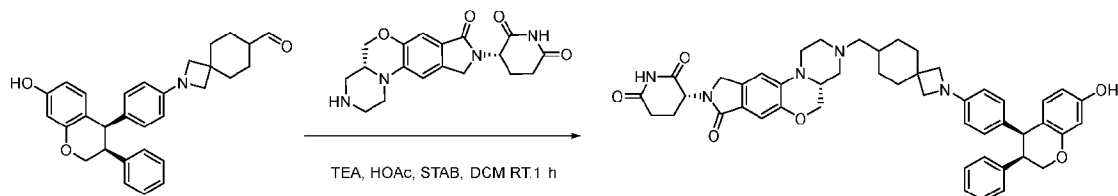
Compound A118 : (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0433] To a mixture of 2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (S)-3-((S)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (26 mg, 0.072 mmol, 1.1 eq.), TEA (6.7 mg, 0.066 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/0.05% formic acid) to afford (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (20.78 mg, 39.5% yield) as a yellow solid. LC-MS purity: 98.4% (UV at 254 nm), 794.4 [M+H]⁺.

[0434] ¹H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.27 – 7.10 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.82 – 6.71 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.38 – 6.21 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.37 – 4.09 (m, 6H), 3.92 – 3.77 (m, 2H), 3.51 – 3.47 (m, 1H), 3.41 – 3.32 (m, 5H), 3.18 – 3.12 (m, 1H), 2.96 – 2.84 (m, 3H), 2.80 – 2.71 (m, 1H), 2.62 – 2.54 (m, 1H), 2.39 – 2.30 (m, 1H), 2.17 – 2.03 (m, 3H), 1.98 – 1.91 (m, 1H), 1.87 – 1.76 (m, 2H), 1.75 – 1.62 (m, 3H), 1.54 – 1.38 (m, 3H), 1.00 – 0.80 (m, 2H).

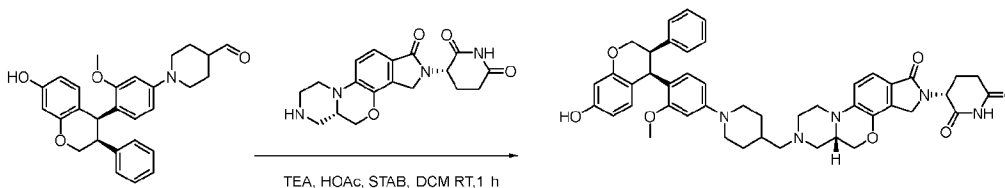
Compound A120 : (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0435] To a mixture of 2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (S)-3-((R)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (26 mg, 0.072 mmol, 1.1 eq.), TEA (6.7 mg, 0.066 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/0.05% formic acid) to afford (R)-3-((R)-3-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (17.59 mg, 34.2% yield) as a white solid. LC-MS purity: 98.4% (UV at 254 nm), 794.4 [M+H]⁺.

[0436] ¹H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.19 – 7.05 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.79 – 6.70 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.41 – 6.21 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.38 – 4.23 (m, 3H), 4.21 – 4.07 (m, 3H), 3.93 – 3.78 (m, 2H), 3.51 – 3.47 (m, 1H), 3.43 – 3.30 (m, 5H), 3.18 – 3.12 (m, 1H), 2.94 – 2.83 (m, 3H), 2.78 – 2.71 (m, 1H), 2.61 – 2.54 (m, 1H), 2.38 – 2.28 (m, 1H), 2.18 – 2.02 (m, 3H), 1.98 – 1.90 (m, 1H), 1.88 – 1.77 (m, 2H), 1.75 – 1.62 (m, 3H), 1.55 – 1.33 (m, 3H), 0.98 – 0.80 (m, 2H).

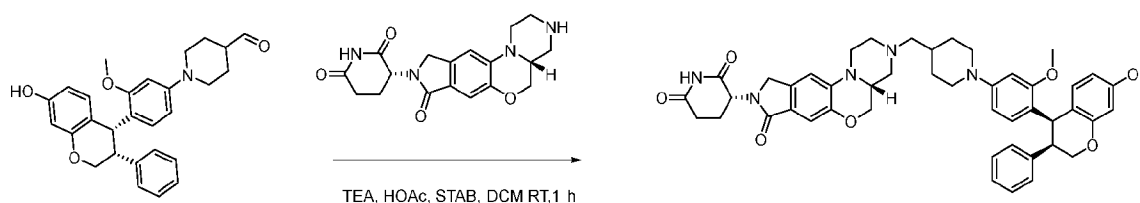
Compound A121 : (R)-3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0437] To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (80 mg, 0.180 mmol, 1 eq.), (S)-3-((S)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (71 mg, 0.198 mmol, 1.1 eq.), TEA (18.2 mg, 0.180 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (21.6 mg, 0.360 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (76 mg, 0.360 mmol, 2.0 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/0.05% formic acid) to afford (R)-3-((S)-7-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (64.14 mg, 45.4% yield) as a white solid.. LC-MS purity: 98.1% (UV at 254 nm), 784.2 [M+H]⁺.

[0438] ¹H NMR (400 MHz, DMSO) δ 11.18 (s, 1H), 10.94 (s, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.19 – 7.05 (m, 4H), 6.77 – 6.55 (m, 4H), 6.37 – 6.23 (m, 2H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.76 – 4.65 (m, 1H), 4.46 – 4.39 (m, 1H), 4.33 – 4.06 (m, 6H), 3.97 – 3.87 (m, 1H), 3.69 – 3.48 (m, 9H), 3.19 – 3.03 (m, 6H), 2.98 – 2.83 (m, 2H), 2.71 – 2.52 (m, 3H), 2.46 – 2.33 (m, 1H), 2.27 – 1.88 (m, 4H), 1.71 (s, 1H).

Compound A122 : (R)-3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione

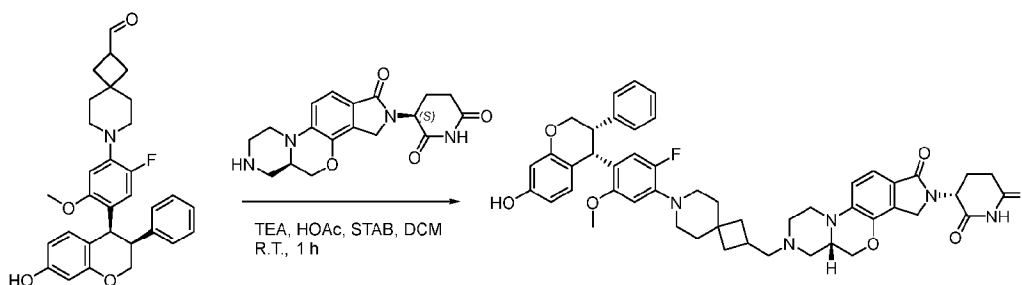


[0439] To a mixture of 1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (80 mg, 0.180 mmol, 1 eq.), (R)-3-((R)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (71 mg, 0.198 mmol, 1.1 eq.), TEA (18.2 mg, 0.180 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (21.6 mg, 0.360 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (76 mg, 0.360 mmol, 2.0 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/

0.05% formic acid)) to afford (R)-3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (70.36 mg, 49.5% yield) as a white solid. LC-MS purity: 99.5% (UV at 254 nm), 784.4 [M+H]⁺.

[0440] ¹H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.29 – 6.95 (m, 5H), 6.71 – 6.41 (m, 5H), 6.38 – 6.18 (m, 3H), 5.08 – 4.99 (m, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.38 – 4.16 (m, 7H), 4.08 – 4.00 (m, 2H), 3.75 – 3.56 (m, 5H), 3.50 – 3.44 (m, 1H), 3.26 – 3.16 (m, 1H), 3.17 – 3.05 (m, 3H), 2.95 – 2.84 (m, 2H), 2.78 – 2.66 (m, 2H), 2.64 – 2.52 (m, 3H), 2.41 – 2.32 (m, 1H), 2.07 – 1.75 (m, 4H), 1.43 – 1.27 (m, 2H).

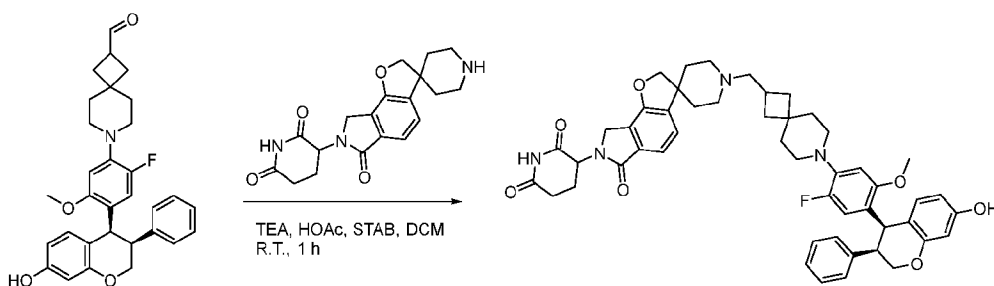
Compound A125: (R)-3-((S)-7-((7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0441] To a mixture of 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (35 mg, 0.07 mmol, 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione hydrochloride (33 mg, 0.084 mmol, 1.2 eq.), TEA (10.6 mg, 0.10 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.1 mg, 0.119 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30 mg, 0.14 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0–50% acetonitrile/ 0.05% formic acid)) to afford (R)-3-((S)-7-((7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (10.79 mg, 18% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 842.5 [M+H]⁺.

[0442] ^1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.32 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.14 – 7.07 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.77 – 6.66 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.34 – 6.19 (m, 4H), 5.06 – 4.99 (m, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.39 – 4.21 (m, 3H), 4.16 – 4.05 (m, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.80 (d, J = 11.6 Hz, 1H), 3.50 – 3.46 (m, 1H), 3.20 – 3.10 (m, 1H), 3.05 (s, 3H), 2.96 – 2.70 (m, 8H), 2.62 – 2.53 (m, 1H), 2.47 – 2.32 (m, 4H), 2.11 (t, J = 10.2 Hz, 1H), 2.01 – 1.89 (m, 3H), 1.79 – 1.63 (m, 3H), 1.62 – 1.52 (m, 2H), 1.44 (t, J = 9.4 Hz, 2H).

Compound A130 : 3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione

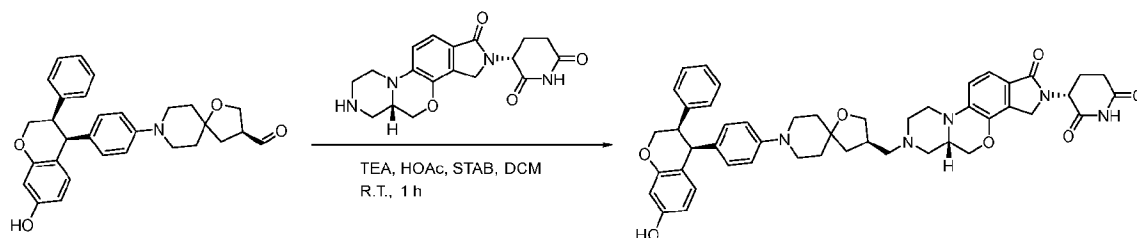


[0443] To a mixture of 7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonane-2-carbaldehyde (35 mg, 0.07 mmol, 1 eq.), 3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione hydrochloride (33 mg, 0.084 mmol, 1.2 eq.), TEA (10.6 mg, 0.10 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.1 mg, 0.119 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30 mg, 0.14 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/0.05% formic acid) to afford 3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (13.71 mg, 23.3% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 841.5 $[\text{M}+\text{H}]^+$.

[0444] ^1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.29 (s, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 3.6 Hz, 3H), 6.78 – 6.68 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.35 – 6.21 (m, 4H), 5.12 – 5.04 (m, 1H), 4.65 (d, J = 5.2 Hz, 1H), 4.55 – 4.46 (m, 2H), 4.42 – 4.27 (m, 2H), 4.21 (d, J = 17.0 Hz, 1H), 4.08 (d, J = 7.8 Hz, 1H), 3.50 – 3.48 (m, 1H), 3.05 (s, 3H), 2.94 –

2.75 (m, 7H), 2.59 (d, $J = 16.6$ Hz, 1H), 2.47 – 2.33 (m, 4H), 2.05 – 1.84 (m, 7H), 1.72 – 1.52 (m, 6H), 1.43 (t, $J = 9.4$ Hz, 2H).

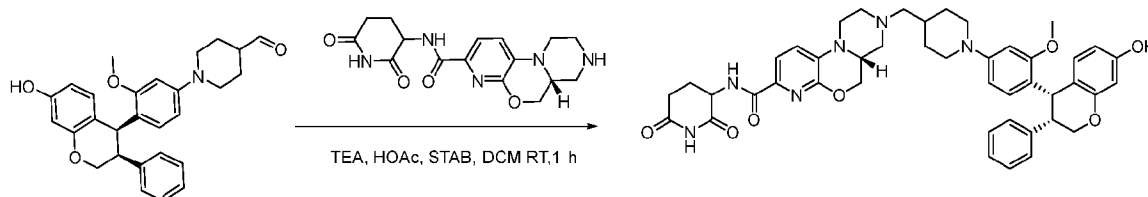
Compound A132 : (R)-3-((S)-7-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione



[0445] To a mixture of (S)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (R)-3-((S)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford (R)-3-((S)-7-(((R)-8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-c]isoindol-2-yl)piperidine-2,6-dione (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.8% (UV at 254 nm), 785.1 $[M+H]^+$.

[0446] ^1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 7.23 – 7.07 (m, 4H), 7.01 (d, $J = 8.0$ Hz, 1H), 6.80 – 6.70 (m, 2H), 6.69 – 6.55 (m, 3H), 6.37 (d, $J = 8.8$ Hz, 2H), 6.31 – 6.22 (m, 2H), 5.10 – 4.98 (m, 1H), 4.39 – 4.24 (m, 3H), 4.21 – 4.12 (m, 2H), 4.08 (s, 1H), 4.00 – 3.94 (m, 1H), 3.87 (d, $J = 7.8$ Hz, 1H), 3.81 (s, 1H), 3.55 – 3.47 (m, 1H), 3.43 (d, $J = 7.6$ Hz, 1H), 3.33 (s, 4H), 3.06 (s, 3H), 2.88 (d, $J = 12.6$ Hz, 1H), 2.70 (d, $J = 16.0$ Hz, 1H), 2.37 – 2.32 (m, 2H), 2.12 (s, 1H), 2.01 – 1.91 (m, 3H), 1.83 – 1.72 (m, 1H), 1.64 – 1.52 (m, 4H), 1.40 – 1.20 (m, 4H).

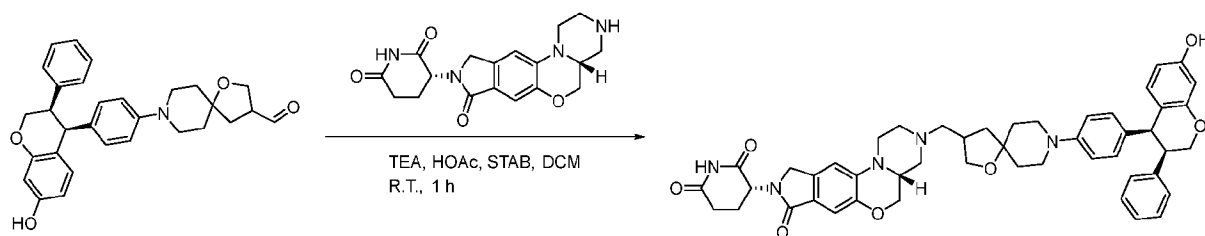
Compound A134 : (4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide



[0447] To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (30 mg, 0.068 mmol, 1 eq.), (4aR)-N-(2,6-dioxopiperidin-3-yl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (26 mg, 0.074 mmol, 1.1 eq.), TEA (6.8 mg, 0.068 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (8.1 mg, 0.136 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (29 mg, 0.136 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/0.05% formic acid) to afford (4aR)-N-(2,6-dioxopiperidin-3-yl)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-1,2,3,4,4a,5-hexahydropyrazino[1,2-d]pyrido[2,3-b][1,4]oxazine-8-carboxamide (20.95 mg, 39.9% yield) as a yellow solid. LC-MS purity: 99.6% (UV at 254 nm), 773.4 [M+H]⁺.

[0448] ¹H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.31 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.17 – 7.04 (m, 3H), 6.74 – 6.64 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 7.6 Hz, 1H), 6.31 – 6.21 (m, 2H), 6.18 (s, 1H), 4.76 – 4.66 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.51 – 4.38 (m, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.13 – 4.00 (m, 2H), 3.78 (d, J = 11.6 Hz, 1H), 3.65 – 3.56 (m, 2H), 3.49 – 3.39 (m, 2H), 3.23 – 3.17 (m, 1H), 3.05 – 2.92 (m, 5H), 2.84 – 2.70 (m, 2H), 2.63 – 2.55 (m, 2H), 2.25 – 1.94 (m, 5H), 1.84 – 1.62 (m, 4H), 1.25 – 1.11 (m, 2H).

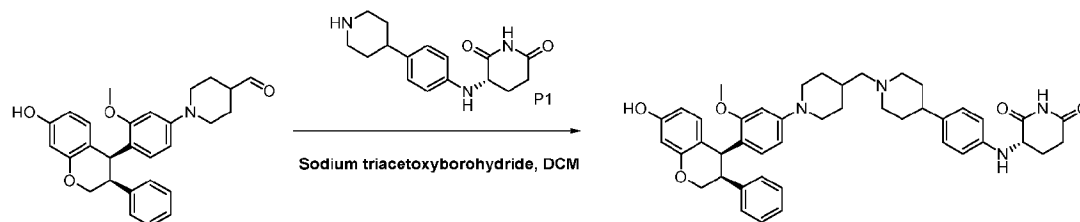
Compound A139 : (3R)-3-((4aR)-3-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0449] To a mixture of 8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (30 mg, 0.063 mmol, 1 eq.), (R)-3-((R)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (30 mg, 0.07 mmol, 1.2 eq.), TEA (9.6 mg, 0.095 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (6.4 mg, 0.11 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.13 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford (3R)-3-(((4aR)-3-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (12.78 mg, 39.7% yield) as white solid. LC-MS purity: 99.5% (UV at 254 nm), 810.2 [M+H]⁺.

[0450] ¹H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.17 – 7.11 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.80 – 6.72 (m, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.21 (m, 2H), 5.05 – 4.98 (m, 1H), 4.71 – 3.89 (m, 7H), 3.88 – 3.67 (m, 2H), 3.51 (d, J = 4.0 Hz, 1H), 3.44 (t, J = 7.8 Hz, 1H), 3.35 (s, 1H), 3.15 (s, 1H), 3.06 (s, 2H), 2.95 – 2.84 (m, 2H), 2.76 (s, 1H), 2.63 – 2.54 (m, 2H), 2.33 (t, J = 8.8 Hz, 3H), 2.17 – 2.07 (m, 1H), 1.98 – 1.88 (m, 2H), 1.76 – 1.68 (m, 1H), 1.66 – 1.33 (m, 5H), 1.24 (s, 2H).

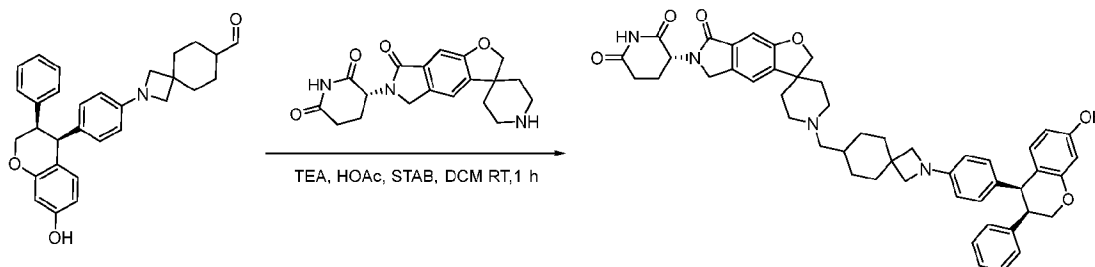
Compound A149: (S)-3-((4-(1-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione



[0451] To a mixture of 1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidine-4-carbaldehyde (30 mg, 0.068 mmol, 1 eq.), (S)-3-((4-(piperidin-4-

yl)phenyl)amino)piperidine-2,6-dione (22 mg, 0.074 mmol 1.1 eq.) in DCM (3 mL) was added sodium triacetoxyborohydride (29 mg, 0.136 mmol 2.0 eq.) at room temperature for 1 hour. LCMS showed the reaction was completed. The reaction was cooled to 20 °C and concentrated under vacuum. The residue was purified by Prep-HPLC (acetonitrile/ 0.01% formic acid) to afford (S)-3-((4-(1-((1-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (34.35 mg, 70.9 % yield) as a white solid. LC-MS (ESI, m/z): mass calcd. For C₄₄H₅₀N₄O₅, 714.4; found, 715.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.10 (s, 3H), 6.95 (d, J = 6.8 Hz, 2H), 6.69 – 6.54 (m, 5H), 6.48 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.30 – 6.22 (m, 2H), 6.17 (s, 1H), 5.64 (d, J = 6.4 Hz, 1H), 4.64 – 4.57 (m, 1H), 4.34 – 4.19 (m, 2H), 4.04 (d, J = 9.6 Hz, 1H), 3.65 – 3.54 (m, 3H), 3.47 – 3.39 (m, 2H), 3.02 (s, 3H), 2.93 (d, J = 10.4 Hz, 2H), 2.78 – 2.67 (m, 1H), 2.60 – 2.53 (m, 3H), 2.36 – 2.26 (m, 1H), 2.21 – 2.06 (m, 3H), 2.01 – 1.92 (m, 2H), 1.80 – 1.72 (m, 2H), 1.70 – 1.52 (m, 5H), 1.23 – 1.08 (m, 2H).

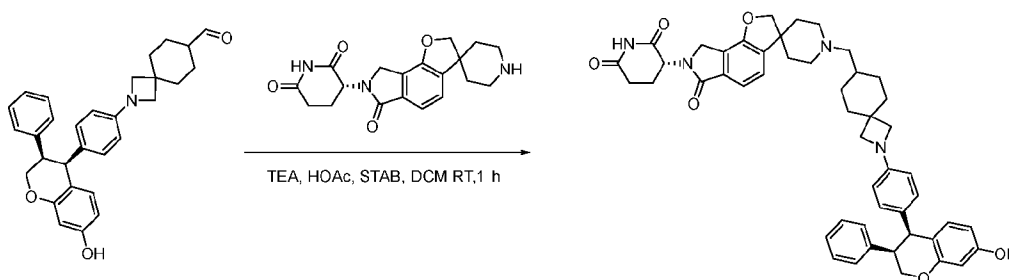
Compound A153 : (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione



[0452] To a mixture of rac-2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), rac-(R)-3-(7-oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (26 mg, 0.072 mmol, 1.1 eq.), TEA (6.7 mg, 0.068 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/ 0.05% formic acid)) to afford (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-7-

oxo-5,7-dihydro-2H,6H-spiro[furo[2,3-f]isoindole-3,4'-piperidin]-6-yl)piperidine-2,6-dione (21.29 mg, 40.6 % yield) as a white solid. LC-MS purity: 99.6% (UV at 254 nm), 793.4 [M+H]⁺. **[0453]** ¹H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 7.45 (s, 1H), 7.22 – 7.08 (m, 3H), 7.00 (s, 1H), 6.81 – 6.71 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.37 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.38 – 4.28 (m, 2H), 4.24 – 4.11 (m, 3H), 3.54 – 3.44 (m, 2H), 3.41 – 3.39 (m, 2H), 3.36 – 3.33 (m, 2H), 2.97 – 2.77 (m, 3H), 2.64 – 2.54 (m, 1H), 2.42 – 2.30 (m, 1H), 2.11 (d, J = 6.8 Hz, 2H), 1.99 – 1.80 (m, 7H), 1.73 – 1.63 (m, 4H), 1.53 – 1.38 (m, 3H), 0.98 – 0.83 (m, 2H).

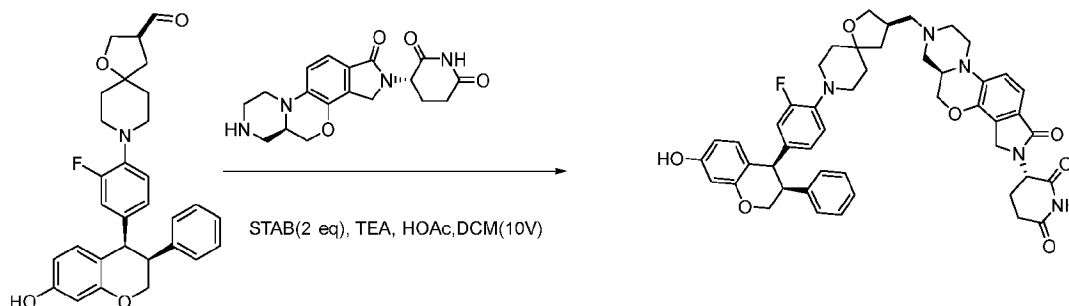
Compound A154: (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



[0454] To a mixture of 2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonane-7-carbaldehyde (30 mg, 0.066 mmol, 1 eq.), (R)-3-(6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (26 mg, 0.072 mmol, 1.1 eq.), TEA (6.7 mg, 0.068 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.9 mg, 0.132 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (28 mg, 0.132 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% acetonitrile/ 0.05% formic acid)) to afford (R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione (2.11 mg, 4.1% yield) as a gentle red solid. LC-MS purity: 96.8% (UV at 254 nm), 793.4 [M+H]⁺. **[0455]** ¹H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.26 (s, 1H), 7.42 – 7.22 (m, 2H), 7.18 – 7.07 (m, 3H), 6.79 – 6.72 (m, 2H), 6.70 – 6.58 (m, 1H), 6.36 – 6.25 (m, 4H), 6.12 – 6.06 (m, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.51 (s, 2H), 4.40 – 4.29 (m, 2H), 4.24 – 4.13 (m, 3H), 3.52 – 3.46 (m, 1H), 3.44 – 3.37 (m, 2H), 3.38 – 3.34 (m, 2H), 2.99 – 2.73 (m, 3H), 2.63 – 2.56 (m, 1H), 2.46 –

2.27 (m, 1H), 2.18 – 2.06 (m, 2H), 2.02 – 1.79 (m, 6H), 1.74 – 1.64 (m, 3H), 1.53 – 1.37 (m, 3H), 1.28 – 1.21 (m, 2H), 0.98 – 0.83 (m, 2H).

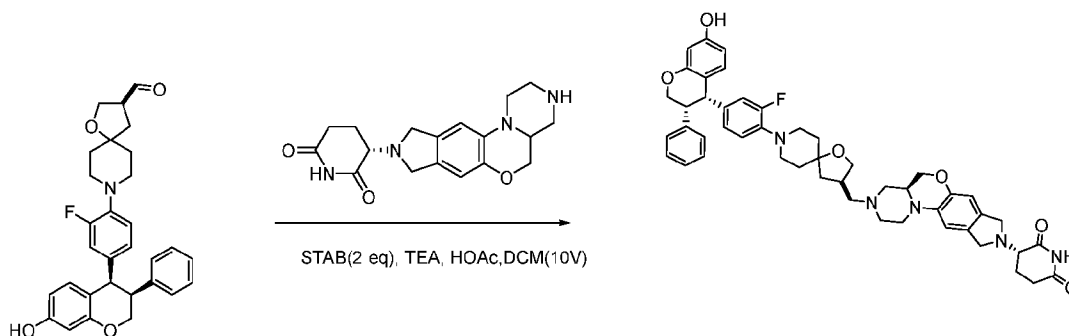
Compound A157: (S)-3-((R)-7-(((R)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione



[0456] To a mixture of (S)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-carbaldehyde (35 mg, 0.072 mmol, 1 eq.), (S)-3-((R)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (31mg, 0.09 mmol, 1.2 eq.), TEA (16.1 mg, 0.108 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.3 mg, 0.12 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30.5 mg, 0.14 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford (S)-3-((R)-7-(((R)-8-(2-fluoro-4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione (22.53 mg, 38.9% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 828.4 [M+H]⁺.

[0457] ¹H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.29 (s, 1H), 7.19 – 7.15 (m, 1H), 7.14 – 7.08 (m, 3H), 7.01 (d, J = 8.6 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 – 6.26 (m, 3H), 5.06 – 4.99 (m, 1H), 4.46 (d, J = 5.2 Hz, 1H), 4.38 – 4.22 (m, 3H), 4.17 – 4.06 (m, 2H), 3.99 – 3.78 (m, 3H), 3.56 – 3.48 (m, 2H), 3.16 – 3.08 (m, 5H), 3.04 – 2.98 (m, 1H), 2.94 – 2.84 (m, 2H), 2.76 – 2.66 (m, 2H), 2.39 – 2.32 (m, 3H), 2.17 – 2.04 (m, 1H), 2.00 – 1.90 (m, 2H), 1.82 – 1.70 (m, 1H), 1.68 – 1.53 (m, 4H), 1.38 – 1.30 (m, 1H).

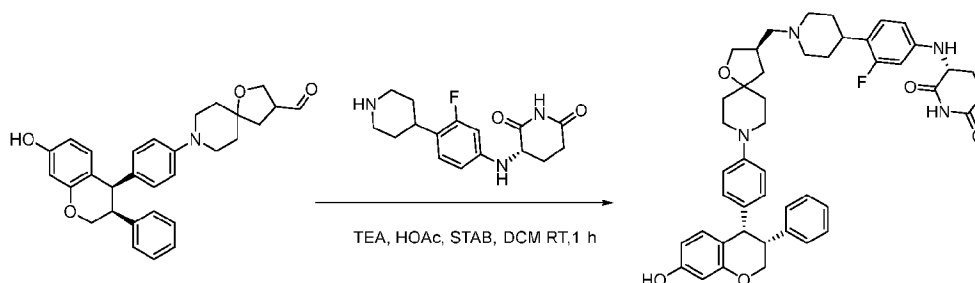
Compound A161: (S)-3-((S)-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione



[0458] To a mixture of (3S,4R)-4-(4-((S)-3-(dimethoxymethyl)-1-oxa-8-azaspiro[4.5]decan-8-yl)-3-fluorophenyl)-3-phenylchroman-7-ol (30 mg, 0.072 mmol, 1 eq.), (3S)-3-(1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (30 mg, 0.09 mmol, 1.2 eq.), TEA (16.1 mg, 0.108 mmol, 1.5 eq.) in DCM (2.0 mL) was added acetic acid (7.3 mg, 0.12 mmol, 1.7 eq.) followed by sodium triacetoxyborohydride (30.5 mg, 0.14 mmol, 2 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford (S)-3-((S)-3-(((R)-8-(2-fluoro-4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione (7.46 mg, 12.7% yield) as white solid. LC-MS purity: 100% (UV at 254 nm), 828.4 [M+H]⁺.

[0459] ¹H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.27 (s, 1H), 7.14 – 7.09 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.78 – 6.74 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 (s, 1H), 6.33 (s, 1H), 6.32 – 6.28 (m, 2H), 6.28 – 6.26 (m, 1H), 5.02 (dd, J = 13.4, 5.0 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.38 – 4.25 (m, 3H), 4.22 (s, 1H), 4.18 – 4.10 (m, 2H), 3.93 – 3.85 (m, 2H), 3.84 – 3.77 (m, 1H), 3.18 – 3.08 (m, 6H), 3.06 – 2.83 (m, 4H), 2.76 (s, 2H), 2.37 – 2.32 (m, 3H), 2.13 – 2.04 (m, 1H), 2.01 – 1.89 (m, 3H), 1.72 – 1.57 (m, 5H), 1.38 – 1.31 (m, 1H).

Compound A162: 3-((3-fluoro-4-(1-(((R)-8-(4-((3RS,4SR)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione



[0460] To a mixture of 8-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decane-3-carbaldehyde (30 mg, 0.064 mmol, 1 eq.), (S)-3-((3-fluoro-4-(piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (22 mg, 0.070 mmol, 1.1 eq.), TEA (6.4 mg, 0.064 mmol, 1.0 eq.) in DCM (2.0 mL) was added acetic acid (7.6 mg, 0.128 mmol, 2.0 eq.) followed by sodium triacetoxyborohydride (27 mg, 0.128 mmol, 2.0 eq.). The mixture was stirred at room temperature for 30 minutes and concentrated. The residue was purified by reverse-phase chromatography (0-50% Acetonitrile/ 0.05% Formic acid) to afford (RS)-3-((3-fluoro-4-(1-(((R)-8-(4-((3RS,4SR)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)piperidin-4-yl)phenyl)amino)piperidine-2,6-dione (14.85 mg, 30.5% yield) as a white solid. LC-MS purity: 98.7% (UV at 254 nm), 759.5 [M+H]⁺.

[0461] ¹H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, *J* = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, *J* = 7.6 Hz, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, *J* = 7.2 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.42 (d, *J* = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, *J* = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, *J* = 12.4, 8.0 Hz, 1H).

[0462] Compounds shown in the following table were prepared in a manner analogous to Compound **A154** by reductive amination.

Table 4. Characterization Data for Compounds A1 to A165

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A1	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.26 (s, 1H), 7.18 – 7.09 (m, 3H), 6.99 (d, <i>J</i> = 44.2 Hz, 2H), 6.81 – 6.72 (m, 2H), 6.64 (dd, <i>J</i> = 19.4, 8.4 Hz, 3H), 6.42 – 6.24 (m, 4H), 5.06 – 4.98 (m, 1H), 4.38 – 4.10 (m, 6H), 3.85 (d, <i>J</i> = 37.8 Hz, 2H), 3.60 – 3.47 (m, 3H), 3.17 (s, 1H), 3.01 – 2.82 (m,	B	754.4	754.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	3H), 2.41 – 2.03 (m, 7H), 1.81 – 1.62 (m, 4H), 1.24 (s, 4H).			
A2	¹ H NMR (400 MHz, MeOD) δ 7.29 (d, J = 8.4 Hz, 1H), 7.18 – 7.11 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.80 – 6.66 (m, 4H), 6.40 – 6.28 (m, 3H), 6.20 (d, J = 14.0 Hz, 1H), 5.11 – 5.04 (m, 1H), 4.58 (s, 3H), 4.44 – 4.17 (m, 6H), 4.08 – 3.98 (m, 1H), 3.84 (d, J = 10.0 Hz, 1H), 3.61 – 3.50 (m, 1H), 3.09 – 2.72 (m, 5H), 2.65 – 2.54 (m, 2H), 2.53 – 2.39 (m, 1H), 2.36 – 2.08 (m, 4H), 1.93 – 1.56 (m, 4H), 1.44 – 1.25 (m, 4H).	F	772.3	772.3
A3	¹ H NMR (400 MHz, CD3OD) δ 7.29 (d, J = 8.4 Hz, 1H), 7.16 – 7.07 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.75 – 6.67 (m, 5H), 6.48 (d, J = 8.6 Hz, 2H), 6.39 – 6.28 (m, 2H), 5.11 – 5.01 (m, 1H), 4.47 – 4.26 (m, 4H), 4.24 – 4.11 (m, 2H), 4.08 – 4.00 (m, 1H), 3.89 – 3.80 (m, 1H), 3.70 – 3.33 (m, 4H), 3.17 – 3.07 (m, 1H), 3.02 – 2.97 (m, 1H), 2.94 – 2.82 (m, 2H), 2.78 – 2.69 (m, 1H), 2.68 – 2.54 (m, 2H), 2.53 – 2.41 (m, 1H), 2.39 – 2.24 (m, 3H), 2.17 – 2.07 (m, 1H), 1.96 – 1.61 (m, 4H), 1.42 – 1.25 (m, 2H).	C	794.3	794.5
A4	¹ H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 8.41 (s, 1H), 7.80 (s, 2H), 7.22 – 7.01 (m, 3H), 6.76 (s, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.4 Hz, 2H), 6.32 – 6.23 (m, 2H), 5.18 – 5.06 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.22 – 4.14 (m, 2H), 4.09 (s, 4H), 3.61 (s, 2H), 3.45 (s, 4H), 3.01 (s, 4H), 2.94 – 2.83 (m, 1H), 2.68 – 2.55 (m, 3H), 2.11 – 2.00 (m, 1H), 1.52 (s, 4H), 1.40 (d, J = 16.4 Hz, 4H).	E	772.3	772.3
A5	¹ H NMR (400 MHz, DMSO-d6) δ 11.37 (s, 1H), 7.85 (s, 2H), 7.46 (s, 2H), 7.22-7.19 (m, 3H), 6.91 (d, J = 7.6 Hz, 2H), 6.69 (d, J = 8.8 Hz, 1H),	C	754.4	754.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	6.32-6.30 (m, 2H), 5.17-5.12 (m, 1H), 4.29 (d, J = 6.8 Hz, 1H), 4.19 (d, J = 5.6 Hz, 1H), 3.61-3.59 (m, 3H), 3.48-3.45 (m, 2H), 3.41-3.39 (m, 2H), 2.94-2.84 (m, 1H), 2.67-2.56 (m, 1H), 2.08-2.05 (m, 1H), 1.85-1.79 (m, 1H), 1.55-1.48 (m, 11H), 0.95-0.91 (m, 6H).			
A6	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.12 (s, 1H), 7.88 (s, 2H), 7.46 (s, 2H), 7.25-7.19 (m, 3H), 6.93-6.91 (m, 2H), 6.88 (d, J = 9.2 Hz, 1H), 6.32-6.30 (m, 2H), 5.17-5.12 (m, 1H), 4.29 (d, J = 7.6 Hz, 1H), 4.20 (d, J = 5.2 Hz, 1H), 3.64-3.56 (m, 4H), 3.49 (s, 2H), 3.39 (s, 2H), 2.94-2.86 (m, 1H), 2.68-2.55 (m, 1H), 2.08-2.05 (m, 1H), 1.85-1.76 (m, 1H), 1.65-1.49 (m, 11H), 0.95-0.93 (m, 6H).	C	772.4	772.5
A7	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.39 (s, 1H), 7.21 – 7.13 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.86 – 6.62 (m, 4H), 6.37 – 6.22 (m, 3H), 6.20 – 6.08 (m, 1H), 5.09 – 4.96 (m, 1H), 4.41 – 4.16 (m, 5H), 4.10 (d, J = 16.8 Hz, 1H), 4.03 – 3.91 (m, 1H), 3.83 (d, J = 10.2 Hz, 1H), 3.56 – 3.53 (m, 1H), 3.25 – 3.14 (m, 4H), 2.99 – 2.82 (m, 3H), 2.75 (t, J = 11.4 Hz, 1H), 2.61 – 2.53 (m, 2H), 2.44 – 2.33 (m, 1H), 2.27 – 2.05 (m, 3H), 1.98 – 1.90 (m, 1H), 1.84 – 1.56 (m, 4H), 1.34 – 1.13 (m, 2H).	E	754.4	754.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A8	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.20 – 7.11 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.81 – 6.72 (m, 2H), 6.69 – 6.57 (m, 3H), 6.38 (d, J = 8.6 Hz, 2H), 6.33 – 6.23 (m, 2H), 5.07 – 4.99 (m, 1H), 4.39 – 4.06 (m, 6H), 4.03 – 3.93 (m, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.59 – 3.47 (m, 3H), 3.30 (s, 1H), 3.22 – 3.13 (m, 1H), 2.98 – 2.83 (m, 3H), 2.80 – 2.70 (m, 1H), 2.63 – 2.53 (m, 2H), 2.42 – 2.35 (m, 1H), 2.24 – 2.05 (m, 3H), 2.00 – 1.91 (m, 1H), 1.80 – 1.59 (m, 4H), 1.24 – 1.10 (m, 2H).	E	754.3	754.6
A9	¹ H NMR (400 MHz, MeOD) δ 7.29 (d, J = 8.4 Hz, 1H), 7.18 – 7.11 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.80 – 6.66 (m, 4H), 6.40 – 6.28 (m, 3H), 6.20 (d, J = 14.0 Hz, 1H), 5.11 – 5.04 (m, 1H), 4.58 (s, 3H), 4.44 – 4.17 (m, 6H), 4.08 – 3.98 (m, 1H), 3.84 (d, J = 10.0 Hz, 1H), 3.61 – 3.50 (m, 1H), 3.09 – 2.72 (m, 5H), 2.65 – 2.54 (m, 2H), 2.53 – 2.39 (m, 1H), 2.36 – 2.08 (m, 4H), 1.93 – 1.56 (m, 4H), 1.44 – 1.25 (m, 4H).	F	772.3	772.3
A10	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H).	B	756.4	756.5
A11	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.26 (s, 1H), 7.18 – 7.09 (m, 3H), 6.99 (d, J = 44.2 Hz, 2H), 6.81 – 6.72 (m, 2H), 6.64 (dd, J = 19.4, 8.4 Hz, 3H), 6.42 – 6.24 (m, 4H), 5.06 – 4.98 (m, 1H), 4.38 – 4.10 (m, 6H), 3.85 (d, J = 37.8 Hz, 2H), 3.60 – 3.47 (m, 3H), 3.17 (s, 1H), 3.01 – 2.82 (m,	B	754.4	754.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	3H), 2.41 – 2.03 (m, 7H), 1.81 – 1.62 (m, 4H), 1.24 (s, 4H).			
A12	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.26 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.2 Hz, 1H), 6.75 – 6.58 (m, 7H), 6.40 (d, J = 8.6 Hz, 2H), 6.33 – 6.21 (m, 2H), 5.07 – 4.98 (m, 1H), 4.39 – 4.21 (m, 3H), 4.17 – 4.06 (m, 3H), 4.03 – 3.92 (m, 1H), 3.83 (d, J = 9.8 Hz, 1H), 3.68 (s, 3H), 3.62 – 3.40 (m, 3H), 3.23 – 3.12 (m, 1H), 3.00 – 2.84 (m, 3H), 2.75 (t, J = 11.2 Hz, 1H), 2.62 – 2.56 (m, 1H), 2.43 – 2.35 (m, 1H), 2.25 – 2.14 (m, 2H), 1.99 – 1.91 (m, 1H), 1.81 – 1.62 (m, 4H), 1.29 – 1.10 (m, 5H).	F	784.4	784.5
A13	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.75 – 6.59 (m, 7H), 6.40 (d, J = 8.4 Hz, 2H), 6.34 – 6.22 (m, 2H), 5.07 – 4.98 (m, 1H), 4.39 – 4.22 (m, 3H), 4.17 – 4.07 (m, 3H), 4.02 – 3.93 (m, 1H), 3.83 (d, J = 10.8 Hz, 1H), 3.68 (s, 3H), 3.56 (d, J = 10.2 Hz, 2H), 3.48 – 3.42 (m, 1H), 3.23 – 3.13 (m, 1H), 3.00 – 2.83 (m, 3H), 2.75 (t, J = 10.8 Hz, 1H), 2.62 – 2.52 (m, 3H), 2.44 – 2.32 (m, 1H), 2.25 – 2.06 (m, 3H), 2.01 – 1.90 (m, 1H), 1.84 – 1.61 (m, 5H), 1.25 – 1.09 (m, 2H).	F	784.4	784.5
A14	¹ H NMR (400 MHz, DMSO) δ 11.00 (s, 1H), 9.32 (s, 1H), 7.41 (d, J = 9.2 Hz, 1H), 7.25 – 7.13 (m, 4H), 7.03 (s, 1H), 6.82 – 6.64 (m, 4H), 6.36 – 6.24 (m, 3H), 6.15 (d, J = 14.8 Hz, 1H), 5.69 – 5.59 (m, 1H), 4.36 – 4.17 (m, 3H), 3.59 – 3.50 (m, 1H), 3.22 (d, J = 10.0 Hz, 2H), 3.10 (s, 4H), 2.90 – 2.78 (m, 1H), 2.74 – 2.64 (m, 2H), 2.61 – 2.52 (m, 5H), 2.41 (s, 3H), 2.27 – 2.15 (m, 3H), 1.82 – 1.57 (m, 3H), 1.30 – 1.16 (m, 3H).	F	743.4	743.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A15	¹ H NMR (400 MHz, MeOD) δ 7.67 (s, 1H), 6.50 (d, J = 8.4 Hz, 1H), 6.22 (d, J = 8.4 Hz, 1H), 5.97 – 5.79 (m, 7H), 5.71 (d, J = 8.4 Hz, 2H), 5.57 – 5.47 (m, 2H), 4.33 – 4.23 (m, 1H), 3.63 – 3.45 (m, 4H), 3.38 – 3.19 (m, 3H), 3.06 (d, J = 11.6 Hz, 1H), 2.93 (s, 3H), 2.84 – 2.62 (m, 3H), 2.33 – 1.93 (m, 5H), 1.83 (t, J = 11.8 Hz, 2H), 1.73 – 1.30 (m, 5H), 1.16 – 0.88 (m, 4H), 0.61 – 0.45 (m, 2H).	E	784.4	784.5
A16	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.46 (s, 1H), 7.18 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.76 – 6.58 (m, 7H), 6.40 (d, J = 7.8 Hz, 2H), 6.33 – 6.22 (m, 2H), 5.08 – 4.96 (m, 1H), 4.37 – 4.23 (m, 2H), 4.18 – 4.05 (m, 3H), 4.03 – 3.91 (m, 1H), 3.88 – 3.78 (m, 1H), 3.68 (s, 3H), 3.62 – 3.52 (m, 2H), 2.99 – 2.82 (m, 3H), 2.81 – 2.69 (m, 1H), 2.43 – 2.29 (m, 2H), 2.27 – 2.05 (m, 3H), 2.04 – 1.89 (m, 2H), 1.83 – 1.59 (m, 4H), 1.33 – 1.11 (m, 6H).	E	784.4	784.5
A17	¹ H NMR (400 MHz, MeOD) δ 7.44 (d, J = 9.2 Hz, 1H), 7.32 – 7.22 (m, 1H), 7.21 – 7.05 (m, 4H), 6.75 – 6.64 (m, 5H), 6.48 (d, J = 8.6 Hz, 2H), 6.39 – 6.27 (m, 2H), 5.61 – 5.52 (m, 1H), 4.57 (s, 2H), 4.41 (t, J = 11.0 Hz, 1H), 4.22 – 4.13 (m, 2H), 3.56 – 3.45 (m, 1H), 3.26 (s, 2H), 3.06 – 3.00 (m, 2H), 2.98 – 2.91 (m, 6H), 2.89 – 2.82 (m, 3H), 2.79 – 2.73 (m, 1H), 2.69 – 2.63 (m, 1H), 2.50 (s, 3H), 2.39 – 2.28 (m, 1H), 2.15 – 2.04 (m, 2H), 1.85 – 1.71 (m, 2H), 1.67 – 1.52 (m, 4H), 1.37 – 1.24 (m, 3H).	F	765.4	765.6

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A18	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H).	B	756.4	756.5
A19	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H).	B	756.4	756.5
A20	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H).	B	756.4	756.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A21	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.26 (s, 1H), 7.20 – 7.09 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.80 – 6.71 (m, 2H), 6.68 – 6.56 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.23 (m, 2H), 5.11 – 4.92 (m, 1H), 4.36 – 4.04 (m, 6H), 4.02 – 3.90 (m, 1H), 3.80 (d, J = 10.6 Hz, 1H), 3.54 – 3.48 (m, 1H), 3.17 – 3.11 (m, 1H), 3.02 – 2.81 (m, 7H), 2.76 – 2.66 (m, 1H), 2.63 – 2.53 (m, 2H), 2.43 – 2.30 (m, 3H), 2.17 – 1.87 (m, 4H), 1.79 – 1.58 (m, 3H), 1.55 – 1.34 (m, 4H).	F	794.4	794.4
A22	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.36 (s, 1H), 7.21 – 7.09 (m, 4H), 7.00 (d, J = 8.0 Hz, 1H), 6.75 (s, 2H), 6.68 – 6.56 (m, 3H), 6.42 – 6.23 (m, 4H), 5.06 – 4.99 (m, 1H), 4.36 – 4.08 (m, 6H), 4.00 – 3.92 (m, 1H), 3.84 – 3.78 (m, 1H), 3.52 – 3.49 (m, 1H), 3.16 – 3.12 (m, 1H), 3.00 – 2.84 (m, 7H), 2.76 – 2.67 (m, 1H), 2.61 – 2.54 (m, 2H), 2.43 – 2.34 (m, 3H), 2.16 – 1.88 (m, 4H), 1.78 – 1.59 (m, 3H), 1.53 – 1.37 (m, 4H).	F	794.4	794.4
A23	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.27 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.09 – 6.97 (m, 2H), 6.77 – 6.60 (m, 4H), 6.49 – 6.21 (m, 6H), 5.03 (dd, J = 13.2, 4.8 Hz, 1H), 4.41 – 4.05 (m, 6H), 4.02 – 3.78 (m, 2H), 3.61 – 3.43 (m, 6H), 3.23 – 3.12 (m, 1H), 2.99 – 2.83 (m, 3H), 2.81 – 2.69 (m, 1H), 2.62 – 2.53 (m, 3H), 2.46 – 2.31 (m, 2H), 2.27 – 1.88 (m, 5H), 1.27 – 1.15 (m, 4H).	C	784.4	784.5
A24	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.26 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.09 – 6.99 (m, 2H), 6.73 – 6.61 (m, 4H), 6.46 – 6.23 (m, 6H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.41 – 4.21 (m, 3H), 4.21 – 4.06 (m, 3H), 3.98 (dd, J = 19.4, 9.2 Hz, 1H), 3.62 – 3.43 (m, 6H), 3.18 (s, 1H), 3.01 –	C	784.4	784.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	2.82 (m, 3H), 2.60 – 2.55 (m, 2H), 2.46 – 2.28 (m, 2H), 2.27 – 2.05 (m, 3H), 1.97 – 1.90 (m, 1H), 1.85 – 1.61 (m, 4H), 1.29 – 1.10 (m, 4H).			
A25	¹ H NMR (400 MHz, DMSO) δ 11.01 (s, 1H), 8.32 (s, 1H), 7.40 (d, J = 9.2 Hz, 1H), 7.27 – 7.08 (m, 4H), 7.02 (s, 1H), 6.81 – 6.70 (m, 2H), 6.68 – 6.56 (m, 3H), 6.43 – 6.23 (m, 4H), 5.67 – 5.60 (m, 1H), 4.32 (t, J = 11.2 Hz, 1H), 4.22 – 4.12 (m, 2H), 3.53 – 3.48 (m, 2H), 3.10 – 3.03 (m, 4H), 3.01 – 2.96 (m, 2H), 2.93 – 2.87 (m, 2H), 2.85 – 2.79 (m, 1H), 2.72 – 2.65 (m, 2H), 2.56 – 2.52 (m, 3H), 2.46 – 2.38 (m, 6H), 2.24 – 2.17 (m, 1H), 1.92 (t, J = 9.6 Hz, 2H), 1.68 – 1.59 (m, 2H), 1.56 – 1.48 (m, 2H), 1.47 – 1.38 (m, 2H).	F	764.4	764.4
A26	¹ H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.35 (s, 1H), 7.80 (s, 2H), 7.15-7.13 (m, 3H), 6.76-6.66 (m, 2H), 6.64-6.61 (m, 3H), 6.37 (d, J = 8.4 Hz, 2H), 6.30-6.25 (m, 2H), 5.15-5.12 (m, 1H), 4.33-4.30 (m, 1H), 4.18-4.16 (m, 2H), 4.10 (s, 4H), 3.88 (s, 2H), 3.60 (s, 2H), 3.11-2.94 (m, 4H), 2.62-2.55 (m, 1H), 2.17-2.07 (m, 1H), 1.75-1.73 (m, 4H), 1.74-1.48 (m, 2H), 0.96-0.93 (m, 3H).	F	766.4	766.5
A27	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.36 (s, 1H), 7.18 – 7.09 (m, 3H), 7.03 (s, 1H), 6.92 (s, 1H), 6.79 – 6.71 (m, 2H), 6.69 – 6.56 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.23 (m, 2H), 5.05 – 4.99 (m, 1H), 4.35 – 4.14 (m, 6H), 3.92 – 3.76 (m, 3H), 3.53 – 3.50 (m, 1H), 3.16 – 3.11 (m, 1H), 3.00 – 2.85 (m, 7H), 2.77 – 2.70 (m, 1H), 2.60 – 2.54 (m, 1H), 2.42 – 2.30 (m, 3H), 2.09 (t, J = 10.4 Hz, 1H), 1.98 – 1.88 (m, 3H), 1.77 – 1.59 (m, 3H), 1.54 – 1.37 (m, 4H).	F	794.4	794.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A28	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.33 (s, 1H), 7.17 – 7.09 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.55 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.07 – 4.97 (m, 1H), 4.35 – 4.12 (m, 6H), 3.92 – 3.76 (m, 3H), 3.52 – 3.50 (m, 1H), 3.17 – 3.11 (m, 1H), 3.00 – 2.84 (m, 7H), 2.77 – 2.68 (m, 1H), 2.61 – 2.53 (m, 1H), 2.43 – 2.32 (m, 3H), 2.14 – 2.04 (m, 1H), 1.98 – 1.88 (m, 3H), 1.75 – 1.59 (m, 3H), 1.53 – 1.37 (m, 4H).	F	794.4	794.5
A29	¹ H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 9.33 (s, 1H), 7.26 – 7.08 (m, 3H), 6.87 – 6.63 (m, 5H), 6.57 – 6.36 (m, 2H), 6.35 – 6.24 (m, 3H), 6.21 – 6.06 (m, 1H), 5.81 (d, J = 7.8 Hz, 1H), 4.37 – 4.17 (m, 4H), 3.59 – 3.51 (m, 1H), 3.21 (d, J = 8.2 Hz, 2H), 2.87 (s, 4H), 2.75 – 2.67 (m, 1H), 2.58 – 2.52 (m, 7H), 2.32 – 2.03 (m, 3H), 1.93 – 1.55 (m, 4H), 1.31 – 1.13 (m, 2H).	F	722.3	722.3
A30	¹ H NMR (400 MHz, DMSO) δ 10.82 (s, 1H), 9.33 (s, 1H), 7.27 – 7.15 (m, 3H), 6.93 – 6.78 (m, 3H), 6.69 (dd, J = 21.8, 8.6 Hz, 3H), 6.57 (dd, J = 15.2, 2.4 Hz, 1H), 6.51 – 6.39 (m, 3H), 6.38 – 6.28 (m, 2H), 5.85 (d, J = 7.6 Hz, 1H), 4.42 – 4.20 (m, 4H), 3.65 – 3.55 (m, 3H), 2.92 (s, 4H), 2.83 – 2.68 (m, 2H), 2.67 – 2.57 (m, 5H), 2.25 (s, 2H), 2.19 – 2.01 (m, 2H), 1.99 – 1.75 (m, 4H), 1.75 – 1.49 (m, 2H).	D	704.4	704.5
A31	¹ H NMR (400 MHz, DMSO-d6) δ 11.10 (s, 1H), 8.40 (s, 1H), 7.81 (s, 2H), 7.14-7.12 (m, 3H), 6.75 (s, 2H), 6.66-6.59 (m, 3H), 6.38-6.36 (m, 2H), 6.27-6.25 (m, 2H), 5.15-5.10 (m, 1H), 4.32-4.29 (m, 1H), 4.18-4.14 (m, 2H), 4.08 (s, 4H), 3.75-3.50	B	794.4	794.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 2H), 3.01 (s, 4H), 1.52-1.38 (m, 13H), 0.98-0.95 (m, 4H).			
A32	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.13 (s, 1H), 9.31 (s, 1H), 7.92 (s, 2H), 7.15-7.14 (m, 3H), 6.79-6.77 (m, 2H), 6.64-6.62 (d, J = 8.4 Hz, 1H), 6.34-6.25 (m, 4H), 6.18 (d, J = 8.0 Hz, 2H), 5.18-5.13 (m, 1H), 5.03 (s, 2H), 4.77 (s, 2H), 4.33-4.30 (m, 1H), 4.19-4.13 (m, 2H), 3.50-3.46 (m, 1H), 3.36-3.32 (m, 2H), 3.16-2.90 (m, 5H), 2.75-2.69 (m, 4H), 2.08-2.07 (m, 1H), 2.00-1.92 (m, 2H), 1.76-1.73 (m, 2H), 1.23 (s, 2H).	B	812.4	814.5
A33	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.32 (s, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.11 – 6.94 (m, 2H), 6.76 – 6.57 (m, 4H), 6.40 (dd, J = 20.2, 7.6 Hz, 3H), 6.32 – 6.19 (m, 3H), 5.11 – 4.95 (m, 1H), 4.43 – 4.21 (m, 3H), 4.19 – 4.05 (m, 3H), 4.04 – 3.91 (m, 1H), 3.82 (d, J = 10.8 Hz, 1H), 3.56 (s, 5H), 3.50 – 3.42 (m, 1H), 3.18 (s, 1H), 3.03 – 2.82 (m, 3H), 2.80 – 2.69 (m, 1H), 2.64 – 2.53 (m, 3H), 2.47 – 2.31 (m, 2H), 2.27 – 2.03 (m, 3H), 1.95 (s, 1H), 1.85 – 1.49 (m, 5H).	C	784.4	784.4
A34	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 9.29 (s, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.09 – 6.98 (m, 2H), 6.73 – 6.61 (m, 4H), 6.40 (dd, J = 19.8, 8.0 Hz, 3H), 6.32 – 6.23 (m, 3H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.40 – 4.21 (m, 3H), 4.19 – 4.06 (m, 3H), 3.97 (dd, J = 19.2, 9.4 Hz, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.62 – 3.52 (m, 5H), 3.51 – 3.43 (m, 1H), 3.22 – 3.11 (m, 1H), 2.98 – 2.83 (m, 3H), 2.75 (t, J = 11.2 Hz, 1H), 2.60 – 2.52 (m, 3H), 2.46 – 2.30 (m, 2H), 2.22 – 2.05 (m, 3H), 2.01 – 1.85 (m, 2H), 1.79 – 1.60 (m, 4H).	C	784.4	784.4
A35	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H),	B	756.4	756.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H).			
A36	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.45 (s, 2H), 7.24-7.20 (m, 3H), 7.04 (s, 1H), 6.93 – 6.91 (m, 3H), 6.70 (d, J = 8.8 Hz, 1H), 6.32 – 6.30 (m, 2H), 5.05 – 5.00 (m, 1H), 4.97 – 4.66 (m, 2H), 4.30 – 4.11 (m, 6H), 3.92-3.79 (m, 2H), 3.58-3.53 (m, 1H), 3.19-3.14 (m, 1H), 2.37-1.94 (m, 4H), 1.80-1.66 (m, 5H), 0.98-0.95 (m, 2H).	B	756.4	756.5
A37	¹ H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.29 (s, 1H), 7.20 – 7.10 (m, 4H), 7.01 (d, J = 8.4 Hz, 1H), 6.81 – 6.70 (m, 2H), 6.70 – 6.54 (m, 3H), 6.41 – 6.24 (m, 4H), 5.08 – 4.98 (m, 1H), 4.38 – 4.07 (m, 6H), 4.02 – 3.91 (m, 1H), 3.81 (d, J = 10.4 Hz, 1H), 3.54 – 3.49 (m, 1H), 3.17 – 3.11 (m, 1H), 3.03 – 2.83 (m, 7H), 2.72 (t, J = 11.6 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.47 – 2.33 (m, 4H), 2.11 (t, J = 11.4 Hz, 1H), 2.00 – 1.87 (m, 3H), 1.79 – 1.58 (m, 3H), 1.55 – 1.36 (m, 4H).	F	794.4	794.4
A38	¹ H NMR (400 MHz, DMSO-d6) δ 11.11 (s, 1H), 9.31 (s, 1H), 7.80 (s, 2H), 7.14(s, 3H), 6.76-6.74 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 6.35-6.26 (m, 4H), 6.09(d, J = 5.2 Hz, 2H), 5.15-5.11 (m, 1H), 4.32-4.28 (m, 1H), 4.19-4.14 (m, 2H), 4.08 (s, 4H), 3.61 (s, 2H), 3.50-3.44 (m, 7H), 2.91-2.89 (m, 1H), 2.67-2.53 (m, 2H), 2.09-2.07 (m, 1H), 2.04-1.65 (m, 4H), 1.24 (s, 2H).	C	766.4	766.5
A39	¹ H NMR (400 MHz, MeOD-d4) δ 8.51 (s, 1H), 7.75 (s, 2H), 7.12-7.09	C	766.4	766.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 2H), 6.72-6.67 (m, 5H), 6.47 (d, J = 8.4 Hz, 2H), 6.35-6.29 (m, 2H), 5.15-5.10 (m, 1H), 4.42 (t, J = 10.8 Hz, 1H), 4.19-4.15 (m, 5H), 4.00 (s, 2H), 3.76 (s, 2H), 3.53-3.50 (m, 3H), 3.11-2.97 (m, 4H), 2.84-2.74 (m, 2H), 2.17-2.15 (m, 1H), 1.90-1.87 (m, 4H), 1.30 (s, 2H).			
A40	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.11 (s, 1H), 9.27 (s, 1H), 7.88 (s, 2H), 7.15-7.13 (m, 3H), 6.78-6.74 (m, 2H), 6.66-6.60 (s, 3H), 6.39-6.36 (m, 2H), 6.30-6.26 (m, 2H), 5.15-5.11 (m, 1H), 4.33-4.30 (m, 1H), 4.19-4.16 (m, 2H), 4.09 (s, 4H), 3.61 (s, 2H), 3.52-3.45 (m, 4H), 3.03-3.01 (m, 4H), 1.53-1.47 (m, 7H), 1.73-1.38 (m, 6H).	B	794.4	794.5
A41	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.99 (s, 1H), 8.36 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 3.6 Hz, 1H), 7.15-7.13 (m, 3H), 6.77-6.76 (m, 2H), 6.66-6.59 (m, 3H), 6.38-6.36 (m, 2H), 6.31-6.26 (m, 2H), 5.14-5.11 (m, 1H), 5.01-4.98 (m, 2H), 4.71 (d, J = 7.2 Hz, 2H), 4.47-4.43 (m, 1H), 4.34-4.30 (m, 2H), 4.20-4.16 (m, 2H), 3.53-3.48 (m, 3H), 3.25 (s, 3H), 3.01-2.98 (m, 4H), 2.97-2.89 (m, 1H), 2.67-2.59 (m, 1H), 2.47-2.41 (m, 2H), 2.03-1.97 (m, 1H), 1.48-1.46 (m, 8H).	C	780.4	780.6

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A42	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.99 (s, 1H), 9.27 (s, 1H), 7.74 (s, 1H), 7.60 (s, 1H), 7.15-7.13 (m, 3H), 6.78-6.76 (m, 2H), 6.66-6.61 (m, 3H), 6.39-6.37 (m, 2H), 6.31-6.26 (m, 2H), 5.14-5.09 (m, 1H), 5.00-4.97 (m, 2H), 4.76 (d, J = 7.6 Hz, 2H), 4.49-4.44 (m, 1H), 4.36-4.30 (m, 2H), 4.20-4.17 (m, 2H), 3.54-3.50 (m, 1H), 3.02 (s, 4H), 2.98-2.87 (m, 2H), 2.67-2.59 (m, 2H), 2.50-2.41 (m, 1H), 2.02-1.99 (m, 2H), 1.62-1.38 (m, 8H), 1.27-1.24 (m, 3H).	C	780.4	780.6
A43	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.12 (s, 1H), 8.30 (s, 2H), 7.92 (s, 2H), 7.15-7.13 (m, 3H), 6.77-6.75 (m, 2H), 6.66-6.60 (m, 3H), 6.38-6.36 (m, 2H), 6.30-6.25 (m, 2H), 5.67-5.61 (m, 1H), 5.16 (s, 2H), 4.77 (s, 2H), 4.33-4.31 (m, 1H), 4.18-4.16 (m, 2H), 3.52-3.49 (m, 2H), 3.23 (s, 4H), 3.00-2.88 (m, 6H), 2.61-2.56 (m, 3H), 2.17-2.08 (m, 1H), 1.49-1.46 (m, 8H).	C	840.4	840.6
A44	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.11 (s, 1H), 7.83 (s, 2H), 7.15-7.13 (m, 3H), 6.77-6.74 (m, 2H), 6.65-6.63 (m, 1H), 6.36-6.25 (m, 4H), 6.12-6.10 (d, J = 8.4 Hz, 2H), 5.16-5.11 (m, 1H), 4.35-4.29 (m, 1H), 4.19-4.14 (m, 6H), 4.77 (s, 2H), 3.51-3.44 (m, 8H), 2.89-2.86 (m, 1H), 2.64-2.55 (m, 2H), 2.07-2.05 (m, 1H), 1.72-1.67 (m, 4H), 1.24-0.93 (m, 2H).	C	766.4	766.6
A45	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.03 (s, 1H), 10.48 (s, 1H), 9.32 (s, 1H), 7.76 (d, J = 11.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.15-7.10 (m, 3H), 6.77-6.63 (m, 2H), 6.62-6.57 (m, 3H), 6.41-6.38 (m, 2H), 6.30-6.26 (m, 3H), 5.14-5.12 (m, 1H), 4.88 (d, J = 5.6 Hz, 2H), 4.78 (m, 2H),	B	798.4	798.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	4.50-4.45 (m, 3H), 4.36-4.29 (m, 2H), 4.20-4.18 (m, 2H), 4.09-4.04 (m, 3H), 3.93-3.90 (m, 1H), 3.54-3.49 (m, 2H), 3.06-2.92 (m, 4H), 2.18-2.09 (m, 1H), 1.96-1.87 (m, 1H), 2.07-1.80 (m, 5H).			
A46	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.12 (s, 1H), 9.62 (s, 1H), 7.91 (d, J = 3.6 Hz, 2H), 7.15-7.13 (m, 3H), 6.76-6.74 (m, 2H), 6.63(d, J = 8.4 Hz, 1H), 6.35-6.26 (m, 4H), 6.10 (d, J = 8.4 Hz, 2H), 5.17-5.13 (m, 1H), 5.07 (s, 2H), 4.78 (s, 2H), 4.32-4.19 (m, 1H), 4.18-4.14 (m, 2H), 3.47-3.43 (m, 5H), 3.22(s, 3H), 2.91-2.88 (m, 1H), 2.67-2.58 (m, 2H), 2.46-2.43 (m, 3H), 2.11-2.08 (m, 1H), 1.73-1.71 (m, 4H).	B	812.4	812.5
A47	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.12 (s, 1H), 8.36 (s, 1H), 7.91 (d, J = 3.6 Hz, 2H), 7.15-7.13 (m, 3H), 6.76-6.74 (m, 2H), 6.62(d, J = 8.0 Hz, 1H), 6.34-6.26 (m, 4H), 6.10 (d, J = 8.4 Hz, 2H), 5.17-5.12 (m, 1H), 5.07 (s, 2H), 4.78 (s, 2H), 4.33-4.31 (m, 1H), 4.18-4.14 (m, 2H), 3.50-3.41 (m, 4H), 3.22 (s, 4H), 2.87-2.80 (m, 1H), 2.63-2.57 (m, 2H), 2.43-2.40 (m, 4H), 1.72 (s, 4H).	B	766.4	766.5
A48	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.98 (s, 1H), 9.25 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 6.0Hz, 1H), 7.15-7.13 (m, 3H), 6.76-6.74 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 6.35-6.25 (m, 4H), 6.10 (d, J = 8.4 Hz, 2H), 5.09-5.07 (m, 1H), 4.98 (d, J = 10.4 Hz, 2H), 4.71 (d, J = 7.6 Hz, 2H), 4.47-4.43 (m, 1H), 4.34-4.30 (m, 2H), 4.18-4.141 (m, 2H), 3.50-3.42 (m, 7H), 3.21-3.17 (m, 2H), 2.93-2.89 (m, 1H), 2.67-2.57 (m, 2H), 2.43-2.39 (m, 2H), 2.12-1.97 (m, 1H), 1.72 (s, 4H).	C	798.4	798.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A49	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.98 (s, 1H), 8.33 (s, 1H), 7.68 (d, J = 9.6 Hz, 1H), 7.56 (d, J = 6.4 Hz, 1H), 7.15-7.13 (m, 3H), 6.76-6.74 (m, 2H), 6.63 (d, J = 8.4 Hz, 1H), 6.35-6.26 (m, 4H), 6.12-6.10 (m, 2H), 5.11-5.07 (m, 1H), 5.01-4.98 (m, 2H), 4.71 (m, 2H), 4.47-4.43 (m, 1H), 4.34-4.29 (m, 2H), 4.21-4.14 (m, 2H), 3.50-3.47 (m, 4H), 3.20 (s, 3H), 2.90-2.87 (m, 1H), 2.71-2.63 (m, 2H), 2.43-2.38 (m, 4H), 2.02-1.97 (m, 1H), 1.72 (s, 4H).	C	752.4	752.4
A50	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.32 (s, 1H), 7.20 – 7.10 (m, 4H), 7.00 (d, J = 8.6 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.70 – 6.56 (m, 3H), 6.42 – 6.23 (m, 4H), 5.08 – 4.97 (m, 1H), 4.36 – 4.07 (m, 6H), 4.01 – 3.91 (m, 1H), 3.80 (d, J = 9.8 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.16 – 3.12 (m, 1H), 3.01 – 2.95 (m, 2H), 2.94 – 2.83 (m, 5H), 2.75 – 2.69 (m, 1H), 2.62 – 2.52 (m, 2H), 2.44 – 2.34 (m, 3H), 2.18 – 2.05 (m, 1H), 2.01 – 1.86 (m, 3H), 1.80 – 1.57 (m, 3H), 1.56 – 1.34 (m, 4H).	F	794.4	794.5
A51	¹ H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.26 (s, 1H), 7.21 – 7.08 (m, 3H), 6.85 – 6.71 (m, 3H), 6.68 – 6.56 (m, 3H), 6.54 – 6.45 (m, 1H), 6.43 – 6.24 (m, 5H), 5.79 (d, J = 7.6 Hz, 1H), 4.35 – 4.15 (m, 4H), 3.53 – 3.50 (m, 1H), 3.01 – 2.78 (m, 9H), 2.62 – 2.52 (m, 2H), 2.47 – 2.38 (m, 6H), 2.12 – 2.04 (m, 1H), 1.94 – 1.81 (m, 3H), 1.64 – 1.37 (m, 6H).	F	744.4	744.4
A52	¹ H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.26 (s, 1H), 7.17 – 7.11 (m, 3H), 6.84 – 6.73 (m, 3H), 6.68 – 6.57 (m, 3H), 6.55 – 6.45 (m, 1H), 6.43 – 6.34 (m, 3H), 6.32 – 6.24 (m, 2H), 5.79 (d, J = 7.4 Hz, 1H), 4.35 – 4.16 (m, 4H), 3.52 – 3.49 (m, 1H), 3.00 –	F	744.4	744.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	2.96 (m, 2H), 2.91 – 2.86 (m, 2H), 2.85 – 2.78 (m, 4H), 2.75 – 2.69 (m, 1H), 2.62 – 2.53 (m, 2H), 2.47 – 2.43 (m, 4H), 2.38 (d, J = 7.0 Hz, 2H), 2.13 – 2.04 (m, 1H), 1.95 – 1.81 (m, 3H), 1.65 – 1.59 (m, 2H), 1.52 – 1.37 (m, 4H).			
A53	¹ H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.21 – 7.11 (m, 3H), 7.03 (s, 1H), 6.94 (s, 1H), 6.76 (s, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.38 – 6.25 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.10 – 4.95 (m, 1H), 4.32 – 4.12 (m, 6H), 3.98 – 3.78 (m, 3H), 3.39 – 3.34 (m, 4H), 3.18 – 3.04 (m, 2H), 2.96 – 2.85 (m, 3H), 2.80 – 2.71 (m, 1H), 2.61 – 2.54 (m, 1H), 2.41 – 2.29 (m, 1H), 2.21 – 2.05 (m, 3H), 2.02 – 1.92 (m, 1H), 1.87 – 1.79 (m, 2H), 1.68 (d, J = 9.8 Hz, 3H), 1.56 – 1.39 (m, 3H), 0.99 – 0.80 (m, 2H).	C	794.4	794.5
A54	¹ H NMR (400 MHz, DMSO-d6) δ 11.13 (s, 1H), 9.64 (s, 1H), 9.27 (s, 1H), 7.97 (s, 1H), 7.15-7.13 (m, 3H), 6.78-6.75 (m, 2H), 6.71-6.64 (m, 3H), 6.42-6.40 (m, 2H), 6.32-6.30 (m, 2H), 5.16-5.14 (m, 1H), 4.96 (s, 2H), 4.88 (s, 2H), 4.33-4.30 (m, 3H), 4.21-4.18 (m, 2H), 3.38-3.33 (m, 3H), 3.27-3.18 (m, 2H), 3.11-3.04 (m, 4H), 2.87-2.80 (m, 1H), 2.77-2.61 (m, 2H).. 2.15-2.07 (m, 1H), 1.87-1.81 (m, 2H), 1.69-1.66 (m, 4H), 1.47 (s, 2H).	C	840.4	840.6
A55	¹ H NMR (400 MHz, DMSO-d6) δ 11.02 (s, 1H), 9.23 (s, 1H), 7.91 (d, J = 2.0 Hz, 2H), 7.15-7.13 (m, 3H), 6.76-6.72 (m, 2H), 6.64-6.60 (m, 3H), 6.36 (d, J = 8.8 Hz, 2H), 6.27-6.25 (m, 2H), 5.17-5.13 (m, 1H), 4.97 (s, 2H), 4.74 (s, 2H), 4.32 (d, J = 10.8 Hz, 1H), 4.19-4.16 (m, 2H), 3.52-3.49 (m, 1H), 3.82-3.78 (m, 2H). 3.01 (s, 4H), 2.96 (s, 4H), 2.91-2.87 (m,	B	812.4	812.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	1H), 2.66-2.58 (m, 2H), 2.08-2.06 (m, 1H), 1.75-1.72 (m, 4H).			
A56	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.98 (s, 1H), 9.25 (s, 1H), 8.24 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 6.4 Hz, 1H), 7.15-7.13 (m, 3H), 6.77-6.73 (m, 2H), 6.66-6.60 (m, 3H), 6.38-6.36 (m, 2H), 6.31-6.25 (m, 3H), 5.12-5.09 (m, 1H), 4.89-4.85 (m, 2H), 4.70-4.65 (m, 2H), 4.47-4.45 (m, 1H), 4.34-4.29 (m, 2H), 4.19-4.16 (m, 2H), 3.54-3.48 (m, 2H), 3.15-3.01 (m, 4H), 2.97-2.95 (m, 4H), 2.93-2.87 (m, 1H), 2.61-2.54 (m, 2H), 2.43-2.38 (m, 1H), 2.08-1.97 (m, 1H), 1.75-1.72 (m, 4H).	B	798.4	798.4
A57	¹ H NMR (400 MHz, DMSO-d ₆) δ 11.14 (s, 1H), 9.57 (s, 1H), 7.98-7.96 (m, 2H), 7.14-7.11 (m, 3H), 6.77-6.65 (m, 5H), 6.45-6.43 (m, 2H), 6.31-6.26 (m, 2H), 5.24-5.15 (m, 2H), 5.04-4.81 (m, 3H), 4.42-4.30 (m, 2H), 4.21 (s, 2H), 3.26-3.23 (s, 3H), 3.07 (s, 5H), 2.95-2.93 (m, 1H), 2.67-2.56 (m, 2H), 2.13-2.08 (m, 1H), 1.88-1.67 (m, 5H), 1.54-1.41 (m, 6H), 1.21 (s, 1H).	C	808.4	808.5
A58	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.17 – 7.11 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.80 – 6.71 (m, 2H), 6.67 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.08 – 4.98 (m, 1H), 4.34 – 4.13 (m, 6H), 3.94 – 3.76 (m, 2H), 3.54 – 3.47 (m, 1H), 3.17 – 3.09 (m, 1H), 3.02 – 2.95 (m, 2H), 2.93 – 2.84 (m, 5H), 2.78 – 2.67 (m, 1H), 2.61 – 2.53 (m, 2H), 2.43 – 2.34 (m, 3H), 2.10 (t, J = 10.6 Hz, 1H), 1.98 – 1.87 (m, 3H), 1.72 (t, J = 10.6 Hz, 1H), 1.66 – 1.59 (m, 2H), 1.55 – 1.47 (m, 2H), 1.41 (t, J = 9.8 Hz, 2H).	E	794.4	794.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A59	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.28 (s, 1H), 7.18 – 7.09 (m, 3H), 7.03 (s, 1H), 6.92 (s, 1H), 6.80 – 6.71 (m, 2H), 6.69 – 6.55 (m, 3H), 6.42 – 6.23 (m, 4H), 5.09 – 4.95 (m, 1H), 4.35 – 4.13 (m, 6H), 3.92 – 3.76 (m, 2H), 3.53 – 3.50 (m, 1H), 3.15 – 3.13 (m, 1H), 3.00 – 2.86 (m, 7H), 2.79 – 2.70 (m, 1H), 2.61 – 2.55 (m, 2H), 2.44 – 2.37 (m, 3H), 2.10 (t, J = 10.6 Hz, 1H), 2.02 – 1.87 (m, 3H), 1.75 – 1.59 (m, 3H), 1.54 – 1.37 (m, 4H).	F	794.4	794.5
A60	¹ H NMR (400 MHz, DMSO-d ₆) δ 10.98 (s, 1H), 9.26 (s, 1H), 7.68 (d, J = 10.4 Hz, 1H), 7.56 (d, J = 5.2 Hz, 1H), 7.15-7.13 (m, 3H), 6.77-6.75 (m, 2H), 6.66-6.64 (m, 1H), 6.58 (d, J = 8.8 Hz, 2H), 6.35 (d, J = 8.4 Hz, 2H), 6.30-6.25 (m, 2H), 5.16-5.09 (m, 2H), 5.01-4.95 (m, 1H), 4.72 (d, J = 8.4 Hz, 2H), 4.49-4.43 (m, 1H), 4.35-4.30 (m, 2H), 4.20-4.15 (m, 2H), 3.73-3.65 (m, 4H), 3.52-3.49 (m, 2H), 3.26 (s, 3H), 2.98-2.88 (m, 6H), 2.74-2.62 (m, 4H), 2.03-1.99 (m, 1H), 1.45-1.36 (m, 8H).	B	824.4	824.5
A61	DMSO-d ₆ : δ 10.93 (s, 1H), 9.31 (s, 1H), 8.13 (s, 1H), 7.29 – 7.16 (m, 4H), 6.99 (s, 1H), 6.89 – 6.81 (m, 2H), 6.75 – 6.64 (m, 2H), 6.61 – 6.47 (m, 1H), 6.36 – 6.22 (m, 2H), 5.10 – 4.96 (m, 1H), 4.41 – 4.07 (m, 9H), 4.05 – 3.50 (m, 4H), 3.24 – 3.02 (m, 2H), 2.99 – 2.83 (m, 2H), 2.77 – 2.54 (m, 4H), 2.42 – 2.30 (m, 1H), 2.27 – 1.91 (m, 3H), 1.87 – 1.64 (m, 3H), 1.09 (s, 2H).	E	755.4	755.4
A62	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.22 – 7.01 (m, 6H), 6.81 – 6.73 (m, 2H), 6.63 (dd, J = 20.8, 8.4 Hz, 3H), 6.38 (d, J = 8.6 Hz, 2H), 6.33 – 6.24 (m, 2H), 5.04 (dd, J =	B	726.4	726.4

Compound No	¹ HNMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	13.4, 5.2 Hz, 1H), 4.41 – 4.13 (m, 6H), 3.62 – 3.47 (m, 4H), 3.30 – 3.22 (m, 5H), 2.63 – 2.53 (m, 5H), 2.19 (d, <i>J</i> = 6.6 Hz, 2H), 2.07 – 1.87 (m, 2H), 1.84 – 1.49 (m, 4H).			
A63	¹ H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.14 (s, 3H), 7.04 (s, 1H), 6.94 (s, 1H), 6.76 (s, 2H), 6.65 (d, <i>J</i> = 8.2 Hz, 1H), 6.36 – 6.24 (m, 4H), 6.09 (d, <i>J</i> = 8.0 Hz, 2H), 5.09 – 4.98 (m, 1H), 4.38 – 4.20 (m, 4H), 4.21 – 4.13 (m, 3H), 3.93 – 3.76 (m, 4H), 3.41 – 3.35 (m, 4H), 3.19 – 3.14 (m, 1H), 2.93 – 2.85 (m, 3H), 2.80 – 2.69 (m, 2H), 2.62 – 2.56 (m, 1H), 2.41 – 2.34 (m, 1H), 2.13 – 2.06 (m, 2H), 2.06 – 1.93 (m, 2H), 1.86 – 1.78 (m, 2H), 1.70 – 1.64 (m, 2H), 1.47 – 1.39 (m, 2H), 0.97 – 0.85 (m, 2H).	C	794.4	794.5
A64	DMSO-d ₆ : δ 10.93 (s, 1H), 8.24 (s, 1H), 7.26 (s, 1H), 7.22 – 7.12 (m, 4H), 7.01 (d, <i>J</i> = 8.4 Hz, 1H), 6.89 – 6.79 (m, 2H), 6.67 (d, <i>J</i> = 8.2 Hz, 2H), 6.51 (d, <i>J</i> = 8.8 Hz, 1H), 6.35 – 6.22 (m, 2H), 5.03 (dd, 1H), 4.43 – 4.04 (m, 8H), 4.02 – 3.93 (m, 1H), 3.82 (d, <i>J</i> = 10.4 Hz, 1H), 3.57 – 3.52 (m, 1H), 3.20 – 3.16 (m, 1H), 2.99 – 2.81 (m, 3H), 2.79 – 2.55 (m, 4H), 2.44 – 2.30 (m, 1H), 2.25 – 2.03 (m, 3H), 2.00 – 1.88 (m, 1H), 1.82 – 1.64 (m, 4H), 1.12 – 0.96 (m, 2H).	E	755.4	755.4
A65	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.43 (s, 1H), 7.28 – 7.11 (m, 5H), 7.05 – 6.94 (m, 1H), 6.88 – 6.73 (m, 2H), 6.70 – 6.57 (m, 2H), 6.54 – 6.44 (m, 1H), 6.35 – 6.20 (m, 2H), 5.03 (d, <i>J</i> = 13.2 Hz, 1H), 4.35 – 4.05 (m, 6H), 4.01 – 3.90 (m, 1H), 3.83 – 3.74 (m, 1H), 3.57 – 3.45 (m, 2H), 3.27 – 3.22 (m, 3H), 3.19 – 3.06 (m, 2H), 2.94 – 2.81 (m, 3H), 2.76 – 2.62 (m, 2H), 2.43 – 2.34 (m, 3H), 2.18 – 2.04 (m, 1H), 1.99 – 1.87 (m, 3H),	C	795.4	795.5

Compound No	¹ HNMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	1.80 – 1.66 (m, 1H), 1.54 (s, 2H), 1.42 (s, 4H).			
A66	DMSO-d6: δ 10.93 (s, 1H), 8.27 (s, 2H), 7.28 – 7.14 (m, 5H), 7.00 (d, J = 8.4 Hz, 1H), 6.88 – 6.77 (m, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.8 Hz, 1H), 6.36 – 6.23 (m, 2H), 5.07 – 4.96 (m, 1H), 4.39 – 4.16 (m, 5H), 4.09 (d, J = 16.4 Hz, 1H), 4.03 – 3.92 (m, 1H), 3.87 – 3.77 (m, 1H), 3.60 – 3.49 (m, 2H), 3.26 – 3.09 (m, 5H), 2.96 – 2.84 (m, 3H), 2.75 – 2.66 (m, 1H), 2.63 – 2.55 (m, 1H), 2.44 – 2.32 (m, 3H), 2.18 – 2.06 (m, 1H), 2.02 – 1.89 (m, 3H), 1.81 – 1.68 (m, 1H), 1.60 – 1.50 (m, 2H), 1.48 – 1.35 (m, 4H).	E	795.4	795.5
A67	¹ HNMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.38 (s, 1H), 7.51 (d, J=8 Hz 1H), 7.24-7.05 (m, 7H), 6.84 (s, 2H), 6.67-6.65 (m, 2H), 6.52-6.50 (m, 1H), 6.31-6.28 (m, 2H), 5.05-5.02 (m, 1H), 4.34-4.18 (m, 6H), 3.25 (s, 9H), 3.09-2.86 (m, 3H), 2.74-2.34 (m, 3H), 1.95-1.93 (m, 4H), 1.54-1.42 (m, 7H).	B	767.4	767.5
A68	DMSO-d6: δ 10.95 (s, 1H), 9.65 (s, 1H), 9.35 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.33 – 7.12 (m, 6H), 6.97 – 6.85 (m, 2H), 6.80 – 6.44 (m, 4H), 6.38 – 6.24 (m, 2H), 5.06 (dd, 1H), 4.41 – 4.20 (m, 5H), 4.08 – 3.95 (m, 2H), 3.66 – 3.49 (m, 3H), 3.28 – 3.25 (m, 2H), 3.21 – 3.03 (m, 5H), 2.99 – 2.84 (m, 1H), 2.79 – 2.55 (m, 2H), 2.45 – 2.28 (m, 2H), 2.13 – 1.90 (m, 3H), 1.70 – 1.40 (m, 6H).	B	767.4	767.5
A69	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.34 (s, 1H), 7.28 – 7.14 (m, 5H), 7.01 (d, J = 8.2 Hz, 1H), 6.91 – 6.78 (m, 2H), 6.67 (d, J = 8.4 Hz, 2H), 6.51 (d, J = 8.8 Hz, 1H), 6.38 – 6.23 (m, 2H), 5.09 – 4.97 (m, 1H), 4.37 – 4.08 (m, 8H), 4.03 – 3.91 (m,	E	755.4	755.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	1H), 3.82 (d, J = 9.8 Hz, 1H), 3.56 – 3.50 (m, 1H), 3.20 – 3.14 (m, 1H), 2.97 – 2.85 (m, 3H), 2.77 – 2.58 (m, 4H), 2.42 – 2.33 (m, 1H), 2.22 – 2.05 (m, 3H), 2.00 – 1.84 (m, 1H), 1.73 (d, J = 10.0 Hz, 4H), 1.03 (d, J = 11.6 Hz, 2H).			
A70	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.31 (s, 1H), 7.29 – 7.14 (m, 4H), 7.04 (s, 1H), 6.93 (s, 1H), 6.89 – 6.80 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.51 (d, J = 8.8 Hz, 1H), 6.36 – 6.24 (m, 2H), 5.08 – 4.97 (m, 1H), 4.34 – 4.05 (m, 8H), 3.94 – 3.76 (m, 2H), 3.56 – 3.50 (m, 1H), 3.20 – 3.14 (m, 1H), 2.98 – 2.59 (m, 7H), 2.38 – 2.27 (m, 1H), 2.23 – 2.03 (m, 3H), 2.01 – 1.89 (m, 1H), 1.81 – 1.63 (m, 4H), 1.12 – 0.93 (m, 2H).	F	755.4	755.4
A71	¹ H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 8.20 (s, 1H), 7.44 (s, 1H), 7.21 – 7.08 (m, 3H), 7.00 (s, 1H), 6.82 – 6.54 (m, 5H), 6.44 – 6.20 (m, 4H), 5.12 – 5.02 (m, 1H), 4.50 – 4.40 (m, 2H), 4.38 – 4.27 (m, 2H), 4.25 – 4.14 (m, 3H), 3.53 – 3.50 (m, 1H), 3.01 – 2.95 (m, 2H), 2.93 – 2.85 (m, 3H), 2.79 (d, J = 9.4 Hz, 2H), 2.64 – 2.54 (m, 1H), 2.45 – 2.30 (m, 4H), 2.02 – 1.84 (m, 7H), 1.71 – 1.57 (m, 4H), 1.55 – 1.46 (m, 2H), 1.41 (t, J = 9.8 Hz, 2H).	F	793.4	793.5
A72	¹ H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.33 (s, 1H), 7.24 – 7.16 (m, 3H), 7.04 (t, J = 8.6 Hz, 1H), 6.86 – 6.79 (m, 2H), 6.70 (dd, J = 20.4, 8.4 Hz, 3H), 6.55 – 6.41 (m, 4H), 6.39 – 6.30 (m, 2H), 6.07 (d, J = 7.4 Hz, 1H), 4.48 – 4.31 (m, 2H), 4.30 – 4.18 (m, 2H), 3.63 – 3.54 (m, 4H), 3.13 – 2.85 (m, 2H), 2.87 – 2.63 (m, 3H), 2.42 – 1.86 (m, 8H), 1.88 – 1.62 (m, 8H).	B	703.4	703.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A73	1H NMR (400 MHz, DMSO) δ 11.07 (s, 1H), 8.30 (s, 1H), 7.17 – 7.07 (m, 4H), 7.01 – 6.87 (m, 2H), 6.79 – 6.73 (m, 2H), 6.67 – 6.58 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.24 (m, 2H), 5.37 – 5.29 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.17 (t, J = 6.8 Hz, 2H), 3.52 – 3.50 (m, 1H), 3.32 (s, 3H), 3.01 – 2.95 (m, 2H), 2.94 – 2.86 (m, 5H), 2.73 – 2.58 (m, 2H), 2.44 – 2.34 (m, 4H), 2.02 – 1.88 (m, 5H), 1.72 – 1.60 (m, 6H), 1.54 – 1.47 (m, 2H), 1.45 – 1.36 (m, 2H).	E	780.4	780.4
A74	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.24 (s, 1H), 7.24 – 6.93 (m, 5H), 6.71 – 6.20 (m, 8H), 5.03 (s, 1H), 4.63 (s, 1H), 4.36 – 3.99 (m, 6H), 3.90 – 3.42 (m, 6H), 3.13 – 2.85 (m, 7H), 2.78 – 2.61 (m, 2H), 2.17 – 1.67 (m, 6H), 1.61 – 1.08 (m, 5H).	F	784.4	784.4
A75	1H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 8.30 (s, 2H), 7.18 – 7.08 (m, 3H), 6.97 (t, J = 8.8 Hz, 1H), 6.81 – 6.71 (m, 2H), 6.67 – 6.57 (m, 3H), 6.47 – 6.34 (m, 4H), 6.32 – 6.24 (m, 2H), 5.99 (d, J = 7.6 Hz, 1H), 4.38 – 4.24 (m, 2H), 4.21 – 4.13 (m, 2H), 3.53 – 3.50 (m, 1H), 3.01 – 2.94 (m, 2H), 2.88 (d, J = 7.2 Hz, 4H), 2.78 – 2.67 (m, 1H), 2.61 – 2.52 (m, 2H), 2.37 (d, J = 6.4 Hz, 2H), 2.12 – 2.04 (m, 1H), 2.01 – 1.85 (m, 5H), 1.65 – 1.57 (m, 6H), 1.53 – 1.46 (m, 2H), 1.39 (t, J = 9.8 Hz, 2H).	E	743.4	743.4
A76	1H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 9.25 (s, 1H), 7.21 – 7.00 (m, 5H), 6.69 – 6.16 (m, 8H), 5.03 (dd, J = 12.8, 4.8 Hz, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.39 – 4.22 (m, 3H), 4.14 – 3.94 (m, 3H), 3.83 (d, J = 11.2 Hz, 1H), 3.53 (M, 3H), 3.01 (M, 4H), 2.96 – 2.82 (m, 3H), 2.78 – 2.58 (m, 3H), 2.42 – 2.30 (m, 1H), 2.16 (M,	F	784.4	784.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	3H), 1.80 (M, 5H), 1.33 – 1.10 (m, 3H).			
A77	DMSO-d ₆ : δ 10.93 (s, 1H), 9.24 (s, 1H), 7.13 – 7.03 (m, 4H), 6.94 (s, 1H), 6.72 – 6.65 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.49 (d, J = 8.2 Hz, 1H), 6.36 (d, J = 8.0 Hz, 1H), 6.31 – 6.23 (m, 2H), 6.18 (s, 1H), 5.03 (dd, 1H), 4.62 (d, J = 4.8 Hz, 1H), 4.37 – 4.22 (m, 3H), 4.19 – 4.00 (m, 2H), 3.97 – 3.77 (m, 2H), 3.68 – 3.54 (m, 2H), 3.50 – 3.40 (m, 1H), 3.23 – 3.12 (m, 1H), 3.02 (s, 3H), 2.98 – 2.79 (m, 3H), 2.75 – 2.55 (m, 4H), 2.43 – 2.04 (m, 4H), 1.99 – 1.88 (m, 1H), 1.83 – 1.60 (m, 4H), 1.32 – 1.11 (m, 2H).	E	784.4	784.4
A78	¹ H NMR (400 MHz, DMSO) δ 11.19 (s, 1H), 9.34 (s, 1H), 7.96 (d, J = 18.8 Hz, 2H), 7.25 – 7.15 (m, 3H), 6.85 – 6.78 (m, 2H), 6.71 (dd, J = 17.4, 8.4 Hz, 3H), 6.45 (d, J = 8.6 Hz, 2H), 6.38 – 6.31 (m, 2H), 5.22 (dd, J = 12.8, 5.4 Hz, 1H), 5.12 (s, 2H), 4.82 (s, 2H), 4.39 (t, J = 11.2 Hz, 1H), 4.28 – 4.19 (m, 2H), 3.68 (d, J = 11.2 Hz, 2H), 3.61 – 3.54 (m, 1H), 3.11 – 2.88 (m, 3H), 2.67 – 2.58 (m, 3H), 2.42 – 2.00 (m, 5H), 1.92 – 1.74 (m, 4H), 1.76 – 1.47 (m, 5H).	C	794.4	794.5
A79	¹ H NMR (400 MHz, DMSO) δ 11.19 (s, 1H), 9.35 (s, 1H), 7.96 (d, J = 18.4 Hz, 2H), 7.24 – 7.11 (m, 3H), 6.86 – 6.77 (m, 2H), 6.71 (dd, J = 15.6, 8.4 Hz, 3H), 6.45 (d, J = 8.4 Hz, 2H), 6.39 – 6.30 (m, 2H), 5.22 (dd, J = 12.8, 5.2 Hz, 1H), 5.12 (s, 2H), 4.83 (s, 2H), 4.39 (t, J = 11.2 Hz, 1H), 4.30 – 4.19 (m, 2H), 3.68 (d, J = 11.2 Hz, 2H), 3.59 – 3.56 (m, 1H), 3.12 – 2.90 (m, 3H), 2.73 – 2.61 (m, 3H), 2.43 – 2.27 (m, 2H), 2.20 – 2.01 (m, 3H), 1.93 – 1.77 (m, 4H), 1.73 – 1.52 (m, 5H).	C	794.4	794.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A80	¹ H NMR (400 MHz, DMSO) δ 11.05 (s, 1H), 9.35 (s, 1H), 7.75 (d, <i>J</i> = 13.8 Hz, 1H), 7.62 (d, <i>J</i> = 12.6 Hz, 1H), 7.24 – 7.16 (m, 3H), 6.85 – 6.79 (m, 2H), 6.70 (dd, <i>J</i> = 16.4, 8.4 Hz, 3H), 6.44 (d, <i>J</i> = 8.6 Hz, 2H), 6.39 – 6.31 (m, 2H), 5.17 (dd, <i>J</i> = 13.2, 5.2 Hz, 1H), 5.06 (d, <i>J</i> = 6.2 Hz, 2H), 4.77 (d, <i>J</i> = 7.8 Hz, 2H), 4.52 (d, <i>J</i> = 17.2 Hz, 1H), 4.44 – 4.34 (m, 2H), 4.29 – 4.18 (m, 2H), 3.71 – 3.60 (m, 3H), 3.10 – 2.96 (m, 3H), 2.74 – 2.63 (m, 2H), 2.46 – 2.29 (m, 3H), 2.11 – 2.02 (m, 2H), 1.90 – 1.52 (m, 10H).	C	780.4	780.4
A81	¹ H NMR (400 MHz, DMSO) δ 11.05 (s, 1H), 9.34 (s, 1H), 7.75 (d, <i>J</i> = 13.8 Hz, 1H), 7.62 (d, <i>J</i> = 12.8 Hz, 1H), 7.28 – 7.17 (m, 3H), 6.86 – 6.78 (m, 2H), 6.71 (dd, <i>J</i> = 14.8, 8.4 Hz, 3H), 6.45 (d, <i>J</i> = 8.4 Hz, 2H), 6.40 – 6.30 (m, 2H), 5.17 (dd, <i>J</i> = 13.2, 5.2 Hz, 1H), 5.06 (d, <i>J</i> = 4.8 Hz, 2H), 4.77 (d, <i>J</i> = 8.0 Hz, 2H), 4.52 (d, <i>J</i> = 17.4 Hz, 1H), 4.44 – 4.33 (m, 2H), 4.29 – 4.20 (m, 2H), 3.73 – 3.58 (m, 3H), 3.14 – 2.91 (m, 3H), 2.73 – 2.62 (m, 3H), 2.48 – 2.31 (m, 3H), 2.12 – 2.01 (m, 2H), 1.92 – 1.82 (m, 4H), 1.76 – 1.67 (m, 2H), 1.63 – 1.53 (m, 3H).	C	780.4	780.4
A82	DMSO-d ₆ : δ 10.25 (s, 1H), 8.29 (s, 1H), 7.20 – 7.08 (m, 5H), 6.92 (d, <i>J</i> = 8.4 Hz, 2H), 6.81 – 6.73 (m, 2H), 6.63 (dd, 3H), 6.42 – 6.24 (m, 4H), 4.33 (d, <i>J</i> = 11.2 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.69 (t, <i>J</i> = 6.4 Hz, 2H), 3.60 – 3.38 (m, 8H), 3.15 – 2.94 (m, 5H), 2.68 (d, <i>J</i> = 6.0 Hz, 2H), 2.19 (d, <i>J</i> = 6.8 Hz, 2H), 1.83 – 1.57 (m, 3H), 1.24 – 1.08 (m, 2H).	E	672.3	672.3
A83	¹ H NMR (400 MHz, DMSO) δ 10.25 (s, 1H), 8.24 (s, 1H), 7.18 – 7.07 (m, 5H), 6.91 (d, <i>J</i> = 9.0 Hz, 2H), 6.80 – 6.71 (m, 2H), 6.68 – 6.55 (m, 3H), 6.37 (d, <i>J</i> = 8.6 Hz, 2H), 6.32 – 6.24	E	712.4	712.4

Compound No	¹ HNMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 2H), 4.32 (t, J = 11.0 Hz, 1H), 4.22 – 4.12 (m, 2H), 3.69 (t, J = 6.6 Hz, 2H), 3.53 – 3.48 (m, 1H), 3.13 – 3.04 (m, 4H), 3.01 – 2.94 (m, 2H), 2.92 – 2.85 (m, 2H), 2.67 (t, J = 6.6 Hz, 2H), 2.48 – 2.45 (m, 5H), 2.39 (d, J = 6.8 Hz, 2H), 1.92 (t, J = 9.8 Hz, 2H), 1.67 – 1.58 (m, 2H), 1.53 – 1.47 (m, 2H), 1.41 (t, J = 9.8 Hz, 2H).			
A84	DMSO-d ₆ : δ 10.94 (s, 1H), 9.24 (s, 1H), 7.28 – 6.95 (m, 5H), 6.72 – 6.65 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.53 – 6.44 (m, 1H), 6.35 (d, J = 9.0 Hz, 1H), 6.31 – 6.23 (m, 2H), 6.18 (s, 1H), 5.03 (dd, 1H), 4.62 (d, J = 5.4 Hz, 1H), 4.42 – 4.22 (m, 3H), 4.16 – 3.94 (m, 3H), 3.92 – 3.78 (m, 1H), 3.69 – 3.53 (m, 2H), 3.51 – 3.41 (m, 1H), 3.23 – 3.13 (m, 1H), 3.01 (s, 3H), 2.98 – 2.84 (m, 3H), 2.81 – 2.56 (m, 4H), 2.45 – 2.07 (m, 4H), 2.01 – 1.60 (m, 5H), 1.36 – 1.10 (m, 2H).	E	784.4	784.4
A85	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.37 – 8.14 (m, 2H), 7.85 (d, J = 8.8 Hz, 1H), 7.48 – 7.32 (m, 1H), 7.22 – 7.05 (m, 3H), 6.82 – 6.54 (m, 5H), 6.44 – 6.19 (m, 4H), 4.79 – 4.68 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.23 – 4.12 (m, 2H), 3.54 – 3.47 (m, 2H), 3.31 (s, 4H), 3.03 – 2.85 (m, 4H), 2.84 – 2.75 (m, 1H), 2.48 – 2.37 (m, 7H), 2.24 – 2.12 (m, 1H), 2.05 – 1.84 (m, 3H), 1.63 (s, 2H), 1.54 – 1.38 (m, 4H).	F	755.4	755.4
A86	DMSO-d ₆ : δ 10.96 (s, 1H), 8.30 (s, 1H), 7.46 (s, 1H), 7.21 – 7.10 (m, 3H), 7.00 (s, 1H), 6.83 – 6.73 (m, 2H), 6.63 (dd, 3H), 6.38 (d, J = 8.4 Hz, 2H), 6.33 – 6.22 (m, 2H), 5.07 (dd, 1H), 4.46 (s, 2H), 4.37 – 4.29 (m, 2H), 4.24 – 4.10 (m, 3H), 3.59 – 3.50 (m, 3H), 2.98 – 2.76 (m, 3H), 2.69 – 2.55 (m, 2H), 2.39 – 2.32 (m,	E	753.4	753.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	2H), 2.22 – 2.14 (m, 2H), 2.00 – 1.86 (m, 5H), 1.79 – 1.63 (m, 5H), 1.22 – 1.09 (m, 2H).			
A87	¹ H NMR (400 MHz, DMSO) δ 10.25 (s, 1H), 9.28 (s, 1H), 7.14 (s, 5H), 6.94 (s, 2H), 6.82 – 6.53 (m, 5H), 6.39 (s, 2H), 6.34 – 6.21 (m, 2H), 4.25 (d, J = 54.9 Hz, 3H), 3.93 (dd, J = 35.0, 15.7 Hz, 4H), 3.68 (s, 4H), 3.51 (d, J = 14.2 Hz, 1H), 3.14 (d, J = 9.8 Hz, 2H), 2.98 (d, J = 13.9 Hz, 4H), 2.66 (d, J = 14.6 Hz, 4H), 1.79 (dd, J = 43.0, 8.6 Hz, 6H), 1.39 – 1.13 (m, 3H).	C	812.4	812.5
A88	DMSO-d ₆ : δ 10.84 (s, 1H), 9.27 (s, 1H), 8.73 (d, J = 8.2 Hz, 1H), 8.32 (s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.50 – 7.34 (m, 1H), 7.20 – 7.05 (m, 3H), 6.85 – 6.71 (m, 2H), 6.69 – 6.56 (m, 3H), 6.38 (d, J = 8.4 Hz, 2H), 6.32 – 6.22 (m, 2H), 4.82 – 4.69 (m, 1H), 4.33 (t, J = 11.0 Hz, 1H), 4.24 – 4.12 (m, 2H), 3.61 – 3.48 (m, 3H), 3.32 – 3.05 (m, 8H), 2.86 – 2.73 (m, 1H), 2.69 – 2.54 (m, 3H), 2.35 – 2.11 (m, 3H), 2.05 – 1.96 (m, 1H), 1.84 – 1.60 (m, 3H), 1.26 – 1.10 (m, 2H).	E	715.4	715.4
A89	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.23 (s, 1H), 7.24 – 7.08 (m, 4H), 7.00 (d, J = 8.4 Hz, 1H), 6.80 – 6.72 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 8.6 Hz, 2H), 6.37 (d, J = 8.6 Hz, 2H), 6.33 – 6.23 (m, 2H), 5.09 – 4.90 (m, 1H), 4.36 – 4.08 (m, 6H), 4.01 – 3.90 (m, 1H), 3.80 (d, J = 11.4 Hz, 1H), 3.52 – 3.47 (m, 1H), 3.18 – 3.12 (m, 1H), 3.01 – 2.94 (m, 2H), 2.92 – 2.82 (m, 5H), 2.77 – 2.67 (m, 1H), 2.61 – 2.53 (m, 2H), 2.43 – 2.37 (m, 3H), 2.10 (t, J = 10.2 Hz, 1H), 2.00 – 1.88 (m, 3H), 1.73 (t, J = 10.6 Hz, 1H), 1.67 – 1.58 (m, 2H), 1.56 – 1.36 (m, 4H).	A	794.4	794.5

Compound No	¹ HNMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A90	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.25 (s, 1H), 7.21 – 7.08 (m, 4H), 7.00 (d, J = 8.2 Hz, 1H), 6.75 (s, 2H), 6.69 – 6.54 (m, 3H), 6.43 – 6.21 (m, 4H), 5.08 – 4.98 (m, 1H), 4.36 – 4.09 (m, 6H), 4.02 – 3.93 (m, 1H), 3.81 (d, J = 11.4 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.16 – 3.11 (m, 1H), 2.98 (s, 2H), 2.93 – 2.83 (m, 5H), 2.70 (t, J=11.6 Hz, 1H), 2.62 – 2.54 (m, 2H), 2.43 – 2.34 (m, 3H), 2.12 (t, J = 10.4 Hz, 1H), 2.00 – 1.85 (m, 3H), 1.74 (t, J=10.4 Hz, 1H), 1.63 (s, 2H), 1.50 (s, 2H), 1.41 (t, J=8.6 Hz, 2H).	A	794.4	794.5
A91	DMSO-d6: δ 10.82 (s, 1H), 7.18 – 7.08 (m, 4H), 6.83 – 6.46 (m, 7H), 6.39 – 6.17 (m, 5H), 4.47 – 4.19 (m, 7H), 3.67 – 3.46 (m, 8H), 3.08 (s, 5H), 2.86 – 2.56 (m, 2H), 2.20 – 1.75 (m, 8H).	B	750.3	750.3
A92	1H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 8.30 (s, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.28 – 7.13 (m, 4H), 7.04 (d, J = 7.8 Hz, 2H), 6.90 – 6.78 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 8.8 Hz, 1H), 6.36 – 6.25 (m, 2H), 5.13 – 4.96 (m, 1H), 4.33 – 4.14 (m, 5H), 3.36 – 3.21 (m, 10H), 2.96 – 2.85 (m, 1H), 2.65 – 2.56 (m, 1H), 2.50 – 2.34 (m, 8H), 2.02 – 1.87 (m, 3H), 1.59 – 1.48 (m, 2H), 1.46 – 1.36 (m, 4H).	C	767.4	767.4
A93	1H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 8.27 (s, 1H), 7.63 – 7.46 (m, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.19 – 7.07 (m, 3H), 6.81 – 6.69 (m, 2H), 6.69 – 6.54 (m, 3H), 6.41 – 6.22 (m, 4H), 4.77 – 4.64 (m, 1H), 4.47 – 4.38 (m, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.22 – 4.13 (m, 2H), 4.09 – 3.99 (m, 1H), 3.78 – 3.73 (m, 1H), 3.50 – 3.48 (m, 2H), 3.22 – 3.13 (m, 2H), 3.01 – 2.95 (m, 2H), 2.93 – 2.86 (m, 4H), 2.79 – 2.69 (m,	B	783.4	783.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	2H), 2.43 – 2.36 (m, 2H), 2.19 – 2.04 (m, 2H), 2.01 – 1.88 (m, 3H), 1.71 (t, J = 10.8 Hz, 1H), 1.65 – 1.48 (m, 4H), 1.46 – 1.35 (m, 2H).			
A94	¹ H NMR (400 MHz, DMSO) δ 10.73 (s, 1H), 8.18 (s, 1H), 7.23 – 7.04 (m, 3H), 6.81 – 6.70 (m, 2H), 6.68 – 6.54 (m, 4H), 6.36 (d, J = 8.8 Hz, 2H), 6.31 – 6.24 (m, 2H), 6.21 – 6.09 (m, 2H), 5.32 – 5.20 (m, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.20 – 4.08 (m, 4H), 3.81 (d, J = 9.6 Hz, 1H), 3.55 – 3.46 (m, 3H), 3.01 – 2.95 (m, 2H), 2.92 – 2.65 (m, 7H), 2.60 – 2.52 (m, 1H), 2.43 – 2.33 (m, 2H), 2.14 – 2.02 (m, 2H), 1.95 – 1.87 (m, 2H), 1.86 – 1.74 (m, 1H), 1.68 (t, J = 10.8 Hz, 1H), 1.64 – 1.46 (m, 4H), 1.44 – 1.35 (m, 2H).	B	754.4	754.4
A95	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.27 (s, 1H), 7.19 – 7.08 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.69 – 6.53 (m, 5H), 6.40 – 6.21 (m, 4H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.40 – 4.05 (m, 7H), 3.91 – 3.84 (m, 1H), 3.78 (d, J = 11.6 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.13 (d, J = 9.6 Hz, 1H), 3.01 – 2.94 (m, 2H), 2.92 – 2.80 (m, 5H), 2.78 – 2.67 (m, 1H), 2.63 – 2.54 (m, 1H), 2.43 – 2.29 (m, 3H), 2.09 (d, J = 10.4 Hz, 1H), 2.00 – 1.83 (m, 3H), 1.71 (d, J = 10.8 Hz, 1H), 1.65 – 1.47 (m, 4H), 1.45 – 1.33 (m, 2H).	B	794.4	794.5
A96	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.19 (s, 1H), 7.21 – 7.08 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.80 – 6.68 (m, 2H), 6.67 – 6.49 (m, 3H), 6.44 – 6.21 (m, 4H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.42 – 4.22 (m, 3H), 4.20 – 4.06 (m, 3H), 3.98 – 3.72 (m, 3H), 3.53 – 3.46 (m, 2H), 3.17 – 3.10 (m, 1H), 3.03 – 2.95 (m, 2H), 2.93 – 2.80 (m, 5H), 2.77 – 2.65 (m, 1H), 2.62 – 2.54 (m, 1H), 2.44 – 2.30	B	794.4	794.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 3H), 2.10 (d, J = 10.4 Hz, 1H), 2.00 – 1.87 (m, 3H), 1.72 (t, J = 10.8 Hz, 1H), 1.65 – 1.46 (m, 4H), 1.44 – 1.35 (m, 2H).			
A97	¹ H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 8.61 (d, J = 8.4 Hz, 1H), 8.19 (s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.18 – 7.10 (m, 3H), 6.82 – 6.70 (m, 2H), 6.68 – 6.56 (m, 3H), 6.41 – 6.21 (m, 4H), 4.79 – 4.66 (m, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.21 – 4.12 (m, 2H), 4.00 (s, 3H), 3.58 – 3.41 (m, 3H), 3.12 – 2.85 (m, 9H), 2.83 – 2.73 (m, 1H), 2.53 (s, 3H), 2.42 – 2.36 (m, 2H), 2.27 – 2.13 (m, 1H), 2.04 – 1.86 (m, 3H), 1.66 – 1.47 (m, 4H), 1.46 – 1.37 (m, 2H).	C	785.4	785.4
A98	¹ H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 9.35 (s, 1H), 8.15 (s, 1H), 7.52 (d, J = 8.8 Hz, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.21 – 7.10 (m, 3H), 7.05 (d, J = 7.8 Hz, 2H), 6.91 – 6.79 (m, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.52 (d, J = 8.8 Hz, 1H), 6.41 – 6.25 (m, 2H), 5.10 – 4.99 (m, 1H), 4.40 – 4.16 (m, 6H), 3.58 – 3.54 (m, 2H), 3.39 – 3.32 (m, 3H), 3.31 – 3.20 (m, 7H), 2.93 – 2.84 (m, 1H), 2.64 – 2.54 (m, 2H), 2.47 – 2.29 (m, 3H), 2.01 – 1.89 (m, 3H), 1.61 – 1.50 (m, 2H), 1.49 – 1.33 (m, 4H).	C	767.4	767.4
A99	¹ H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 7.45 (s, 1H), 7.24 – 7.07 (m, 3H), 7.00 (s, 1H), 6.82 – 6.72 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.39 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.49 – 4.40 (m, 2H), 4.37 – 4.27 (m, 2H), 4.25 – 4.11 (m, 3H), 3.54 – 3.46 (m, 2H), 3.42 – 3.39 (m, 2H), 3.37 – 3.33 (m, 2H), 2.95 – 2.78 (m, 3H), 2.62 – 2.55 (m, 1H), 2.41 – 2.30 (m, 1H), 2.12 (d, J = 6.8 Hz, 2H), 2.02 – 1.79 (m, 7H), 1.73 – 1.60 (m, 4H),	C	793.4	793.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	1.55 – 1.37 (m, 3H), 0.98 – 0.83 (m, 2H).			
A100	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.38 – 8.22 (m, 1H), 7.92 – 7.76 (m, 1H), 7.47 – 7.28 (m, 1H), 7.21 – 7.10 (m, 3H), 6.85 – 6.58 (m, 4H), 6.35 – 6.23 (m, 3H), 6.15 (d, J = 13.2 Hz, 1H), 4.81 – 4.69 (m, 1H), 4.40 – 4.08 (m, 3H), 3.61 – 3.48 (m, 2H), 3.41 – 3.14 (m, 9H), 2.97 – 2.64 (m, 2H), 2.60 – 2.53 (m, 2H), 2.38 – 1.90 (m, 5H), 1.81 – 1.59 (m, 3H), 1.34 – 1.08 (m, 2H).	C	733.3	733.3
A101	¹ H NMR (400 MHz, DMSO) δ 10.87 (s, 1H), 9.02 (d, J = 8.4 Hz, 1H), 8.58 (s, 1H), 8.22 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.96 – 7.84 (m, 1H), 7.23 – 7.12 (m, 3H), 6.81 – 6.64 (m, 4H), 6.38 – 6.24 (m, 3H), 6.23 – 6.10 (m, 1H), 4.86 – 4.72 (m, 1H), 4.41 – 4.17 (m, 4H), 3.58 – 3.53 (m, 2H), 3.22 (d, J = 8.4 Hz, 2H), 3.02 – 2.94 (m, 2H), 2.86 – 2.75 (m, 1H), 2.73 – 2.62 (m, 1H), 2.22 (d, J = 7.2 Hz, 3H), 2.07 – 1.96 (m, 3H), 1.81 – 1.69 (m, 6H), 1.66 – 1.58 (m, 1H), 1.30 – 1.17 (m, 2H).	C	732.2	732.3
A102	¹ H NMR (400 MHz, DMSO) δ 10.88 (s, 1H), 9.47 – 9.11 (m, 1H), 8.61 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.21 – 7.13 (m, 3H), 6.87 – 6.61 (m, 4H), 6.35 – 6.23 (m, 3H), 6.19 – 6.08 (m, 1H), 4.80 – 4.65 (m, 1H), 4.37 – 4.15 (m, 3H), 4.01 (s, 3H), 3.62 – 3.51 (m, 1H), 3.45 – 3.28 (m, 4H), 3.25 – 3.14 (m, 3H), 3.10 (s, 4H), 2.89 – 2.71 (m, 1H), 2.61 – 2.54 (m, 2H), 2.26 – 2.14 (m, 3H), 2.07 – 1.95 (m, 1H), 1.76 (d, J = 11.8 Hz, 2H), 1.67 – 1.57 (m, 1H), 1.31 – 1.10 (m, 2H).	C	763.4	763.4
A103	¹ H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.62	C	761.3	761.3

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	– 7.51 (m, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.23 – 7.06 (m, 3H), 6.83 – 6.64 (m, 4H), 6.38 – 6.25 (m, 3H), 6.15 (d, J = 13.2 Hz, 1H), 4.76 – 4.66 (m, 1H), 4.48 – 4.40 (m, 1H), 4.36 – 4.17 (m, 3H), 4.12 – 4.03 (m, 1H), 3.78 (d, J = 11.2 Hz, 1H), 3.58 – 3.51 (m, 2H), 3.31 – 3.07 (m, 5H), 2.99 – 2.92 (m, 2H), 2.82 – 2.70 (m, 2H), 2.39 – 1.85 (m, 6H), 1.84 – 1.58 (m, 4H), 1.33 – 1.14 (m, 2H).			
A104	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.50 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.17 (s, 3H), 6.86 – 6.63 (m, 4H), 6.32 (d, J = 5.8 Hz, 3H), 6.23 – 6.08 (m, 1H), 4.79 – 4.63 (m, 1H), 4.51 – 4.41 (m, 1H), 4.40 – 4.18 (m, 3H), 4.14 – 4.02 (m, 1H), 3.85 – 3.73 (m, 1H), 3.60 – 3.50 (m, 4H), 3.27 – 3.14 (m, 4H), 2.95 (d, J = 9.8 Hz, 2H), 2.88 – 2.73 (m, 2H), 2.29 – 2.08 (m, 4H), 2.03 – 1.93 (m, 1H), 1.87 – 1.61 (m, 4H), 1.30 – 1.17 (m, 2H).	C	761.3	761.3
A105	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.36 (s, 1H), 7.27 – 6.96 (m, 5H), 6.78 – 6.53 (m, 3H), 6.41 – 6.19 (m, 4H), 5.07 – 4.97 (m, 1H), 4.66 (d, J = 4.4 Hz, 1H), 4.42 – 4.20 (m, 3H), 4.16 – 4.05 (m, 2H), 3.97 (d, J = 9.6 Hz, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.53 – 3.44 (m, 2H), 3.22 – 3.12 (m, 2H), 3.06 (s, 3H), 3.00 – 2.85 (m, 3H), 2.80 – 2.72 (m, 1H), 2.70 – 2.53 (m, 3H), 2.43 – 2.33 (m, 1H), 2.28 – 2.17 (m, 2H), 2.15 – 2.06 (m, 1H), 2.01 – 1.89 (m, 1H), 1.87 – 1.58 (m, 4H), 1.37 – 1.16 (m, 2H).	C	802.4	802.5
A106	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.32 (s, 1H), 7.22 – 6.96 (m, 5H), 6.77 – 6.55 (m, 3H), 6.36 – 6.20 (m, 4H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.66 (d, J = 5.6 Hz, 1H), 4.38 – 4.20 (m, 3H), 4.14 – 4.04 (m, 2H),	C	802.4	802.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	4.03 – 3.91 (m, 1H), 3.83 (d, J = 11.2 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.29 – 3.22 (m, 2H), 3.21 – 3.14 (m, 1H), 3.06 (s, 3H), 2.97 – 2.85 (m, 3H), 2.80 – 2.68 (m, 1H), 2.66 – 2.52 (m, 3H), 2.43 – 2.32 (m, 1H), 2.27 – 2.18 (m, 2H), 2.14 – 2.04 (m, 1H), 2.01 – 1.90 (m, 1H), 1.85 – 1.59 (m, 4H), 1.36 – 1.17 (m, 2H).			
A107	¹ H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.33 (s, 2H), 7.25 – 7.06 (m, 5H), 6.91 (d, J = 9.2 Hz, 2H), 6.80 – 6.73 (m, 2H), 6.63 (dd, J = 22.6, 8.4 Hz, 3H), 6.39 (d, J = 8.6 Hz, 2H), 6.33 – 6.23 (m, 2H), 4.33 (t, J = 11.2 Hz, 1H), 4.24 – 4.15 (m, 2H), 3.69 (t, J = 6.6 Hz, 3H), 3.16 – 3.08 (m, 3H), 3.07 – 2.94 (m, 7H), 2.68 (t, J = 6.6 Hz, 2H), 2.45 – 2.40 (m, 4H), 1.94 (t, J = 9.8 Hz, 2H), 1.72 – 1.64 (m, 2H), 1.60 – 1.52 (m, 2H), 1.50 – 1.39 (m, 2H).	B	712.4	712.4
A108	DMSO-d ₆ : δ 10.88 (s, 1H), 9.26 (s, 1H), 8.62 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 7.0 Hz, 1H), 7.19 – 7.10 (m, 3H), 6.81 – 6.72 (m, 2H), 6.64 (d, J = 8.2 Hz, 1H), 6.41 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 4.79 – 4.67 (m, 1H), 4.32 (d, J = 11.0 Hz, 1H), 4.22 – 4.12 (m, 2H), 4.01 (s, 3H), 3.54 – 3.35 (m, 6H), 3.10 (s, 4H), 2.89 – 2.75 (m, 1H), 2.66 – 2.54 (m, 2H), 2.44 – 1.94 (m, 6H), 1.84 (d, J = 12.0 Hz, 2H), 1.69 (d, J = 11.4 Hz, 2H), 1.51 – 1.38 (m, 2H), 1.04 – 0.84 (m, 2H).	E	785.4	785.5
A109	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 9.32 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.32 (d, J = 2.8 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 8.8, 2.8 Hz, 1H), 7.20 – 6.98 (m, 3H), 6.79 – 6.55 (m, 3H), 6.35 – 6.16 (m, 4H), 4.79 – 4.62 (m, 2H), 4.32 (d, J = 11.2 Hz, 1H), 4.13 – 4.04 (m, 1H),	B	763.4	763.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	3.52 – 3.44 (m, 1H), 3.36 – 3.26 (m, 1H), 3.06 (s, 3H), 2.84 – 2.73 (m, 1H), 2.69 – 2.54 (m, 2H), 2.27 – 2.12 (m, 3H), 2.05 – 1.93 (m, 1H), 1.85 – 1.57 (m, 3H), 1.35 – 1.13 (m, 2H).			
A110	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.4 Hz, 1H), 8.32 (s, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.12 (s, 3H), 6.80 – 6.53 (m, 3H), 6.41 – 6.18 (m, 4H), 4.81 – 4.62 (m, 2H), 4.32 (d, J = 11.2 Hz, 1H), 4.09 (d, J = 8.4 Hz, 1H), 3.56 – 3.44 (m, 2H), 3.40 – 3.21 (m, 1H), 3.06 (s, 3H), 2.84 – 2.72 (m, 1H), 2.68 – 2.57 (m, 2H), 2.28 – 2.11 (m, 3H), 2.05 – 1.96 (m, 1H), 1.87 – 1.59 (m, 3H), 1.32 – 1.16 (m, 2H).	B	763.4	763.4
A111	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 9.27 (s, 1H), 8.68 (d, J = 8.1 Hz, 1H), 8.29 (d, J = 2.7 Hz, 1H), 8.16 (s, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.41 – 7.35 (m, 1H), 7.17 – 7.10 (m, 3H), 6.76 (d, J = 3.8 Hz, 2H), 6.63 (dd, J = 17.4, 8.5 Hz, 3H), 6.37 (d, J = 8.5 Hz, 2H), 6.32 – 6.24 (m, 2H), 4.78 – 4.67 (m, 1H), 4.32 (t, J = 11.3 Hz, 1H), 4.18 (t, J = 5.9 Hz, 2H), 3.91 (d, J = 12.4 Hz, 2H), 3.51 (dd, J = 14.6, 5.0 Hz, 1H), 3.11 (s, 4H), 2.96 (s, 4H), 2.80 (dd, J = 24.4, 12.5 Hz, 3H), 2.67 (s, 1H), 2.33 (s, 2H), 2.24 – 2.10 (m, 1H), 2.05 – 1.94 (m, 1H), 1.75 (d, J = 14.9 Hz, 6H), 1.55 (dd, J = 18.2, 9.2 Hz, 1H), 1.19 (dd, J = 23.8, 12.8 Hz, 2H).	B	755.4	755.5
A112	¹ H NMR (400 MHz, DMSO) δ 10.24 (s, 1H), 8.27 (s, 1H), 7.22 – 7.03 (m, 5H), 6.91 (d, J = 8.8 Hz, 2H), 6.83 – 6.71 (m, 2H), 6.62 (dd, J = 22.6, 8.4 Hz, 3H), 6.38 (d, J = 8.4 Hz, 2H), 6.35 – 6.18 (m, 2H), 4.31 (t, J = 11.2 Hz, 1H), 4.24 – 4.13 (m, 2H), 3.68 (t, J = 6.6 Hz, 2H), 3.56 – 3.46 (m, 2H), 3.14 – 3.06 (m, 2H), 3.04 – 2.94 (m,	C	712.4	712.4

Compound No	¹ HNMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	6H), 2.67 (t, <i>J</i> = 6.6 Hz, 2H), 2.44 – 2.36 (m, 6H), 1.97 – 1.89 (m, 2H), 1.71 – 1.62 (m, 2H), 1.59 – 1.51 (m, 2H), 1.47 – 1.39 (m, 2H).			
A113	DMSO-d ₆ :δ 10.97 (s, 1H), 9.49 – 9.02 (m, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 1H), 7.26 (d, <i>J</i> = 7.6 Hz, 1H), 7.21 – 7.07 (m, 3H), 6.79 – 6.71 (m, 2H), 6.63 (dd, 3H), 6.37 (d, <i>J</i> = 8.6 Hz, 2H), 6.31 – 6.24 (m, 2H), 5.08 (dd, 1H), 4.51 (s, 2H), 4.42 – 4.28 (m, 2H), 4.25 – 4.11 (m, 3H), 3.52 – 3.48 (m, 1H), 3.02 – 2.85 (m, 5H), 2.83 – 2.76 (m, 2H), 2.70 – 2.53 (m, 2H), 2.43 – 2.31 (m, 3H), 2.02 – 1.83 (m, 7H), 1.70 – 1.59 (m, 4H), 1.54 – 1.47 (m, 2H), 1.45 – 1.35 (m, 2H).	E	792.4	794.5
A114	DMSO-d ₆ :δ 10.97 (s, 1H), 9.27 (s, 1H), 7.39 (d, <i>J</i> = 7.6 Hz, 1H), 7.26 (d, <i>J</i> = 7.6 Hz, 1H), 7.19 – 7.09 (m, 3H), 6.80 – 6.72 (m, 2H), 6.65 (d, <i>J</i> = 8.2 Hz, 1H), 6.42 – 6.23 (m, 4H), 6.09 (d, <i>J</i> = 8.4 Hz, 2H), 5.08 (dd, 1H), 4.51 (s, 2H), 4.41 – 4.28 (m, 2H), 4.25 – 4.11 (m, 3H), 3.54 – 3.37 (m, 5H), 2.97 – 2.77 (m, 3H), 2.68 – 2.55 (m, 1H), 2.43 – 2.30 (m, 1H), 2.12 (d, <i>J</i> = 6.8 Hz, 2H), 2.01 – 1.81 (m, 7H), 1.75 – 1.62 (m, 4H), 1.55 – 1.38 (m, 3H), 0.99 – 0.84 (m, 2H).	E	792.4	794.5
A115	DMSO-d ₆ :δ 10.93 (s, 1H), 9.26 (s, 1H), 7.23 – 7.10 (m, 4H), 7.07 – 6.97 (m, 1H), 6.81 – 6.71 (m, 2H), 6.64 (d, <i>J</i> = 8.2 Hz, 1H), 6.40 – 6.22 (m, 4H), 6.09 (d, <i>J</i> = 8.2 Hz, 2H), 5.08 – 4.98 (m, 1H), 4.45 – 4.07 (m, 6H), 4.02 – 3.75 (m, 2H), 3.67 – 3.36 (m, 5H), 3.24 – 3.13 (m, 1H), 2.99 – 2.83 (m, 3H), 2.79 – 2.70 (m, 1H), 2.67 – 2.56 (m, 1H), 2.49 – 2.30 (m, 2H), 2.19 – 2.03 (m, 2H), 2.00 – 1.92 (m, 1H), 1.89 – 1.80 (m, 2H), 1.77 – 1.63 (m, 3H), 1.58 – 1.37 (m, 3H), 1.04 – 0.81 (m, 2H).	E	794.4	794.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A116	¹ H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 8.85 (d, J = 8.2 Hz, 1H), 8.27 (s, 1H), 8.04 (s, 1H), 7.55 (s, 1H), 7.19 – 7.07 (m, 3H), 6.81 – 6.71 (m, 2H), 6.69 – 6.56 (m, 3H), 6.42 – 6.22 (m, 4H), 4.80 – 4.69 (m, 1H), 4.32 (t, J = 11.0 Hz, 1H), 4.22 – 4.13 (m, 2H), 3.93 (s, 3H), 3.53 – 3.47 (m, 2H), 3.10 (s, 4H), 3.01 – 2.86 (m, 4H), 2.85 – 2.74 (m, 1H), 2.59 – 2.52 (m, 2H), 2.48 – 2.37 (m, 5H), 2.24 – 2.13 (m, 1H), 2.05 – 1.86 (m, 3H), 1.62 – 1.36 (m, 6H).	E	784.4	784.4
A117	¹ H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.26 (s, 1H), 8.86 (d, J = 8.2 Hz, 1H), 8.05 (s, 1H), 7.57 (s, 1H), 7.14 (s, 3H), 6.76 (s, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.38 – 6.20 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 4.75 (t, J = 12.8 Hz, 1H), 4.31 (d, J = 11.2 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.93 (s, 3H), 3.49 (d, J = 11.2 Hz, 2H), 3.13 (s, 6H), 2.93 – 2.62 (m, 2H), 2.45 – 2.13 (m, 4H), 2.11 – 1.98 (m, 2H), 1.97 – 1.60 (m, 5H), 1.59 – 1.24 (m, 4H), 1.24 (s, 1H), 0.98 – 0.79 (m, 2H).	E	784.4	784.4
A118	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.27 – 7.10 (m, 3H), 7.03 (s, 1H), 6.93 (s, 1H), 6.82 – 6.71 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.38 – 6.21 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.37 – 4.09 (m, 6H), 3.92 – 3.77 (m, 2H), 3.51 – 3.47 (m, 1H), 3.41 – 3.32 (m, 5H), 3.18 – 3.12 (m, 1H), 2.96 – 2.84 (m, 3H), 2.80 – 2.71 (m, 1H), 2.62 – 2.54 (m, 1H), 2.39 – 2.30 (m, 1H), 2.17 – 2.03 (m, 3H), 1.98 – 1.91 (m, 1H), 1.87 – 1.76 (m, 2H), 1.75 – 1.62 (m, 3H), 1.54 – 1.38 (m, 3H), 1.00 – 0.80 (m, 2H).	C	794.4	794.5
A119	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.17 – 7.08 (m, 3H), 7.03 (s,	C	794.4	794.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	1H), 6.91 (d, J = 12.4 Hz, 1H), 6.80 – 6.70 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.40 – 6.20 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.02 (dd, J = 13.2, 5.2 Hz, 1H), 4.38 – 4.11 (m, 6H), 3.92 – 3.76 (m, 2H), 3.52 – 3.47 (m, 1H), 3.41 – 3.33 (m, 5H), 3.19 – 3.13 (m, 1H), 2.96 – 2.83 (m, 3H), 2.80 – 2.71 (m, 1H), 2.61 – 2.53 (m, 1H), 2.37 – 2.27 (m, 1H), 2.18 – 2.02 (m, 3H), 1.99 – 1.89 (m, 1H), 1.87 – 1.78 (m, 2H), 1.73 – 1.61 (m, 3H), 1.54 – 1.36 (m, 3H), 0.98 – 0.82 (m, 2H).			
A120	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 7.19 – 7.05 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.79 – 6.70 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.41 – 6.21 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.38 – 4.23 (m, 3H), 4.21 – 4.07 (m, 3H), 3.93 – 3.78 (m, 2H), 3.51 – 3.47 (m, 1H), 3.43 – 3.30 (m, 5H), 3.18 – 3.12 (m, 1H), 2.94 – 2.83 (m, 3H), 2.78 – 2.71 (m, 1H), 2.61 – 2.54 (m, 1H), 2.38 – 2.28 (m, 1H), 2.18 – 2.02 (m, 3H), 1.98 – 1.90 (m, 1H), 1.88 – 1.77 (m, 2H), 1.75 – 1.62 (m, 3H), 1.55 – 1.33 (m, 3H), 0.98 – 0.80 (m, 2H).	C	794.4	794.5
A121	¹ H NMR (400 MHz, DMSO) δ 11.18 (s, 1H), 10.94 (s, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.19 – 7.05 (m, 4H), 6.77 – 6.55 (m, 4H), 6.37 – 6.23 (m, 2H), 5.03 (dd, J = 13.2, 5.2 Hz, 1H), 4.76 – 4.65 (m, 1H), 4.46 – 4.39 (m, 1H), 4.33 – 4.06 (m, 6H), 3.97 – 3.87 (m, 1H), 3.69 – 3.48 (m, 9H), 3.19 – 3.03 (m, 6H), 2.98 – 2.83 (m, 2H), 2.71 – 2.52 (m, 3H), 2.46 – 2.33 (m, 1H), 2.27 – 1.88 (m, 4H), 1.71 (s, 1H).	C	784.4	784.5
A122	¹ H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 7.29 – 6.95 (m, 5H), 6.71 – 6.41 (m, 5H), 6.38 – 6.18 (m, 3H), 5.08 – 4.99 (m, 1H), 4.65 (d, J = 5.2	C	784.4	784.5

Compound No	¹ HNMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	Hz, 1H), 4.38 – 4.16 (m, 7H), 4.08 – 4.00 (m, 2H), 3.75 – 3.56 (m, 5H), 3.50 – 3.44 (m, 1H), 3.26 – 3.16 (m, 1H), 3.17 – 3.05 (m, 3H), 2.95 – 2.84 (m, 2H), 2.78 – 2.66 (m, 2H), 2.64 – 2.52 (m, 3H), 2.41 – 2.32 (m, 1H), 2.07 – 1.75 (m, 4H), 1.43 – 1.27 (m, 2H).			
A123	¹ H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 7.38 (s, 1H), 7.26 (d, J = 2.4 Hz, 1H), 7.20 – 7.11 (m, 4H), 6.85 – 6.78 (m, 3H), 6.71 (d, J = 8.4 Hz, 1H), 6.54 (d, J = 8.8 Hz, 1H), 6.37 – 6.30 (m, 2H), 5.11 (dd, J = 13.2, 5.2 Hz, 1H), 4.55 (s, 2H), 4.44 – 4.32 (m, 3H), 4.26 – 4.19 (m, 2H), 3.58 – 3.51 (m, 1H), 3.39 – 3.35 (m, 2H), 3.30 – 3.29 (m, 3H), 3.03 – 2.94 (m, 2H), 2.91 – 2.84 (m, 1H), 2.81 – 2.65 (m, 4H), 2.54 – 2.42 (m, 1H), 2.27 – 2.02 (m, 6H), 1.99 – 1.89 (m, 2H), 1.81 – 1.46 (m, 7H).	C	794.4	794.5
A124	¹ H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.71 (d, J = 8.4 Hz, 1H), 8.32 (s, 2H), 7.86 (d, J = 8.8 Hz, 1H), 7.41 (dd, J = 8.8, 2.8 Hz, 1H), 7.17 – 7.03 (m, 3H), 6.73 – 6.63 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.39 – 6.32 (m, 1H), 6.30 – 6.21 (m, 2H), 6.20 – 6.13 (m, 1H), 4.79 – 4.68 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.31 (d, J = 11.2 Hz, 1H), 4.09 – 3.97 (m, 1H), 3.63 – 3.55 (m, 3H), 3.48 – 3.41 (m, 3H), 3.38 – 3.28 (m, 6H), 3.02 (s, 3H), 2.83 – 2.74 (m, 1H), 2.64 – 2.58 (m, 2H), 2.24 – 2.11 (m, 3H), 2.05 – 1.95 (m, 1H), 1.82 – 1.63 (m, 3H), 1.26 – 1.11 (m, 2H).	C	745.4	745.4
A125	¹ H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.32 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.14 – 7.07 (m, 3H), 7.01 (d, J = 8.4 Hz, 1H), 6.77 – 6.66 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.34 – 6.19 (m, 4H), 5.06 – 4.99 (m, 1H),	E	842.4	842.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	4.65 (d, J = 5.2 Hz, 1H), 4.39 – 4.21 (m, 3H), 4.16 – 4.05 (m, 2H), 3.95 (t, J = 9.6 Hz, 1H), 3.80 (d, J = 11.6 Hz, 1H), 3.50 – 3.46 (m, 1H), 3.20 – 3.10 (m, 1H), 3.05 (s, 3H), 2.96 – 2.70 (m, 8H), 2.62 – 2.53 (m, 1H), 2.47 – 2.32 (m, 4H), 2.11 (t, J = 10.2 Hz, 1H), 2.01 – 1.89 (m, 3H), 1.79 – 1.63 (m, 3H), 1.62 – 1.52 (m, 2H), 1.44 (t, J = 9.4 Hz, 2H).			
A126	¹ H NMR (400 MHz, DMSO) δ 10.94 (s, 1H), 8.33 (s, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.13 – 7.07 (m, 3H), 7.00 (d, J = 8.6 Hz, 1H), 6.77 – 6.66 (m, 2H), 6.59 (d, J = 8.2 Hz, 1H), 6.35 – 6.19 (m, 4H), 5.07 – 4.99 (m, 1H), 4.65 (d, J = 5.0 Hz, 1H), 4.39 – 4.22 (m, 3H), 4.14 – 4.04 (m, 2H), 3.99 – 3.91 (m, 1H), 3.80 (d, J = 11.8 Hz, 1H), 3.51 – 3.47 (m, 1H), 3.19 – 3.11 (m, 1H), 3.05 (s, 3H), 2.96 – 2.68 (m, 8H), 2.62 – 2.53 (m, 1H), 2.47 – 2.32 (m, 4H), 2.11 (t, J = 10.6 Hz, 1H), 2.02 – 1.89 (m, 3H), 1.79 – 1.38 (m, 7H).	E	842.4	842.5
A127	¹ H NMR (400 MHz, DMSO) δ 10.86 (s, 1H), 9.51 – 9.12 (m, 2H), 8.86 (d, J = 8.4 Hz, 1H), 8.14 (s, 1H), 7.64 (s, 1H), 7.15 – 7.00 (m, 3H), 6.72 – 6.38 (m, 5H), 6.32 – 6.19 (m, 3H), 4.80 – 4.69 (m, 1H), 4.64 (d, J = 5.6 Hz, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.06 (d, J = 7.2 Hz, 1H), 3.97 (s, 3H), 3.50 – 3.44 (m, 3H), 3.24 – 3.11 (m, 6H), 3.04 (s, 3H), 2.86 – 2.76 (m, 1H), 2.71 – 2.65 (m, 2H), 2.54 – 2.53 (m, 3H), 2.36 – 2.11 (m, 2H), 2.07 – 1.93 (m, 2H), 1.86 – 1.76 (m, 2H), 1.40 – 1.24 (m, 2H).	C	775.4	775.5
A128	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.69 (d, J = 8.2 Hz, 1H), 8.38 – 8.17 (m, 2H), 7.83 (d, J = 8.8 Hz, 1H), 7.39 (dd, J = 8.8, 2.6 Hz, 1H), 7.22 – 7.04 (m, 3H), 6.84 – 6.72 (m,	C	715.4	715.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	2H), 6.63 (dd, <i>J</i> = 18.8, 8.4 Hz, 3H), 6.47 – 6.20 (m, 4H), 4.82 – 4.64 (m, 1H), 4.33 (t, <i>J</i> = 11.2 Hz, 1H), 4.25 – 4.13 (m, 2H), 3.93 (d, <i>J</i> = 12.4 Hz, 2H), 3.61 – 3.44 (m, 1H), 3.01 (s, 4H), 2.91 – 2.73 (m, 3H), 2.47 – 2.39 (m, 5H), 2.25 – 2.10 (m, 3H), 2.06 – 1.95 (m, 1H), 1.80 (d, <i>J</i> = 10.6 Hz, 3H), 1.26 – 1.10 (m, 2H).			
A129	¹ H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.70 (d, <i>J</i> = 8.0 Hz, 1H), 8.31 – 8.26 (m, 2H), 7.84 (d, <i>J</i> = 8.8 Hz, 1H), 7.43 – 7.36 (m, 1H), 7.20 – 7.11 (m, 3H), 6.83 – 6.72 (m, 2H), 6.64 (dd, <i>J</i> = 19.2, 8.4 Hz, 3H), 6.44 – 6.25 (m, 4H), 4.79 – 4.68 (m, 1H), 4.34 (t, <i>J</i> = 11.2 Hz, 1H), 4.24 – 4.15 (m, 2H), 3.93 (d, <i>J</i> = 12.2 Hz, 2H), 3.01 (s, 5H), 2.90 – 2.75 (m, 4H), 2.45 (s, 4H), 2.19 (d, <i>J</i> = 6.0 Hz, 3H), 2.07 – 1.96 (m, 1H), 1.81 (d, <i>J</i> = 10.8 Hz, 3H), 1.25 – 1.13 (m, 2H).	B	715.4	715.4
A130	¹ H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.29 (s, 1H), 7.38 (d, <i>J</i> = 7.6 Hz, 1H), 7.26 (d, <i>J</i> = 7.6 Hz, 1H), 7.11 (d, <i>J</i> = 3.6 Hz, 3H), 6.78 – 6.68 (m, 2H), 6.59 (d, <i>J</i> = 8.2 Hz, 1H), 6.35 – 6.21 (m, 4H), 5.12 – 5.04 (m, 1H), 4.65 (d, <i>J</i> = 5.2 Hz, 1H), 4.55 – 4.46 (m, 2H), 4.42 – 4.27 (m, 2H), 4.21 (d, <i>J</i> = 17.0 Hz, 1H), 4.08 (d, <i>J</i> = 7.8 Hz, 1H), 3.50 – 3.48 (m, 1H), 3.05 (s, 3H), 2.94 – 2.75 (m, 7H), 2.59 (d, <i>J</i> = 16.6 Hz, 1H), 2.47 – 2.33 (m, 4H), 2.05 – 1.84 (m, 7H), 1.72 – 1.52 (m, 6H), 1.43 (t, <i>J</i> = 9.4 Hz, 2H).	E	841.4	841.5
A131	¹ H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 8.19 (s, 1H), 7.38 (d, <i>J</i> = 7.6 Hz, 1H), 7.27 (d, <i>J</i> = 7.6 Hz, 1H), 7.16 – 7.07 (m, 3H), 6.77 – 6.68 (m, 2H), 6.59 (d, <i>J</i> = 8.4 Hz, 1H), 6.35 – 6.21 (m, 4H), 5.12 – 5.05 (m, 1H), 4.65 (d, <i>J</i> = 5.4 Hz, 1H), 4.56 – 4.48	E	841.4	841.6

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 2H), 4.41 – 4.27 (m, 2H), 4.21 (d, J = 17.0 Hz, 1H), 4.13 – 4.05 (m, 1H), 3.51 – 3.47 (m, 1H), 3.05 (s, 3H), 2.94 – 2.76 (m, 7H), 2.59 (d, J = 16.0 Hz, 1H), 2.48 – 2.33 (m, 4H), 2.11 – 1.85 (m, 7H), 1.73 – 1.62 (m, 4H), 1.60 – 1.52 (m, 2H), 1.49 – 1.39 (m, 2H).			
A132	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 7.23 – 7.07 (m, 4H), 7.01 (d, J = 8.0 Hz, 1H), 6.80 – 6.70 (m, 2H), 6.69 – 6.55 (m, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.31 – 6.22 (m, 2H), 5.10 – 4.98 (m, 1H), 4.39 – 4.24 (m, 3H), 4.21 – 4.12 (m, 2H), 4.08 (s, 1H), 4.00 – 3.94 (m, 1H), 3.87 (d, J = 7.8 Hz, 1H), 3.81 (s, 1H), 3.55 – 3.47 (m, 1H), 3.43 (d, J = 7.6 Hz, 1H), 3.33 (s, 4H), 3.06 (s, 3H), 2.88 (d, J = 12.6 Hz, 1H), 2.70 (d, J = 16.0 Hz, 1H), 2.37 – 2.32 (m, 2H), 2.12 (s, 1H), 2.01 – 1.91 (m, 3H), 1.83 – 1.72 (m, 1H), 1.64 – 1.52 (m, 4H), 1.40 – 1.20 (m, 4H).	D	810.4	810.5
A133	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.22 – 7.10 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H), 6.78 – 6.71 (m, 2H), 6.70 – 6.56 (m, 3H), 6.42 – 6.31 (m, 2H), 6.31 – 6.23 (m, 2H), 5.09 – 5.00 (m, 1H), 4.44 – 4.22 (m, 3H), 4.19 – 4.12 (m, 2H), 4.08 (s, 1H), 3.95 (d, J = 9.4 Hz, 1H), 3.89 – 3.76 (m, 2H), 3.56 – 3.48 (m, 1H), 3.46 – 3.40 (m, 1H), 3.32 (s, 4H), 3.16 (s, 1H), 3.06 (s, 3H), 2.91 (d, J = 12.6 Hz, 1H), 2.73 (s, 1H), 2.38 – 2.34 (m, 2H), 2.13 (d, J = 12.0 Hz, 1H), 2.01 – 1.88 (m, 3H), 1.81 – 1.70 (m, 1H), 1.64 – 1.47 (m, 4H), 1.37 – 1.29 (m, 1H), 1.24 (s, 2H).	E	810.4	810.5
A134	¹ H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.31 (s, 1H), 8.50 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.17 – 7.04	B	773.4	773.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 3H), 6.74 – 6.64 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 7.6 Hz, 1H), 6.31 – 6.21 (m, 2H), 6.18 (s, 1H), 4.76 – 4.66 (m, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.51 – 4.38 (m, 1H), 4.30 (d, J = 11.2 Hz, 1H), 4.13 – 4.00 (m, 2H), 3.78 (d, J = 11.6 Hz, 1H), 3.65 – 3.56 (m, 2H), 3.49 – 3.39 (m, 2H), 3.23 – 3.17 (m, 1H), 3.05 – 2.92 (m, 5H), 2.84 – 2.70 (m, 2H), 2.63 – 2.55 (m, 2H), 2.25 – 1.94 (m, 5H), 1.84 – 1.62 (m, 4H), 1.25 – 1.11 (m, 2H).			
A135	¹ H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.27 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.16 – 7.02 (m, 3H), 6.72 – 6.64 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.30 – 6.21 (m, 2H), 6.21 – 6.13 (m, 1H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.57 – 4.48 (m, 2H), 4.40 – 4.16 (m, 3H), 4.08 – 4.00 (m, 1H), 3.63 – 3.55 (m, 2H), 3.48 – 3.42 (m, 2H), 3.02 (s, 3H), 2.92 – 2.76 (m, 2H), 2.68 – 2.55 (m, 3H), 2.44 – 2.30 (m, 1H), 2.19 (d, J = 6.8 Hz, 2H), 2.03 – 1.85 (m, 5H), 1.82 – 1.59 (m, 5H), 1.26 – 1.12 (m, 2H).	B	783.4	783.4
A136	¹ H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 9.23 (s, 1H), 7.46 (s, 1H), 7.16 – 7.02 (m, 3H), 7.00 (s, 1H), 6.72 – 6.64 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 6.39 – 6.31 (m, 1H), 6.30 – 6.22 (m, 2H), 6.17 (s, 1H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.49 – 4.43 (m, 2H), 4.37 – 4.16 (m, 3H), 4.09 – 4.00 (m, 1H), 3.63 – 3.54 (m, 2H), 3.48 – 3.41 (m, 2H), 3.02 (s, 3H), 2.94 – 2.79 (m, 2H), 2.63 – 2.54 (m, 3H), 2.41 – 2.31 (m, 1H), 2.19 (d, J = 6.8 Hz, 2H), 2.02 – 1.84 (m, 5H),	B	783.4	783.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	1.81 – 1.60 (m, 5H), 1.26 – 1.11 (m, 2H).			
A137	¹ H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.27 (s, 1H), 8.14 (s, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.16 – 7.08 (m, 3H), 6.80 – 6.72 (m, 2H), 6.69 – 6.56 (m, 3H), 6.38 (d, J = 8.8 Hz, 2H), 6.34 – 6.24 (m, 2H), 5.08 (dd, 5.0 Hz, 1H), 4.56 – 4.49 (m, 2H), 4.40 – 4.24 (m, 2H), 4.23 – 4.13 (m, 3H), 3.87 (t, J = 7.8 Hz, 1H), 3.55 – 3.41 (m, 3H), 3.06 (s, 4H), 2.98 – 2.61 (m, 4H), 2.56 (s, 1H), 2.34 (d, J = 7.0 Hz, 2H), 1.99 – 1.90 (m, 4H), 1.71 – 1.55 (m, 6H), 1.39 – 1.28 (m, 1H), 1.24 (s, 2H).	A	809.4	809.5
A138	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.17 – 7.11 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.80 – 6.72 (m, 2H), 6.69 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.21 (m, 2H), 5.05 – 4.98 (m, 1H), 4.71 – 3.89 (m, 7H), 3.88 – 3.67 (m, 2H), 3.51 (d, J = 4.0 Hz, 1H), 3.44 (t, J = 7.8 Hz, 1H), 3.35 (s, 1H), 3.15 (s, 1H), 3.06 (s, 2H), 2.95 – 2.84 (m, 2H), 2.76 (s, 1H), 2.63 – 2.54 (m, 2H), 2.33 (t, J = 8.8 Hz, 3H), 2.17 – 2.07 (m, 1H), 1.98 – 1.88 (m, 2H), 1.76 – 1.68 (m, 1H), 1.66 – 1.33 (m, 5H), 1.24 (s, 2H).	A	810.4	810.5
A139	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.27 (s, 1H), 7.18 – 7.07 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.78 – 6.71 (m, 2H), 6.69 – 6.60 (m, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.31 – 6.23 (m, 2H), 5.08 – 4.97 (m, 1H), 4.36 – 4.21 (m, 3H), 4.20 – 4.11 (m, 3H), 3.93 – 3.84 (m, 2H), 3.81 (d, J = 12.6 Hz, 1H), 3.51 (d, J = 11.4 Hz, 1H), 3.43 (d, J = 8.2 Hz, 1H), 3.06 (s, 4H), 2.96 – 2.84 (m, 2H), 2.76 (s, 1H), 2.60 (s, 1H), 2.33 (s, 3H), 2.05 – 1.91	A	810.4	810.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 3H), 1.61 (d, J = 14.0 Hz, 4H), 1.28 (d, J = 18.2 Hz, 3H).			
A140	¹ H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 7.21 – 7.06 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H), 6.79 – 6.70 (m, 2H), 6.69 – 6.54 (m, 3H), 6.37 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.63 (d, J = 7.2 Hz, 1H), 4.35 – 4.13 (m, 4H), 3.51 – 3.45 (m, 1H), 3.41 – 3.39 (m, 2H), 3.35 – 3.33 (m, 2H), 2.91 (d, J = 10.8 Hz, 2H), 2.77 – 2.68 (m, 1H), 2.61 – 2.57 (m, 1H), 2.35 – 2.28 (m, 1H), 2.14 – 2.04 (m, 3H), 2.00 – 1.91 (m, 2H), 1.89 – 1.78 (m, 3H), 1.74 – 1.37 (m, 10H), 0.95 – 0.84 (m, 2H).	C	725.4	725.4
A141	¹ H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 7.22 – 7.03 (m, 3H), 6.94 (d, J = 8.4 Hz, 2H), 6.80 – 6.71 (m, 2H), 6.69 – 6.54 (m, 3H), 6.45 – 6.18 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.64 (d, J = 6.4 Hz, 1H), 4.35 – 4.11 (m, 6H), 3.51 – 3.47 (m, 1H), 3.41 – 3.29 (m, 4H), 3.01 – 2.91 (m, 2H), 2.78 – 2.69 (m, 1H), 2.62 – 2.53 (m, 1H), 2.38 – 2.27 (m, 1H), 2.24 – 2.15 (m, 2H), 2.13 – 1.98 (m, 3H), 1.91 – 1.77 (m, 3H), 1.73 – 1.57 (m, 6H), 1.53 – 1.35 (m, 2H), 0.97 – 0.84 (m, 2H).	C	725.4	725.4
A142	¹ H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.21 – 7.09 (m, 3H), 6.79 – 6.69 (m, 2H), 6.64 (d, J = 8.4 Hz, 1H), 6.36 – 6.23 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 4.74 – 4.66 (m, 1H), 4.47 – 4.38 (m, 1H), 4.37 – 4.27 (m, 1H), 4.20 – 4.02 (m, 3H), 3.77 (d, J = 11.2 Hz, 1H), 3.52 – 3.46 (m, 2H), 3.40 – 3.38 (m, 2H), 3.36 – 3.34 (m, 2H), 3.24 – 3.14 (m, 2H), 2.92 (d, J = 10.4 Hz, 2H), 2.81 – 2.71 (m, 2H), 2.21 – 1.96 (m, 5H), 1.83 (d, J = 12.8 Hz, 2H), 1.76 – 1.62 (m, 3H), 1.54 – 1.37 (m, 3H), 0.97 – 0.85 (m, 2H).	C	783.4	783.4

Compound No	¹ HNMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A143	1H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.27 (s, 1H), 7.59 (dd, J = 7.6, 2.0 Hz, 1H), 7.39 – 7.25 (m, 3H), 7.15 – 7.10 (m, 3H), 6.76 (dd, J = 6.4, 2.8 Hz, 2H), 6.63 (dd, J = 19.6, 8.8 Hz, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.31 – 6.23 (m, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.57 – 4.50 (m, 2H), 4.39 – 4.29 (m, 2H), 4.23 – 4.14 (m, 3H), 3.53 – 3.48 (m, 1H), 2.99 (s, 3H), 2.90 (s, 3H), 2.58 (d, J = 18.4 Hz, 3H), 2.29 (d, J = 33.2 Hz, 2H), 1.95 (t, J = 9.6 Hz, 6H), 1.74 (d, J = 10.0 Hz, 2H), 1.57 (d, J = 47.2 Hz, 4H), 1.48 – 1.40 (m, 2H).	C	793.4	793.4
A144	1H NMR (400 MHz, DMSO) δ 10.85 (s, 1H), 9.27 (s, 1H), 8.86 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.57 (s, 1H), 7.25 – 7.01 (m, 3H), 6.82 – 6.71 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.36 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 4.79 – 4.71 (m, 1H), 4.32 (d, J = 11.2 Hz, 1H), 4.21 – 4.10 (m, 2H), 3.93 (s, 3H), 3.52 – 3.46 (m, 1H), 3.41 – 3.38 (m, 2H), 3.36 – 3.33 (m, 3H), 3.12 (s, 4H), 2.84 – 2.74 (m, 1H), 2.51 – 2.50 (m, 4H), 2.25 – 2.09 (m, 3H), 2.04 – 1.94 (m, 1H), 1.83 (d, J = 12.8 Hz, 2H), 1.69 (d, J = 10.8 Hz, 2H), 1.54 – 1.37 (m, 3H), 0.99 – 0.84 (m, 2H).	C	785.4	785.4
A145	1H NMR (400 MHz, DMSO) δ 10.84 (s, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.39 (s, 4H), 8.31 (d, J = 2.8 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.14 (d, J = 3.6 Hz, 3H), 6.75 (d, J = 3.6 Hz, 2H), 6.68 – 6.58 (m, 5H), 6.37 (d, J = 8.6 Hz, 2H), 6.31 – 6.25 (m, 2H), 5.32 (t, J = 4.6 Hz, 2H), 4.75 (d, J = 12.8 Hz, 1H), 4.32 (t, J = 11.2 Hz, 1H), 4.16 (d, J = 4.2 Hz, 2H), 3.91 – 3.83 (m, 2H), 3.33 – 3.31 (m, 3H), 3.06 (s, 3H), 2.77 (d, J = 11.4 Hz, 1H), 2.33 (s, 2H), 2.15 (d, J	E	771.4	771.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	= 12.4 Hz, 1H), 1.94 (d, J = 13.0 Hz, 2H), 1.62 – 1.59 (m, 2H), 1.45 (s, 1H), 1.28 (s, 2H), 0.85 (d, J = 7.2 Hz, 2H).			
A146	¹ H NMR (400 MHz, CD ₃ OD_SPE) δ 8.43 (s, 1H), 7.38 (q, 2H), 7.14 – 7.09 (m, 3H), 6.73 – 6.65 (m, 5H), 6.47 (d, J = 8.6 Hz, 2H), 6.34 (d, J = 2.2 Hz, 1H), 6.30 (dd, 1H), 5.12 (dd, 1H), 4.64 – 4.56 (m, 3H), 4.42 (dt, J = 11.0, 8.5 Hz, 3H), 4.22 – 4.12 (m, 2H), 4.09 – 4.02 (m, 1H), 3.57 (t, J = 8.2 Hz, 1H), 3.52 – 3.43 (m, 1H), 3.12 (s, 4H), 2.87 – 2.74 (m, 4H), 2.65 – 2.44 (m, 3H), 2.20 – 2.08 (m, 4H), 1.90 (d, J = 13.4 Hz, 2H), 1.82 – 1.63 (m, 4H), 1.49 (dd, 1H), 1.30 (d, J = 18.0 Hz, 1H).	D	809.4	809.5
A147	¹ H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.27 (s, 1H), 8.49 (d, J = 8.2 Hz, 1H), 8.18 (s, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.19 – 7.07 (m, 3H), 6.79 – 6.73 (m, 2H), 6.65 (t, J = 8.4 Hz, 1H), 6.61 (d, J = 8.6 Hz, 2H), 6.37 (d, J = 8.6 Hz, 2H), 6.32 – 6.22 (m, 2H), 4.76 – 4.64 (m, 1H), 4.47 – 4.41 (m, 1H), 4.31 (d, J = 11.0 Hz, 1H), 4.17 (t, J = 6.0 Hz, 2H), 4.11 – 4.04 (m, 1H), 3.87 (t, J = 7.8 Hz, 1H), 3.77 (d, J = 12.4 Hz, 1H), 3.57 – 3.42 (m, 3H), 3.20 (s, 1H), 3.05 (d, J = 5.6 Hz, 3H), 2.94 (d, J = 10.0 Hz, 1H), 2.82 – 2.72 (m, 2H), 2.68 – 2.55 (m, 1H), 2.35 (d, J = 7.0 Hz, 2H), 2.21 – 2.08 (m, 2H), 2.00 – 1.93 (m, 2H), 1.74 (t, J = 11.0 Hz, 1H), 1.65 – 1.53 (m, 4H), 1.35 (d, J = 12.0 Hz, 1H), 1.24 (s, 2H).	E	799.4	799.5
A148	¹ H NMR (400 MHz, DMSO) δ 10.83 (s, 1H), 9.28 (s, 1H), 8.49 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.6 Hz, 1H), 7.15 – 7.07 (m, 3H), 6.80 – 6.71 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.60 (s, 2H), 6.37 (d,	E	799.4	799.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	J = 8.6 Hz, 2H), 6.31 – 6.22 (m, 2H), 4.79 – 4.62 (m, 1H), 4.43 (dd, 2.8 Hz, 1H), 4.32 (t, J = 10.8 Hz, 1H), 4.17 (t, J = 6.2 Hz, 2H), 4.12 – 4.01 (m, 1H), 3.87 (t, J = 7.8 Hz, 1H), 3.77 (d, J = 11.0 Hz, 1H), 3.56 – 3.42 (m, 3H), 3.19 (s, 1H), 3.06 (s, 3H), 2.94 (s, 1H), 2.82 – 2.74 (m, 2H), 2.41 – 2.32 (m, 3H), 2.19 – 2.05 (m, 2H), 2.04 – 1.91 (m, 3H), 1.76 – 1.68 (m, 1H), 1.58 (d, J = 13.6 Hz, 3H), 1.37 – 1.32 (m, 1H), 1.24 (s, 2H).			
A149	¹ H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.10 (s, 3H), 6.95 (d, J = 6.8 Hz, 2H), 6.69 – 6.54 (m, 5H), 6.48 (d, J = 8.4 Hz, 1H), 6.35 (d, J = 8.4 Hz, 1H), 6.30 – 6.22 (m, 2H), 6.17 (s, 1H), 5.64 (d, J = 6.4 Hz, 1H), 4.64 – 4.57 (m, 1H), 4.34 – 4.19 (m, 2H), 4.04 (d, J = 9.6 Hz, 1H), 3.65 – 3.54 (m, 3H), 3.47 – 3.39 (m, 2H), 3.02 (s, 3H), 2.93 (d, J = 10.4 Hz, 2H), 2.78 – 2.67 (m, 1H), 2.60 – 2.53 (m, 3H), 2.36 – 2.26 (m, 1H), 2.21 – 2.06 (m, 3H), 2.01 – 1.92 (m, 2H), 1.80 – 1.72 (m, 2H), 1.70 – 1.52 (m, 5H), 1.23 – 1.08 (m, 2H).	B	715.4	715.4
A150	¹ H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 7.14 – 7.04 (m, 3H), 6.95 (d, J = 8.4 Hz, 2H), 6.72 – 6.65 (m, 2H), 6.63 – 6.54 (m, 3H), 6.48 (d, J = 8.4 Hz, 1H), 6.40 – 6.31 (m, 1H), 6.29 – 6.22 (m, 2H), 6.17 (d, J = 2.0 Hz, 1H), 5.64 (d, J = 7.2 Hz, 1H), 4.62 (d, J = 5.2 Hz, 1H), 4.34 – 4.22 (m, 2H), 4.07 – 4.00 (m, 1H), 3.62 – 3.55 (m, 2H), 3.49 – 3.38 (m, 2H), 3.02 (s, 3H), 2.94 (d, J = 10.4 Hz, 2H), 2.78 – 2.67 (m, 1H), 2.61 – 2.53 (m, 3H), 2.36 – 2.28 (m, 1H), 2.19 (d, J = 6.8 Hz, 2H), 2.13 – 2.06 (m, 1H), 1.98 (t, J = 10.8 Hz, 2H), 1.90 – 1.82 (m, 1H), 1.79 – 1.72 (m, 2H), 1.71 – 1.55 (m, 5H), 1.25 – 1.08 (m, 2H).	B	715.4	715.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
A151	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.28 (s, 1H), 7.18 – 7.12 (m, 3H), 7.05 (s, 1H), 6.93 (s, 1H), 6.77 – 6.72 (m, 2H), 6.65 – 6.56 (m, 3H), 6.37 (d, J = 8.8 Hz, 2H), 6.33 – 6.23 (m, 2H), 5.09 – 4.98 (m, 1H), 4.37 – 4.23 (m, 4H), 4.16 – 4.10 (m, 2H), 3.93 – 3.78 (m, 4H), 3.51 (d, J = 4.6 Hz, 1H), 3.40 (d, J = 18.2 Hz, 2H), 3.16 (s, 2H), 3.06 (s, 3H), 2.89 (t, J = 12.8 Hz, 2H), 2.73 (d, J = 11.8 Hz, 1H), 2.58 (d, J = 6.8 Hz, 1H), 2.35 (s, 2H), 2.09 (d, J = 10.2 Hz, 1H), 2.01 – 1.88 (m, 3H), 1.74 (t, J = 10.8 Hz, 1H), 1.62 (s, 3H), 1.38 – 1.28 (m, 2H), 1.24 – 1.22 (m, 1H).	E	810.4	810.5
A152	1H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 9.28 (s, 1H), 7.16 – 7.09 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.76 – 6.69 (m, 2H), 6.67 – 6.57 (m, 3H), 6.37 (d, J = 8.6 Hz, 2H), 6.31 – 6.22 (m, 2H), 5.09 – 4.95 (m, 1H), 4.33 – 4.23 (m, 3H), 4.18 – 4.08 (m, 3H), 3.92 – 3.79 (m, 3H), 3.55 – 3.39 (m, 3H), 3.14 (s, 1H), 3.06 (s, 3H), 2.91 (d, J = 12.6 Hz, 2H), 2.74 (d, J = 9.0 Hz, 1H), 2.61 – 2.55 (m, 2H), 2.35 (d, J = 12.4 Hz, 3H), 2.18 – 2.07 (m, 1H), 1.97 – 1.89 (m, 2H), 1.79 – 1.68 (m, 1H), 1.60 – 1.55 (m, 2H), 1.31 (s, 1H), 1.24 (s, 1H).	B	810.4	810.4
A153	1H NMR (400 MHz, DMSO) δ 10.96 (s, 1H), 7.45 (s, 1H), 7.22 – 7.08 (m, 3H), 7.00 (s, 1H), 6.81 – 6.71 (m, 2H), 6.65 (d, J = 8.4 Hz, 1H), 6.37 – 6.22 (m, 4H), 6.09 (d, J = 8.4 Hz, 2H), 5.07 (dd, J = 13.2, 5.2 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.38 – 4.28 (m, 2H), 4.24 – 4.11 (m, 3H), 3.54 – 3.44 (m, 2H), 3.41 – 3.39 (m, 2H), 3.36 – 3.33 (m, 2H), 2.97 – 2.77 (m, 3H), 2.64 – 2.54 (m, 1H), 2.42 – 2.30 (m, 1H), 2.11 (d, J = 6.8 Hz, 2H), 1.99 – 1.80 (m, 7H), 1.73 – 1.63 (m, 4H),	C	793.4	793.4

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	1.53 – 1.38 (m, 3H), 0.98 – 0.83 (m, 2H).			
A154	¹ H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 9.26 (s, 1H), 7.42 – 7.22 (m, 2H), 7.18 – 7.07 (m, 3H), 6.79 – 6.72 (m, 2H), 6.70 – 6.58 (m, 1H), 6.36 – 6.25 (m, 4H), 6.12 – 6.06 (m, 2H), 5.08 (dd, J = 13.2, 5.2 Hz, 1H), 4.51 (s, 2H), 4.40 – 4.29 (m, 2H), 4.24 – 4.13 (m, 3H), 3.52 – 3.46 (m, 1H), 3.44 – 3.37 (m, 2H), 3.38 – 3.34 (m, 2H), 2.99 – 2.73 (m, 3H), 2.63 – 2.56 (m, 1H), 2.46 – 2.27 (m, 1H), 2.18 – 2.06 (m, 2H), 2.02 – 1.79 (m, 6H), 1.74 – 1.64 (m, 3H), 1.53 – 1.37 (m, 3H), 1.28 – 1.21 (m, 2H), 0.98 – 0.83 (m, 2H).	C	793.4	793.5
A155	¹ H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 8.16 (s, 1H), 7.12 (d, J = 7.0 Hz, 3H), 7.01 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 6.2 Hz, 2H), 6.67 – 6.62 (m, 3H), 6.60 – 6.57 (m, 2H), 6.38 – 6.23 (m, 3H), 5.84 (d, J = 7.6 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.33 (dd, J = 21.6, 10.5 Hz, 2H), 4.14 (d, J = 7.7 Hz, 1H), 3.84 (dd, J = 15.4, 7.8 Hz, 1H), 3.12 (s, 5H), 3.00 (d, J = 9.8 Hz, 1H), 2.80 – 2.64 (m, 2H), 2.31 (d, J = 7.3 Hz, 4H), 2.11 (s, 5H), 2.04 – 1.94 (m, 2H), 1.88 (d, J = 12.6 Hz, 3H), 1.62 – 1.56 (m, 3H), 1.28 – 1.20 (m, 1H), 0.85 (d, J = 7.0 Hz, 1H).	B	828.4	828.5
A156	¹ H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 8.27 (s, 1H), 7.13 – 7.10 (m, 3H), 7.01 (d, J = 8.2 Hz, 2H), 6.76 (d, J = 6.0 Hz, 2H), 6.68 – 6.60 (m, 4H), 6.59 (d, J = 4.4 Hz, 2H), 6.38 – 6.24 (m, 3H), 5.84 (d, J = 7.4 Hz, 1H), 4.46 (d, J = 5.2 Hz, 1H), 4.39 – 4.25 (m, 2H), 4.14 (d, J = 8.2 Hz, 1H), 3.88 – 3.79 (m, 1H), 3.52 (d, J = 10.6 Hz, 2H), 3.00 (d, J = 10.4 Hz, 1H), 2.80 – 2.64 (m, 2H), 2.36 – 2.25 (m, 3H), 2.19 – 2.04 (m, 5H), 2.04 – 1.95	B	807.4	807.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 1H), 1.94 – 1.80 (m, 3H), 1.62 – 1.57 (m, 2H), 1.36 – 1.19 (m, 5H), 0.88 – 0.82 (m, 1H).			
A157	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.29 (s, 1H), 7.19 – 7.15 (m, 1H), 7.14 – 7.08 (m, 3H), 7.01 (d, J = 8.6 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 – 6.26 (m, 3H), 5.06 – 4.99 (m, 1H), 4.46 (d, J = 5.2 Hz, 1H), 4.38 – 4.22 (m, 3H), 4.17 – 4.06 (m, 2H), 3.99 – 3.78 (m, 3H), 3.56 – 3.48 (m, 2H), 3.16 – 3.08 (m, 5H), 3.04 – 2.98 (m, 1H), 2.94 – 2.84 (m, 2H), 2.76 – 2.66 (m, 2H), 2.39 – 2.32 (m, 3H), 2.17 – 2.04 (m, 1H), 2.00 – 1.90 (m, 2H), 1.82 – 1.70 (m, 1H), 1.68 – 1.53 (m, 4H), 1.38 – 1.30 (m, 1H).	B	828.4	828.4
A158	¹ H NMR (400 MHz, DMSO) δ 10.92 (s, 1H), 8.29 (s, 1H), 7.19 – 7.15 (m, 1H), 7.14 – 7.08 (m, 3H), 7.01 (d, J = 8.6 Hz, 1H), 6.78 – 6.74 (m, 2H), 6.65 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 – 6.26 (m, 3H), 5.06 – 4.99 (m, 1H), 4.46 (d, J = 5.2 Hz, 1H), 4.38 – 4.22 (m, 3H), 4.17 – 4.06 (m, 2H), 3.99 – 3.78 (m, 3H), 3.56 – 3.48 (m, 2H), 3.16 – 3.08 (m, 5H), 3.04 – 2.98 (m, 1H), 2.94 – 2.84 (m, 2H), 2.76 – 2.66 (m, 2H), 2.39 – 2.32 (m, 3H), 2.17 – 2.04 (m, 1H), 2.00 – 1.90 (m, 2H), 1.82 – 1.70 (m, 1H), 1.68 – 1.53 (m, 4H), 1.38 – 1.30 (m, 1H).	B	828.4	828.4
A159	¹ H NMR (400 MHz, DMSO) δ 10.76 (s, 1H), 9.29 (s, 1H), 8.17 (s, 1H), 7.14 – 7.09 (m, 3H), 7.01 (d, J = 8.0 Hz, 2H), 6.78 – 6.74 (m, 2H), 6.64 (t, J = 8.8 Hz, 3H), 6.60 – 6.57 (m, 2H), 6.37 – 6.32 (m, 1H), 6.31 – 6.26 (m, 2H), 5.84 (d, J = 7.4 Hz, 1H), 4.46 (d, J = 5.4 Hz, 1H), 4.37 – 4.26 (m, 2H), 4.18 – 4.11 (m, 1H), 3.87 – 3.80 (m,	C	806.4	806.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	1H), 3.55 – 3.50 (m, 1H), 3.44 – 3.42 (m, 1H), 3.14 – 3.11 (m, 3H), 2.69 – 2.66 (m, 3H), 2.33 – 2.31 (m, 2H), 2.16 – 2.06 (m, 5H), 1.93 – 1.84 (m, 3H), 1.82 – 1.77 (m, 1H), 1.63 – 1.53 (m, 5H), 1.35 – 1.28 (m, 1H).			
A160	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.27 (s, 1H), 7.14 – 7.09 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.78 – 6.74 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 (s, 1H), 6.33 (s, 1H), 6.32 – 6.28 (m, 2H), 6.28 – 6.26 (m, 1H), 5.02 (dd, J = 13.4, 5.0 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.38 – 4.25 (m, 3H), 4.22 (s, 1H), 4.18 – 4.10 (m, 2H), 3.93 – 3.85 (m, 2H), 3.84 – 3.77 (m, 1H), 3.18 – 3.08 (m, 6H), 3.06 – 2.83 (m, 4H), 2.76 (s, 2H), 2.37 – 2.32 (m, 3H), 2.13 – 2.04 (m, 1H), 2.01 – 1.89 (m, 3H), 1.72 – 1.57 (m, 5H), 1.38 – 1.31 (m, 1H).	C	828.4	828.5
A161	¹ H NMR (400 MHz, DMSO) δ 10.93 (s, 1H), 8.27 (s, 1H), 7.14 – 7.09 (m, 3H), 7.04 (s, 1H), 6.93 (s, 1H), 6.78 – 6.74 (m, 2H), 6.66 (d, J = 8.2 Hz, 1H), 6.61 – 6.57 (m, 2H), 6.37 (s, 1H), 6.33 (s, 1H), 6.32 – 6.28 (m, 2H), 6.28 – 6.26 (m, 1H), 5.02 (dd, J = 13.4, 5.0 Hz, 1H), 4.46 (d, J = 5.0 Hz, 1H), 4.38 – 4.25 (m, 3H), 4.22 (s, 1H), 4.18 – 4.10 (m, 2H), 3.93 – 3.85 (m, 2H), 3.84 – 3.77 (m, 1H), 3.18 – 3.08 (m, 6H), 3.06 – 2.83 (m, 4H), 2.76 (s, 2H), 2.37 – 2.32 (m, 3H), 2.13 – 2.04 (m, 1H), 2.01 – 1.89 (m, 3H), 1.72 – 1.57 (m, 5H), 1.38 – 1.31 (m, 1H).	C	828.4	828.5
A162	¹ H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, J = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, J = 7.6 Hz, 1H), 4.36 –	B	759.4	759.5

Compound No	¹ H NMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, <i>J</i> = 7.2 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.42 (d, <i>J</i> = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, <i>J</i> = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, <i>J</i> = 12.4, 8.0 Hz, 1H).			
A163	¹ H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, <i>J</i> = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, <i>J</i> = 7.6 Hz, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, <i>J</i> = 7.2 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.42 (d, <i>J</i> = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, <i>J</i> = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, <i>J</i> = 12.4, 8.0 Hz, 1H).	B	759.4	759.5
A164	¹ H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, <i>J</i> = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, <i>J</i> = 7.6 Hz, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, <i>J</i> = 7.2 Hz, 1H), 3.52 – 3.48 (m, 1H), 3.42 (d, <i>J</i> = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, <i>J</i> = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, <i>J</i> = 12.4, 8.0 Hz, 1H).	B	759.4	759.5
A165	¹ H NMR (400 MHz, DMSO) δ 10.77 (s, 1H), 8.19 (s, 1H), 7.17 – 7.09 (m, 3H), 6.98 (d, <i>J</i> = 8.8 Hz, 1H), 6.79 – 6.71 (m, 2H), 6.68 – 6.58 (m, 3H), 6.46 – 6.34 (m, 4H), 6.33 – 6.25 (m, 2H), 5.98 (d, <i>J</i> = 7.6 Hz, 1H), 4.36 – 4.27 (m, 2H), 4.20 – 4.14 (m, 2H), 3.84 (d, <i>J</i> = 7.2 Hz, 1H), 3.52 – 3.48	B	759.4	759.5

Compound No	¹ HNMR	LCMS method	Calcd. (M+H) ⁺	Found. (M+H) ⁺
	(m, 1H), 3.42 (d, <i>J</i> = 6.0 Hz, 1H), 3.09 – 3.03 (m, 4H), 2.95 – 2.90 (m, 1H), 2.76 – 2.69 (m, 1H), 2.59 – 2.55 (m, 2H), 2.33 (d, <i>J</i> = 7.2 Hz, 2H), 2.10 – 1.83 (m, 6H), 1.73 – 1.49 (m, 9H), 1.32 (dd, <i>J</i> = 12.4, 8.0 Hz, 1H).			

FOR COMPOUNDS B1 to B5**Table 5. Characterization Data for Compounds B1 to B5**

Compound No	LC-MS ([M+H] ⁺)
B1	754.36
B2	794.31
B3	794.33
B4	793.31
B5	794.3

II. BIOLOGICAL ASSAYS FOR COMPOUNDS 1-165

In vitro Assay: IC₅₀ Measurements for binding to CRBN/DDB1

[0463] The binding potency was determined using HTRF assay technology (Perkin Elmer). Compounds were serially diluted in DMSO and 0.2 μ L volume was transferred to white 384-well plate. The reaction was conducted in total volume of 20 μ L with addition of 2 nM His tagged CRBN+DDB-DLS7+CXU4 (Wuxi, catalogue # RP210521GA) to compounds followed by addition of 60 nM Fluorescent probe Cy5-labeled Thalidomide (Tenova Pharma, catalogue # T52461), and 0.4 nM of MAb Anti-6HIS Tb cryplate Gold (Cisbio, catalogue # 61HI2TLA in the assay buffer (50 mM HEPES pH 7.5, 1 mM TCEP, 0.01% Brij-35, 50 mM NaCl, and 0.1% BSA). After one hour incubation at room temperature, the HTRF signals were read on Envision reader (Perkin Elmer). Data was analyzed using XLfit using four parameters dose response curve to determine IC₅₀s. The binding IC₅₀ data for compounds are summarized in **Table 6**.

Table 6. Binding IC₅₀ to CRBN/DDB1

Compound No.	CRBN HTRF IC ₅₀ (nM)
A1	D
A2	D
A3	B
A4	C
A5	C
A6	B
A7	B
A8	B
A9	B
A10	C
A11	D
A12	B
A13	B
A14	C
A15	B
A16	B
A17	B
A18	C
A19	B

Compound No.	CRBN HTRF IC ₅₀ (nM)
A20	A
A21	A
A22	A
A23	A
A24	A
A25	B
A26	B
A27	C
A28	D
A29	C
A30	C
A31	B
A32	C
A33	A
A34	B
A35	B
A36	B
A37	A
A38	B
A39	B
A40	B
A41	B
A42	B
A43	D
A44	B
A45	B
A46	C
A47	C
A48	B
A49	B
A50	B
A51	C
A52	B
A53	C

Compound No.	CRBN HTRF IC ₅₀ (nM)
A54	C
A55	C
A56	B
A57	D
A58	C
A59	B
A60	B
A61	B
A62	B
A63	C
A64	B
A65	B
A67	B
A69	B
A70	B
A71	B
A72	B
A73	A
A74	C
A75	B
A76	B
A77	C
A78	C
A79	C
A80	C
A81	C
A82	C
A83	D
A84	C
A85	D
A86	B
A87	D
A88	D
A89	A

Compound No.	CRBN HTRF IC ₅₀ (nM)
A90	D
A91	D
A92	D
A93	C
A94	C
A95	C
A96	B
A97	C
A98	B
A99	B
A100	D
A101	D
A102	C
A103	C
A104	C
A105	A
A106	A
A107	D
A108	C
A109	D
A110	D
A111	C
A112	D
A113	A
A114	A
A115	B
A116	C
A117	C
A118	C
A119	C
A120	C
A121	C
A122	B
A123	B

Compound No.	CRBN HTRF IC ₅₀ (nM)
A124	D
A125	B
A126	A
A127	D
A128	D
A129	D
A130	B
A131	A
A132	A
A133	A
A134	C
A135	A
A136	A
A137	A
A138	B
A139	C
A140	C
A141	B
A142	C
A144	C
A145	D
A146	A
A147	C
A148	C
A149	B
A150	B
A151	B
A152	B
A153	B
A154	A
A155	A
A156	C
A157	A
A158	A

Compound No.	CRBN HTRF IC ₅₀ (nM)
A159	C
A160	C
A161	B
A162	A
A163	B
A164	A
A165	B

Note: IC₅₀: "A": < 50 nM; "B": 50-500 nM; "C": > 500 and <5000 nM; "D": >=5000 nM.

***In vitro* Assay: IC₅₀ Measurements for binding to ER α _LBD (GST)**

• *Final assay conditions:*

1. ER α _LBD(GST) protein: 4 nM
2. Tb Anti-GST: 2nM
3. Fluormone ES2 Green tracer: 3nM
4. Incubation time: 60 min
5. DMSO: 1%
6. Assay buffer: Adding 1M DTT to Nuclear receptor Buffer K for final 5mM DTT.
7. ZPE: 1% DMSO
8. HPE: 1 μ M ARV_471
9. Lanthascreen® TR-FRET ER α Competitive Binding Assay (ThermoFisher, # A15887)

• *100x Compound preparation:*

- 1) Cherry pick 2 μ L 10mM compound stock to column 1 of a 384 intermediate plate
- 2) Add 18 μ L DMSO to column 1 to dilute compound to 1mM.
- 3) Transfer 10 μ L 1mM compound to column 1 of a LDV plate.
- 2) Add 6 μ L DMSO to column 2-10 of the LDV plate.
- 3) Compounds undergo 3-fold serial dilution (3 μ L+6 μ L) in DMSO.
- 4) Transfer 120 nL compound solution to assay plate.

ZPE: 120 nL 100% DMSO

• *Procedure:*

[0464] Prepare complete nuclear receptor buffer K by adding 1 M DTT to nuclear receptor buffer K for a final concentration of 5 mM DTT. Complete nuclear receptor buffer K must be prepared fresh daily. Prepare 2X protein solution using complete nuclear receptor buffer K containing 8nM

ER α _LBD(GST) and 4nM Tb Anti-GST. Then, prepare 2X Fluormone ES2 Green tracer (6 nM) using complete nuclear receptor buffer K. Add 6 μ L 2X Fluormone ES2 green tracer into a compound plate (PerkinElmer 6008289) by dragonfly with one-tips-addition. Subsequently, add 6 μ L 2X protein solution into the plate. Briefly and gently mix the 384-well plate on a plate shaker and incubate at room temperature protected from light for 60min. The plate is sealed with a cover to minimize evaporation. Read the plate at wavelengths of 520 nm and 495 nm. Calculate the TR-FRET ratio by dividing the emission signal at 520 nm by the emission signal at 495 nm. Generate a binding curve by plotting the emission ratio vs. the log [ligand]. To determine the IC₅₀ value, fit the data using XL-fit for a sigmoidal dose-response. The ER α binding IC₅₀ data are summarized in **Table 7**.

Table 7. ER α binding IC₅₀

Compound No	ER α HTRF IC ₅₀ (nM)
A8	A
A9	A
A21	A
A22	
A23	
A24	
A25	
A26	A
A27	A
A35	A
A36	
A37	
A38	
A39	
A40	B
A41	B
A44	A
A49	A
A50	A
A53	A
A56	A

Compound No	ER α HTRF IC ₅₀ (nM)
A58	A
A59	A
A62	A
A64	A
A66	B
A68	A
A77	A
A78	
A79	
A80	
A81	A
A84	A
A99	A
A106	A
A110	A
A113	A
A114	A
A115	A
A117	A
A118	A
A120	A
A121	A
A122	A
A125	A
A130	A
A132	A
A137	A
A138	A
A140	A
A142	A
A145	A
A146	B
A147	A
A150	A

Compound No	ER α HTRF IC ₅₀ (nM)
A153	A
A154	A

Note: IC₅₀: "A": < 5 nM; "B": $\geq$ 5 nM.

In-cell Western (ICW) assays in MCF-7 and T47D cell lines.

- Reagents and Consumables for ICW*

- 1) MCF-7 from HDB
- 2) T47D from HDB
- 3) CS-FBS, BI, Cat#04-201-1
- 4) phenol red-free RPMI1640, Thermo, Cat#11835
- 5) P/S, Biosera Liquid, Cat#XC-A4122
- 6) 384-well cell plate(black), Corning, Cat#3764
- 7) PFA, Electron Microscopy Sciences, Cat#15710
- 8) Intercept (PBS) Blocking Buffer, Licor, Cat# 927-70001
- 9) Triton X-100, Sigma, Cat#X-100
- 10) ER antibody, CST, Cat#13258
- 11) IRDye 800CW Goat anti-Rabbit IgG, LiCor, Cat#926-32211
- 12) CellTag 700 Stain, Licor, Cat# 926-41090
- 13) Odyssey® DLx Imaging System, LiCor
- 14) EnVision, PerkinElmer

- Procedures for ICW assays*

In vitro Assay: MCF-7 and T47D ICW assay

[0465] Day1: MCF-7 and T47D cell (From HDB) were seeded in 384-well black plate with phenol red-free RPMI1640 + 10% CS-FBS + 1% P/S medium (1×10^4 for MCF-7 and 1.5×10^4 for T47D cells/well, 30ul medium) for overnight at 37°C, 5%CO₂ incubator.

[0466] Day 2: Cells were treated at desired compound concentrations (0.02 to 300 nM) and DMSO as vehicle control for 16 hrs at 37°C, 5%CO₂ incubator.

[0467] Day 3: After 16 hrs of compounds treatment, cells were fixed by 4% PFA and

[0468] permeabilized with elution buffer (0.1% Triton X-100 in 1% PBS Solution). Subsequently, cells were blocked with Intercept (PBS) Blocking Buffer (Li-COR, Odyssey Blocking Buffer), and were stained with ER (1:500, Cell signaling) primary antibody for overnight at cold room.

[0469] Day 4: Remove the buffer, add IRDye 800CW Goat anti-Rabbit IgG Secondary Antibody (1:2000) and CellTag 700 Stain (1:500) in Intercept (PBS) Blocking Buffer. Finally, cell plate is placed in incubator to dry. Image and signal were captured on Odyssey® DLx Imaging System. Data was further analyzed using XLfit using four parameters dose response curve to determine DC_{50} and D_{max} .

- *Data analysis*

[0470] Data are analyzed by image studio V5.2 and XLfit.

[0471] Half maximal degradation concentration values (DC_{50}) and maximal degradation percentage (D_{max} , %) of ER are summarized in **Table 8**.

Table 8. ER degradation by in-cell western (ICW) assays

Compound No	MCF7 DC_{50} (nM)	MCF7 D_{max} %	T47D DC_{50} (nM)	T47D D_{max} %
A1	B	B		
A2	B	B		
A3	B	C		
A6	B	B		
A7	B	B		
A8	B	B		
A9	B	B		
A14	B	C		
A16	A	B		
A17	A	B		
A27	B	B		
A33	B	B	B	B
A34	B	C		
A35	B	C	B	B
A36	C	C		
A37	B	C		

Compound No	MCF7 DC ₅₀ (nM)	MCF7 D _{max} %	T47D DC ₅₀ (nM)	T47D D _{max} %
A38	C	C		
A39	D	D		
A40	B	B	A	B
A41	B	B	A	A
A42	D	D		
A43	D	D		
A44	B	B	A	B
A45	D	D		
A46	D	D		
A47	C	C		
A48	D	D		
A49	B	B	B	B
A50	B	B	A	B
A51	A	C	A	C
A52	D	D	A	C
A53	B	B	B	A
A54	C	C	B	A
A55	D	D	D	D
A56	B	B	A	A
A57	D	D	D	D
A58	B	C	B	B
A59	B	B	A	A
A60	A	C	B	D
A61	B	C	B	B
A62	A	B	A	B
A63	D	D	D	D
A64	B	C	B	B
A65	B	D	B	C

Compound No	MCF7 DC ₅₀ (nM)	MCF7 D _{max} %	T47D DC ₅₀ (nM)	T47D D _{max} %
A66	B	B	B	B
A67	D	D	C	D
A68	B	B	B	A
A69	B	D	B	C
A70	D	D	B	C
A71	A	B	A	B
A72	D	D	A	C
A73	A	B	A	B
A74	A	D	B	C
A75	A	C	B	B
A76			D	D
A77	A	B	A	B
A78			C	C
A79	A	A	A	A
A80			C	B
A81	A	A	A	A
A82			B	C
A83			D	D
A84	A	B	A	B
A85	A	B	B	B
A86			A	C
A87			B	C
A88	B	B	B	B
A89	A	A	A	A
A90	B	B	A	B
A91	B	B	B	B
A92	A	B	A	B
A93	B	B	A	B

Compound No	MCF7 DC ₅₀ (nM)	MCF7 D _{max} %	T47D DC ₅₀ (nM)	T47D D _{max} %
A94			B	B
A95	B	B	B	B
A96	A	B	A	B
A97			A	C
A98	A	A	A	A
A99	A	B	A	B
A100	B	B	B	B
A101			A	D
A102	A	B		
A103	B	B	B	B
A104	B	A	B	A
A105	C	C	B	C
A106	A	A	A	A
A107	B	C	A	C
A108	B	B	A	A76.29
A109	C	C	B	C
A110	A	B	A	B
A111	A	B	A	B
A112	D	D	B	D
A113	A	B	A	B
A114	A	A	A	A
A115	A	A	A	A
A116	A	B	A	B
A117	A	A	A	A
A118	B	A	B	A
A119	B	B	B	B
A120	B	A	A	A
A121	A	A	A	A

Compound No	MCF7 DC ₅₀ (nM)	MCF7 D _{max} %	T47D DC ₅₀ (nM)	T47D D _{max} %
A122	A	A	A	A
A123	A	B	A	B
A124	A	B	A	B
A125	A	A	A	A
A126	B	C	A	B
A127	A	B	A	C
A128	A	B	A	B
A129	C	C	C	B
A130	A	A	A	A
A131	B	B	B	B
A132	B	B	B	B
A133	B	C	A	C
A134	A	A	A	A
A135	A	C	A	C
A136	A	B	A	B
A137	A	B	A	B
A138	A	A	A	B
A139	A	B	A	B
A140	A	B	A	B
A141	B	B	B	B
A142	B	B	A	B
A143	C	C	C	C
A144	C	C	D	D
A145	B	B	A	B
A146	B	B	B	C
A147	A	B	A	B
A148	A	B	A	B
A149	A	B	A	B

Compound No	MCF7 DC ₅₀ (nM)	MCF7 D _{max} %	T47D DC ₅₀ (nM)	T47D D _{max} %
A150	A	C	A	C
A151	A	B	A	B
A152	C	B	B	B
A153	A	B	A	A
A154	A	B	A	A
A155	D	D	B	C
A156	D	D	A	C
A157	A	B	A	A
A158	A	B	A	A
A159	B	C	B	B
A160	B	D	B	C
A161	A	B	A	A
A162	A	C	A	A
A163	A	C	A	B
A164	A	C	B	B
A165	0.31	C	A	B

Note: IC₅₀: "A": < 1 nM; "B": 1-10 nM; "C": >10 and <100 nM; "D": ≥100 nM.

D_{max}: "A": ≥75%; "B": >50% and <75%; "C": 25%-50%; "D": <25%.

CellTiter-Glo® (CTG) assays in MCF-7 and T47D cell lines.

- *Reagents and Consumables for CTG*

- 1) MCF-7 from HDB
- 2) T47D from HDB
- 3) CS-FBS, BI, Cat#04-201-1
- 4) phenol red-free RPMI1640, Thermo, Cat#11835
- 5) P/S, Biosera Liquid, Cat#XC-A4122
- 6) 384-well cell plate(white), Corning, Cat#3765
- 7) Cell TiterGlo reagent, Promega, Cat#G7573
- 8) EnVision, PerkinElmer

- *Medium*

1) Cell culture medium: phenol red-free RPMI1640+10%CS-FBS,1% P/S

- *Procedures for CTG assay*

In vitro Assay: MCF-7 and T47D CTG assay

[0472] Day-1: MCF-7 and T47D cell (From HDB) were cultured in 384-well white plate with phenol red-free RPMI1640 + 10% CS-FBS + 1% P/S medium (1,000cells/well) for overnight at 37°C, 5%CO₂ incubator.

[0473] Day 0: Cells were treated at desired compound concentrations (0.5 to 10000nM) (DMSO and Staurosporine as control) for Day 6 at 37°C,5%CO₂ incubator.

[0474] Day 0 and Day 6: add Cell TiterGlo reagent and read on EnVision after 30min incubation for data generation.

- *Data analysis*

[0475] Data are analyzed by image studio V5.2 and XLfit.

[0476] The IC₅₀ data on day 6 were summarized in **Table 9**.

Table 9. CellTiter-Glo® (proliferation) data

Compound No.	MCF7 Proliferation IC ₅₀ (nM)	T47D Proliferation IC ₅₀ (nM)
A50	B	B
A51	B	B
A53	B	B
A56	A	A
A58	B	B
A59	B	B
A62	A	A
A92	A	A
A95	B	A
A96	A	A
A98	A	A
A113	A	D
A114	A	A
A115	B	B
A116	A	B

Compound No.	MCF7 Proliferation IC ₅₀ (nM)	T47D Proliferation IC ₅₀ (nM)
A117	A	A
A118	B	B
A119	B	C
A120	B	B
A121	A	B
A122	A	A
A138	A	A
A150	B	B
A154	A	A
A161	A	

Note: IC₅₀: "A": < 50 nM; "B": 50-500 nM; "C": > 500 and <5000 nM; "D": ≥5000 nM.

FOR COMPOUND B1 to B5

[0477] In-cell western blot analysis. a. seed cells in black-sided/clear bottom 96- or 384-well plates at 40,000 or 10,000 cells/well, overnight; b. add diluted compounds (final 0.5% DMSO), 16 hours. 16 h later, remove medium, add 100 µL or 25 µL of 3.7-4.0% formaldehyde (PBS:FA=9:1), RT 20 min, no shaking; c. wash with PBS, and permeabilized with 100 µL or 25 µL/well of 1X PBS + 0.1% Triton X-100 10 minutes; d. block with 100 µL or 25 µL Licor blocking buffer (Li-Cor), RT 1h, moderate shaking; d. Add 100 µL or 25 µL of anti-ER (cs-8644, 1:500-1,000) + GAPDH(Millipore MAB374, 1:1000) in Block + 0.05%Tween 20. RT 2h, gentle shaking. Negative control: cells plus secondary antibodies (no primary antibodies); e. wash x 4 with PBS +0.05-0.1% Tween 20, gentel shaking; f. anti-rabbit-680 and anti-mouse-800 (both 1:1000 in LiCor block +0.05% Tween20, RT 1h, gentle shaking, no light. LI-COR: 0.2% to reduce background; g. wash x 4 with PBS +0.05% Tween 20, gental shaking; h. add 100 µL or 25 µL of PBS to each well and read on CLX plate reader. The relative ER percentage in treated cells were obtained by comparing the values of treated wells to those in untreated and DMSO-treated wells as 100%.

[0478] Western Blot Analysis. Western blot analysis was performed essentially as described previously. The cells treated with indicated compounds were lysed in Radioimmunoprecipitation

Assay Protein Lysis and Extraction Buffer (25 mmol/L Tris.HCl, pH 7.6, 150 mmol/L NaCl, 1% Nonidet P-40, 1% sodium deoxycholate, and 0.1% sodium dodecyl sulfate) containing proteinase inhibitor cocktail (Roche Diagnostics, Mannheim, Germany). Equal amounts of total protein were electrophoresed through 10% SDS-polyacrylamide gels after determination of protein concentration by BCA assay (Fisher Scientific, Pittsburgh, PA). The separated protein bands were transferred onto PVDF membranes (GE Healthcare Life Sciences, Marlborough, MA) and blotted against different antibodies, as indicated. The blots were scanned, and the band intensities were quantified using GelQuant.NET software provided by biochemlabsolutions.com. The relative mean intensity of target proteins was expressed after normalization to the intensity of glyceraldehyde-3-phosphate dehydrogenase bands.

[0479] Cell Growth Assay. The cells were seeded at 1500/well in 96 well plates overnight. One day after the seeding, they were treated with indicated doses of compounds respectively. 4 days after the compound treatment, 10% WST-8 reagent was added to the culture medium and incubate in a CO2 incubator at 37°C for 2.5 hours. Before reading, the plate was mixed gently on an orbital shaker for one minute to ensure homogeneous distribution of color. The absorbance was measured of each sample using a microplate reader at a wavelength of 450 nm. The relative absorbance was calculated against the vehicle control from three individually repeats.

[0480] In vivo pharmacodynamic and efficacy studies. To develop breast cancer cell line xenografts, mice was given 4 ug/ml 17 β -Estradiol in 0.05% EtOH drinking water for 1 week, followed with 8 ug/ml 17 β -Estradiol in 0.1% EtOH drinking water thereafter. Five million cells in 50% Matrigel were injected subcutaneously into SCID mice. when tumors reached 100–400 mm³, mice were treated with vehicle control (5%DMSO, 10%solulol, 85%Water) or indicated dose of the drugs, sacrificed at indicated time-points, and tumor tissue was harvested for analysis. For in vivo efficacy experiments, when tumors reached 80–200 mm³, mice were randomized into groups. vehicle control (5%DMSO, 10%solulol, 85%Water) was given at the dose and with the duration indicated. Tumor sizes and animal weights were measured 2–3 times per week. Tumor volume (mm³) = (length $\times$ width²)/2. Tumor growth inhibition was calculated as TGI (%) = (Vc–Vt)/(Vc–Vo) $\times$ 100, where Vc, Vt are the median of control and treated groups at the end of the study and Vo at the start. All the in vivo studies were performed under an animal protocol (PRO00005315) approved by the University Committee on Use and Care of Animals of the

University of Michigan, in accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health.

Table 10.

Compound No.	ICW DC ₅₀ (nM)	Cell Growth Inhibition in T47D cell line IC ₅₀ (nM)
B1	C	C
B2	C	C
B3	C	C
B4	C	C
B5	C	C

Note:

DC₅₀: "A": < 10 nM; "B": 10-100 nM; "C": > 100 nM

IC₅₀: "A": < 1 nM; "B": 1-10 nM; "C": > 10 nM

In vitro efficacy studies

ER degradation in breast cancer cell lines

[0481] ER degradation is measured using several different breast cancer cell lines in multiple cellular assays. Cell lines to be used for this purpose include, but are not limited to, MCF-7 cells (ATCC, catalog # HB-22), T47D cells (ATCC, catalog # HTB-133), or CAMA1 cells (ATCC, catalog # HTB-21) expressing wild type ER, or breast cancer cell lines expressing clinically relevant ER gene mutations, such as MCF-7 cells engineered to express Q380E, Y537S, or D538G ER. Endogenous ER in breast cancer cell lines is measured using Western blot, in-cell Western assay or HiBiT assay in cells engineered to express a HiBiT-tagged version of ER. ER degradation is measured at times, e.g., between 2 and 24 hours. Cells are treated with vehicle control (DMSO) or the compound at various concentrations (e.g., ranging from 0.005 nM to 100 nM). Some assays are conducted in the presence of estradiol, while other assays are conducted in the absence of estradiol. The compounds of this disclosure are expected to degrade ER protein in breast cancer cell lines.

Cell growth inhibition in breast cancer cell lines

[0482] Cell growth inhibition is measured using several different cell lines (e.g., the ones mentioned above) to test whether ER degradation with the compounds of this disclosure impacts cell growth inhibition in breast cancer cell lines. Cells are treated with vehicle control (DMSO)

or the compound at various concentrations (e.g., ranging from 0.003 nM to 100 nM) for about 144 hours. Briefly cells per well are plated in each well of a 384-well plate. 24 hours later, the compound is dispensed into the wells. 144 hours after compound is added to wells, CellTiter-Glo (Promega) is added to wells and plates are read on an EnVision® Plate Reader (Perkin Elmer). The compounds of this disclosure are expected to inhibit or retard cell growth in breast cancer cell lines.

***In vivo* Pharmacokinetic and Pharmacodynamic (PKPD) and efficacy studies**

ER degradation in MCF-7 tumor model

[0483] To evaluate the ability of compounds of this disclosure to reduce ER protein levels *in vivo*, an orthotopic human breast cancer MCF7 xenograft model in female NOD/SCID mice is used. Each mouse is implanted subcutaneously with estrogen pellets at the right flank before the tumor inoculation. Each mouse is inoculated at the right third mammary fat pad with MCF7 tumor cells (2×10^7) in 0.2 mL of PBS with Matrigel (1:1) for tumor development. Mice are treated with vehicle control (e.g., 5% DMSO, 10% solutol, 85% water) or the compound for 6 or 24 hours past the 3rd dose once tumors reach 400-500 mm³. Tumors are harvested at given times, bisected and flash frozen. Half of the tumor is analyzed for compound concentration in the tumor or plasma and the other half is analyzed using Western blot to quantify the extent of ER degradation. The compounds of this disclosure are expected to demonstrate dose-dependent ER degradation in MCF-7 tumor model.

Tumor growth inhibition and regression in mice

[0484] To evaluate the ability of compounds of this disclosure to inhibit tumor growth and/or cause tumor growth regression *in vivo*, the MCF-7 human breast carcinoma female athymic nude mouse model is used. Mice are supplemented with 10 µg/mL 17 beta-estradiol in their drinking water 3 days prior to cell implantation and then for the duration of the study. Mice are injected with 1×10^7 MCF-7 tumor cells in PBS subcutaneously in the flank. Mice are treated with vehicle control (e.g., 5% DMSO, 10% solutol, 85% Water) or the compound once tumors reach 150-200 mm³, and sacrificed when tumor volume reaches 2000 mm³ or at the end of the study (whichever occurs first). Tumor sizes and animal weights and caliper measurements of tumors are collected 2-3 times per week. Tumor volume (mm³) = (length×width²)/2. Tumor growth inhibition is calculated using $^{D/T/D/C} \text{ TGI (\%)} = (1 - ((T_e - T_0)/(C_e - C_0))) * 100$, where $^{D/T/D/C}$ is the difference (delta) or change in

test vs control TGI; T_e = Test tumor volume endpoint, T_0 = Test tumor volume at start of dosing, C_e = Vehicle control tumor volume endpoint, C_0 = Vehicle control tumor volume at start of dosing. Tumor growth regression is calculated using % Tumor Regression = $-(1-(T_e/T_0))*100$ where T_e = Test tumor volume (TV) endpoint, Test T_0 = TV at start of dosing. The compounds of this disclosure are expected to inhibit tumor growth and induce tumor shrinkage over a range of doses.

INCORPORATION BY REFERENCE

[0485] All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

EQUIVALENTS

[0486] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an agent” includes a plurality of such agents, and reference to “the cell” includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth.

[0487] While specific embodiments of the subject invention have been discussed, the above specification is illustrative and not restrictive. Many variations of the invention will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the invention should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

WHAT IS CLAIMED IS:

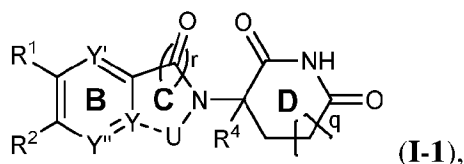
1. A compound of Formula I:

T-L-C (I),

or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof,

wherein:

C is of Formula **I-1**



wherein:

R^1 is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u;

R^2 is *-Cy²-, wherein * denotes attachment to **L**;

-Cy²- is C₃₋₁₂ carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u; or

R^1 and R^2 , together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted C₃₋₁₂ carbocycle or 5- to 16-membered heterocycle;

Y'' is N or CR³;

R^3 is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl,

alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; or

R^2 and R^3 , together with the intervening carbon atoms, form Ring A attached to **L**, wherein Ring A is optionally substituted 5- to 16-membered heterocycle;

provided that R^1 and R^2 , and R^2 and R^3 , do not both form Ring A attached to **L**;

Y' is N or $CR^{Y'}$;

$R^{Y'}$ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

--- denotes an optional covalent bond between Y and U;

when the bond between Y and U is absent:

r is 0 or 1;

Y is N or CR^Y ;

R^Y is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u ;

U is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u ;

when the bond between Y and U is present:

r is 1;

Y is C;

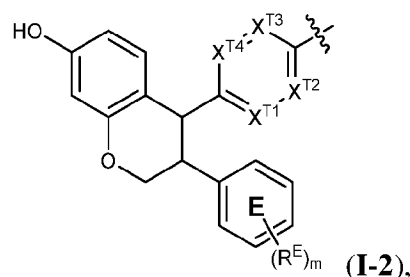
U is -CH₂-, -C(=O)-, -(C=O)-N(R^U)-*, or -N=C(R^U)-*;

R^U is H or C₁₋₆ alkyl optionally substituted with one or more R^u , and * denotes attachment to Ring B;

R^4 is hydrogen, deuterium, C₁₋₆ haloalkyl, or C₁₋₆ alkyl; and

q is an integer from 0 to 2,

T is of Formula **I-2**:



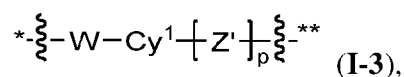
wherein:

each of $\mathbf{X}^{\text{T1}}$, $\mathbf{X}^{\text{T2}}$, $\mathbf{X}^{\text{T3}}$, and $\mathbf{X}^{\text{T4}}$ is independently $\mathbf{N}$ or $\mathbf{CR}^{\text{T}}$;

each R^E is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

m is an integer selected from 0 to 5,

L is of Formula I-3:



wherein:

* denotes attachment to **T** and ** denotes attachment to **C**;

W is absent; or

W is C₁₋₃ alkylene, -O-, -NR^W-, or -(C=O)-, wherein the alkylene is optionally substituted by one or more R^u;

Cy¹ is absent; or

Cy¹ is 6-membered heteroarylene, C₆ arylene, C₃₋₁₂ membered carbocyclylene, or 3- to 12-membered heterocyclylene, wherein the arylene, heteroarylene, carbocyclylene, or heterocyclylene is optionally substituted by one or more R^u;

Z' is absent; or

each Z' is independently C₁₋₃ alkylene, -O-, -NR^W-, -(C=O)-, C₃₋₁₂ membered carbocyclene, or 3- to 12-membered heterocyclene, wherein the alkylene, carbocyclene, or heterocyclene is optionally substituted by one or more R^u;
 R^W is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u; and
 p is an integer selected from 0 to 8,

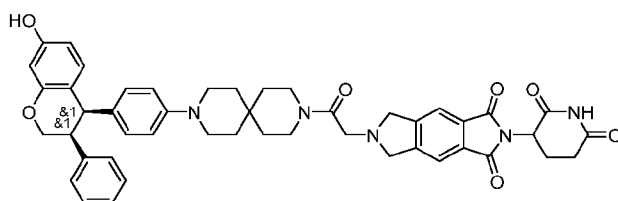
wherein:

each R^u is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d; wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more substituents selected from oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, and 3- to 6-membered heterocyclyl; or
 two R^u, together with the one or more intervening atoms, form C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl or 3- to 12-membered heterocyclyl;
 each R^a is independently C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl;
 each R^b is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; and
 each R^c and R^d is independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, C₆₋₁₀ aryl, or 5- to 10-membered heteroaryl; or
 R^c and R^d, together with the nitrogen atom to which they are attached, form 3- to 12-membered heterocyclyl,
 wherein each of R^a, R^b, R^c, and R^d is independently and optionally substituted with one or more R^z; and
 each R^z is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ carbocyclyl, or 3- to 6-membered heterocyclyl.

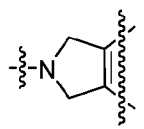
2. The compound of claim 1, wherein

1) when the bond between Y and U is present, U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$, and r is 1, then either R^1 and R^2 , or R^2 and R^3 , together with the intervening carbon atoms, form Ring A attached to **L**; and

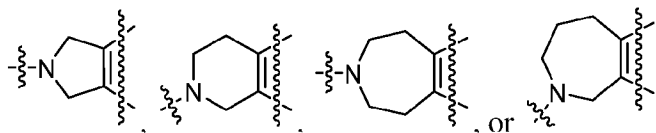
2) the compound is not



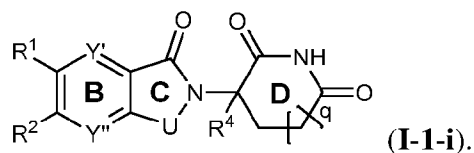
3. The compound of claim 1 or 2, wherein when the bond between Y and U is present, U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$, and r is 1, then Ring A is not



4. The compound of any one of claims 1-3, wherein when the bond between Y and U is present, U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$, and r is 1, then Ring A is not

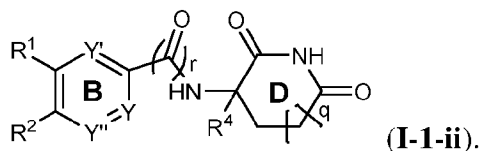


5. The compound of any one of claims 1-4, wherein **C** is of Formula **I-1-i**

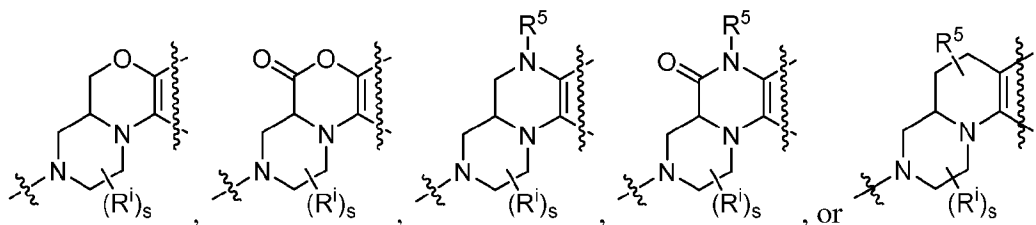


6. The compound of claim 5, wherein U is $-\text{CH}_2-$ or $-\text{C}(=\text{O})-$.

7. The compound of any one of claims 1-4, wherein **C** is of Formula **I-1-ii**



8. The compound of claim 7, wherein Y is N.
9. The compound of claim 7, wherein Y is CR^Y, and R^Y is hydrogen, halogen, or C₁₋₆ alkoxy, wherein the alkoxy is optionally substituted with one or more R^u.
10. The compound of any one of claims 1-9, wherein R¹ and R², together with the intervening carbon atoms, form Ring A attached to L, wherein the Ring A is optionally substituted 5- to 16-membered heterocycle.
11. The compound of claim 10, wherein Ring A is optionally substituted 7- to 16-membered fused heterocycle.
12. The compound of claim 11, wherein Ring A is



wherein:

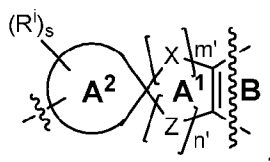
R⁵ is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u;

each Rⁱ is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -

$C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and s is an integer selected from 0 to 8, as valency permits.

13. The compound of claim 10, wherein Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

14. The compound of claim 13, wherein Ring A is:



wherein:

Ring A^2 is C_{3-8} carbocycle or 3- to 8-membered heterocycle;

each X is independently $-C(R^{X1})_2-$, $-NR^{X2}-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

each Z is independently $-C(R^{Z1})_2-$, $-NR^{Z2}-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

two geminal R^{X1} or two geminal R^{Z1} together form oxo; or

two R^{X1} or two R^{Z1} , together with the intervening carbon atom(s), form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

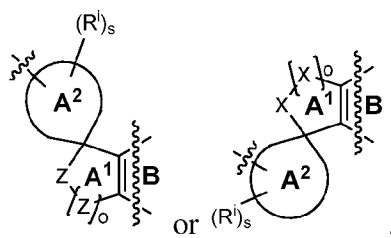
each occurrence of R^{X2} and R^{Z2} is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

m' and n' are independently an integer selected from 0-3, wherein m' and n' are not both 0;

each R^i is independently oxo, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OH}$, $-\text{NH}_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-\text{SR}^b$, $-\text{S}(=\text{O})\text{R}^a$, $-\text{S}(=\text{O})_2\text{R}^a$, $-\text{S}(=\text{O})_2\text{OR}^b$, $-\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^c\text{S}(=\text{O})_2\text{R}^a$, $-\text{NR}^c\text{S}(=\text{O})\text{R}^a$, $-\text{NR}^c\text{S}(=\text{O})_2\text{OR}^b$, $-\text{NR}^c\text{S}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{NR}^b\text{C}(=\text{O})\text{R}^a$, $-\text{NR}^b\text{C}(=\text{O})\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{R}^a$, $-\text{OS}(=\text{O})_2\text{OR}^b$, $-\text{OS}(=\text{O})_2\text{NR}^c\text{R}^d$, $-\text{OC}(=\text{O})\text{R}^a$, $-\text{OC}(=\text{O})\text{OR}^b$, $-\text{OC}(=\text{O})\text{NR}^c\text{R}^d$, $-\text{C}(=\text{O})\text{R}^a$, $-\text{C}(=\text{O})\text{OR}^b$, or $-\text{C}(=\text{O})\text{NR}^c\text{R}^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and s is an integer selected from 0 to 8, as valency permits, provided that when none of m' and n' is 0, then Ring A^1 is 4- to 9-membered heterocycle.

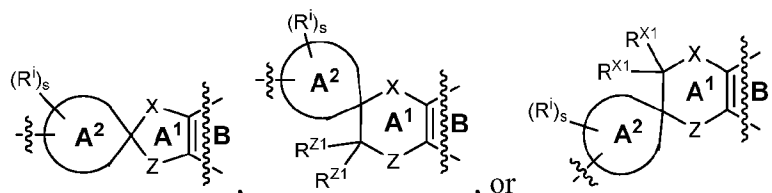
15. The compound of claim 14, wherein Ring A is:

1)



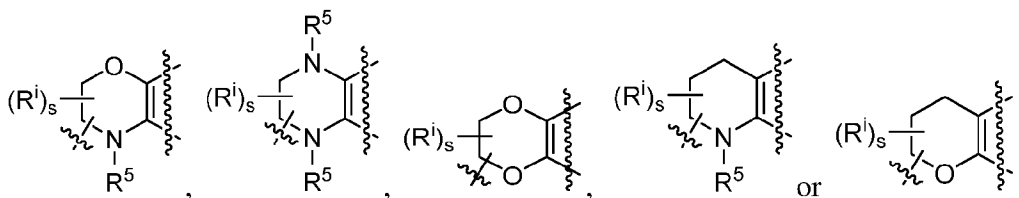
wherein o is 0 or 1; or

2)



16. The compound of claim 10, wherein Ring A is optionally substituted 5- to 6-membered heterocycle.

17. The compound of claim 16, wherein Ring A is



wherein:

R⁵ is hydrogen or C₁₋₆ alkyl optionally substituted with one or more R^u;

each Rⁱ is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u; and

s is an integer selected from 0 to 8, as valency permits.

18. The compound of any one of claims 10-17, wherein Y'' is N.

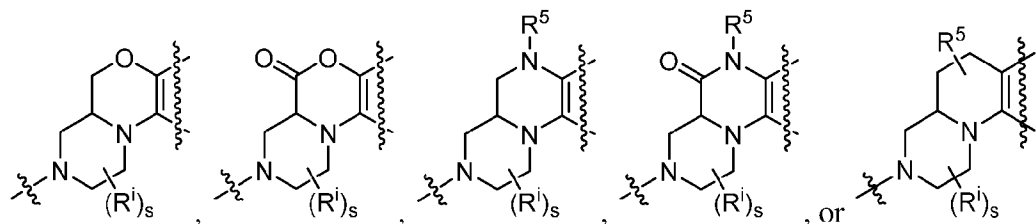
19. The compound of any one of claims 10-17, wherein Y'' is CR³, and R³ is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u.

20. The compound of claim 19, wherein R³ is hydrogen, halogen, or C₁₋₆ alkoxy, wherein the alkoxy is optionally substituted with one or more R^u.

21. The compound of any one of claims 1-9, wherein R² and R³, together with the intervening carbon atoms, form Ring A attached to L, wherein the Ring A is optionally substituted 5- to 16-membered heterocycle.

22. The compound of claim 21, wherein Ring A is optionally substituted 7- to 16-membered fused heterocycle.

23. The compound of claim 22, wherein Ring A is



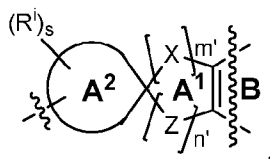
wherein:

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

each R^i is independently oxo, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and s is an integer selected from 0 to 8, as valency permits.

24. The compound of claim 21, wherein Ring A is optionally substituted 7- to 16-membered spiro heterocycle.

25. The compound of claim 24, wherein Ring A is:



wherein:

Ring A^2 is C_{3-8} carbocycle or 3- to 8-membered heterocycle;

each X is independently $-C(R^{X1})_2-$, $-NR^{X2}-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

each Z is independently $-C(R^{Z1})_2-$, $-NR^{Z2}-$, $-O-$, $-S-$, $-S(=O)-$, or $-S(=O)_2-$;

each occurrence of R^{X1} and R^{Z1} is independently hydrogen, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-6} carbocyclyl, 3- to 6-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ;

two geminal R^{X1} or two geminal R^{Z1} together form oxo; or

two R^{X1} or two R^{Z1} , together with the intervening carbon atom(s), form C_{3-12} carbocyclyl or 3- to 12-membered heterocyclyl, wherein the carbocyclyl or heterocyclyl is optionally substituted with one or more R^u ;

each occurrence of R^{X2} and R^{Z2} is independently hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

m' and n' are independently an integer selected from 0-3, wherein m' and n' are not both 0;

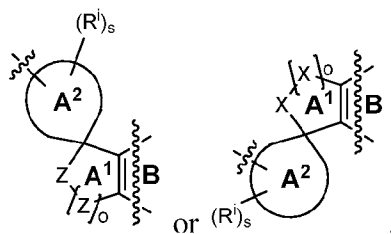
each R^i is independently oxo, halogen, $-CN$, $-NO_2$, $-OH$, $-NH_2$, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, $-SR^b$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2OR^b$, $-S(=O)_2NR^cR^d$, $-NR^cS(=O)_2R^a$, $-NR^cS(=O)R^a$, $-NR^cS(=O)_2OR^b$, $-NR^cS(=O)_2NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-OS(=O)_2R^a$, $-OS(=O)_2OR^b$, $-OS(=O)_2NR^cR^d$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, $-C(=O)R^a$, $-C(=O)OR^b$, or $-C(=O)NR^cR^d$, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and

s is an integer selected from 0 to 8, as valency permits,

provided that when none of m' and n' is 0, then Ring A^1 is 4- to 9-membered heterocycle.

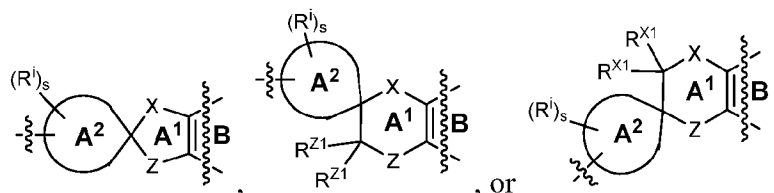
26. The compound of claim 25, wherein Ring A is:

1)



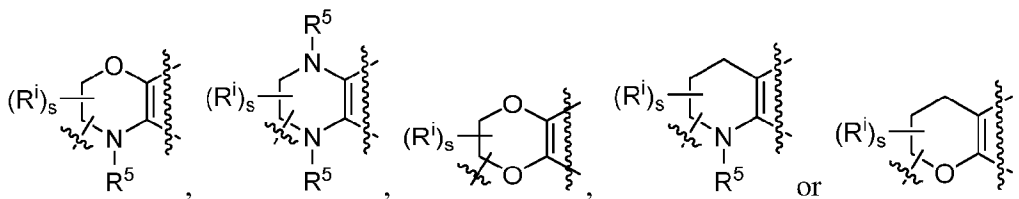
wherein o is 0 or 1; or

2)



27. The compound of claim 21, wherein Ring A is optionally substituted 5- to 6-membered heterocycle.

28. The compound of claim 27, wherein Ring A is



wherein:

R^5 is hydrogen or C_{1-6} alkyl optionally substituted with one or more R^u ;

each R^i is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, 3- to 12-membered heterocyclyl, -SR^b, -S(=O)R^a, -S(=O)₂R^a, -S(=O)₂OR^b, -S(=O)₂NR^cR^d, -NR^cS(=O)₂R^a, -NR^cS(=O)R^a, -NR^cS(=O)₂OR^b, -NR^cS(=O)₂NR^cR^d, -NR^bC(=O)NR^cR^d, -NR^bC(=O)R^a, -NR^bC(=O)OR^b, -OS(=O)₂R^a, -OS(=O)₂OR^b, -OS(=O)₂NR^cR^d, -OC(=O)R^a, -OC(=O)OR^b, -OC(=O)NR^cR^d, -C(=O)R^a, -C(=O)OR^b, or -C(=O)NR^cR^d, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl is optionally substituted with one or more R^u ; and s is an integer selected from 0 to 8, as valency permits.

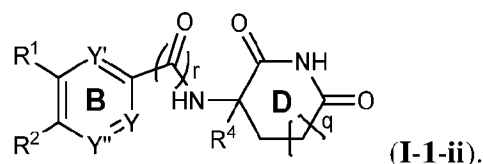
29. The compound of any one of claims 21-28, wherein R^1 is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

30. The compound of claim 29, wherein R^1 is hydrogen, halogen, or C₁₋₆ alkoxy, wherein the alkoxy is optionally substituted with one or more R^u .

31. The compound of any one of claims 10-30, wherein each R^i is independently oxo, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

32. The compound of claim 31, wherein s is 0.

33. The compound of any one of claims 1-4, wherein **C** is of Formula **I-1-ii**



34. The compound of claim 33, wherein R^2 is *-Cy²-, wherein * denotes attachment to **L**.

35. The compound of claim 33 or 34, wherein -Cy²- is C₅₋₁₂ fused carbocyclylene or 5- to 12-membered fused heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted with one or more R^u .

36. The compound of any one of claims 33-35, wherein R^1 is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl,

alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

37. The compound of claim 36, wherein R^1 is hydrogen, halogen, or C_{1-6} alkoxy, wherein the alkoxy is optionally substituted with one or more R^u .

38. The compound of any one of claims 33-37, wherein Y is N.

39. The compound of any one of claims 33-37, wherein Y is CR^Y , and R^Y is hydrogen, halogen, or C_{1-6} alkoxy, wherein the alkoxy is optionally substituted with one or more R^u .

40. The compound of any one of claims 33-37, wherein Y'' is CR^3 , and R^3 is hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C_{1-6} alkyl, C_{1-6} alkoxy, C_{1-6} alkylamino, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, C_{3-12} carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

41. The compound of claim 40, wherein R^3 is hydrogen, halogen, or C_{1-6} alkoxy, wherein the alkoxy is optionally substituted with one or more R^u .

42. The compound of any one of claims 33-41, wherein r is 0.

43. The compound of any one of claims 33-41, wherein r is 1.

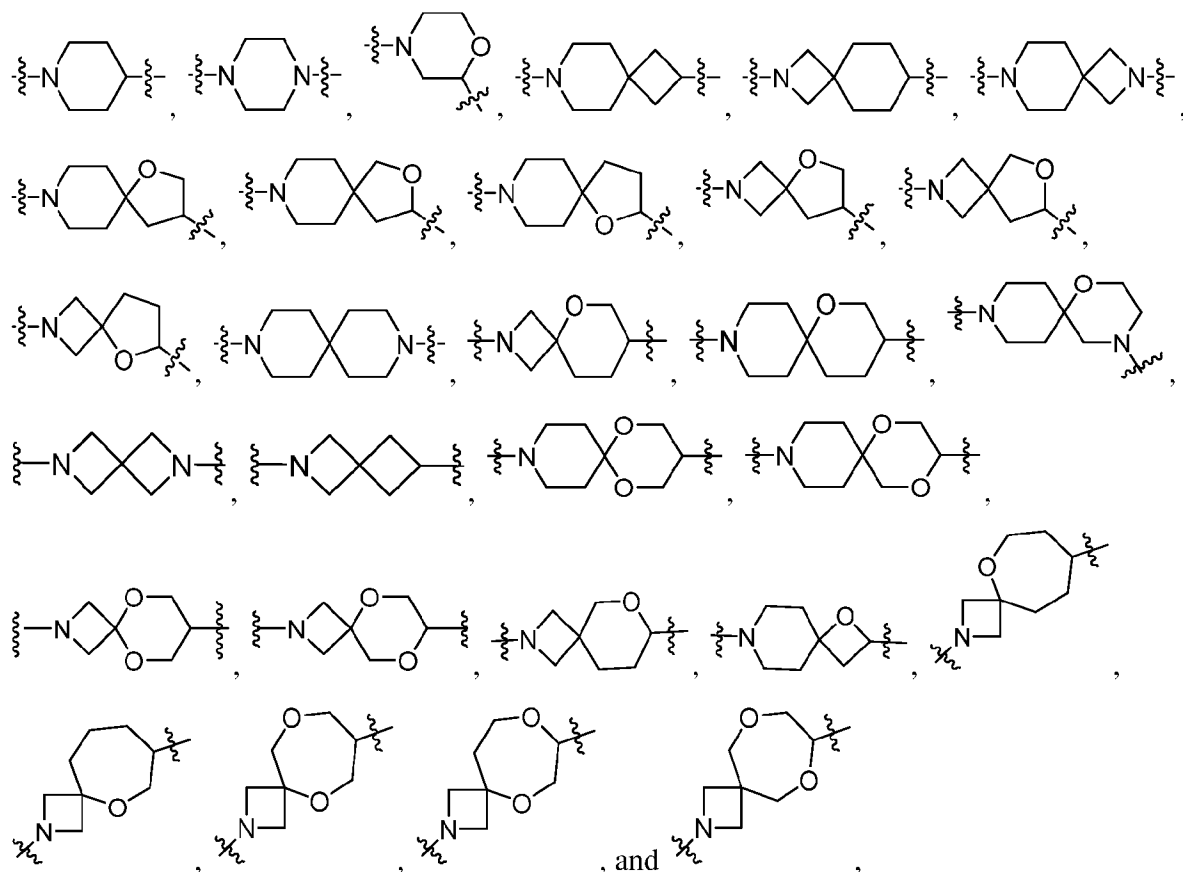
44. The compound of any one of claims 1-43, wherein R^4 is hydrogen.

45. The compound of any one of claims 1-44, wherein q is 1.

46. The compound of any one of claims 1-45, wherein each of X^{T1} , X^{T2} , X^{T3} , and X^{T4} is CR^T .

47. The compound of claim 46, wherein each of X^{T1} , X^{T2} , X^{T3} , and X^{T4} is CH; each of X^{T1} and X^{T4} is CH, one of X^{T2} and X^{T3} is CH, and the other one of X^{T2} and X^{T3} is CF; or one of X^{T1} and X^{T4} is C(OCH₃), the other one of X^{T1} and X^{T4} is CH, and each X^{T2} and X^{T3} is CH.
48. The compound of claim 46, wherein X^{T1} is C(OCH₃), X^{T3} is CF, and each of X^{T2} and X^{T4} is CH; or X^{T2} is CF, X^{T4} is C(OCH₃), and each of X^{T1} and X^{T3} is CH.
49. The compound of any one of claims 1-45, wherein one of X^{T1} , X^{T2} , X^{T3} , and X^{T4} is N.
50. The compound of claim 49, wherein each of X^{T1} and X^{T4} is CH, one of X^{T2} and X^{T3} is CH, and the other one of X^{T2} and X^{T3} is N.
51. The compound of any one of claims 1-45, wherein two of X^{T1} , X^{T2} , X^{T3} , and X^{T4} are N.
52. The compound of claim 51, wherein each of X^{T1} and X^{T4} is CH, and each of X^{T2} and X^{T3} is N.
53. The compound of any one of claims 46-52, wherein each R^T is independently hydrogen, halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .
54. The compound of claim 53, wherein each R^T is independently hydrogen, C₁₋₆ alkoxy, or halogen.
55. The compound of any one of claims 46-54, wherein each R^E is independently halogen, -CN, -NO₂, -OH, -NH₂, C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylamino, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₆₋₁₀ aryl, 5- to 10-membered heteroaryl, C₃₋₁₂ carbocyclyl, or 3- to 12-membered heterocyclyl, wherein the alkyl, alkoxy, alkylamino, alkenyl, alkynyl, aryl, heteroaryl, carbocyclyl, or heterocyclyl is optionally substituted with one or more R^u .

56. The compound of claim 55, wherein R^E is C₁₋₆ alkoxy, wherein the alkoxy is optionally substituted with one or more R^u.
57. The compound of any one of claims 56-58, wherein m is 0.
58. The compound of any one of claims 1-57, wherein Cy¹ is C₃₋₁₂ carbocyclylene or 3- to 12-membered heterocyclylene, wherein the carbocyclylene or heterocyclylene is optionally substituted by one or more R^u.
59. The compound of any one of claims 1-57, wherein Cy¹ is 3- to 12-membered heterocyclylene, wherein the heterocyclylene is optionally substituted by one or more R^u.
60. The compound of claim 59, wherein Cy¹ is 3- to 12-membered heterocyclylene selected from morpholinylene, piperidinylene, piperazinylene, 7-azaspiro[3.5]nonanylene, 2,7-diazaspiro[3.5]nonanylene, 2-azaspiro[3.5]nonanylene, 2,7-diazaspiro[3.5]nonanylene, 1-oxa-8-azaspiro[4.5]decenylene, 2-oxa-8-azaspiro[4.5]decenylene, 5-oxa-2-azaspiro[3.4]octanylene, 6-oxa-2-azaspiro[3.4]octanylene, 3,9-diazaspiro[5.5]undecanylene, 5-oxa-2-azaspiro[3.5]nonanylene, 1-oxa-9-azaspiro[5.5]undecanylene, 1-oxa-4,9-diazaspiro[5.5]undecanylene, 2,6-diazaspiro[3.3]heptanylene, 2-azaspiro[3.3]heptanylene, 1,5-dioxa-9-azaspiro[5.5]undecanylene, 1,4-dioxa-9-azaspiro[5.5]undecanylene, 5,9-dioxa-2-azaspiro[3.5]nonanylene, 5,8-dioxa-2-azaspiro[3.5]nonanylene, 6-oxa-2-azaspiro[3.5]nonanylene, 1-oxa-7-azaspiro[3.5]nonanylene, 5-oxa-2-azaspiro[3.6]decenylene, 5-oxa-2-azaspiro[3.6]decenylene, 5,9-dioxa-2-azaspiro[3.6]decenylene, 5,8-dioxa-2-azaspiro[3.6]decenylene, and 6,9-dioxa-2-azaspiro[3.6]decenylene, wherein the heterocyclylene is optionally substituted by one or more R^u.
61. The compound of claim 59, wherein Cy¹ is 3- to 12-membered heterocyclylene selected from:



wherein the heterocyclene is optionally substituted by one or more R^u .

62. The compound of any one of claims 58-61, wherein W is absent.

63. The compound of any one of claims 58-62, wherein Z' is absent.

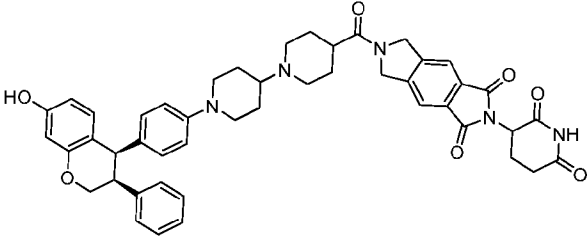
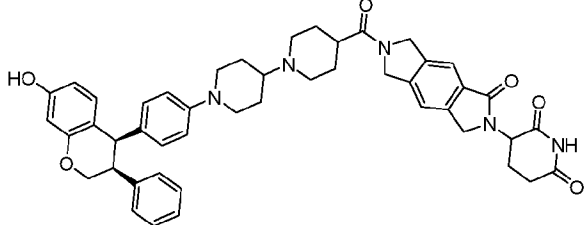
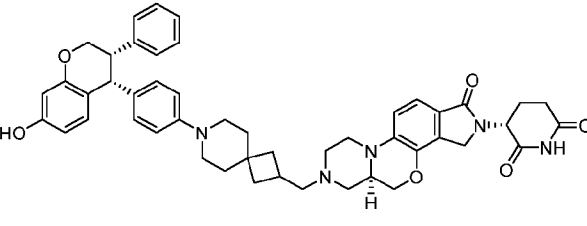
64. The compound of any one of claims 58-62, wherein Z' is $-C(=O)-$, C_{1-6} alkylene, $^*-O-(C_{1-6}$ alkylene)-, $^*-(C_{1-6}$ alkylene)-O-, $^*-C(=O)-(C_{1-6}$ alkylene)-, $^*-(C_{1-6}$ alkylene)- $C(=O)-$, 3- to 12-membered heterocyclene, $^*-C(=O)-(3-$ to 12-membered heterocyclene)-, $^*-(3-$ to 12-membered heterocyclene)- $C(=O)-$, $^*-(3-$ to 12-membered heterocyclene)- $(C_{1-6}$ alkylene)-, $^*-(C_{1-6}$ alkylene)-(3- to 12-membered heterocyclene)- $(C_{1-6}$ alkylene)-, $^*-(C_{1-6}$ alkylene)-(3- to 12-membered heterocyclene)- $C(=O)-$, $^*-(C(=O))-(3-$ to 12-membered heterocyclene)- $(C_{1-6}$ alkylene)-, $^*-(3-$ to 12-membered heterocyclene)- $(C_{1-6}$ alkylene)- $C(=O)-$, $^*-(C(=O))-(C_{1-6}$ alkylene)-(3- to 12-membered heterocyclene)-, $^*-(C_{1-6}$ alkylene)- $C(=O)-(3-$ to 12-membered heterocyclene)-, or $^*-(3-$ to 12-

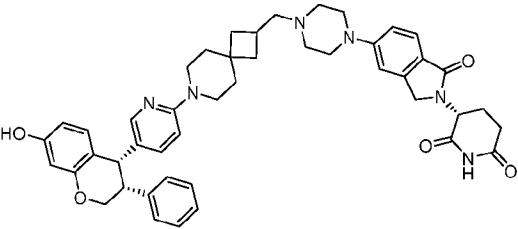
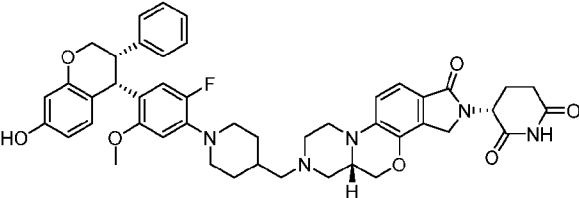
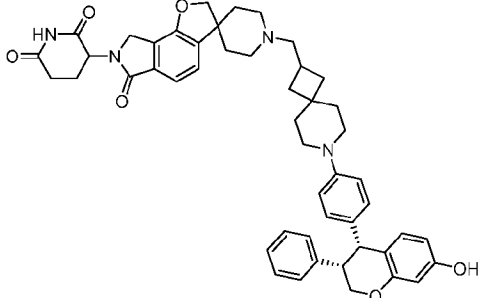
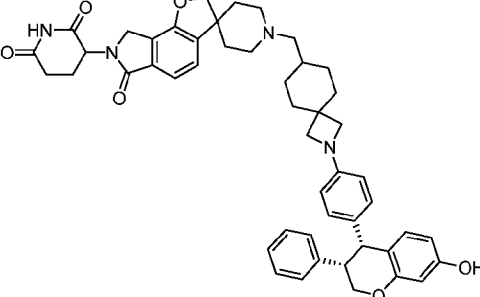
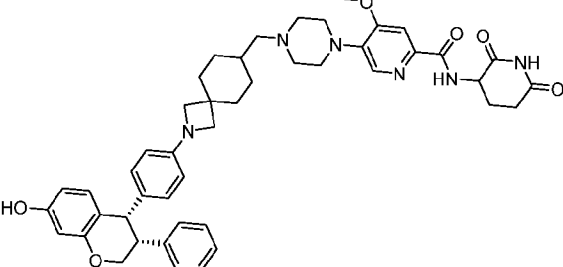
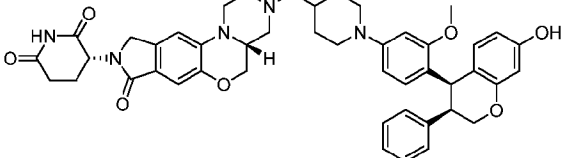
membered heterocyclylene)-(C(=O))-(C₁₋₆ alkylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u, and *denotes attachment to C.

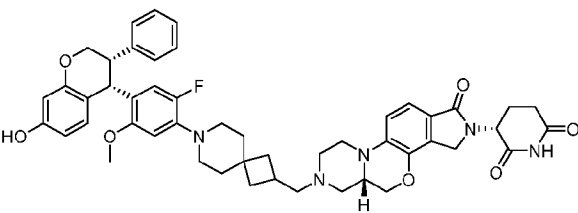
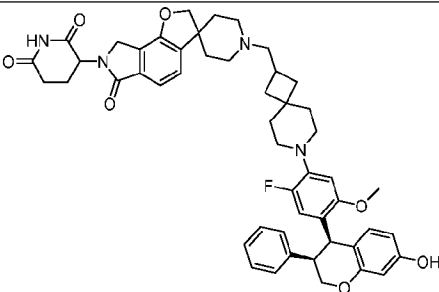
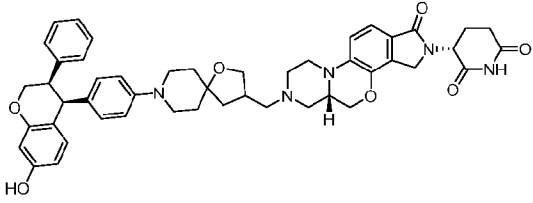
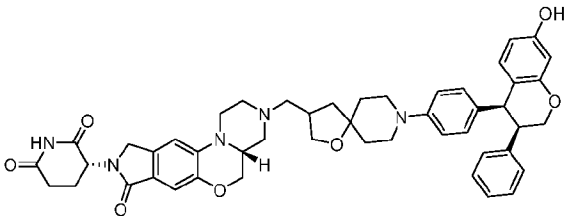
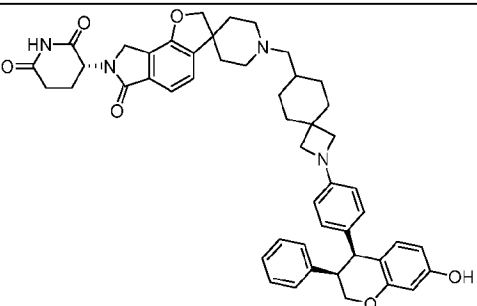
65. The compound of claim 64, wherein Z' is C₁₋₆ alkylene, *-C(=O)-(C₁₋₆ alkylene)-, *-(C₁₋₆ alkylene)-C(=O)-, *-C(=O)-(3- to 12-membered heterocyclylene)-, or *-(3- to 12-membered heterocyclylene)-(C₁₋₆ alkylene)-, wherein the alkylene or heterocyclylene is optionally substituted by one or more R^u, and *denotes attachment to C.

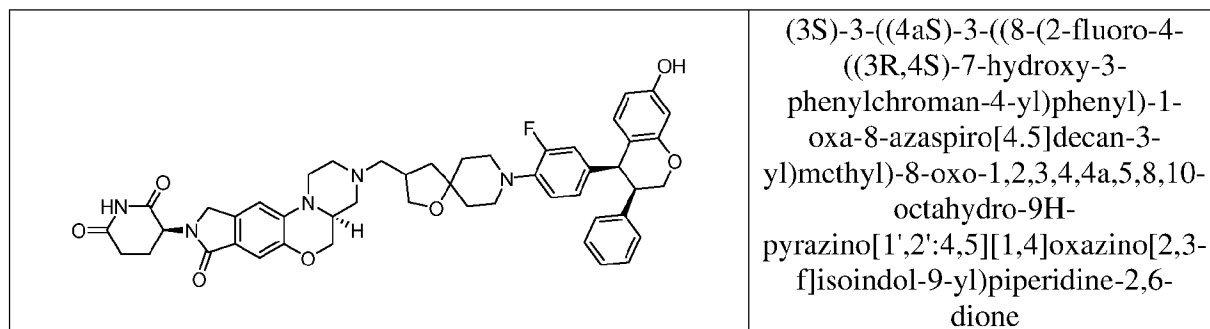
66. A compound selected from the compounds in Tables 1 and 2 or a pharmaceutically acceptable salt thereof.

67. A compound selected from

Structure	Chemical Name
	2-(2,6-dioxopiperidin-3-yl)-6-(1'-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-6,7-dihydropyrrolo[3,4-f]isoindole-1,3(2H,5H)-dione
	3-(6-(1'-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-[1,4'-bipiperidine]-4-carbonyl)-1-oxo-3,5,6,7-tetrahydropyrrolo[3,4-f]isoindol-2(1H)-yl)piperidine-2,6-dione
	(R)-3-((R)-7-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione

	(R)-3-(5-(4-((7-(5-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)pyridin-2-yl)-7-azaspiro[3.5]nonan-2-yl)methyl)piperazin-1-yl)-1-oxoisindolin-2-yl)piperidine-2,6-dione
	(R)-3-((S)-7-((1-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)piperidin-4-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
	3-(1'-((7-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
	3-(1'-((2-(4-((3S,4R)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
	N-(2,6-dioxopiperidin-3-yl)-5-(4-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)piperazin-1-yl)-4-methoxypicolinamide
	(R)-3-((R)-3-((1-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)-3-methoxyphenyl)piperidin-4-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-

	pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
	(R)-3-((S)-7-((7-(2-fluoro-4-((3S,4S)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
	3-(1'-((7-(2-fluoro-4-((3R,4R)-7-hydroxy-3-phenylchroman-4-yl)-5-methoxyphenyl)-7-azaspiro[3.5]nonan-2-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione
	(3R)-3-((5aS)-7-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-1-oxo-1,3,5,5a,6,7,8,9-octahydro-2H-pyrazino[1',2':4,5][1,4]oxazino[2,3-e]isoindol-2-yl)piperidine-2,6-dione
	(3R)-3-((4aR)-3-((8-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-1-oxa-8-azaspiro[4.5]decan-3-yl)methyl)-8-oxo-1,2,3,4,4a,5,8,10-octahydro-9H-pyrazino[1',2':4,5][1,4]oxazino[2,3-f]isoindol-9-yl)piperidine-2,6-dione
	(R)-3-(1'-((2-(4-((3R,4S)-7-hydroxy-3-phenylchroman-4-yl)phenyl)-2-azaspiro[3.5]nonan-7-yl)methyl)-6-oxo-6,8-dihydro-2H,7H-spiro[furo[2,3-e]isoindole-3,4'-piperidin]-7-yl)piperidine-2,6-dione



68. A pharmaceutical composition comprising the compound of any one of claims 1-67, and a pharmaceutically acceptable excipient.
69. A method of degrading an estrogen receptor protein in a patient or biological sample comprising contacting said patient or biological sample with a compound of any one of claims 1-67.
70. Use of a compound of any one of claims 1-67 in the manufacture of a medicament for degrading an estrogen receptor protein in a patient or biological sample.
71. A compound of any one of claims 1-67 for use in degrading an estrogen receptor protein in a patient or biological sample.
72. A method of treating a disease or disorder comprising administering to a patient in need thereof a compound of any one of claims 1-67.
73. Use of a compound of any one of claims 1-67 in the manufacture of a medicament for treating a disease or disorder.
74. A compound of any one of claims 1-67 for use in treating a disease or disorder.
75. The method, use, or compound for use of any one of claims 72-74, wherein the disease or disorder is an estrogen receptor-mediated disease or disorder.

76. The method, use, or compound for use of any one of claims 72-74, wherein the disease or disorder is breast cancer, lung cancer, ovarian cancer, endometrial cancer, prostate cancer, or esophageal cancer.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2023/027435

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D498/14 C07D498/20 C07D487/04 C07D405/14 A61K31/4985
A61K31/438 A61P35/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 2023/183607 A1 (UNIV MICHIGAN [US] ET AL.) 28 September 2023 (2023-09-28) claim 1	1-76
X,P	WO 2022/187588 A1 (UNIV MICHIGAN REGENTS [US]) 9 September 2022 (2022-09-09) claim 1	1-76
X	WO 2021/133886 A1 (ACCUTAR BIOTECHNOLOGY [US]) 1 July 2021 (2021-07-01)	1-6, 44-66, 68-76
Y	claim 1	1-76
X	WO 2021/118629 A1 (ACCUTAR BIOTECHNOLOGY INC [US]) 17 June 2021 (2021-06-17)	1-6, 44-66, 68-76
Y	claim 1	1-76
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance;; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance;; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 October 2023

Date of mailing of the international search report

26/10/2023

Name and mailing address of the ISA/

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Authorized officer

Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2023/027435

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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